Psychopharmacology (2012) 220:647–672
DOI 10.1007/s00213-011-2536-5

REVIEW

Spontaneous object recognition and its relevance to schizophrenia: a review of findings from pharmacological, genetic, lesion and developmental rodent models

L. Lyon · L. M. Saksida · T. J. Bussey

Received: 9 May 2011 / Accepted: 6 October 2011 / Published online: 10 November 2011

Abstract
Rationale Spontaneous (novel) object recognition (SOR) is one of the most widely used rodent behavioural tests. The opportunity for rapid data collection has made SOR a popular choice in studies that explore cognitive impairment in rodent models of schizophrenia, and that test the efficacy of drugs intended to reverse these deficits.
Objectives We provide an overview of the many recent studies that have used SOR to explore the mnemonic effects of manipulation of the key transmitter systems relevant to schizophrenia—the dopamine, glutamate, GABA, acetylcholine, serotonin and cannabinoid systems—alone or in combination. We also review the use of SOR in studying memory in genetically modified mouse models of schizophrenia, as well as in neurodevelopmental and lesion models. We end by discussing the construct and predictive validity, and translational relevance, of SOR with respect to cognitive impairment in schizophrenia.
Results Perturbation of the dopamine or glutamate systems can generate robust and reliable impairment in SOR. Impaired performance is also seen following antagonism of the muscarinic acetylcholine system, or exposure to cannabinoid agonists. Cognitive enhancement has been reported using alpha7-nicotinic acetylcholine receptor agonists and 5-HT_6 antagonists. Among non-pharmacological models, neonatal ventral hippocampal lesions and maternal immune activation can impair SOR, while mixed results have been obtained with mice carrying mutations in schizophrenia risk-associated genes, including neuregulin and COMT.
Conclusions While SOR is not without its limitations, the task represents a useful method for studying manipulations with relevance to cognitive impairment in schizophrenia, as well as the interactions between them.

Keywords Spontaneous object recognition · Novel · Schizophrenia · Memory · Dopamine · Glutamate · Neuregulin · COMT

L. Lyon · L. M. Saksida · T. J. Bussey (✉)
Department of Experimental Psychology,
University of Cambridge,
Downing St,
Cambridge CB2 3EB, UK
e-mail: tjb1000@cam.ac.uk

L. Lyon · L. M. Saksida · T. J. Bussey
The MRC and Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge,
Downing St,
Cambridge CB2 3EB, UK

Introduction

Schizophrenia is a severe psychiatric disorder with great social costs for affected individuals and their caregivers, as well as economic costs for society as a whole. Profound cognitive deficits are also observed in schizophrenia (Goldman-Rakic 1994; Owens and Johnstone 2006) and the severity of these impairments correlates with poor functional outcome (Green 2006). Despite the clear need, however, no treatments have yet been approved for cognitive impairments associated with schizophrenia (CIAS). In an attempt to address this need, the NIMH-sponsored 'Measurement and Treatment Research to Improve Cognition in Schizophrenia' (MATRICS) initiative identified seven of the key cognitive domains impaired in patients, and recommended a battery of neuropsychological tests that could be used to study them. Given that the drug discovery process is heavily dependent upon testing rodent models of impairments in these domains, a 'preclinical

MATRICS' is also required. To this end, Young and colleagues (2009) recently provided a comprehensive overview of the existing rodent tasks that might map onto the cognitive domains identified by MATRICS. The aim of the present review is to examine in more detail one of the most widely used of all these tasks, spontaneous object recognition (SOR).

SOR (sometimes referred to as 'novel object recognition', NOR) is proposed to map onto the MATRICS 'visual learning and memory' domain (Young et al. 2009). SOR exploits the natural tendency of rodents to explore a novel object more than a familiar one, and uses this spontaneous behaviour as an index of memory for a previously presented, and thus now familiar, object. The use of a spontaneous behaviour offers many advantages. Lengthy training in rule acquisition is not required, allowing for rapid data collection. The SOR task is non-aversive, avoiding confounding effects of stress on learning and memory, and performance is unaffected by motivation to work for a food reward. A single cohort of animals can be tested on multiple occasions using different sets of objects, making the SOR task well-suited to pharmacological manipulations that require a within-subjects design. It is also amenable to investigation of stages of memory—encoding, consolidation/storage, retrieval—separately (Nilsson et al. 2007; Winters et al. 2008). These advantages have made SOR a popular choice in studies that explore cognitive impairment in rodent models of schizophrenia, and that test the efficacy of drugs intended to reverse these deficits.

A wealth of evidence has revealed schizophrenia to be a complex, brain-wide disorder that affects multiple transmitter systems, which interact in complex ways. As a relatively straightforward, rapid test of memory, the SOR task may be well-suited to exploring these interactions. The present review will therefore summarise findings from studies that have used SOR to investigate the effects on memory of manipulating neurotransmitter systems relevant to schizophrenia, and to cognitive impairments therein. These include the dopamine, glutamate, GABA, acetylcholine, serotonin and cannabinoid systems. Given their importance in studying schizophrenia aetiology, genetic mouse models that have been tested on SOR, including COMT and neuregulin 1 knockout mice, will also be described. So too will animal models that attempt to reproduce the neurodevelopmental nature of schizophrenia, including maternal immune activation, obstetric complications and neonatal ventral hippocampal lesions. Finally, the construct and predictive validity, as well as the translational relevance, of SOR will be discussed with respect to CIAS. The present review has focused mainly on recent developments in the field; for a review of findings prior to 2007, see Dere et al. (2007). To set these findings in context, however, the origins of the SOR task used in these studies will first be briefly summarised.

A brief history of spontaneous object recognition

Impairments in the ability to recognise a previously encountered object have long been described in human patients that have sustained damage to the medial temporal lobes, the best known example being patient H.M. (Scoville and Milner 1957). Attempts to model these deficits in non-human primates and then rodents led to the development of the delayed nonmatching-to-sample (DNMS) task (Gaffan 1974; Mishkin and Delacour 1975; Aggleton et al. 1986; Rothblat and Hayes 1987; Mumby et al. 1990). In DNMS, subjects are rewarded for choosing the item that was not presented to them in the preceding sample phase. Lesion studies have confirmed the importance of the medial temporal lobes in mediating this task, although the relative contribution of the hippocampus and the surrounding cortical areas, most notably perirhinal cortex, has been a matter of ongoing debate (see Winters et al. 2008, 2010 for discussion).

A shift in direction occurred with the realisation that both primates and rodents display a spontaneous preference for exploring novel over familiar items, and that this innate tendency can be used to test memory for a previously encountered item, without the requirement for additional reward, or for prolonged training in the nonmatching-to-sample rule. In the first report of the spontaneous one-trial object recognition (SOR) task, Ennaceur and Delacour (1988) described how a rat that had been allowed to explore two copies of a sample object in an arena would, upon being returned to that arena 24 h later, prefer to explore a novel object over a new copy of the sample object. Preference for the novel object can be expressed quantitatively as a discrimination ratio (DR), sometimes called a 'D2 score' (e.g. Aggleton et al. 1997), where $DR = (n-f)/(n+f)$, with 'n' being the time spent exploring the novel object, and 'f' being the time spent exploring the familiar object. This measure takes into account differences between animals in their overall exploration levels. As with DNMS, performance in SOR has been reported to be impaired by lesions of rhinal cortex (Bussey et al. 1999, 2000; Ennaceur et al. 1996), although not usually by hippocampal damage (Winters et al. 2004; Forwood et al. 2005; but see e.g. Clark et al. 2000). The SOR task thus employs the same principle as DNMS, but a quantitative index of memory can now be obtained in a single trial.

The value of the SOR task is greatly increased, however, if multiple trials are run using different sample-choice intervals ('delays'). This is because factors other than memory can affect an animal's performance on SOR, including their activity levels, motivation, perceptual skills and innate novelty preference. By lengthening the delay, an experimenter can increase the memory load while leaving these non-mnemonic factors

largely unchanged.[1] To conclude definitively that a perturbation affects memory selectively one needs, at minimum, to show that performance is spared at a short delay. Similarly, if one tests at a single delay and obtains no effect, it is not appropriate to claim that OR is *normal*. Perhaps there is a relatively subtle impairment, or improvement, that could be revealed by testing at longer delays. Thus, to support the claim that a perturbation leaves OR intact, testing at a long delay, which brings control performance down from ceiling, is required. The use of multiple delays thus provides an important within-study control to help confirm that an experimental manipulation specifically affects recognition memory.

SOR in studying transmitter systems relevant to cognitive impairment in schizophrenia

Dopamine

The original neurotransmitter system-centred hypothesis of schizophrenia was the 'dopamine hypothesis'; the idea that psychotic symptoms could be attributed to excessive activation of the dopaminergic system (Carlsson and Lindqvist 1963). This was based largely on two lines of evidence: drugs that stimulate endogenous dopamine release, such as amphetamine, can be psychotomimetic, while drugs that antagonise D2 receptors are antipsychotic; their antipsychotic efficacy correlating with their D2 receptor occupancy (Seeman and Lee 1975; Creese et al. 1976; Kapur and Remington 2001). In 1991, this generalised dopamine overactivity hypothesis was modified to account for the negative and cognitive symptoms of schizophrenia (Davis et al. 1991). Imaging studies had revealed hypofunction of prefrontal cortex in schizophrenia patients, accompanied by hypoactivation of D1 receptors, which appeared to contribute to the cognitive deficits. The dopamine hypothesis was therefore revised to allow for differential changes in individual dopaminergic pathways, each accounting for distinct arrays of symptoms. Thus, hypofunction of the mesocortical dopamine system may generate negative symptoms and cognitive impairments, while hyperactivity of mesolimbic and mesostriatal pathways may contribute to positive symptoms.

Stimulation of the dopamine system using methamphetamine has long been used to model schizophrenia. Although the primary focus has been on modelling positive symptoms, in humans methamphetamine use also induces cognitive impairments in multiple domains, including decision making, attention and delayed visuospatial memory (Scott et al. 2007; Kalechstein et al. 2003). In rodents, methamphetamine consistently impairs SOR (Table 1). An acute dose reduced novel object exploration with delays ranging across studies from 1 h to 24 h (1 h, Herring et al. 2008; 1.5 h and 24 h, Schroder et al. 2003; 1.5 h, Belcher et al. 2008; 2 h, Camarasa et al. 2010). However, subchronic methamphetamine impaired SOR with a 24-h delay (Kamei et al. 2006; Noda et al. 2010) but had no effect with a 1-h delay (Kamei et al. 2006). Repeated methamphetamine exposure is believed to trigger pharmacodynamic adaptations that attenuate the drug's deleterious effects. Consistent with this, rats that had been exposed to an escalating dose regime were unimpaired in SOR with delays of 3, 4 or 24 h (Clark et al. 2007), and were less impaired following a subsequent acute dose than previously drug-naïve animals (90 min; Belcher et al. 2008). Rats that had repeatedly self-administered methamphetamine, however, were impaired with a delay of either 90 min or 24 h (Reichel et al. 2011). Unfortunately, none of the methamphetamine studies assessed performance using a delay of less than 1 h; the extent to which the observed impairments reflect specific effects on memory is thus unknown.

Methamphetamine has been shown to reduce radioligand binding of dopamine and the dopamine reporter DAT in the striatum, as well as serotonin and the serotonin transporter SERT in the hippocampus and perirhinal cortex (Schroder et al. 2003; Herring et al. 2008; Belcher et al. 2008). The effects of methamphetamine may also impinge upon the glutamatergic and cholinergic systems: a methamphetamine-induced deficit could be rescued by pretreatment with the NMDA and α7-nicotinic acetylcholine receptor (α7-nAChR) antagonist, memantine (2 h, Camarasa et al. 2010), although the mechanism behind this effect is unknown. The mGluR5 positive allosteric modulator CDPPB also reversed a methamphetamine-induced deficit with a delay of 90 min, but not 24 h (Reichel et al. 2011) (see 'Metabotropic glutamate receptors').

Dopamine receptors are metabotropic G protein-coupled receptors, which are divided into two groups: D1-like (D1 and D5) and D2-like (D2, D3, D4). Systemic administration of the D1 antagonist SCH23390 prior to daily methamphetamine administration abolished the deleterious effects of methamphetamine on SOR, while the D2 antagonist raclopride had no effect (Kamei et al. 2006). The same group found that microinjection of a D1 antagonist bilaterally into prefrontal cortex (PFC) also impaired SOR with a 24-h delay, although not with a 1-h delay (Nagai et

[1] There is evidence to suggest that the same structures within the temporal lobe mediate both memory for objects and perceptual discrimination between them (e.g. Cowell et al. 2006; Bussey and Saksida 2005). Thus, perirhinal cortex lesions impair SOR at longer but not shorter delays when standard objects are used, but when perceptually similar objects are used such lesions can produce impairments when there is little or no delay (Bartko et al. 2007). Nevertheless, short delays should be included in experiments using standard objects to rule out gross perceptual (e.g. visual acuity) deficits as a possible reason for impairment at longer delays.

Table 1 Effects of methamphetamine on SOR

Methamphetamine dosing regime	Species and strain	Delay	Effect on SOR	Reference
Acute	S-D rat	1.5 h, 24 h	Impaired	Schroder et al. 2003
Acute	S-D rat	1 h	Impaired	Herring et al. 2008
Acute	L-E rat	2 h	Impaired. Impairment reduced by memantine	Camarasa et al. 2010
Acute/escalating dose followed by acute challenge	S-D rat	1.5 h	Impaired. Exposure to escalating dose regime reduced the deleterious effects of the acute challenge	Belcher et al. 2008
Escalating dose	S-D rat	3 h, 4 h, 24 h	No significant effect	Clark et al. 2007
Self-administered	L-E rat	1.5 h, 24 h	Impaired. 1.5 h, but not 24 h, impairment reduced by CDPPB (mGluR5 PAM)	Reichel et al. 2011
Subchronic	ICR mouse	24 h	Impaired. Impairment reduced by galantamine but not by donepezil	Noda et al. 2010
Subchronic	ICR mouse	1 h, 24 h	Impaired with 24 h, but not 1 h, delay Impairment reduced by clozapine or SCH 23390 (D1 antagonist) Haloperidol and raclopride (D2 antagonist) had no effect	Kamei et al. 2006

L-E Long Evans, *S-D* Sprague Dawley, *PAM* positive allosteric modulator

al. 2007). Kamei and colleagues propose that exposure to a novel object may typically activate D1 receptors in PFC, leading ultimately, via activation of the ERK1/2 signalling pathway (Zanassi et al. 2001), to protein synthesis required for the consolidation of long-term, but not short-term, recognition memory. Subchronic methamphetamine may induce overstimulation of PFC D1 receptors, leading to downregulation of the ERK1/2 signalling pathway and impaired SOR.

The fact that selective delivery of a D1 antagonist into PFC impaired SOR may appear surprising, given that PFC lesions have little effect on SOR in rats (15 min, Ennaceur et al. 1997; 24 hr, Mitchell and Laiacona 1998; 105 min, Hannesson et al. 2004), although they are thought to impair recency judgments (Mitchell and Laiacona 1998; Hannesson et al. 2004). Nevertheless, it has also been suggested that increased PFC dopamine and/or acetylcholine release may underpin the improvements in SOR induced by the D3 antagonist S33138 (4 h; Millan et al. 2008, 2010) and the D4 receptor agonist A-412997 (24 h; Woolley et al. 2008). Since both of these drugs were given systemically, their effect on SOR may well have been mediated outside the PFC (see Beaulieu and Gainetdinov 2011), although the D4 agonist had no effect on hippocampal noradrenaline or acetylcholine release. Another D4 agonist, PD168077, also improved SOR with a 6-h delay, and reduced the impairment induced by subchronic treatment with the NMDA receptor antagonist, phencyclidine, with a 1-min delay (Sood et al. 2010). The D4 receptor has been implicated in novelty-seeking (Ebstein et al. 1996) and D4 expression/function may be altered in schizophrenia (Seeman et al. 1993; Lung et al. 2009). Whether D4 agonists/D3 antagonists would enhance human recognition memory, however, remains to be determined. Despite similarities between the D2 and D3 receptor, the D2 antagonist raclopride had no effect on SOR with delays of 1 or 24 h (Kamei et al. 2006; Nagai et al. 2007). While raclopride did appear to impair SOR with a 1-min delay, impaired performance was seen at doses that also reduced both sample and choice phase exploration (Woolley et al. 2003), arguing against a specific effect on memory.

Glutamate

After dopamine, the neurotransmitter at the forefront of most schizophrenia research has likely been glutamate (see e.g. Coyle 2006 for review). Glutamate binds to two classes of receptors: ionotropic and metabotropic. Ionotropic receptors are ligand-gated ion channels, which are subdivided into three families: NMDA, AMPA and kainate receptors. NMDA receptor antagonists are psychotomimetic in healthy individuals, inducing symptoms such as altered perception, thought disorder and impaired cognition (Krystal et al. 1994; Adler et al. 1999). NMDA receptor antagonists also worsen symptoms in existing schizophrenia patients (Lahti et al. 1995). These effects are believed to result from a disinhibition of glutamate release following blockade of NMDA receptors on GABAergic interneurons (Greene 2001). Many of the most promising candidate schizophrenia susceptibility genes interact with the glutamatergic system (Harrison and Weinberger 2005) and there is some evidence from post-mortem studies, as well as brain imaging, for NMDA receptor hypofunction in schizophrenia. Pharmacological challenge with either acute or subchronic administration of an NMDA receptor antagonist is one of the most widely used animal models of schizophrenia, particularly for

modelling negative symptoms and cognitive deficits. Addressing whether and how the induced deficits can be reversed using other pharmacological agents is, in turn, one of the most popular uses of the SOR task.

NMDA receptor antagonists may be either competitive—competing with the endogenous ligand for access to the binding site, for example AP5—or uncompetitive, binding to a site within the open NMDA receptor channel, for example ketamine, MK-801 or phencyclidine. AP5 has been shown to selectively impair SOR performance when relatively long delays are used (although see Puma and Bizot 1998 in which intra-septal infusion improved SOR with a 24-h delay, but had no effect with a 45-min delay). Pre-sample intra-hippocampal infusion impaired SOR with a delay of 3 h, but not with a delay of 5 min (Baker and Kim 2002). The same result was obtained using pre-sample intra-perirhinal cortex infusion (Winters and Bussey 2005a). In both cases, the intact performance with the shorter delay argues against non-specific actions of the drug on perception, motivation or novelty preference. Pre-sample intra-perirhinal cortex AP5 additionally impaired SOR with a 25-min delay (Abe et al. 2004). When AP5 was infused into the perirhinal cortex post-sample, it impaired SOR with a 180-min delay, but had no effect when infused immediately prior to the choice phase (Winters and Bussey 2005a). This suggests a role for NMDARs in the activity-dependent plasticity required for encoding and consolidation of long-term recognition memory, but not for retrieval. Due to the motoric side-effects that can often accompany AP5, however, as well as its reported inability to cross the blood–brain barrier, more recent studies have tended to use the uncompetitive antagonists, which will thus be described in more detail.

MK-801

Consistent with data from AP5 studies, systemic pre-sample MK-801 impaired SOR in both rats and mice with a delay of 1.5 h or 24 h (de Lima et al. 2005; Nilsson et al. 2007). This implies an essential role for NMDARs in object memory acquisition. An impairment was also seen at both delays in rats with post-sample MK-801 (de Lima et al. 2005), which would support NMDAR involvement in consolidation. Conversely, Nilsson et al. (2007) observed no effect of post-sample MK-801 using a 26-h delay, and enhanced performance with a 1.5-h delay. The reason for this discrepancy is unclear, but may reflect species differences, or at least the particular strain of mice used by Nilsson and colleagues. The vehicle-treated NMR1 mice consistently displayed a relatively weak novelty preference, which may potentially have led to floor effects.

Several putative cognitive enhancers have been shown to reduce the deficit in SOR induced by pre-sample MK-801: an α7-nicotinic acetylcholine receptor (α7-nAChR) agonist improved performance with a 1-h delay (Roncarati et al. 2009), as did an mGluR5 positive allosteric modulator (PAM) with a 24-h delay (Uslaner et al. 2009). A glycine transporter (GlyT1) inhibitor and D-serine each rescued an MK-801-induced impairment with a 2-h delay (Karasawa et al. 2008), while D-serine was also effective with a 24-h delay (Smith et al. 2009b). Glycine and D-serine are ligands for the glycine modulatory site (GMS); a site on the NMDA receptor that must be occupied if glutamate is to be able to open the channel. Increased activation of the GMS may offer the possibility of selectively enhancing phasic NMDA receptor activation, whilst avoiding the increase in tonic activation that would risk excitotoxicity. GMS (partial) agonists are thus being investigated as potential adjunctive therapies in schizophrenia. While mice that lacked the synthetic enzyme for D-serine were not impaired in SOR with a 1-min delay (Devito et al. 2010), mice that lacked GlyT1 in forebrain neurons showed better SOR performance than wild-type controls with a 2-h delay (Singer et al. 2007). Importantly, the GlyT1 knockout mice did not show enhanced performance with a 2-min delay, increasing confidence that the improvement seen after 2 h reflects a specific effect on memory.

Phencyclidine (PCP)

Subchronic PCP is one of the most widely used pharmacological models of negative symptoms and cognitive impairment in schizophrenia. PCP induces robust deficits in SOR with delays as short as 1 min (Grayson et al. 2007; McLean et al. 2009; Snigdha et al. 2010; Sood et al. 2010; Damgaard et al. 2011; Arnt et al. 2010) (but see Hashimoto et al. 2005). This does mean, however, that effects on memory versus those on perceptual or motivational factors can be difficult to disentangle.

PCP-induced SOR deficits can be reversed by compounds that target many different transmitter systems (Table 2). Clozapine and risperidone, but not haloperidol, each reduced PCP-induced deficits when a 1-min delay was used (Grayson et al. 2007). Clozapine also rescued performance with a 1-h delay (Vigano et al. 2009), although risperidone had no effect with this sample-choice interval (McKibben et al. 2010). It has been suggested that an increase in dopamine release may constitute one possible mechanism for reversing PCP-induced impairments. Consistent with this hypothesis, the putative novel antipsychotic asenapine rescued a PCP-induced deficit with a 1-min delay; the rescue effect could be blocked by a D1 antagonist but not by a 5-HT1A antagonist (Snigdha et al. 2010). Asenapine has been shown to increase mPFC and hippocampal dopamine release (Huang et al. 2008; Franberg et al. 2009). I-SPD-A, another putative antipsychotic with D1 agonist/5-HT1A

Table 2 Results from studies that have administered pharmacological agents (listed in column 1) in an attempt to reverse subchronic PCP-induced SOR impairments

Agent administered in an attempt to reverse PCP-induced SOR impairment	Species and strain	Delay	Effect on PCP-induced SOR impairment	Reference
Haloperidol	L-H rat	1 min	No significant effect	Grayson et al. 2007
Clozapine			Reduced	
Risperidone			Reduced	
Haloperidol	ICR mouse	24 h	No significant effect	Nagai et al. 2007
Aripiprazole			Reduced. Rescue effect blocked by SCH 23390 (D1 antagonist) or WAY100635 (5-HT1A antagonist), but not by raclopride (D2 antagonist)	
SKF-38393 (D1-like receptor agonist)	L-H rat	1 min	Reduced	McLean et al. 2009
I-SPD-A (D1 agonist/D2 antagonist/ 5-HT1A partial agonist)	S-D rat	24 h	Reduced	Guo et al. 2009
Clozapine			Reduced	
Asenapine	L-H rat	1 min	Reduced. Rescue effect blocked by SCH 23390 but not by WAY100635	Snigdha et al. 2010
Risperidone (subchronic)	L-H rat	1 h	No significant effect	McKibben et al. 2010
Clozapine	L-H rat	1 h	Reduced Δ9-tetrahydrocannabinol (THC) worsened the PCP-induced impairment	Vigano et al. 2009
MKC-231 (choline uptake inhibitor)	S-D rat	24 h	Reduced	Shirayama et al. 2007
SSR180711 (α7-nAChR agonist)	ICR mouse	24 h	Reduced	Hashimoto et al. 2008
SSR180711 (α7-nAChR agonist)	S-D or Wistar rat	1.5 h	Reduced	Pichat et al. 2007
PNU-282987 (α7-nAChR agonist)	L-H rat	1 min	Reduced	McLean et al. 2011
Donepezil	ICR mouse	24 h	Reduced	Kunitachi et al. 2009
Physostigmine			No significant effect	
PD168077 (D4 agonist)	Rat	1 min	Reduced	Sood et al. 2010
CX546 (AMPAkine)	L-H rat	1 min	Reduced	Damgaard et al. 2010
CX516 (AMPAkine)			Reduced	
Gaboxadol [extrasynaptic GABA(A) receptor agonist]	L-H rat	1 min	Reduced	Damgaard et al. 2011
AA29504 [positive modulator of extrasynaptic GABA(A) receptors]			Reduced	
Lu AE58054 (5-HT6 antagonist)	S-D rat	1 min	Reduced	Arnt et al. 2010

L–H Lister Hooded, *S-D* Sprague Dawley

partial agonist/D2 antagonist efficacy, also rescued a PCP-induced deficit with a 24-h delay (Guo et al. 2009). So too did aripiprazole, acting via a D1/5-HT1A-dependent mechanism (Nagai et al. 2009). These groups propose that activation of 5-HT1A receptors induces PFC dopamine release, which then rescues SOR performance. The mechanism by which this rescue effect might occur, however, is unclear. It should also be noted that the effects of these compounds are unlikely to be limited to the dopaminergic system. Aripiprazole additionally increased serotonin release in rat mPFC (Bortolozzi et al. 2007), while asenapine increased release of both noradrenaline and acetylcholine in mPFC and hippocampus (Huang et al. 2008).

Consistent with an interaction between the cholinergic and dopaminergic systems, a D1 receptor agonist that rescued a PCP-induced SOR deficit (1 min; McLean et al. 2009) has previously been shown to increase hippocampal acetylcholine release (Hersi et al. 1995). Upregulation of cholinergic activity may attenuate the effects of PCP on SOR. Thus, an α7-nAChR agonist reduced a PCP-induced SOR impairment with a delay of 90 min (Pichat et al. 2007) or 24 h (Hashimoto et al. 2008). The choline-uptake inhibitor, MKC-231, also reduced a PCP-induced deficit with a 24-h delay (Shirayama et al. 2007), as did the cholinesterase inhibitor, donepezil; the weaker cholinesterase inhibitor, physostigmine, however, was ineffective (Kunitachi et al. 2009). If increased acetylcholine and dopamine release attenuate PCP-induced deficits, this may account for the beneficial effect of the 5-HT6 antagonist, Lu AE58054 (1 min; Arnt et al. 2010). 5-HT6 receptors are heteroreceptors, thought to modulate the release of multiple transmitters including dopamine, glutamate and acetylcho-

line indirectly via a reduction in GABAergic tone (Marcos et al. 2006). Conversely, upregulation of GABAergic transmission has also been shown to reverse the effects of PCP, again with a 1-min delay (Damgaard et al. 2011). This is consistent with the increasing evidence suggesting that many of the deleterious effects of NMDA receptor antagonists may actually result from *disinhibition* of glutamatergic transmission (see 'GABA').

Memantine

An exception to the rule that NMDA receptor antagonism impairs SOR, the dual NMDA receptor and α7-nAChR antagonist, memantine, reduced a methamphetamine-induced SOR impairment with a 2-h delay (Camarasa et al. 2010). The mechanism behind this effect is unknown but may involve an anxiolytic action. Memantine also improved the SOR performance of 2-year-old rats with a 24-h delay, but not with a 1.5-h delay, as well as reducing oxidative stress damage to proteins in the hippocampus and PFC (Pietá Dias et al. 2007). Again, the mechanism behind the improvement in SOR is unclear. Pieta-Dias and colleagues suggest that oxidative stress damage triggered by NMDA receptor overstimulation may contribute to cognitive decline in normal ageing, with memantine able to reduce this damage. When memantine was given to young healthy adults, however, it actually impaired recognition memory for line drawings of objects (Rammsayer 2001). In schizophrenia patients, memantine has had little effect on cognition (Krivoy et al. 2008; Lieberman et al. 2009), although effects on recognition memory *per se* have yet to be studied.

Metabotropic glutamate receptors (mGluRs)

Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors, which are pharmacologically and structurally classified into three groups: I, comprising mGluR1 and 5; II, mGluR2 and 3; and III, mGluR4, 6, 7 and 8. Activation of group I/II mGluRs within perirhinal cortex may be required for the encoding of long-term recognition memory. Pre-sample intra-perirhinal co-infusion of MPEP (a group I, preferentially mGluR5, antagonist) and LY341495 (a group II mGluR antagonist) impaired SOR with a 24-h delay (Barker et al. 2006). Performance was unimpaired with a 15-min delay, making it unlikely that non-specific changes in perception, alertness or attention could explain the 24-h deficit. Post-sample or pre-choice co-administration of the group I/II antagonists had no effect, suggesting that mGluRs are required specifically for memory acquisition/encoding, rather than later-acting consolidation mechanisms. Administration of either drug alone was also without effect. Reductions in neuronal firing within perirhinal cortex may signal the relative familiarity of stimuli (Brown and Xiang 1998; Warburton et al. 2003). These reductions in neuronal activity may occur via mGluR-dependent long-term depression (LTD) (Brown and Bashir 2002).

Pharmacological manipulation of mGluRs may offer the possibility of cognitive enhancement. An mGluR5 PAM reversed the deleterious effects of methamphetamine with a delay of 90 min, but not 24 h (Reichel et al. 2011). Given that methamphetamine also reduced mGluR5 expression in perirhinal cortex, Reichel and colleagues propose that mGluR5 upregulation may compensate for this reduction and restore mGluR5-dependent LTD. Other mGluR5 PAMs have been shown to facilitate SOR with a delay of 24 h (Liu et al. 2008; Uslaner et al. 2009), possibly via enhanced NMDA receptor-dependent synaptic plasticity. Consistent with this observation, an mGluR5 PAM and an mGluR5 agonist each reduced ketamine-induced deficits with a 24-h delay (Chan et al. 2008). The mGluR2/3 agonist, LY379268, may also have cognitive enhancing potential. LY379268 improved SOR when a 4-h delay was used (Jones et al. 2010). It also rescued the impairment in SOR induced by isolation rearing (2-h delay). Unfortunately, however, LY379268-treated group-housed animals did not show significant novel object preference, making the results more difficult to interpret. An mGluR2/3 agonist prodrug is currently undergoing phase II clinical trials as a novel antipsychotic agent (Patil et al. 2007), but the effects of this drug on human cognition are as yet unknown.

GABA

NMDA receptors expressed on GABAergic interneurons are more sensitive to NMDA receptor antagonists than are their pyramidal cell equivalents. Increasing evidence suggests that many of the deleterious effects of NMDA receptor antagonists may, in fact, result from a reduction in the firing of inhibitory interneurons (Grunze et al. 1996) and the consequent *increase* in pyramidal cell firing (Jackson et al. 2004). Seemingly consistent with this, schizophrenic patients have been shown to display increased brain metabolic activity that is predictive of cognitive impairment (Friston et al. 1992; Malaspina et al. 2004; Heckers et al. 1998), while a group II mGluR agonist, which inhibits glutamate release, is able to reverse working memory impairments induced by PCP (Moghaddam and Adams 1998).

A reduction in the expression of parvalbumin and of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD), is well-documented in schizophrenia (Woo et al. 1997; Lewis et al. 2005; Zhang et al. 2002). There is also evidence for reduced expression in PFC of several GABA (A) receptor subunits, including components both of synaptic receptors (which mediate phasic inhibition) and

extrasynaptic receptors (tonic inhibition) (Hashimoto et al. 2008). Upregulation of extrasynaptic GABA(A) receptor function was found to reduce the impairment in SOR induced by subchronic PCP with a 1-min delay (Damgaard et al. 2011), suggesting that upregulation of tonic inhibition may be therapeutically beneficial. However, mice with increased GABA(A) receptor accumulation at postsynaptic inhibitory synaptic specialisations on CA3 pyramidal neurons displayed unaltered SOR performance with a 24-h delay (Tretter et al. 2009). Mice overexpressing the GABA transporter GAT1 were impaired in SOR with delays of 1 h or 24 h (Hu et al. 2004). Since these mice were also significantly impaired at a zero delay compared to wild-type littermates, at least some of this deficit is likely to have been non-mnemonic in origin.

Acetylcholine

While dysfunction of neocortical and hippocampal cholinergic neurotransmission has traditionally been associated with cognitive impairment in Alzheimer's disease (AD), there is some evidence that perturbations of cholinergic function, mediated either by muscarinic acetylcholine receptors (mAChRs) or by nicotinic receptors (nAChRs), may also contribute to impaired cognition in schizophrenia (see Raedler et al. 2007 for review). Moreover, although the cholinergic system is not considered to be clozapine's principle target, the drug's major metabolite does trigger increased release of both acetylcholine and dopamine via agonist actions at mAChRs (Li et al. 2008).

Muscarinic AChRs (ChRMs)

An M1 preferring agonist improved SOR performance with a 2- or 24-h delay (Bradley et al. 2010; Johnson et al. 2010). Conversely, pre-sample administration of the muscarinic receptor antagonist scopolamine reliably impaired SOR with delays ranging across studies from 1 min to 24 h (1 min, Woolley et al. 2003; 15 min, De Bruin and Pouzet 2006; 60 min, Hirst et al. 2008 and Boultadakis et al. 2010; 180 min, Ballaz et al. 2007; 90 min and 24 h, Botton et al. 2010). Pre-sample infusion of scopolamine directly into perirhinal cortex also impaired SOR (20 min, Warburton et al. 2003; 25 min, Abe et al. 2004; 24 h, Winters et al. 2006), as did selective lesions of the cholinergic basal forebrain input to perirhinal cortex (15 min; Winters and Bussey 2005b). The effects of post-sample scopolamine infusion are more complex (Warburton et al. 2003; Winters et al. 2006) but, overall, the data suggest that cholinergic transmission may influence object memory acquisition/encoding rather than consolidation.

Scopolamine has been shown to impair cognitive performance in healthy human subjects and to worsen existing cognitive deficits in schizophrenia (Minzenberg et al. 2004). These effects are generally considered to reflect deleterious effects on attention, however (Jones and Higgins 1995; Sarter and Bruno 1997). Given that activation of the cholinergic system may also contribute to the fine-tuning of receptive fields (Rasmusson 2000), it is possible that some of the disruptive effects of scopolamine on SOR may likewise reflect altered perception and/or attention. However, there is evidence that cortical acetylcholine may contribute to synaptic plasticity processes. Activation of cholinergic receptors *in vitro* induced an NMDA receptor-independent form of LTD (Massey et al. 2001). Intra-perirhinal infusion of scopolamine disrupted the reduction in neuronal activity that typically occurs in this region in response to repeated presentation of visual stimuli, and also blocked LTD induction in perirhinal slices (Warburton et al. 2003). This would appear to suggest that cholinergic transmission within perirhinal cortex may play a direct role in object memory encoding, and that this process may be disrupted by scopolamine.

Scopolamine-induced impairments in SOR can be reversed by a diverse array of compounds acting via many different receptors and transmitter systems. These include cholinesterase inhibitors, such as donepezil (6 h; Sambeth et al. 2007) and galantamine (15 min; De Bruin and Pouzet 2006). The serotonergic system can also regulate cholinergic transmission (Shirazi-Southall et al. 2002; Steckler and Sahgal 1995). A 5-HT6 antagonist reversed the effects of scopolamine (1 min; Woolley et al. 2003) as did the 5-HT1A antagonist, WAY-101405 (Hirst et al. 2008). WAY-101405 rescued a scopolamine-induced impairment with a 1-h delay and increased hippocampal acetylcholine release; a low dose also significantly improved SOR with a 48-h delay when co-administered with a low dose of donepezil. The nitric oxide-releasing agent NCX 2057 reversed a scopolamine-induced SOR deficit with a 1-h delay (Boultadakis et al. 2010), again possibly via potentiated acetylcholine release (Prast and Philippu 2001). Lastly, caffeine reversed the deleterious effects of scopolamine at both 90-min and 24-h delays (Botton et al. 2010). Caffeine has previously been shown to increase cholinergic transmission via antagonism of adenosine A1 and A2A receptors (Van Dort et al. 2009). In humans, caffeine attenuated the deleterious effects of scopolamine on free recall (Riedel et al. 1995) while chronic caffeine consumption may reduce cognitive decline in AD (Maia and de Mendonca 2002; Ritchie et al. 2007), although its effects in schizophrenia are unknown.

Many of these compounds are likely to act upon more than one target, and to affect multiple transmitter systems to differing degrees. The cholinesterase inhibitor, galantamine, for example, is also an α7-nAChR PAM (Albuquerque et al. 1997). Galantamine, but not donepezil, reduced a methamphetamine-induced SOR

impairment with a 24-h delay (Noda et al. 2010). The rescue effect was accompanied by increased PFC dopamine release, and could be blocked by a D1 receptor antagonist or by mecamylamine—a nAChR antagonist that also prevented the increase in dopamine levels.

Nicotinic AChRs (nAChRs)

Schizophrenia and the nicotinic acetylcholine system are closely linked. More than 80% of schizophrenia patients smoke tobacco, compared to approximately 25% of the general population (de Leon and Diaz 2005), with smoking often beginning in the prodromal phase of the disorder, prior to full symptom onset (Weiser et al. 2004). The genetic locus of the α7-nAChR subunit, 15q14, has been repeatedly linked to schizophrenia (Freedman and Leonard 2001; Freedman et al. 2001; Leonard et al. 1998; Stober et al. 2000; Riley et al. 2000), while expression of CHRNA7, the gene encoding the α7-nAChR subunit, is reduced in post-mortem tissue from patients (Freedman et al. 1995; Marutle et al. 2001). The α7-nAChR receptor has been chosen as a major target for drug development by MATRICS (Bromley 2005).

A number of different α7-nAChR receptor agonists have been shown to improve performance in SOR (Table 3). The majority of these studies used only a 24-h delay (Wishka et al. 2006; Boess et al. 2007; Hauser et al. 2009; Hashimoto et al. 2008), although improvements were also seen at 15 min (Sydserff et al. 2009) and 48 h (Wallace et al. 2011). Pichat and colleagues (2007) observed improved SOR with a 24-h delay in rats and a 48-h delay in mice. While the precise mechanism by which α7-nAChR receptor agonists enhance SOR performance is unclear, activation of α7-nAChR receptors *in vitro* and *in vivo* has been shown to increase extracellular concentrations of multiple transmitters and modulators, including glutamate, acetylcholine and dopamine (Radcliffe and Dani 1998; Biton et al. 2007).

The partial α7-nAChR agonist, SSR180711, for example, improved SOR in rats with a 24-h delay and increased extracellular dopamine levels (albeit this was measured only in the PFC which, as discussed above, is not thought to be necessary for normal SOR performance). The increase in dopamine was blocked by the α7-nAChR antagonist, MLA (Pichat et al. 2007). Another α7-nAChR agonist, AZD0328, improved SOR in mice with a 15-min delay, and increased both extracellular PFC dopamine and the excitability of midbrain dopaminergic ventral tegmental area neurons in rats (Sydserff et al. 2009).

Upregulation of α7-nAChR function has also been shown to reverse the deleterious effects of NMDA receptor antagonism on SOR. Acute treatment with the α7-nAChR agonist, PNU-282987, reversed a subchronic PCP-induced impairment seen with a 1-min delay (McLean et al. 2011), while subchronic, but not acute, treatment with SSR180711 reversed an impairment with a 24-h delay (Hashimoto et al. 2008). Acute SSR180711 also reversed the effects of an acute PCP challenge in rats that had previously been exposed to subchronic PCP (90 min; Pichat et al. 2007). Furthermore, α7-nAChR agonism reversed the effects of MK-801 with a 1-h delay (Roncarati et al. 2009; Pichat et al. 2007). The rescue effect occurred even when MK-801 and the α7-nAChR agonist were co-administered immediately after the sample phase. This suggests that α7-nAChR activation may help to counter the deleterious effects of

Table 3 α7-nicotinic acetylcholine receptor agonists have been shown to improve SOR performance and to reduce the deleterious effects of scopolamine, MK-801 and PCP

α7-nAChR agonist	Species and strain	Delay	Effect on SOR	Reference
PHA-543,613	S-D rat	24 h	Improved	Wishka et al. 2006
ABBF	OF1 mouse	24 h	Improved	Boess et al. 2007
SSR180711	S-D or Wistar rat	24 h	Improved	Pichat et al. 2007
		1 h	Reduced MK-801-induced impairment	
		1.5 h	Reduced subchronic PCP-induced impairment	
	C57Bl/6 J mouse	48 h	Improved performance in wt, but not α7-nAChR ko, mice	
AZD0328	C57Bl/6 mouse	15 min	Improved performance in wt, but not α7-nAChR ko, mice	Sydserff et al. 2009
TC-5619	S-D rat	24 h	Improved	Hauser et al. 2009
RG3487	S-D rat	48 h	Improved	Wallace et al. 2011
SEN12333	Wistar rat	24 h	Improved	Roncarati et al. 2009
		4 h	Reduced scopolamine-induced impairment	
	L-E rat	1 h	Reduced MK-801-induced impairment.	
SSR180711	ICR mouse	24 h	Reduced subchronic PCP-induced impairment	Hashimoto et al. 2008
PNU-282987	L-H rat	1 min	Reduced subchronic PCP-induced impairment	McLean et al. 2011

S-D Sprague Dawley, *L-H* Lister Hooded, *wt* wild-type, *ko* knockout

NMDA receptor antagonism on object memory consolidation. Overall, therefore, it is clear that modulation of the cholinergic system can affect SOR via interaction with several other transmitter systems. A more general discussion of these interactions is beyond the scope of this review, but has been provided by Levin and colleagues (e.g. Levin and Rose 1995; Levin and Simon 1998; Levin and Rezvani 2006).

One final interaction should also be considered: the α7-nAChR shares significant sequence homology with the 5-HT3 receptor (Macor et al. 2001). While a 5-HT3 receptor antagonist did not affect SOR performance (Wallace et al. 2011), it is possible that some of the cognitive enhancing effects of 'α7-nAChR agonists' could occur via modulation of 5-HT3 receptors. However, α7-nAChR agonists did not improve SOR in α7-nAChR knockout mice (Pichat et al. 2007; Sydserff et al. 2009), and their effects could be blocked by selective α7-nAChR antagonists (e.g. Boess et al. 2007; Pichat et al. 2007; Hashimoto et al. 2008; Roncarati et al. 2009; Wallace et al. 2011). Nevertheless, this example illustrates the importance of considering potential off-target drug effects.

Serotonin

Dysfunction of serotonergic PFC circuitry may contribute to the cognitive deficits observed in schizophrenia, particularly due to the involvement of this circuitry in cognitive flexibility and impulsivity (e.g. Robbins 2005). Atypical antipsychotics increase release of acetylcholine and dopamine in PFC via 5-HT1A-dependent mechanisms, and this has been proposed to enhance cognition, particularly attentional processing, in schizophrenia (Rollema et al. 1997; Ichikawa et al. 2002; Diaz-Mataix et al. 2005; McCreary et al. 2007). On the other hand, the large, independent 'Clinical Antipsychotic Trials of Intervention Effectiveness' (CATIE) study did not find any evidence for superior cognitive enhancing effects of atypical antipsychotics over the first-generation drug, perphenazine (Keefe et al. 2007).

The 5-HT1A antagonists WAY 100635 or WAY 100405 reversed the deleterious effects of scopolamine on SOR with a 60-min delay, and enhanced the performance of drug-naive rats with a 24- or 48-h delay (Hirst et al. 2008; Pitsikas et al. 2003). Pitsikas and colleagues found that WAY 100635 improved SOR when administered pre-sample, post-sample or 30 min pre-choice, implying an effect of the drug on acquisition, consolidation and possibly retrieval (Pitsikas et al. 2003). The fact that an improvement was seen using post-sample administration reduces the likelihood that the drug acts solely to enhance attentional processes. In addition, WAY 100635 reversed the deleterious effects of the AMPA receptor antagonist NBQX on SOR with a 3-h delay (Schiapparelli et al. 2006). This finding is consistent with previous suggestions that 5-HT1A antagonists may, by blocking the hyperpolarising actions of endogenous 5-HT on pyramidal neurons, compensate for a reduction in excitatory glutamatergic (or cholinergic) input (Dijk et al. 1995; Carli et al. 1997).

5-HT6 receptors are another promising target for reversing cognitive impairment in schizophrenia (see e.g. Mitchell and Neumaier 2005). Multiple studies have shown them to improve SOR with delays ranging from 1 min (Woolley et al. 2003) to 4 h (King et al. 2004; 2009; Kendall et al. 2011; Schreiber et al. 2007) to 24 h or more (Singer et al. 2009; Hirst et al. 2006; Haydar et al. 2010; although see Lieben et al. 2005) (Table 4). Some 5-HT6 antagonists induce hypophagia (Bentley et al. 1999; Woolley et al. 2000), which would confound interpretation of operant tasks motivated by food rewards. SOR is thus a particularly appropriate task for studying the effects of these drugs. Unfortunately, the majority of studies to date have examined only a single delay, making it difficult to exclude the possibility that non-mnemonic factors may have contributed to the enhanced performance. One exception is the study by King et al. (2009), which revealed that 5-HT6 antagonist-treated rats, but not vehicle-treated controls, displayed significant novel object preference with a 4-h delay. After medial, but not dorsal, raphe lesions, neither drug nor vehicle animals displayed novel object preference with a 4-h delay, but both groups showed good performance with a 1-h delay. This suggests that the medial raphe lesion had indeed specifically disrupted 5-HT6-mediated enhancement of recognition memory. 5-HT6 antagonists have been shown to potentiate release of dopamine (Dawson and Li 2003), glutamate (Dawson et al. 2000, 2001) and acetylcholine (Hirst et al. 2006; Lieben et al. 2005; Riemer et al. 2003), possibly indirectly via a reduction in GABAergic tone (Marcos et al. 2006; West et al. 2009; Doleviczenyi et al. 2008). This may explain why 5-HT6 antagonists are also able to reduce impairments in SOR performance induced by cholinergic (1 h; Lieben et al. 2005) or glutamatergic (1 min; Arnt et al. 2010) antagonism.

Cannabinoids

Cannabis use is highly prevalent among schizophrenia patients, with one study reporting usage rates as high as 51% in first episode patients (Barnett et al. 2007). Some of this usage may represent an attempt at self-medication to reduce the impact of negative symptoms or antipsychotic side-effects (Dixon et al. 1991; Krystal et al. 1999). Meta-analyses of epidemiological studies, however, indicate that cannabis usage itself may significantly increase the risk of developing schizophrenia (Andreasson et al. 1987; Moore et al. 2007), particularly among those who use cannabis in adolescence (Arseneault et al. 2002). Whether cannabis

Table 4 Effects of 5-HT6 receptor antagonists on SOR

5-HT6 antagonist	Species and strain	Delay	Effect on SOR	Reference
SB-271046	L-H rat	4 h	Improved	King et al. 2004
Ro-046790			Improved. Improvement blocked by MK-801	
Ro-046790	L-H rat	4 h	Improved. Improvement blocked by medial raphe lesions	King et al. 2009
Compound 9h	Rat	24 h	Improved	Singer et al. 2009
Compound 18b	Rat	48 h	Improved	Haydar et al. 2010
SB-271046	L-H rat	4 h	Improved	Kendall et al. 2011
Ro-046790			Improved	
			5-HT6 agonists (E-6801 and EMD-386088) also improved performance	
Ro-046790	L-H rat	1 min	Reduced scopolamine-induced impairment	Woolley et al. 2003
Ro-4368554	Wistar rat	24 h	No significant effect	Lieben et al. 2005
		1 h	Reduced impairments induced by scopolamine and tryptophan depletion	
Ro-4368554	L-E rat	4 h	Improved	Schreiber et al. 2007
	Wistar rat	1 h	Reduced scopolamine-induced impairment	
SB-399885	S-D rat	24 h	Reduced scopolamine-induced impairment	Hirst et al. 2006
Lu AE58054	S-D rat	1 min	Reduced subchronic PCP-induced impairment	Arnt et al. 2010

S-D Sprague Dawley, *L-E* Long Evans, *L-H* Lister Hooded

usage 'triggers' schizophrenia *de novo*, or precipitates the development of psychosis in individuals with a pre-existing vulnerability to the disorder, is not clear.

The psychoactive constituent of cannabis is Δ9-tetrahydrocannabinol (THC), which binds to the CB1 receptor. Exposure to cannabinoid agonists has been shown to impair SOR, although the severity of these impairments differs across studies. Subchronic adolescent exposure to THC or to a cannabinoid agonist impaired SOR in rats subsequently tested as adults with a delay of up to 1 h (1 h, Quinn et al. 2008; 30 min, Schneider and Koch 2003; but see Higuera-Matas et al. 2009). Schneider and Koch (2003) observed no impairment with a 2-h delay. Neither acute nor subchronic THC treatment during adulthood impaired SOR with a 1-h delay (Long et al. 2010; Quinn et al. 2008) but chronic hippocampal infusion of the cannabinoid agonist WIN 55,212-2 did impair performance (1 h; Barna et al. 2007). Post-sample infusion of WIN 55,212-2 into CA1 had no effect in adult rats when the delay was 3 h, but did impair performance with a 24-h delay (Clarke et al. 2008). Given that pre-choice administration had no effect, Clarke and colleagues propose that the cannabinoid agonist may block consolidation processes required for the formation of long-term memories. The impairments seen after pre-sample administration in other studies suggest additional involvement in encoding. Overall, however, the somewhat mixed pattern of data is consistent with a modulatory, rather than obligatory, role of the endocannabinoid system in SOR.

Interactions have been reported between the endocannabinoid system and manipulations considered to model aspects of schizophrenia. The deleterious effects of isolation rearing on SOR, for example, could be reduced by chronic, but not acute, treatment with a CB1 antagonist (1 h; Zamberletti et al. 2010). While the mechanism behind this effect is unclear, Zamberletti and colleagues note that cannabinoid receptors have previously been shown to modulate dopaminergic transmission via effects on GABAergic and glutamatergic synapses (Chiu et al. 2010; van der Stelt and Di Marzo 2003). A chronic intermittent PCP regime impaired SOR with a 1-h delay. The PCP-induced deficits were exacerbated in rats that had received chronic THC treatment as adolescents (Vigano et al. 2009), consistent with an interaction between activation of the endocannabinoid system and vulnerability to schizophrenia.

Genetically modified (GM) mice

With heritability estimates of approximately 80% (Sullivan et al. 2003), schizophrenia undeniably has a strong genetic component. Although SOR was initially developed for rats (Ennaceur and Delacour 1988), it can also be used successfully with mice (e.g. Messier 1997). It is therefore a useful tool for phenotyping mouse models of schizophrenia based on altered expression of candidate susceptibility genes. Many of the GM mice tested to date display impaired SOR, although results can vary between laboratories, perhaps highlighting the interaction between genotype and small differences in environmental/testing conditions or genetic background (Crabbe et al. 1999)

(Table 5). Mice heterozygous for a mutation in the transmembrane domain (TM) of neuregulin 1 (NRG1), for example, have been reported to be unimpaired with a 60-min delay (Long et al. 2010) but impaired with a 10-min delay (Duffy et al. 2010). This apparent discrepancy may reflect the use of male mice in one study and females in the other, as the effects of NRG1 disruption may be sex-specific (Taylor et al. 2011; O'Tuathaigh et al. 2006). As is typical among SOR studies, there were also differences in the testing protocol used: Long et al. injected their mice with vehicle (or THC, which did not affect SOR) 75 min prior to the SOR test, whereas Duffy et al.'s animals did not experience injection stress. Exploration levels in Long et al.'s mice were also relatively low (less than 4 s per object), which may reflect the fact that they were not habituated to the arena on the days prior to testing (the mice received 30 min on the day of testing itself). That aside, mice heterozygous for a mutation in the EGF domain common to all NRG1 isoforms were also unimpaired with a 24-h delay (Ehrlichman et al. 2009). Data from male and female animals were pooled in the latter study.

Similar discrepancies exist for mice with mutations in the dopamine catabolic enzyme, catechol-*O*-methyl transferase (COMT). Male and female mice with a heterozygous deletion of COMT were significantly impaired in SOR with a 5-min delay, while males but not females were impaired with a 1-h delay (Babovic et al. 2008). In a subsequent study using an apparently identical protocol, however, the same group found no effect of sex and no impairment at either delay (O'Tuathaigh et al. 2010). In the latter study, the animals had received chronic vehicle injections for 20 days prior to the SOR test. One possibility therefore is that injection stress may have increased arousal, which might have interacted with the genotypes under investigation. Notably, a third study also attempted to test COMT heterozygous and null mutant mice on SOR, but aborted testing due to a confounding reduction in sample phase object exploration in the mutant animals (Papaleo et al. 2008). Transgenic mice overexpressing the human COMT-Val polymorphism, corresponding to the high activity form of the enzyme, were impaired in SOR with a 1-h delay (Papaleo et al. 2008). Interestingly, amphetamine ameliorated the SOR deficit in COMT-Val transgenic mice but tended to impair performance in wild-type animals. This appears broadly consistent with a report that, in humans, amphetamine improves cognition (albeit, in this case, executive function) in COMT-Val/Val genotype individuals, but impairs performance in those with the lower activity

Table 5 Performance of genetically modified mice and their wild-type littermates on SOR

Targeted gene	GM mice tested	Delay	Performance of GM mice on SOR compared to wild-types	Reference
COMT	wt, het, hmz ko (m+f)	5 min, 1 h, 4 h	m+f het mice impaired with 5-min delay m het mice impaired with 1-h delay No novel object preference in any group with 4-h delay	Babovic et al. 2008
COMT	wt, het, hmz ko (m+f)	5 min, 1 h	Unimpaired	O'Tuathaigh et al. 2010
COMT	wt, Val-tg (tg overexpressing human COMT-Val polymorphism) (m)	1 h	Impaired	Papaleo et al. 2008
NRG1	wt, TM domain het (f)	1 h	Unimpaired	Long et al. 2010
NRG1	wt, TM domain het (m)	10 min	Impaired	Duffy et al. 2010
NRG1	wt, EGF domain het (m+f)	24 h	Unimpaired	Ehrlichman et al. 2009
Dysbindin	wt, het, hmz ko (m)	5 min, 24 h	Het and hmz ko mice impaired with 5-min delay No novel object preference in any group with 24-h delay	Bhardwaj et al. 2009
DISC1	wt, DN-DISC1 (tg expressing dominant negative mutant DISC1) (m+f)	1 h	Unimpaired DN-DISC1 impaired following neonatal poly(I:C) treatment	Ibi et al. 2010
Complexin 2	wt, hmz ko (m)	Zero, 1 h	Unimpaired	Radyushkin et al. 2010
GSK3β	wt, GSK3βS9A (tg expressing dysfunctional GSK3β) (m+f)	4 h	Impaired	Dewachter et al. 2009
VGLUT1	wt, het (m+f)	1 h, 24 h	m+f het mice impaired with a 24-h, but not 1-h, delay	Tordera et al. 2007

wt wild-type, *het* heterozygous knockout, *hmz ko* homozygous knockout, *tg* transgenic, *m* male, *f* female, *TM* transmembrane, *EGF* epidermal growth factor

COMT-Met/Met genotype (Mattay et al. 2003). Overall, the findings from studies of COMT mice on SOR are consistent with an inverted U-shaped function between cortical dopamine and cognitive function (e.g. Vijayraghavan et al. 2007).

Mice with a dominant negative mutation in DISC1 were unimpaired in SOR with a 1-h delay, unless they had been treated as neonates with poly(I:C) to induce immune activation. Poly(I:C)-treated DISC1 mutant mice were then impaired relative to poly(I:C) treated wild-type controls (Ibi et al. 2010), demonstrating an interaction between early postnatal environment and underlying genetic susceptibility to schizophrenia.

Neurodevelopmental models

Schizophrenia is widely held to be a neurodevelopmental disorder, in part because adverse events occurring pre- or perinatally increase the risk of developing the disease in adulthood (see Meyer and Feldon 2010 for review). In rodents, pre- or postnatal exposure to a variety of stressors has been used to model the neurodevelopmental nature of schizophrenia. With respect to brain development, the gestational period of rats and mice corresponds approximately to the first and early-middle second trimester of human pregnancy (Clancy et al. 2001), while the first ten postnatal days in rodents correspond to the third trimester in humans. The precise timing of environmental insults is critical as manipulations occurring at different times will be acting upon neuronal populations and neural circuits with differing levels of maturity.

Some of the earliest environmental insults are those that occur during pregnancy itself. In humans, activation of the maternal immune system has been shown to increase subsequent risk of schizophrenia in the offspring (Brown et al. 2004; Brown 2006) and may contribute to the increased incidence of schizophrenia among winter and spring births (Hultman et al. 1999). Several animal models of maternal immune activation have been developed, including treatment with the bacterial cell wall endotoxin, lipopolysaccharide (LPS), and poly(I:C), a synthetic dsRNA. The adult offspring of mice injected with LPS on embryonic day 8 (E8) were impaired in SOR with a 15-min delay (Coyle et al. 2009). The offspring of mice injected daily with poly(I:C) from E12 to E17 were also impaired in SOR with a 1-h delay, when tested as adults (9–10 weeks) but not when tested as juveniles (5 weeks). Both groups were also tested with a 24-h delay, but neither group nor their controls showed convincing novel object preference at this longer interval (Ozawa et al. 2006). Conversely, the adult offspring of mice injected with poly(I:C) on E12.5 displayed significantly enhanced SOR performance with a 5-min delay (Ito et al. 2010). However, the performance of vehicle-treated controls in the latter study was surprisingly poor for the delay used. Early postnatal immune activation appears to have less impact on SOR. Treatment with LPS on postnatal days (P) 7 and 9 had no effect when the animals were tested as either juveniles or adults (1 h; Jenkins et al. 2009), while daily treatment with poly(I:C) from P2 to P6 left SOR similarly unimpaired in wild-type mice tested as adults. As described previously, however, the latter treatment regime did impair performance in DISC1 mutant mice (1 h; Ibi et al. 2010).

Obstetric complications, including the occurrence of asphyxia or hypoxia (Dalman et al. 2001; Byrne et al. 2007) have additionally been linked to increased schizophrenia risk. In rodents, both perinatal asphyxia and postnatal hypoxia impaired SOR. Asphyxia on the last day of gestation led to impaired SOR with a 1-h delay when the animals were tested as adults (Simola et al. 2008; Morales et al. 2010). Performance was intact with a 15-min delay, arguing against a non-mnemonic explanation for the deficit (Simola et al. 2008). Conversely, a single episode of hypoxia–ischaemia (HI) on P7 led to impaired SOR in adolescent rats, using a delay of only 5 min (Pereira et al. 2008). Since the volume of the hippocampus and the striatum ipsilateral to the ischaemia-inducing arterial occlusion was reduced in the HI animals, however, it could be argued that these animals had in effect received partial unilateral neonatal hippocampal lesions.

Neonatal lesions of the ventral hippocampus (NVHL) have been proposed to mimic both positive and negative schizophrenia symptoms, as well as cognitive deficits, in the adult animal (Lipska et al. 1993, 2002; Sams-Dodd et al. 1997). Consistent with a specifically developmental effect, NVHL rats displayed impaired SOR performance compared to sham controls when delays of either 30 min or 2 h were used, while rats that had received equivalent lesions at age P42 were impaired only at the longer delay (Hori et al. 2007). NVHLs have previously been shown to induce cytoarchitectural abnormalities and neuronal loss in perirhinal cortex (Bernstein et al. 1999), consistent with the proposed contribution of this region to SOR.

While the postnatal period in rodents is relatively hyporesponsive to stress (Levine et al. 1994), maternal deprivation is considered to be one of the most potent stressors for pups. Daily maternal deprivation from P2 to P21 impaired SOR in rats with a 1-h delay (Aisa et al. 2008). The impairment was reduced by the glucocorticoid receptor antagonist, mifepristone, and by the β-adrenoreceptor antagonist, propanolol, implicating increased activation of the HPA axis. Daily maternal deprivation from P15 to P21—with or without social isolation from littermates—also impaired SOR in mice (24 h; Niwa et al. 2011). Both forms of isolation stress increased plasma corticosterone levels, and the impairment

in each case could be reduced by clozapine. The effects of isolation stress are not limited to the early postnatal period, however. Rats that were socially isolated during adolescence (approximately P25 to 55) were also impaired in SOR with a 1-h delay (Bianchi et al. 2006). For isolation stress, as for many of the other neurodevelopmental models, comparing the effects of a single stressor at different time points might help to identify specific time periods with particular vulnerability to that stressor, and perhaps aid identification of the underlying mechanisms.

So how relevant is SOR to schizophrenia?

Predictive validity

It is clear that many pharmacological, genetic and environmental manipulations thought to model aspects of CIAS also impair rodent performance in SOR. Moreover, an encouraging number of compounds have been reported to reverse these impairments. If SOR is an effective screening tool, then drugs that improve SOR in the laboratory should also improve cognition in the clinic, and *vice versa*. Given that no drug has yet been approved for the treatment of CIAS, however, the predictive validity of SOR cannot be said to be better or worse than that of any other rodent behavioural task at present. Nevertheless, several classes of compounds that reliably improve performance in SOR have been examined in clinical trials with schizophrenia patients, with mixed results.

Atypical antipsychotics, particularly clozapine, have been shown to reverse the deleterious effects on SOR of manipulations such as methamphetamine, MK-801 and PCP. Dozens of studies have likewise demonstrated greater improvement in cognition in schizophrenia patients given atypical antipsychotics than in those receiving first generation drugs (see Keefe et al. 2007). While such findings are encouraging, many of these clinical studies had methodological limitations such as being open-label, using small sample sizes, or using high (side-effect inducing) doses of older antipsychotics as a comparator. Unfortunately, the results of the large independent multi-site CATIE study, which compared the effects on cognition of four second-generation antipsychotics and the first generation drug, perphenazine, in more than 800 schizophrenia patients, were less encouraging. While all drugs produced a small improvement in cognition, the second generation antipsychotics were no more effective than perphenazine. The results of the CATIE study surprised many and, from the current perspective, it is unfortunate that clozapine was not included in the 'cognitive' phase of the study as it is probably clozapine that has produced the most positive findings in SOR. Nevertheless, it seems fair to say that second generation antipsychotics are more effective at improving SOR, and indeed most other rodent behavioural tasks, than they are in the clinic.

Other promising candidates that have emerged from the SOR literature include 5-HT6 antagonists and compounds that target the glycine modulatory site on the NMDA receptor. Several 5-HT6 antagonists have entered phase I or II trials for CIAS, but the results are as yet unknown. D-serine, which acts as a co-agonist at the NR1 subunit, improved executive function in schizophrenia patients (Tsai et al. 1998), although D-cycloserine had little effect on a cognitive test battery (Goff et al. 2005). The GlyT1 inhibitor, sarcosine, also improved 'global' functioning when given as an adjunct to risperidone but not clozapine (Lane et al. 2006, 2010), but cognition was not examined in detail.

Some of the most striking effects in SOR have been obtained using drugs that modulate the cholinergic system. Galantamine, a cholinesterase inhibitor that also has agonist efficacy at the α7-nAChR, improved cognition in several double-blind placebo-controlled trials (Lee et al. 2007; Schubert et al. 2006; Buchanan et al. 2008, but see Dyer et al. 2008). The improvements were small, however, and the domains affected tended to differ across studies. Logically, one might expect improvement in SOR to most clearly predict an improvement in visual learning and memory. Galantamine did produce an improvement in the Rey Complex Figure Test (Lee et al. 2007), but it had no effect on either the Brief Visuospatial Memory Test (BVMT) (Buchanan et al. 2008) or the Object Memory Matching Task (OMMT) (Schubert et al. 2006).

Donepezil—a more potent cholinesterase inhibitor than galantamine but lacking α7-nAChR activity—has also been shown to improve SOR (see above). However, donepezil has been somewhat less convincing in clinical trials for CIAS. While several small open-label studies did report improvement in patients' cognition using donepezil as an adjunctive agent, the improvements were small and, once again, tended to affect different cognitive domains in different studies (Buchanan et al. 2003; MacEwan et al. 2001; Risch et al. 2001; Chung et al. 2009). Furthermore, a number of double-blind placebo-controlled trials with larger sample sizes observed no significant effect of donepezil on any cognitive domain in schizophrenia (Friedman et al. 2002; Freudenreich et al. 2005; Fagerlund et al. 2007; Keefe et al. 2008), including two that assessed visual memory (Tugal et al. 2004; Akhondzadeh et al. 2008). It is thus possible that donepezil's lower efficacy in treating CIAS compared to cognitive impairments in AD may reflect a lesser contribution of cholinergic abnormalities to these deficits in schizophrenia. This raises the important point that the predictive validity of any cognitive test will be limited by the quality of our rodent models, and the

extent to which these reproduce the biological basis of CIAS.

Nicotinic receptor agonists, particularly those targeting the α7-nicotinic receptor, have produced some of the most convincing improvements in rodent SOR. In schizophrenia clinical trials, nicotine and nicotinic receptor agonists have consistently enhanced performance, but mostly in tests of sustained attention. Improvements were seen sometimes in smokers (Depatie et al. 2002; Smith et al. 2006; Hong et al. 2011) and other times in non-smokers (Harris et al. 2004; Olincy et al. 2006; Shiina et al. 2010), although varenicline—an α4β2 and α7 receptor agonist licensed for smoking cessation therapy—had no effect (Smith et al. 2009a). Effects of nicotinic receptor agonists on memory have been more variable. Varenicline improved verbal learning and memory in schizophrenic smokers (Smith et al. 2009a), although nicotine had no effect (Levin et al. 1996; Smith et al. 2006; Harris et al. 2004). Conversely, nicotine enhanced visuospatial working memory in schizophrenic smokers (Smith et al. 2006) but varenicline did not (Smith et al. 2009a). Nicotine also reversed the deleterious effects of haloperidol on delayed match-to-sample in schizophrenic smokers (Levin et al. 1996). However, the α7-nAChR agonist tropisetron failed to produce a significant improvement in any memory domain within the CANTAB battery in non-smoking patients (Shiina et al. 2010). The partial α7-nAChR agonist DMXB-A was similarly ineffective among schizophrenic non-smokers in the MATRICS Consensus Cognitive Battery (Freedman et al. 2008), although practice effects may have made an improvement more difficult to detect. Relatively few studies have specifically examined visual recognition memory. Nicotinic receptor agonists had no effect on the BVMT (Freedman et al. 2008) or on CANTAB pattern recognition memory (Shiina et al. 2010). Nicotine did improve delayed recognition of abstract geometric shapes in schizophrenic smokers (5-min delay; Myers et al. 2004). However, the benefit was largely due to a reduction in the false alarm rate, which may suggest an improvement in sensory gating rather than in recognition memory *per se*.

Overall therefore, some improvements in cognition have been reported in schizophrenia clinical trials using agents that also improve rodent performance in SOR. In human clinical trials, the improvements tend to be smaller than might be expected from the preclinical data; they also affect differing domains across different studies. Direct comparison with SOR is hindered by the fact that relatively few clinical trials have specifically examined visual recognition memory. Nevertheless, improvement in rodent SOR does not appear to guarantee that an improvement will also be detected in human visual recognition memory when it is examined. This may in part reflect the fact that rodent performance on SOR is influenced by many 'non-specific' factors, including perception, attention and motivation. It is possible that some of the positive results in the SOR literature may reflect improvements in these areas, rather than the anticipated improvements in memory *per se*. The latter would perhaps be more likely to translate into robust improvements in clinical trials.

What does the SOR task measure?

The predictive validity of SOR will also be limited by the extent to which it taps into components of cognition that are impaired in schizophrenia. There is evidence for impaired recognition memory in schizophrenia, with a number of studies, including a large meta-analysis (Pelletier et al. 2005), suggesting that recognition of visual stimuli may be particularly disrupted (e.g. Harvey et al. 2000; Doniger et al. 2002; Heckers et al. 2000; Calkins et al. 2005). While it is likely that deficits in perceptual processing contribute to some of these impairments (e.g. Javitt 2009; Sullivan et al. 1992; Seidman et al. 2003), visual recognition memory would still appear to be a pertinent cognitive domain to assess in putative animal models of schizophrenia.

It could be argued, however, that the methodology in SOR is quite different from the tasks used to assess visual memory in humans. These tasks typically require subjects to memorise abstract geometric shapes or, occasionally, photographs. In addition, human studies generally assess recognition from their subjects' verbal reports, rather than inferring recognition from the preferential exploration of novel objects. It is worth noting, however, that a version of the SOR task that uses preferential looking at novel stimuli is routinely used to assess visual recognition memory in human infants (and non-human primates) (Overman et al. 1993; Nemanic et al. 2004). The visual paired comparison task (VPC) operates on the same principle as SOR, and uses time spent looking at a novel versus familiar image as the index of recognition. It has been suggested that the VPC task can be used in adults to yield a non-verbal measure of explicit or declarative memory (e.g. Manns et al. 2000; Pascalis et al. 2004). McKee and Squire (1993) compared amnesic MTL patients and controls, using photographs as stimuli and delays ranging from 0.5 s to 24 h. Control subjects preferentially viewed the novel images when the delay was an hour or less, whereas amnesic patients were impaired with a delay of only 2 min. Importantly, the amnesic group showed intact performance with a 0.5-s delay, suggesting that their impairment did not reflect gross perceptual deficits or an altered response to novelty.

A related and critical issue is whether the human VPC or rodent SOR tasks tap the appropriate *component* of recognition memory. In human adults, recognition memory could be considered to comprise two components: recollective (episodic) memory, whereby a subject consciously

recalls having encountered a stimulus previously, and familiarity-based processes, whereby the feeling of having previously encountered the stimulus may arise independently of any conscious recollection of having done so (Aggleton and Brown 2006; Yonelinas et al. 2010). In human subjects, the relative contributions of episodic versus familiarity-based processes can be disentangled to some degree using the 'Remember/Know' paradigm (Tulving 1985; Gardiner 1988). Subjects are asked to give a 'remember' response if recognition is accompanied by conscious recollection of an item's previous presentation. They are asked to give a 'know' response if recognition is accompanied by a feeling of familiarity without any conscious recollection. A number of studies have used this paradigm with schizophrenia patients. The findings are reviewed in Danion et al. (2007) and generally suggest that in schizophrenia recollection is impaired to a greater degree than familiarity. Consistent with this idea, there is some suggestion in Pelletier et al.'s (2005) meta-analysis that schizophrenia patients are more impaired in tests that require them to give a 'yes/no' response to indicate recognition of singly presented items, than in tests that require 'forced choice' discrimination between old/new stimulus pairs. If, as seems plausible, subjects can use relative familiarity to a greater degree in forced choice than in yes/no formats, this would seem to suggest that schizophrenia patients are relatively more impaired in recollection-based processes than in familiarity-based ones.

In summary, therefore, recollection and familiarity may both contribute to performance on visual recognition memory tasks, including VPC and SOR. While it is possible that rodents also use explicit memory in SOR, it appears more likely that they rely predominantly on familiarity-based mechanisms. Since familiarity-based processes may be affected rather less in schizophrenia than recollection, this partial mismatch may explain why SOR does not appear to have perfect predictive validity for CIAS. One profitable area of schizophrenia-relevant research might be to explore the use of versions of SOR that may increase the requirement for the use of recollective processes (e.g. Eacott et al. 2005).

Conclusions

As a rapid and technically straightforward test of memory, SOR has many advantages that make it suitable for use in examining the effects of a variety of manipulations on cognition. By using a spontaneous behaviour, SOR avoids confounding effects of stress or differences in motivation to work for an appetitive reward, and is, in this sense, more comparable to the tasks typically used to assess memory in human subjects. There is no requirement for acquisition of a complex rule, meaning that an index of memory can be obtained from a single trial. Moreover, in comparison with incremental learning tasks, it is relatively straightforward to use SOR to examine the effects of a manipulation on different stages of memory formation and recall. Finally, the ability to manipulate 'control' performance by varying the length of the delay or the amount of exposure to the sample objects means that SOR can be used to detect both procognitive and amnestic effects.

As with all tasks, however, there are also a number of limitations. Differences in the apparent preference for a novel object before and after a manipulation can sometimes be confounded by differences in exploration levels before and after the manipulation. These effects can be reduced by use of the discrimination index [(novel−familiar)/(novel+familiar)] to compare the performance of two groups, rather than simply comparing the absolute length of time spent exploring each object. It is also important to remember that factors that affect preference for novelty will also affect performance in SOR, even if they leave memory *per se* unchanged. That said, testing at short as well as long delays helps to mitigate against these and other non-mnemonic interpretations. Lastly, the spontaneous behaviour measured in SOR will, almost by definition, tend to be more variable than a behaviour that has been learned across numerous trials to reliably earn a reward or avoid a punishment. Differences between laboratories in factors such as the duration of the sample and choice phase, as well as the delay, the previous experimental experience of the animals, and whether an open arena or a closed maze is used, can all make it more difficult to confidently compare results between studies. A standardised, automated method would help immensely in this regard.

While SOR is proposed to tap into the visual learning and memory domain highlighted by MATRICS, it is likely that the mechanisms available to humans and to rodents to solve 'visual recognition memory' tasks are not identical. Humans can use both explicit episodic recollection and implicit familiarity while rodents may be biased toward the latter. This partial mismatch in mechanism might explain the apparent lack of predictive validity with respect to CIAS. Nevertheless, several compounds that improve SOR do also have some beneficial effects on cognition in schizophrenia, although the correlation is far from perfect. The predictive validity of SOR could perhaps be increased further if a greater number of studies attempted to control for non-specific drug effects on perception, attention and motivation, via the use of multiple delays.

Studies using SOR have revealed that the effects of many transmitter systems on recognition memory are mediated via interaction with other transmitter systems. Indeed, schizophrenia is itself increasingly recognised to be a complex disorder involving disruption of multiple

transmitter systems and the interactions between them. SOR experiments have also demonstrated that while a drug may preferentially target one receptor or transmitter system, there are highly likely to be other 'off-target' effects. It is important that these effects are acknowledged and studied, partly to avoid the danger that 'cognitive enhancing' upregulation of one transmitter might lead to deleterious effects on another. The silver lining to all this complexity might, however, be the multitude of potential targets within different transmitter systems that might, in theory, eventually offer the possibility of cognitive enhancement.

To conclude, it is perhaps unrealistic to expect a test of spontaneous behaviour in rodents to constitute a perfect screening tool that will accurately and selectively identify any and every drug that will treat CIAS. A better approach is for researchers to take the time to use a multiple task battery in which multiple domains of cognition are assessed, thus providing controls for each other (Bussey et al. 2011); SOR (preferably automated) could provide a valuable element in such a battery. Moreover, it is not clear that any other existing rodent behavioural task would fare any better than SOR, and most of these lack SOR's methodological advantages. Finally, irrespective of its translational relevance, SOR has contributed much valuable information about the role of multiple transmitter systems in memory, and the interactions between them.

Acknowledgements The authors would like to thank Prof. Trevor Robbins and Dr. Mark Tricklebank for comments on an earlier version of the manuscript. This work has received support from the Innovative Medicine Initiative Joint Undertaking under grant agreement n° 115008 of which resources are composed of EFPIA in-kind contribution and financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013).

References

Abe H, Ishida Y, Iwasaki T (2004) Perirhinal N-methyl-D-aspartate and muscarinic systems participate in object recognition in rats. Neurosci Lett 356:191–194

Adler CM, Malhotra AK, Elman I, Goldberg T, Egan M, Pickar D, Breier A (1999) Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. Am J Psychiatry 156:1646–1649

Aggleton JP, Brown MW (2006) Interleaving brain systems for episodic and recognition memory. Trends Cogn Sci 10:455–463

Aggleton JP, Hunt PR, Rawlins JN (1986) The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. Behav Brain Res 19:133–146

Aggleton JP, Keen S, Warburton EC, Bussey TJ (1997) Extensive cytotoxic lesions involving both the rhinal cortices and area TE impair recognition but spare spatial alternation in the rat. Brain Res Bull 43:279–287

Aisa B, Tordera R, Lasheras B, Del Rio J, Ramirez MJ (2008) Effects of maternal separation on hypothalamic-pituitary-adrenal responses, cognition and vulnerability to stress in adult female rats. Neuroscience 154:1218–1226

Akhondzadeh S, Gerami M, Noroozian M, Karamghadiri N, Ghoreishi A, Abbasi SH, Rezazadeh SA (2008) A 12-week, double-blind, placebo-controlled trial of donepezil adjunctive treatment to risperidone in chronic and stable schizophrenia. Prog Neuropsychopharmacol Biol Psychiatr 32:1810–1815

Albuquerque EX, Alkondon M, Pereira EF, Castro NG, Schrattenholz A, Barbosa CT, Bonfante-Cabarcas R, Aracava Y, Eisenberg HM, Maelicke A (1997) Properties of neuronal nicotinic acetylcholine receptors: pharmacological characterization and modulation of synaptic function. J Pharmacol Exp Ther 280:1117–1136

Andreasson S, Allebeck P, Engstrom A, Rydberg U (1987) Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 2:1483–1486

Arnt J, Bang-Andersen B, Grayson B, Bymaster FP, Cohen MP, DeLapp NW, Giethlen B, Kreilgaard M, McKinzie DL, Neill JC, Nelson DL, Nielsen SM, Poulsen MN, Schaus JM, Witten LM (2010) Lu AE58054, a 5-HT(6) antagonist, reverses cognitive impairment induced by subchronic phencyclidine in a novel object recognition test in rats. Int J Neuropsychopharmacol 13:1021–1033

Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE (2002) Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 325:1212–1213

Babovic D, O'Tuathaigh CM, O'Connor AM, O'Sullivan GJ, Tighe O, Croke DT, Karayiorgou M, Gogos JA, Cotter D, Waddington JL (2008) Phenotypic characterization of cognition and social behavior in mice with heterozygous versus homozygous deletion of catechol-O-methyltransferase. Neuroscience 155:1021–1029

Baker KB, Kim JJ (2002) Effects of stress and hippocampal NMDA receptor antagonism on recognition memory in rats. Learn Mem 9:58–65

Ballaz SJ, Akil H, Watson SJ (2007) The 5-HT7 receptor: role in novel object discrimination and relation to novelty-seeking behavior. Neuroscience 149:192–202

Barker GR, Bashir ZI, Brown MW, Warburton EC (2006) A temporally distinct role for group I and group II metabotropic glutamate receptors in object recognition memory. Learn Mem 13:178–186

Barna I, Soproni K, Arszovszki A, Csabai K, Haller J (2007) WIN-55,212-2 chronically implanted into the CA3 region of the dorsal hippocampus impairs learning: a novel method for studying chronic, brain-area-specific effects of cannabinoids. Behav Pharmacol 18:515–520

Barnett JH, Werners U, Secher SM, Hill KE, Brazil R, Masson K, Pernet DE, Kirkbride JB, Murray GK, Bullmore ET, Jones PB (2007) Substance use in a population-based clinic sample of people with first-episode psychosis. Br J Psychiatry 190:515–520

Bartko SJ, Winters BD, Cowell RA, Saksida LM, Bussey TJ (2007) Perceptual functions of perirhinal cortex in rats: zero-delay object recognition and simultaneous oddity discriminations. J Neurosci 27:2548–2559

Beaulieu JM, Gainetdinov RR (2011) The physiology, signaling and pharmacology of dopamine receptors. Pharmacol Rev 63:182–217

Belcher AM, Feinstein EM, O'Dell SJ, Marshall JF (2008) Methamphetamine influences on recognition memory: comparison of escalating and single-day dosing regimens. Neuropsychopharmacology 33:1453–1463

Bentley J, Marsden C, Sleight A, Fone K (1999) Effect of the 5-HT6 antagonist, Ro 04–6790, on food consumption in rats trained to a fixed feeding regime. Br J Pharmacol: U38-U38

Bernstein HG, Grecksch G, Becker A, Hollt V, Bogerts B (1999) Cellular changes in rat brain areas associated with neonatal hippocampal damage. Neuroreport 10:2307–2311

Bhardwaj SK, Baharnoori M, Sharif-Askari B, Kamath A, Williams S, Srivastava LK (2009) Behavioral characterization of dysbindin-1 deficient sandy mice. Behav Brain Res 197:435–441

Bianchi M, Fone KF, Azmi N, Heidbreder CA, Hagan JJ, Marsden CA (2006) Isolation rearing induces recognition memory deficits accompanied by cytoskeletal alterations in rat hippocampus. Eur J Neurosci 24:2894–2902

Biton B, Bergis OE, Galli F, Nedelec A, Lochead AW, Jegham S, Godet D, Lanneau C, Santamaria R, Chesney F, Leonardon J, Granger P, Debono MW, Bohme GA, Sgard F, Besnard F, Graham D, Coste A, Oblin A, Curet O, Vige X, Voltz C, Rouquier L, Souilhac J, Santucci V, Gueudet C, Francon D, Steinberg R, Griebel G, Oury-Donat F, George P, Avenet P, Scatton B (2007) SSR180711, a novel selective alpha7 nicotinic receptor partial agonist: (1) binding and functional profile. Neuropsychopharmacology 32:1–16

Boess FG, De Vry J, Erb C, Flessner T, Hendrix M, Luithle J, Methfessel C, Riedl B, Schnizler K, van der Staay FJ, van Kampen M, Wiese WB, Koenig G (2007) The novel alpha7 nicotinic acetylcholine receptor agonist N-[(3R)-1-azabicyclo [2.2.2]oct-3-yl]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide improves working and recognition memory in rodents. J Pharmacol Exp Ther 321:716–725

Bortolozzi A, Diaz-Mataix L, Toth M, Celada P, Artigas F (2007) In vivo actions of aripiprazole on serotonergic and dopaminergic systems in rodent brain. Psychopharmacology (Berl) 191:745–758

Botton PH, Costa MS, Ardais AP, Mioranzza S, Souza DO, da Rocha JB, Porciuncula LO (2010) Caffeine prevents disruption of memory consolidation in the inhibitory avoidance and novel object recognition tasks by scopolamine in adult mice. Behav Brain Res 214:254–259

Boultadakis A, Liakos P, Pitsikas N (2010) The nitric oxide-releasing derivative of ferulic acid NCX 2057 antagonized delay-dependent and scopolamine-induced performance deficits in a recognition memory task in the rat. Prog Neuropsychopharmacol Biol Psychiatr 34:5–9

Bradley SR, Lameh J, Ohrmund L, Son T, Bajpai A, Nguyen D, Friberg M, Burstein ES, Spalding TA, Ott TR, Schiffer HH, Tabatabaei A, McFarland K, Davis RE, Bonhaus DW (2010) AC-260584, an orally bioavailable M(1) muscarinic receptor allosteric agonist, improves cognitive performance in an animal model. Neuropharmacology 58:365–373

Bromley E (2005) A collaborative approach to targeted treatment development for schizophrenia: a qualitative evaluation of the NIMH-MATRICS project. Schizophr Bull 31:954–961

Brown AS (2006) Prenatal infection as a risk factor for schizophrenia. Schizophr Bull 32:200–202

Brown MW, Bashir ZI (2002) Evidence concerning how neurons of the perirhinal cortex may effect familiarity discrimination. Philos Trans R Soc Lond B Biol Sci 357:1083–1095

Brown MW, Xiang JZ (1998) Recognition memory: neuronal substrates of the judgement of prior occurrence. Prog Neurobiol 55:149–189

Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, Babulas VP, Susser ES (2004) Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 61:774–780

Buchanan RW, Summerfelt A, Tek C, Gold J (2003) An open-labeled trial of adjunctive donepezil for cognitive impairments in patients with schizophrenia. Schizophr Res 59:29–33

Buchanan RW, Conley RR, Dickinson D, Ball MP, Feldman S, Gold JM, McMahon RP (2008) Galantamine for the treatment of cognitive impairments in people with schizophrenia. Am J Psychiatry 165:82–89

Bussey TJ, Saksida LM (2005) Object memory and perception in the medial temporal lobe: an alternative approach. Curr Opin Neurobiol 15:730–737

Bussey TJ, Muir JL, Aggleton JP (1999) Functionally dissociating aspects of event memory: the effects of combined perirhinal and postrhinal cortex lesions on object and place memory in the rat. J Neurosci 19:495–502

Bussey TJ, Duck J, Muir JL, Aggleton JP (2000) Distinct patterns of behavioural impairments resulting from fornix transection or neurotoxic lesions of the perirhinal and postrhinal cortices in the rat. Behav Brain Res 111:187–202

Bussey TJ, Holmes A, Lyon L, Mar AC, McAllister KA, Nithianantharajah J, Oomen CA, Saksida LM (2011) New translational assays for preclinical modelling of cognition in schizophrenia: the touchscreen testing method for mice and rats. Neuropharmacology [Epub ahead of print].

Byrne M, Agerbo E, Bennedsen B, Eaton WW, Mortensen PB (2007) Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. Schizophr Res 97:51–59

Calkins ME, Gur RC, Ragland JD, Gur RE (2005) Face recognition memory deficits and visual object memory performance in patients with schizophrenia and their relatives. Am J Psychiatry 162:1963–1966

Camarasa J, Rodrigo T, Pubill D, Escubedo E (2010) Memantine is a useful drug to prevent the spatial and non-spatial memory deficits induced by methamphetamine in rats. Pharmacol Res 62:450–456

Carli M, Bonalumi P, Samanin R (1997) WAY 100635, a 5-HT1A receptor antagonist, prevents the impairment of spatial learning caused by intrahippocampal administration of scopolamine or 7-chloro-kynurenic acid. Brain Res 774:167–174

Carlsson A, Lindqvist M (1963) Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol Toxicol (Copenh) 20:140–144

Chan MH, Chiu PH, Sou JH, Chen HH (2008) Attenuation of ketamine-evoked behavioral responses by mGluR5 positive modulators in mice. Psychopharmacology (Berl) 198:141–148

Chiu CQ, Puente N, Grandes P, Castillo PE (2010) Dopaminergic modulation of endocannabinoid-mediated plasticity at GABAergic synapses in the prefrontal cortex. J Neurosci 30:7236–7248

Chung YC, Lee CR, Park TW, Yang KH, Kim KW (2009) Effect of donepezil added to atypical antipsychotics on cognition in patients with schizophrenia: an open-label trial. World J Biol Psychiatry 10:156–162

Clancy B, Darlington RB, Finlay BL (2001) Translating developmental time across mammalian species. Neuroscience 105:7–17

Clark RE, Zola SM, Squire LR (2000) Impaired recognition memory in rats after damage to the hippocampus. J Neurosci 20:8853–8860

Clark RE, Kuczenski R, Segal DS (2007) Escalating dose, multiple binge methamphetamine regimen does not impair recognition memory in rats. Synapse 61:515–522

Clarke JR, Rossato JI, Monteiro S, Bevilaqua LR, Izquierdo I, Cammarota M (2008) Posttraining activation of CB1 cannabinoid receptors in the CA1 region of the dorsal hippocampus impairs object recognition long-term memory. Neurobiol Learn Mem 90:374–381

Cowell RA, Bussey TJ, Saksida LM (2006) Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. J Neurosci 26:12186–12197

Coyle JT (2006) Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol 26:365–384

Coyle P, Tran N, Fung JN, Summers BL, Rofe AM (2009) Maternal dietary zinc supplementation prevents aberrant behaviour in an object recognition task in mice offspring exposed to LPS in early pregnancy. Behav Brain Res 197:210–218

Crabbe JC, Wahlsten D, Dudek BC (1999) Genetics of mouse behavior: interactions with laboratory environment. Science 284:1670–1672

Creese I, Burt DR, Snyder SH (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 192:481–483

Dalman C, Thomas HV, David AS, Gentz J, Lewis G, Allebeck P (2001) Signs of asphyxia at birth and risk of schizophrenia. Population-based case–control study. Br J Psychiatry 179:403–408

Damgaard T, Larsen DB, Hansen SL, Grayson B, Neill JC, Plath N (2010) Positive modulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors reverses sub-chronic PCP-induced deficits in the novel object recognition task in rats. Behav Brain Res 207:144–150

Damgaard T, Plath N, Neill JC, Hansen SL (2011) Extrasynaptic GABAA receptor activation reverses recognition memory deficits in an animal model of schizophrenia. Psychopharmacology (Berl) 214:403–413

Danion JM, Huron C, Vidailhet P, Berna F (2007) Functional mechanisms of episodic memory impairment in schizophrenia. Can J Psychiatr 52:693–701

Davis KL, Kahn RS, Ko G, Davidson M (1991) Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 148:1474–1486

Dawson LA, Li P (2003) Effects of 5-HT(6) receptor blockade on the neurochemical outcome of antidepressant treatment in the frontal cortex of the rat. J Neural Transm 110:577–590

Dawson LA, Nguyen HQ, Li P (2000) In vivo effects of the 5-HT(6) antagonist SB-271046 on striatal and frontal cortex extracellular concentrations of noradrenaline, dopamine, 5-HT, glutamate and aspartate. Br J Pharmacol 130:23–26

Dawson LA, Nguyen HQ, Li P (2001) The 5-HT(6) receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. Neuropsychopharmacology 25:662–668

de Bruin N, Pouzet B (2006) Beneficial effects of galantamine on performance in the object recognition task in Swiss mice: deficits induced by scopolamine and by prolonging the retention interval. Pharmacol Biochem Behav 85:253–260

de Leon J, Diaz FJ (2005) A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res 76:135–157

de Lima MN, Laranja DC, Bromberg E, Roesler R, Schröder N (2005) Pre- or post-training administration of the NMDA receptor blocker MK-801 impairs object recognition memory in rats. Behav Brain Res 156:139–143

Depatie L, O'Driscoll GA, Holahan AL, Atkinson V, Thavundayil JX, Kin NN, Lal S (2002) Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. Neuropsychopharmacology 27: 1056–1070

Dere E, Huston JP, De Souza Silva MA (2007) The pharmacology, neuroanatomy and neurogenetics of one-trial object recognition in rodents. Neurosci Biobehav Rev 31:673–704

Devito LM, Balu DT, Kanter BR, Lykken C, Basu AC, Coyle JT, Eichenbaum H (2010) Serine racemase deletion disrupts memory for order and alters cortical dendritic morphology. Genes Brain Behav 10:210–222

Dewachter I, Ris L, Jaworski T, Seymour CM, Kremer A, Borghgraef P, De Vijver H, Godaux E, Van Leuven F (2009) GSK3β, a centre-staged kinase in neuropsychiatric disorders, modulates long term memory by inhibitory phosphorylation at serine-9. Neurobiol Dis 35:193–200

Diaz-Mataix L, Scorza MC, Bortolozzi A, Toth M, Celada P, Artigas F (2005) Involvement of 5-HT1A receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. J Neurosci 25:10831–10843

Dijk SN, Francis PT, Stratmann GC, Bowen DM (1995) NMDA-induced glutamate and aspartate release from rat cortical pyramidal neurones: evidence for modulation by a 5-HT1A antagonist. Br J Pharmacol 115:1169–1174

Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ (1991) Drug abuse in schizophrenic patients: clinical correlates and reasons for use. Am J Psychiatry 148:224–230

Doleviczenyi Z, Vizi ES, Gacsalyi I, Pallagi K, Volk B, Harsing LG Jr, Halmos G, Lendvai B, Zelles T (2008) 5-HT6/7 receptor antagonists facilitate dopamine release in the cochlea via a GABAergic disinhibitory mechanism. Neurochem Res 33:2364–2372

Doniger GM, Foxe JJ, Murray MM, Higgins BA, Javitt DC (2002) Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch Gen Psychiatry 59:1011–1020

Duffy L, Cappas E, Lai D, Boucher AA, Karl T (2010) Cognition in transmembrane domain neuregulin 1 mutant mice. Neuroscience 170:800–807

Dyer MA, Freudenreich O, Culhane MA, Pachas GN, Deckersbach T, Murphy E, Goff DC, Evins AE (2008) High-dose galantamine augmentation inferior to placebo on attention, inhibitory control and working memory performance in nonsmokers with schizophrenia. Schizophr Res 102:88–95

Eacott MJ, Easton A, Zinkivskav A (2005) Recollection in an episodic-like memory task in the rat. Learn Mem 12:221–223

Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH (1996) Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. Nat Genet 12:78–80

Ehrlichman RS, Luminais SN, White SL, Rudnick ND, Ma N, Dow HC, Kreibich AS, Abel T, Brodkin ES, Hahn CG, Siegel SJ (2009) Neuregulin 1 transgenic mice display reduced mismatch negativity, contextual fear conditioning and social interactions. Brain Res 1294:116–127

Ennaceur A, Delacour J (1988) A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. Behav Brain Res 31:47–59

Ennaceur A, Neave N, Aggleton JP (1996) Neurotoxic lesions of the perirhinal cortex do not mimic the behavioural effects of fornix transection in the rat. Behav Brain Res 80:9–25

Ennaceur A, Neave N, Aggleton JP (1997) Spontaneous object recognition and object location memory in rats: the effects of lesions in the cingulate cortices, the medial prefrontal cortex, the cingulum bundle and the fornix. Exp Brain Res 113:509–519

Fagerlund B, Soholm B, Fink-Jensen A, Lublin H, Glenthoj BY (2007) Effects of donepezil adjunctive treatment to ziprasidone on cognitive deficits in schizophrenia: a double-blind, placebo-controlled study. Clin Neuropharmacol 30:3–12

Forwood SE, Winters BD, Bussey TJ (2005) Hippocampal lesions that abolish spatial maze performance spare object recognition memory at delays of up to 48 hours. Hippocampus 15:347–355

Franberg O, Marcus MM, Ivanov V, Schilstrom B, Shahid M, Svensson TH (2009) Asenapine elevates cortical dopamine, noradrenaline and serotonin release. Evidence for activation of cortical and subcortical dopamine systems by different mechanisms. Psychopharmacology (Berl) 204:251–264

Freedman R, Leonard S (2001) Genetic linkage to schizophrenia at chromosome 15q14. Am J Med Genet 105:655–657

Freedman R, Hall M, Adler LE, Leonard S (1995) Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 38:22–33

Freedman R, Leonard S, Gault JM, Hopkins J, Cloninger CR, Kaufmann CA, Tsuang MT, Farone SV, Malaspina D, Svrakic DM, Sanders A, Gejman P (2001) Linkage disequilibrium for schizophrenia at the chromosome 15q13–14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7). Am J Med Genet 105:20–22

Freedman R, Olincy A, Buchanan RW, Harris JG, Gold JM, Johnson L, Allensworth D, Guzman-Bonilla A, Clement B, Ball MP,

Kutnick J, Pender V, Martin LF, Stevens KE, Wagner BD, Zerbe GO, Soti F, Kem WR (2008) Initial phase 2 trial of a nicotinic agonist in schizophrenia. Am J Psychiatry 165:1040–1047

Freudenreich O, Herz L, Deckersbach T, Evins AE, Henderson DC, Cather C, Goff DC (2005) Added donepezil for stable schizophrenia: a double-blind, placebo-controlled trial. Psychopharmacology (Berl) 181:358–363

Friedman JI, Adler DN, Howanitz E, Harvey PD, Brenner G, Temporini H, White L, Parrella M, Davis KL (2002) A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for the cognitive impairment of schizophrenia. Biol Psychiatry 51:349–357

Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RS (1992) The left medial temporal region and schizophrenia. A PET study. Brain 115(Pt 2):367–382

Gaffan D (1974) Recognition impaired and association intact in the memory of monkeys after transection of the fornix. J Comp Physiol Psychol 86:1100–1109

Gardiner JM (1988) Recognition failures and free-recall failures: implications for the relation between recall and recognition. Mem Cognit 16:446–451

Goff DC, Herz L, Posever T, Shih V, Tsai G, Henderson DC, Freudenreich O, Evins AE, Yovel I, Zhang H, Schoenfeld D (2005) A six-month, placebo-controlled trial of D-cycloserine co-administered with conventional antipsychotics in schizophrenia patients. Psychopharmacology (Berl) 179:144–150

Goldman-Rakic PS (1994) Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 6:348–357

Grayson B, Idris NF, Neill JC (2007) Atypical antipsychotics attenuate a sub-chronic PCP-induced cognitive deficit in the novel object recognition task in the rat. Behav Brain Res 184:31–38

Green MF (2006) Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatr 67:e12

Greene R (2001) Circuit analysis of NMDAR hypofunction in the hippocampus, in vitro, and psychosis of schizophrenia. Hippocampus 11:569–577

Grunze HC, Rainnie DG, Hasselmo ME, Barkai E, Hearn EF, McCarley RW, Greene RW (1996) NMDA-dependent modulation of CA1 local circuit inhibition. J Neurosci 16:2034–2043

Guo Y, Zhang H, Chen X, Cai W, Cheng J, Yang Y, Jin G, Zhen X (2009) Evaluation of the antipsychotic effect of bi-acetylated l-stepholidine (l-SPD-A), a novel dopamine and serotonin receptor dual ligand. Schizophr Res 115:41–49

Hannesson DK, Vacca G, Howland JG, Phillips AG (2004) Medial prefrontal cortex is involved in spatial temporal order memory but not spatial recognition memory in tests relying on spontaneous exploration in rats. Behav Brain Res 153:273–285

Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, Zerbe G, Freedman R (2004) Effects of nicotine on cognitive deficits in schizophrenia. Neuropsychopharmacology 29:1378–1385

Harrison PJ, Weinberger DR (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatr 10:40–68, image 5

Harvey PD, Moriarty PJ, Friedman JI, White L, Parrella M, Mohs RC, Davis KL (2000) Differential preservation of cognitive functions in geriatric patients with lifelong chronic schizophrenia: less impairment in reading compared with other skill areas. Biol Psychiatry 47:962–968

Hashimoto K, Fujita Y, Shimizu E, Iyo M (2005) Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of clozapine, but not haloperidol. Eur J Pharmacol 519:114–117

Hashimoto K, Ishima T, Fujita Y, Matsuo M, Kobashi T, Takahagi M, Tsukada H, Iyo M (2008) Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the novel selective alpha7 nicotinic receptor agonist SSR180711. Biol Psychiatry 63:92–97

Hauser TA, Kucinski A, Jordan KG, Gatto GJ, Wersinger SR, Hesse RA, Stachowiak EK, Stachowiak MK, Papke RL, Lippiello PM, Bencherif M (2009) TC-5619: an alpha7 neuronal nicotinic receptor-selective agonist that demonstrates efficacy in animal models of the positive and negative symptoms and cognitive dysfunction of schizophrenia. Biochem Pharmacol 78:803–812

Haydar SN, Yun H, Andrae PM, Mattes J, Zhang J, Kramer A, Smith DL, Huselton C, Graf R, Aschmies S, Schechter LE, Comery TA, Robichaud AJ (2010) 5-Cyclic amine-3-arylsulfonylindazoles as novel 5-HT6 receptor antagonists. J Med Chem 53:2521–2527

Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM (1998) Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nat Neurosci 1:318–323

Heckers S, Curran T, Goff D, Rauch SL, Fischman AJ, Alpert NM, Schacter DL (2000) Abnormalities in the thalamus and prefrontal cortex during episodic object recognition in schizophrenia. Biol Psychiatry 48:651–657

Herring NR, Schaefer TL, Gudelsky GA, Vorhees CV, Williams MT (2008) Effect of +−methamphetamine on path integration learning, novel object recognition, and neurotoxicity in rats. Psychopharmacology (Berl) 199:637–650

Hersi AI, Richard JW, Gaudreau P, Quirion R (1995) Local modulation of hippocampal acetylcholine release by dopamine D1 receptors: a combined receptor autoradiography and in vivo dialysis study. J Neurosci 15:7150–7157

Higuera-Matas A, Botreau F, Miguens M, Del Olmo N, Borcel E, Perez-Alvarez L, Garcia-Lecumberri C, Ambrosio E (2009) Chronic periadolescent cannabinoid treatment enhances adult hippocampal PSA-NCAM expression in male Wistar rats but only has marginal effects on anxiety, learning and memory. Pharmacol Biochem Behav 93:482–490

Hirst WD, Stean TO, Rogers DC, Sunter D, Pugh P, Moss SF, Bromidge SM, Riley G, Smith DR, Bartlett S, Heidbreder CA, Atkins AR, Lacroix LP, Dawson LA, Foley AG, Regan CM, Upton N (2006) SB-399885 is a potent, selective 5-HT6 receptor antagonist with cognitive enhancing properties in aged rat water maze and novel object recognition models. Eur J Pharmacol 553:109–119

Hirst WD, Andree TH, Aschmies S, Childers WE, Comery TA, Dawson LA, Day M, Feingold IB, Grauer SM, Harrison BL, Hughes ZA, Kao J, Kelly MG, van der Lee H, Rosenzweig-Lipson S, Saab AL, Smith DL, Sullivan K, Rizzo SJ, Tio C, Zhang MY, Schechter LE (2008) Correlating efficacy in rodent cognition models with in vivo 5-hydroxytryptamine1a receptor occupancy by a novel antagonist, (R)-N-(2-methyl-(4-indolyl-1-piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexan e carboxamide (WAY-101405). J Pharmacol Exp Ther 325:134–145

Hong LE, Schroeder M, Ross TJ, Buchholz B, Salmeron BJ, Wonodi I, Thaker GK, Stein EA (2011) Nicotine enhances but does not normalize visual sustained attention and the associated brain network in schizophrenia. Schizophr Bull 37:416–425

Hori SE, Powell KJ, Robertson GS (2007) Darbepoetin alfa (Aranesp) improves recognition memory in adult rats that have sustained bilateral ventral hippocampal lesions as neonates or young adults. Neuroscience 144:1–7

Hu JH, Ma YH, Jiang J, Yang N, Duan SH, Jiang ZH, Mei ZT, Fei J, Guo LH (2004) Cognitive impairment in mice over-expressing gamma-aminobutyric acid transporter 1 (GAT1). Neuroreport 15:9–12

Huang M, Li Z, Dai J, Shahid M, Wong EH, Meltzer HY (2008) Asenapine increases dopamine, norepinephrine, and acetylcholine efflux in the rat medial prefrontal cortex and hippocampus. Neuropsychopharmacology 33:2934–2945

Hultman CM, Sparen P, Takei N, Murray RM, Cnattingius S (1999) Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case–control study. BMJ 318:421–426

Ibi D, Nagai T, Koike H, Kitahara Y, Mizoguchi H, Niwa M, Jaaro-Peled H, Nitta A, Yoneda Y, Nabeshima T, Sawa A, Yamada K (2010) Combined effect of neonatal immune activation and mutant DISC1 on phenotypic changes in adulthood. Behav Brain Res 206:32–37

Ichikawa J, Li Z, Dai J, Meltzer HY (2002) Atypical antipsychotic drugs, quetiapine, iloperidone, and melperone, preferentially increase dopamine and acetylcholine release in rat medial prefrontal cortex: role of 5-HT1A receptor agonism. Brain Res 956:349–357

Ito HT, Smith SE, Hsiao E, Patterson PH (2010) Maternal immune activation alters nonspatial information processing in the hippocampus of the adult offspring. Brain Behav Immun 24:930–941

Jackson ME, Homayoun H, Moghaddam B (2004) NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. Proc Natl Acad Sci USA 101:8467–8472

Javitt DC (2009) Sensory processing in schizophrenia: neither simple nor intact. Schizophr Bull 35:1059–1064

Jenkins TA, Harte MK, Stenson G, Reynolds GP (2009) Neonatal lipopolysaccharide induces pathological changes in parvalbumin immunoreactivity in the hippocampus of the rat. Behav Brain Res 205:355–359

Johnson DJ, Forbes IT, Watson SP, Garzya V, Stevenson GI, Walker GR, Mudhar HS, Flynn ST, Wyman PA, Smith PW, Murkitt GS, Lucas AJ, Mookherjee CR, Watson JM, Gartlon JE, Bradford AM, Brown F (2010) The discovery of a series of N-substituted 3-(4-piperidinyl)-1,3-benzoxazolinones and oxindoles as highly brain penetrant, selective muscarinic M1 agonists. Bioorg Med Chem Lett 20:5434–5438

Jones DN, Higgins GA (1995) Effect of scopolamine on visual attention in rats. Psychopharmacology (Berl) 120:142–149

Jones CA, Brown AM, Auer DP, Fone KC (2010) The mGluR2/3 agonist LY379268 reverses post-weaning social isolation-induced recognition memory deficits in the rat. Psychopharmacology (Berl) 214:269–283

Kalechstein AD, Newton TF, Green M (2003) Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. J Neuropsychiatry Clin Neurosci 15:215–220

Kamei H, Nagai T, Nakano H, Togan Y, Takayanagi M, Takahashi K, Kobayashi K, Yoshida S, Maeda K, Takuma K, Nabeshima T, Yamada K (2006) Repeated methamphetamine treatment impairs recognition memory through a failure of novelty-induced ERK1/2 activation in the prefrontal cortex of mice. Biol Psychiatry 59:75–84

Kapur S, Remington G (2001) Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry 50:873–883

Karasawa J, Hashimoto K, Chaki S (2008) D-Serine and a glycine transporter inhibitor improve MK-801-induced cognitive deficits in a novel object recognition test in rats. Behav Brain Res 186:78–83

Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hsiao JK, Lieberman JA (2007) Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry 64:633–647

Keefe RS, Malhotra AK, Meltzer HY, Kane JM, Buchanan RW, Murthy A, Sovel M, Li C, Goldman R (2008) Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology 33:1217–1228

Kendall I, Slotten HA, Codony X, Burgueno J, Pauwels PJ, Vela JM, Fone KC (2011) E-6801, a 5-HT6 receptor agonist, improves recognition memory by combined modulation of cholinergic and glutamatergic neurotransmission in the rat. Psychopharmacology (Berl) 213:413–430

King MV, Sleight AJ, Woolley ML, Topham IA, Marsden CA, Fone KC (2004) 5-HT6 receptor antagonists reverse delay-dependent deficits in novel object discrimination by enhancing consolidation–an effect sensitive to NMDA receptor antagonism. Neuropharmacology 47:195–204

King MV, Spicer CH, Sleight AJ, Marsden CA, Fone KC (2009) Impact of regional 5-HT depletion on the cognitive enhancing effects of a typical 5-ht(6) receptor antagonist, Ro 04–6790, in the Novel Object Discrimination task. Psychopharmacology (Berl) 202:111–123

Krivoy A, Weizman A, Laor L, Hellinger N, Zemishlany Z, Fischel T (2008) Addition of memantine to antipsychotic treatment in schizophrenia inpatients with residual symptoms: a preliminary study. Eur Neuropsychopharmacol 18:117–121

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Krystal JH, D'Souza DC, Madonick S, Petrakis IL (1999) Toward a rational pharmacotherapy of comorbid substance abuse in schizophrenic patients. Schizophr Res 35(Suppl):S35–S49

Kunitachi S, Fujita Y, Ishima T, Kohno M, Horio M, Tanibuchi Y, Shirayama Y, Iyo M, Hashimoto K (2009) Phencyclidine-induced cognitive deficits in mice are ameliorated by subsequent subchronic administration of donepezil: role of sigma-1 receptors. Brain Res 1279:189–196

Lahti AC, Koffel B, LaPorte D, Tamminga CA (1995) Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19

Lane HY, Huang CL, Wu PL, Liu YC, Chang YC, Lin PY, Chen PW, Tsai G (2006) Glycine transporter I inhibitor, N-methylglycine (sarcosine), added to clozapine for the treatment of schizophrenia. Biol Psychiatry 60:645–649

Lane HY, Lin CH, Huang YJ, Liao CH, Chang YC, Tsai GE (2010) A randomized, double-blind, placebo-controlled comparison study of sarcosine (N-methylglycine) and D-serine add-on treatment for schizophrenia. Int J Neuropsychopharmacol 13:451–460

Lee SW, Lee JG, Lee BJ, Kim YH (2007) A 12-week, double-blind, placebo-controlled trial of galantamine adjunctive treatment to conventional antipsychotics for the cognitive impairments in chronic schizophrenia. Int Clin Psychopharmacol 22:63–68

Leonard S, Gault J, Moore T, Hopkins J, Robinson M, Olincy A, Adler LE, Cloninger CR, Kaufmann CA, Tsuang MT, Faraone SV, Malaspina D, Svrakic DM, Freedman R (1998) Further investigation of a chromosome 15 locus in schizophrenia: analysis of affected sibpairs from the NIMH Genetics Initiative. Am J Med Genet 81:308–312

Levin ED, Rezvani AH (2006) Nicotinic-antipsychotic drug interactions and cognitive function. EXS 98:185–205

Levin ED, Rose JE (1995) Acute and chronic nicotinic interactions with dopamine systems and working memory performance. Ann N Y Acad Sci 757:245–252

Levin ED, Simon BB (1998) Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology (Berl) 138:217–230

Levin ED, Wilson W, Rose JE, McEvoy J (1996) Nicotine–haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology 15:429–436

Levine S, Berkenbosch F, Suchecki D, Tilders FJ (1994) Pituitary–adrenal and interleukin-6 responses to recombinant interleukin-1 in neonatal rats. Psychoneuroendocrinology 19:143–153

Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6:312–324

Li Z, Snigdha S, Roseman AS, Dai J, Meltzer HY (2008) Effect of muscarinic receptor agonists xanomeline and sabcomeline on acetylcholine and dopamine efflux in the rat brain; comparison with effects of 4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one (AC260584) and N-desmethylclozapine. Eur J Pharmacol 596:89–97

Lieben CK, Blokland A, Sik A, Sung E, van Nieuwenhuizen P, Schreiber R (2005) The selective 5-HT6 receptor antagonist Ro4368554 restores memory performance in cholinergic and serotonergic models of memory deficiency in the rat. Neuropsychopharmacology 30:2169–2179

Lieberman JA, Papadakis K, Csernansky J, Litman R, Volavka J, Jia XD, Gage A (2009) A randomized, placebo-controlled study of memantine as adjunctive treatment in patients with schizophrenia. Neuropsychopharmacology 34:1322–1329

Lipska BK, Jaskiw GE, Weinberger DR (1993) Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. Neuropsychopharmacology 9:67–75

Lipska BK, Aultman JM, Verma A, Weinberger DR, Moghaddam B (2002) Neonatal damage of the ventral hippocampus impairs working memory in the rat. Neuropsychopharmacology 27:47–54

Liu F, Grauer S, Kelley C, Navarra R, Graf R, Zhang G, Atkinson PJ, Popiolek M, Wantuch C, Khawaja X, Smith D, Olsen M, Kouranova E, Lai M, Pruthi F, Pulicicchio C, Day M, Gilbert A, Pausch MH, Brandon NJ, Beyer CE, Comery TA, Logue S, Rosenzweig-Lipson S, Marquis KL (2008) ADX47273 [S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]-piperidin-1-yl}-methanone]: a novel metabotropic glutamate receptor 5-selective positive allosteric modulator with preclinical antipsychotic-like and procognitive activities. J Pharmacol Exp Ther 327:827–839

Long LE, Chesworth R, Arnold JC, Karl T (2010) A follow-up study: acute behavioural effects of Delta(9)-THC in female heterozygous neuregulin 1 transmembrane domain mutant mice. Psychopharmacology (Berl) 211:277–289

Lung FW, Shu BC, Kao WT, Chen CN, Ku YC, Tzeng DS (2009) Association of DRD4 uVNTR and TP53 codon 72 polymorphisms with schizophrenia: a case–control study. BMC Med Genet 10:147

MacEwan GW, Ehmann TS, Khanbhai I, Wrixon C (2001) Donepezil in schizophrenia—is it helpful? An experimental design case study. Acta Psychiatr Scand 104:469–472

Macor JE, Gurley D, Lanthorn T, Loch J, Mack RA, Mullen G, Tran O, Wright N, Gordon JC (2001) The 5-HT3 antagonist tropisetron (ICS 205–930) is a potent and selective alpha7 nicotinic receptor partial agonist. Bioorg Med Chem Lett 11:319–321

Maia L, de Mendonca A (2002) Does caffeine intake protect from Alzheimer's disease? Eur J Neurol 9:377–382

Malaspina D, Harkavy-Friedman J, Corcoran C, Mujica-Parodi L, Printz D, Gorman JM, Van Heertum R (2004) Resting neural activity distinguishes subgroups of schizophrenia patients. Biol Psychiatry 56:931–937

Manns JR, Stark CE, Squire LR (2000) The visual paired-comparison task as a measure of declarative memory. Proc Natl Acad Sci USA 97:12375–12379

Marcos B, Gil-Bea FJ, Hirst WD, Garcia-Alloza M, Ramirez MJ (2006) Lack of localization of 5-HT6 receptors on cholinergic neurons: implication of multiple neurotransmitter systems in 5-HT6 receptor-mediated acetylcholine release. Eur J Neurosci 24:1299–1306

Marutle A, Zhang X, Court J, Piggott M, Johnson M, Perry R, Perry E, Nordberg A (2001) Laminar distribution of nicotinic receptor subtypes in cortical regions in schizophrenia. J Chem Neuroanat 22:115–126

Massey PV, Bhabra G, Cho K, Brown MW, Bashir ZI (2001) Activation of muscarinic receptors induces protein synthesis-dependent long-lasting depression in the perirhinal cortex. Eur J Neurosci 14:145–152

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR (2003) Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci USA 100:6186–6191

McCreary AC, Glennon JC, Ashby CR Jr, Meltzer HY, Li Z, Reinders JH, Hesselink MB, Long SK, Herremans AH, van Stuivenberg H, Feenstra RW, Kruse CG (2007) SLV313 (1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-4- [5-(4-fluoro-phenyl)-pyridin-3-ylmethyl]-piperazine monohydrochloride): a novel dopamine D2 receptor antagonist and 5-HT1A receptor agonist potential antipsychotic drug. Neuropsychopharmacology 32:78–94

McKee RD, Squire LR (1993) On the development of declarative memory. J Exp Psychol Learn Mem Cogn 19:397–404

McKibben CE, Jenkins TA, Adams HN, Harte MK, Reynolds GP (2010) Effect of pretreatment with risperidone on phencyclidine-induced disruptions in object recognition memory and prefrontal cortex parvalbumin immunoreactivity in the rat. Behav Brain Res 208:132–136

McLean SL, Woolley ML, Thomas D, Neill JC (2009) Role of 5-HT receptor mechanisms in sub-chronic PCP-induced reversal learning deficits in the rat. Psychopharmacology (Berl) 206:403–414

McLean SL, Grayson B, Idris NF, Lesage AS, Pemberton DJ, Mackie C, Neill JC (2011) Activation of alpha7 nicotinic receptors improves phencyclidine-induced deficits in cognitive tasks in rats: implications for therapy of cognitive dysfunction in schizophrenia. Eur Neuropsychopharmacol 21:333–343

Messier C (1997) Object recognition in mice: improvement of memory by glucose. Neurobiol Learn Mem 67:172–175

Meyer U, Feldon J (2010) Epidemiology-driven neurodevelopmental animal models of schizophrenia. Prog Neurobiol 90:285–326

Millan MJ, Mannoury la Cour C, Novi F, Maggio R, Audinot V, Newman-Tancredi A, Cussac D, Pasteau V, Boutin JA, Dubuffet T, Lavielle G (2008) S33138 [N-[4-[2-[(3aS,9bR)-8-cyano-1,3a,4,9b-tetrahydro[1]-benzopyrano[3,4-c]pyrr ol-2(3H)-yl)-ethyl]phenylacetamide], a preferential dopamine D3 versus D2 receptor antagonist and potential antipsychotic agent: I. Receptor-binding profile and functional actions at G-protein-coupled receptors. J Pharmacol Exp Ther 324:587–599

Millan MJ, Buccafusco JJ, Loiseau F, Watson DJ, Decamp E, Fone KC, Thomasson-Perret N, Hill M, Mocaer E, Schneider JS (2010) The dopamine D(3) receptor antagonist, S33138, counters cognitive impairment in a range of rodent and primate procedures. Int J Neuropsychopharmacol 13:1035–1051

Minzenberg MJ, Poole JH, Benton C, Vinogradov S (2004) Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. Am J Psychiatry 161:116–124

Mishkin M, Delacour J (1975) An analysis of short-term visual memory in the monkey. J Exp Psychol Anim Behav Process 1:326–334

Mitchell JB, Laiacona J (1998) The medial frontal cortex and temporal memory: tests using spontaneous exploratory behaviour in the rat. Behav Brain Res 97:107–113

Mitchell ES, Neumaier JF (2005) 5-HT6 receptors: a novel target for cognitive enhancement. Pharmacol Ther 108:320–333

Moghaddam B, Adams BW (1998) Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science 281:1349–1352

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2007) Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370:319–328

Morales P, Simola N, Bustamante D, Lisboa F, Fiedler J, Gebicke-Haerter PJ, Morelli M, Tasker RA, Herrera-Marschitz M (2010) Nicotinamide prevents the long-term effects of perinatal asphyxia on apoptosis, non-spatial working memory and anxiety in rats. Exp Brain Res 202:1–14

Mumby DG, Pinel JP, Wood ER (1990) Nonrecurring-items nonmatching-to-sample in rats: a new paradigm for testing non-spatial working memory. Psychobiology 18:321–326

Myers CS, Robles O, Kakoyannis AN, Sherr JD, Avila MT, Blaxton TA, Thaker GK (2004) Nicotine improves delayed recognition in schizophrenic patients. Psychopharmacology (Berl) 174:334–340

Nagai T, Takuma K, Dohniwa M, Ibi D, Mizoguchi H, Kamei H, Nabeshima T, Yamada K (2007) Repeated methamphetamine treatment impairs spatial working memory in rats: reversal by clozapine but not haloperidol. Psychopharmacology (Berl) 194:21–32

Nagai T, Murai R, Matsui K, Kamei H, Noda Y, Furukawa H, Nabeshima T (2009) Aripiprazole ameliorates phencyclidine-induced impairment of recognition memory through dopamine D1 and serotonin 5-HT1A receptors. Psychopharmacology (Berl) 202:315–328

Nemanic S, Alvarado MC, Bachevalier J (2004) The hippocampal/parahippocampal regions and recognition memory: insights from visual paired comparison versus object-delayed nonmatching in monkeys. J Neurosci 24:2013–2026

Nilsson M, Hansson S, Carlsson A, Carlsson ML (2007) Differential effects of the N-methyl-d-aspartate receptor antagonist MK-801 on different stages of object recognition memory in mice. Neuroscience 149:123–130

Niwa M, Matsumoto Y, Mouri A, Ozaki N, Nabeshima T (2011) Vulnerability in early life to changes in the rearing environment plays a crucial role in the aetiopathology of psychiatric disorders. Int J Neuropsychopharmacol 14:459–477

Noda Y, Mouri A, Ando Y, Waki Y, Yamada SN, Yoshimi A, Yamada K, Ozaki N, Wang D, Nabeshima T (2010) Galantamine ameliorates the impairment of recognition memory in mice repeatedly treated with methamphetamine: involvement of allosteric potentiation of nicotinic acetylcholine receptors and dopaminergic-ERK1/2 systems. Int J Neuropsychopharmacol 13:1343–1354

Olincy A, Harris JG, Johnson LL, Pender V, Kongs S, Allensworth D, Ellis J, Zerbe GO, Leonard S, Stevens KE, Stevens JO, Martin L, Adler LE, Soti F, Kem WR, Freedman R (2006) Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch Gen Psychiatry 63:630–638

O'Tuathaigh CM, O'Sullivan GJ, Kinsella A, Harvey RP, Tighe O, Croke DT, Waddington JL (2006) Sexually dimorphic changes in the exploratory and habituation profiles of heterozygous neuregulin-1 knockout mice. Neuroreport 17:79–83

O'Tuathaigh CM, Hryniewiecka M, Behan A, Tighe O, Coughlan C, Desbonnet L, Cannon M, Karayiorgou M, Gogos JA, Cotter DR, Waddington JL (2010) Chronic adolescent exposure to Delta-9-tetrahydrocannabinol in COMT mutant mice: impact on psychosis-related and other phenotypes. Neuropsychopharmacology 35:2262–2273

Overman WH, Bachevalier J, Sewell F, Drew J (1993) A comparison of children's performance on two recognition memory tasks: delayed nonmatch-to-sample versus visual paired-comparison. Dev Psychobiol 26:345–357

Owens DG, Johnstone EC (2006) Precursors and prodromata of schizophrenia: findings from the Edinburgh High Risk Study and their literature context. Psychol Med 36:1501–1514

Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M (2006) Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia. Biol Psychiatry 59:546–554

Papaleo F, Crawley JN, Song J, Lipska BK, Pickel J, Weinberger DR, Chen J (2008) Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. J Neurosci 28:8709–8723

Pascalis O, Hunkin NM, Holdstock JS, Isaac CL, Mayes AR (2004) Visual paired comparison performance is impaired in a patient with selective hippocampal lesions and relatively intact item recognition. Neuropsychologia 42:1293–1300

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, Mosolov SN, Neznanov NG, Reznik AM, Smulevich AB, Tochilov VA, Johnson BG, Monn JA, Schoepp DD (2007) Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. Nat Med 13:1102–1107

Pelletier M, Achim AM, Montoya A, Lal S, Lepage M (2005) Cognitive and clinical moderators of recognition memory in schizophrenia: a meta-analysis. Schizophr Res 74:233–252

Pereira LO, Strapasson AC, Nabinger PM, Achaval M, Netto CA (2008) Early enriched housing results in partial recovery of memory deficits in female, but not in male, rats after neonatal hypoxia–ischemia. Brain Res 1218:257–266

Pichat P, Bergis OE, Terranova JP, Urani A, Duarte C, Santucci V, Gueudet C, Voltz C, Steinberg R, Stemmelin J, Oury-Donat F, Avenet P, Griebel G, Scatton B (2007) SSR180711, a novel selective alpha7 nicotinic receptor partial agonist: (II) efficacy in experimental models predictive of activity against cognitive symptoms of schizophrenia. Neuropsychopharmacology 32:17–34

Pietá Dias C, Martins de Lima MN, Presti-Torres J, Dornelles A, Garcia VA, Siciliani Scalco F, Rewsaat Guimarães M, Constantino L, Budni P, Dal-Pizzol F, Schröder N (2007) Memantine reduces oxidative damage and enhances long-term recognition memory in aged rats. Neuroscience 146:1719–1725

Pitsikas N, Rigamonti AE, Cella SG, Muller EE (2003) The 5-HT 1A receptor antagonist WAY 100635 improves rats performance in different models of amnesia evaluated by the object recognition task. Brain Res 983:215–222

Prast H, Philippu A (2001) Nitric oxide as modulator of neuronal function. Prog Neurobiol 64:51–68

Puma C, Bizot JC (1998) Intraseptal infusions of a low dose of AP5, a NMDA receptor antagonist, improves memory in an object recognition task in rats. Neurosci Lett 248:183–186

Quinn HR, Matsumoto I, Callaghan PD, Long LE, Arnold JC, Gunasekaran N, Thompson MR, Dawson B, Mallet PE, Kashem MA, Matsuda-Matsumoto H, Iwazaki T, McGregor IS (2008) Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. Neuropsychopharmacology 33:1113–1126

Radcliffe KA, Dani JA (1998) Nicotinic stimulation produces multiple forms of increased glutamatergic synaptic transmission. J Neurosci 18:7075–7083

Radyushkin K, El-Kordi A, Boretius S, Castaneda S, Ronnenberg A, Reim K, Bickeböller H, Frahm J, Brose N, Ehrenreich H (2010) Complexin2 null mutation requires a 'second hit' for induction of phenotypic changes relevant to schizophrenia. Genes Brain Behav 9:592–602

Raedler TJ, Bymaster FP, Tandon R, Copolov D, Dean B (2007) Towards a muscarinic hypothesis of schizophrenia. Mol Psychiatr 12:232–246

Rammsayer TH (2001) Effects of pharmacologically induced changes in NMDA-receptor activity on long-term memory in humans. Learn Mem 8:20–25

Rasmusson DD (2000) The role of acetylcholine in cortical synaptic plasticity. Behav Brain Res 115:205–218

Reichel CM, Schwendt M, McGinty JF, Foster Olive M, See RE (2011) Loss of object recognition memory produced by extended access to methamphetamine self-administration is reversed by positive allosteric modulation of metabotropic glutamate receptor 5. Neuropsychopharmacology 36:782–792

Riedel W, Hogervorst E, Leboux R, Verhey F, van Praag H, Jolles J (1995) Caffeine attenuates scopolamine-induced memory impairment in humans. Psychopharmacology (Berl) 122:158–168

Riemer C, Borroni E, Levet-Trafit B, Martin JR, Poli S, Porter RH, Bos M (2003) Influence of the 5-HT6 receptor on acetylcholine release in the cortex: pharmacological characterization of 4-(2-bromo-6-pyrrolidin-1-ylpyridine-4-sulfonyl)phenylamine, a potent and selective 5-HT6 receptor antagonist. J Med Chem 46:1273–1276

Riley BP, Makoff A, Mogudi-Carter M, Jenkins T, Williamson R, Collier D, Murray R (2000) Haplotype transmission disequilibrium and evidence for linkage of the CHRNA7 gene region to schizophrenia in Southern African Bantu families. Am J Med Genet 96:196–201

Risch SC, McGurk S, Horner MD, Nahas Z, Owens SD, Molloy M, Gilliard C, Christie S, Markowitz JS, DeVane CL, Mintzer J, George MS (2001) A double-blind placebo-controlled case study of the use of donepezil to improve cognition in a schizoaffective disorder patient: functional MRI correlates. Neurocase 7:105–110

Ritchie K, Carriere I, de Mendonca A, Portet F, Dartigues JF, Rouaud O, Barberger-Gateau P, Ancelin ML (2007) The neuroprotective effects of caffeine: a prospective population study (the Three City Study). Neurology 69:536–545

Robbins TW (2005) Synthesizing schizophrenia: a bottom-up, symptomatic approach. Schizophr Bull 31:854–864

Rollema H, Lu Y, Schmidt AW, Zorn SH (1997) Clozapine increases dopamine release in prefrontal cortex by 5-HT1A receptor activation. Eur J Pharmacol 338:R3–R5

Roncarati R, Scali C, Comery TA, Grauer SM, Aschmi S, Bothmann H, Jow B, Kowal D, Gianfriddo M, Kelley C, Zanelli U, Ghiron C, Haydar S, Dunlop J, Terstappen GC (2009) Procognitive and neuroprotective activity of a novel alpha7 nicotinic acetylcholine receptor agonist for treatment of neurodegenerative and cognitive disorders. J Pharmacol Exp Ther 329:459–468

Rothblat LA, Hayes LL (1987) Short-term object recognition memory in the rat: nonmatching with trial-unique junk stimuli. Behav Neurosci 101:587–590

Sambeth A, Riedel WJ, Smits LT, Blokland A (2007) Cholinergic drugs affect novel object recognition in rats: relation with hippocampal EEG? Eur J Pharmacol 572:151–159

Sams-Dodd F, Lipska BK, Weinberger DR (1997) Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. Psychopharmacology (Berl) 132:303–310

Sarter M, Bruno JP (1997) Trans-synaptic stimulation of cortical acetylcholine and enhancement of attentional functions: a rational approach for the development of cognition enhancers. Behav Brain Res 83:7–14

Schiapparelli L, Simon AM, Del Rio J, Frechilla D (2006) Opposing effects of AMPA and 5-HT1A receptor blockade on passive avoidance and object recognition performance: correlation with AMPA receptor subunit expression in rat hippocampus. Neuropharmacology 50:897–907

Schneider M, Koch M (2003) Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. Neuropsychopharmacology 28:1760–1769

Schreiber R, Vivian J, Hedley L, Szczepanski K, Secchi RL, Zuzow M, van Laarhoven S, Moreau JL, Martin JR, Sik A, Blokland A (2007) Effects of the novel 5-HT(6) receptor antagonist RO4368554 in rat models for cognition and sensorimotor gating. Eur Neuropsychopharmacol 17:277–288

Schroder N, O'Dell SJ, Marshall JF (2003) Neurotoxic methamphetamine regimen severely impairs recognition memory in rats. Synapse 49:89–96

Schubert MH, Young KA, Hicks PB (2006) Galantamine improves cognition in schizophrenic patients stabilized on risperidone. Biol Psychiatry 60:530–533

Scott JC, Woods SP, Matt GE, Meyer RA, Heaton RK, Atkinson JH, Grant I (2007) Neurocognitive effects of methamphetamine: a critical review and meta-analysis. Neuropsychol Rev 17:275–297

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21

Seeman P, Lee T (1975) Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. Science 188:1217–1219

Seeman P, Guan HC, Van Tol HH (1993) Dopamine D4 receptors elevated in schizophrenia. Nature 365:441–445

Seidman LJ, Lanca M, Kremen WS, Faraone SV, Tsuang MT (2003) Organizational and visual memory deficits in schizophrenia and bipolar psychoses using the Rey–Osterrieth complex figure: effects of duration of illness. J Clin Exp Neuropsychol 25:949–964

Shiina A, Shirayama Y, Niitsu T, Hashimoto T, Yoshida T, Hasegawa T, Haraguchi T, Kanahara N, Shiraishi T, Fujisaki M, Fukami G, Nakazato M, Iyo M, Hashimoto K (2010) A randomised, double-blind, placebo-controlled trial of tropisetron in patients with schizophrenia. Ann Gen Psychiatr 9:27

Shirayama Y, Yamamoto A, Nishimura T, Katayama S, Kawahara R (2007) Subsequent exposure to the choline uptake enhancer MKC-231 antagonizes phencyclidine-induced behavioral deficits and reduction in septal cholinergic neurons in rats. Eur Neuropsychopharmacol 17:616–626

Shirazi-Southall S, Rodriguez DE, Nomikos GG (2002) Effects of typical and atypical antipsychotics and receptor selective compounds on acetylcholine efflux in the hippocampus of the rat. Neuropsychopharmacology 26:583–594

Simola N, Bustamante D, Pinna A, Pontis S, Morales P, Morelli M, Herrera-Marschitz M (2008) Acute perinatal asphyxia impairs non-spatial memory and alters motor coordination in adult male rats. Exp Brain Res 185:595–601

Singer P, Boison D, Möhler H, Feldon J, Yee BK (2007) Enhanced recognition memory following glycine transporter 1 deletion in forebrain neurons. Behav Neurosci 121:815–825

Singer JM, Wilson MW, Johnson PD, Graham SR, Cooke LW, Roof RL, Boxer PA, Gold LH, Meltzer LT, Janssen A, Roush N, Campbell JE, Su TZ, Hurst SI, Stoner CL, Schwarz JB (2009) Synthesis and SAR of tolylamine 5-HT6 antagonists. Bioorg Med Chem Lett 19:2409–2412

Smith RC, Warner-Cohen J, Matute M, Butler E, Kelly E, Vaidhyanathaswamy S, Khan A (2006) Effects of nicotine nasal spray on cognitive function in schizophrenia. Neuropsychopharmacology 31:637–643

Smith RC, Lindenmayer JP, Davis JM, Cornwell J, Noth K, Gupta S, Sershen H, Lajtha A (2009a) Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder. Schizophr Res 110:149–155

Smith SM, Uslaner JM, Yao L, Mullins CM, Surles NO, Huszar SL, McNaughton CH, Pascarella DM, Kandebo M, Hinchliffe RM, Sparey T, Brandon NJ, Jones B, Venkatraman S, Young MB,

Sachs N, Jacobson MA, Hutson PH (2009b) The behavioral and neurochemical effects of a novel D-amino acid oxidase inhibitor compound 8 [4H-thieno [3,2-b]pyrrole-5-carboxylic acid] and D-serine. J Pharmacol Exp Ther 328:921–930

Snigdha S, Idris N, Grayson B, Shahid M, Neill JC (2010) Asenapine improves phencyclidine-induced object recognition deficits in the rat: evidence for engagement of a dopamine D(1) receptor mechanism. Psychopharmacology (Berl) 214:843–853

Sood P, Idris NF, Cole S, Grayson B, Neill JC, Young AM (2010) PD168077, a D4 receptor agonist, reverses object recognition deficits in rats: potential role for D4 receptor mechanisms in improving cognitive dysfunction in schizophrenia. J Psychopharmacol 25:792–800

Steckler T, Sahgal A (1995) The role of serotonergic–cholinergic interactions in the mediation of cognitive behaviour. Behav Brain Res 67:165–199

Stober G, Saar K, Ruschendorf F, Meyer J, Nurnberg G, Jatzke S, Franzek E, Reis A, Lesch KP, Wienker TF, Beckmann H (2000) Splitting schizophrenia: periodic catatonia-susceptibility locus on chromosome 15q15. Am J Hum Genet 67:1201–1207

Sullivan EV, Mathalon DH, Ha CN, Zipursky RB, Pfefferbaum A (1992) The contribution of constructional accuracy and organizational strategy to nonverbal recall in schizophrenia and chronic alcoholism. Biol Psychiatry 32:312–333

Sullivan PF, Kendler KS, Neale MC (2003) Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 60:1187–1192

Sydserff S, Sutton EJ, Song D, Quirk MC, Maciag C, Li C, Jonak G, Gurley D, Gordon JC, Christian EP, Doherty JJ, Hudzik T, Johnson E, Mrzljak L, Piser T, Smagin GN, Wang Y, Widzowski D, Smith JS (2009) Selective alpha7 nicotinic receptor activation by AZD0328 enhances cortical dopamine release and improves learning and attentional processes. Biochem Pharmacol 78:880–888

Taylor SB, Markham JA, Taylor AR, Kanaskie BZ, Koenig JI (2011) Sex-specific neuroendocrine and behavioral phenotypes in hypomorphic Type II Neuregulin 1 rats. Behav Brain Res 224:223–232

Tordera RM, Totterdell S, Wojcik SM, Brose N, Elizalde N, Lasheras B, Del Rio J (2007) Enhanced anxiety, depressive-like behaviour and impaired recognition memory in mice with reduced expression of the vesicular glutamate transporter 1 (VGLUT1). Eur J Neurosci 25:281–290

Tretter V, Revilla-Sanchez R, Houston C, Terunuma M, Havekes R, Florian C, Jurd R, Vithlani M, Michels G, Couve A, Sieghart W, Brandon N, Abel T, Smart TG, Moss SJ (2009) Deficits in spatial memory correlate with modified {gamma}-aminobutyric acid type A receptor tyrosine phosphorylation in the hippocampus. Proc Natl Acad Sci USA 106:20039–20044

Tsai G, Yang P, Chung LC, Lange N, Coyle JT (1998) D-serine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 44:1081–1089

Tugal O, Yazici KM, Anil Yagcioglu AE, Gogus A (2004) A double-blind, placebo controlled, cross-over trial of adjunctive donepezil for cognitive impairment in schizophrenia. Int J Neuropsychopharmacol 7:117–123

Tulving E (1985) How many memory systems are there? Am Psychol 40:385–398

Uslaner JM, Parmentier-Batteur S, Flick RB, Surles NO, Lam JS, McNaughton CH, Jacobson MA, Hutson PH (2009) Dose-dependent effect of CDPPB, the mGluR5 positive allosteric modulator, on recognition memory is associated with GluR1 and CREB phosphorylation in the prefrontal cortex and hippocampus. Neuropharmacology 57:531–538

van der Stelt M, Di Marzo V (2003) The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. Eur J Pharmacol 480:133–150

Van Dort CJ, Baghdoyan HA, Lydic R (2009) Adenosine A(1) and A (2A) receptors in mouse prefrontal cortex modulate acetylcholine release and behavioral arousal. J Neurosci 29:871–881

Vigano D, Guidali C, Petrosino S, Realini N, Rubino T, Di Marzo V, Parolaro D (2009) Involvement of the endocannabinoid system in phencyclidine-induced cognitive deficits modelling schizophrenia. Int J Neuropsychopharmacol 12:599–614

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF (2007) Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci 10:376–384

Wallace TL, Callahan PM, Tehim A, Bertrand D, Tombaugh G, Wang S, Xie W, Rowe WB, Ong V, Graham E, Terry AV Jr, Rodefer JS, Herbert B, Murray M, Porter R, Santarelli L, Lowe DA (2011) RG3487, a novel nicotinic alpha7 receptor partial agonist, improves cognition and sensorimotor gating in rodents. J Pharmacol Exp Ther 336:242–253

Warburton EC, Koder T, Cho K, Massey PV, Duguid G, Barker GR, Aggleton JP, Bashir ZI, Brown MW (2003) Cholinergic neurotransmission is essential for perirhinal cortical plasticity and recognition memory. Neuron 38:987–996

Weiser M, Reichenberg A, Grotto I, Yasvitzky R, Rabinowitz J, Lubin G, Nahon D, Knobler HY, Davidson M (2004) Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. Am J Psychiatry 161:1219–1223

West PJ, Marcy VR, Marino MJ, Schaffhauser H (2009) Activation of the 5-HT(6) receptor attenuates long-term potentiation and facilitates GABAergic neurotransmission in rat hippocampus. Neuroscience 164:692–701

Winters BD, Bussey TJ (2005a) Glutamate receptors in perirhinal cortex mediate encoding, retrieval, and consolidation of object recognition memory. J Neurosci 25:4243–4251

Winters BD, Bussey TJ (2005b) Removal of cholinergic input to perirhinal cortex disrupts object recognition but not spatial working memory in the rat. Eur J Neurosci 21:2263–2270

Winters BD, Forwood SE, Cowell RA, Saksida LM, Bussey TJ (2004) Double dissociation between the effects of peri-postrhinal cortex and hippocampal lesions on tests of object recognition and spatial memory: heterogeneity of function within the temporal lobe. J Neurosci 24:5901–5908

Winters BD, Saksida LM, Bussey TJ (2006) Paradoxical facilitation of object recognition memory after infusion of scopolamine into perirhinal cortex: implications for cholinergic system function. J Neurosci 26:9520–9529

Winters BD, Saksida LM, Bussey TJ (2008) Object recognition memory: neurobiological mechanisms of encoding, consolidation and retrieval. Neurosci Biobehav Rev 32:1055–1070

Winters BD, Bartko SJ, Saksida LM, Bussey TJ (2010) Muscimol, AP5, or scopolamine infused into perirhinal cortex impairs two-choice visual discrimination learning in rats. Neurobiol Learn Mem 93:221–228

Wishka DG, Walker DP, Yates KM, Reitz SC, Jia S, Myers JK, Olson KL, Jacobsen EJ, Wolfe ML, Groppi VE, Hanchar AJ, Thornburgh BA, Cortes-Burgos LA, Wong EH, Staton BA, Raub TJ, Higdon NR, Wall TM, Hurst RS, Walters RR, Hoffmann WE, Hajos M, Franklin S, Carey G, Gold LH, Cook KK, Sands SB, Zhao SX, Soglia JR, Kalgutkar AS, Arneric SP, Rogers BN (2006) Discovery of N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide, an agonist of the alpha7 nicotinic acetylcholine receptor, for the potential treatment of cognitive deficits in schizophrenia: synthesis and structure–activity relationship. J Med Chem 49:4425–4436

Woo TU, Miller JL, Lewis DA (1997) Schizophrenia and the parvalbumin-containing class of cortical local circuit neurons. Am J Psychiatry 154:1013–1015

Woolley M, Marsden C, Sleight A, Fone K (2000) Reversal of a scopolamine-induced deficit in object discrimination by a selective 5-HT6 receptor antagonist, Ro 046790, in rats. Br J Pharmacol: U39-U39.

Woolley ML, Marsden CA, Sleight AJ, Fone KC (2003) Reversal of a cholinergic-induced deficit in a rodent model of recognition memory by the selective 5-HT6 receptor antagonist, Ro 04–6790. Psychopharmacology (Berl) 170:358–367

Woolley ML, Waters KA, Reavill C, Bull S, Lacroix LP, Martyn AJ, Hutcheson DM, Valerio E, Bate S, Jones DN, Dawson LA (2008) Selective dopamine D4 receptor agonist (A-412997) improves cognitive performance and stimulates motor activity without influencing reward-related behaviour in rat. Behav Pharmacol 19:765–776

Yonelinas AP, Aly M, Wang WC, Koen JD (2010) Recollection and familiarity: examining controversial assumptions and new directions. Hippocampus 20:1178–1194

Young JW, Powell SB, Risbrough V, Marston HM, Geyer MA (2009) Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia. Pharmacol Ther 122:150–202

Zamberletti E, Vigano D, Guidali C, Rubino T, Parolaro D (2010) Long-lasting recovery of psychotic-like symptoms in isolation-reared rats after chronic but not acute treatment with the cannabinoid antagonist AM251. Int J Neuropsychopharmacol: 1–14.

Zanassi P, Paolillo M, Feliciello A, Avvedimento EV, Gallo V, Schinelli S (2001) cAMP-dependent protein kinase induces cAMP-response element-binding protein phosphorylation via an intracellular calcium release/ERK-dependent pathway in striatal neurons. J Biol Chem 276:11487–11495

Zhang Z, Sun J, Reynolds GP (2002) A selective reduction in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia patients. Chin Med J (Engl) 115:819–823