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Effect of Psychotomimetic and Schizophrenia-associated Drugs on Rat Visual Perceptual Grouping

Effect of Psychotomimetic and Schizophrenia-associated Drugs on Rat Visual Perceptual Grouping

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Contents

Abstract

Background and Purpose Abnormalities in visual perception are associated with a number of neurological diseases, particularly schizophrenia, and may represent a novel avenue of treatment for such disorders. However, translatability of pre-clinical models of psychosis to patient populations is lacking, particular with regards to the study of perception in these models. The purpose of the present study was to investigate the effect of pro-psychotic and schizophrenia-associated compounds on the ability of rats to perform a task of visual integration by proximity.

Experimental Approach Rats were trained in a touchscreen operant environment to perform a visual discrimination between stimuli that were composed of rows of dots differing only in their relative horizontal and vertical proximity, a process thought to measure visual integration. Animals were then tested under the influence of glutamatergic (memantine, NVP-AAM077, CP-101,606), serotonergic (psilocybin, ketanserin) and dopaminergic (D-amphetamine, methylphenidate, haloperidol) compounds while performing the visual discrimination task with a range of altered stimuli.

Key Results The GluN2B-selective NMDA antagonist CP-101,606 impaired perceptual grouping on the task in a dose-dependent manner, while a GluN2A-selective antagonist showed increased ability on the task through a mechanism independent of grouping. Paradoxical results were encountered in agonist/antagonist drug pairings; the dopamine-releasing agent D-amphetamine and the antipsychotic haloperidol both impaired perceptual grouping, whereas both agonist and antagonist at 5HT-2A, psilocybin and ketanserin, respectively increased accuracy, in a non-stimulus-specific manner, suggesting an underlying mechanism potentially distinct from perceptual grouping enhancement.

Conclusions and Implications My findings add to the evidence that NMDA antagonists are strongly associated with alterations in visual cognition. They indicate GluN2B antagonism results in an impairment of visual grouping by proximity, whereas GluN2A antagonism increases task accuracy though in a non stimulus-specific manner. The findings also indicate potentially paradoxical interactions of monoaminergic pharmacology on visual perception, which will require investigation to understand further.

Lay Abstract

Mental illnesses and neurological diseases are most commonly understood in terms of the symptoms present when interacting with people and the world – for example, Alzheimer's disease is associated with forgetfulness and wandering, while schizophrenia is associated with confused speech and delusions. However, the disruption of normal visual perception, which is also a feature of both of these disorders, is relatively unstudied. Visual perception deficits may contribute to higher-level symptoms; studies that focus on visual perception may lead to new ways to treat these and other disorders.

In these studies, I used a task that may measure perceptual grouping. This is the ability to view objects with similar properties as associated with each other. This ability is disrupted in schizophrenia patients, but pre-clinical research is still lacking. Translatability between pre-clinical animal models of disease and clinical human research is important to be able to extrapolate experimental findings to predictive outcomes in humans.

My research focused on drugs associated with receptor systems thought to be disrupted in schizophrenia, and the effects of which produce schizophrenia-like symptoms: NMDA antagonists, serotonin-2A agonists, and dopamine-releasers. To quantify their effect on perceptual grouping, I trained rats to discriminate between rows of dots that were aligned either horizontally or vertically. The rats then performed the discrimination task under the influence of a variety of drugs, to see how each affected their ability to complete it.

My investigation revealed that perceptual grouping deficits caused by NMDA antagonists may be localized to receptors containing the NR2B subunit. I also found grouping ability to be disrupted by the stimulant D-amphetamine and the antipsychotic haloperidol. The 5HT-2A agonist and antagonist psilocybin and ketanserin both increased accuracy on t task, the underlying mechanism of which is unknown.

Introduction

Vision is the primary sensory modality in humans. A disruption in visual perception would have significant effects on the way one can interact with the world, and may have knock-on effects on the wide array of cognitive mechanisms that rely on visual sensory input at some stage of their processing.

Several neurological conditions have been demonstrated to express various visual perceptual deficits as part of their symptomology. These include Alzheimer's disease (Cronin-Golomb 1995; Holroyd & Shepherd 2001; Kirby et al. 2009) and autism-spectrum disorder (ASD) (Brosnan et al. 2004; Robertson et al. 2014). Perhaps the disorder most associated with dysfunction of visual perception is schizophrenia, which is partially characterized by visual and auditory hallucinations. In addition, schizophrenic populations seem to show an extremely high prevalence of deficits in perceptual organization - the ability to extract and resolve elements of a complex scene into distinct and identifiable objects (Kurylo et al. 2007; Silverstein & Keane 2011; Uhlhaas & Silverstein 2005). The potential contribution of these impairments to the overall pathology of these diseases is surprisingly unexplored, considering that impairments in the ability to process information about external reality would, in theory, affect every cognitive process that relies on a form of sensory input. Investigating these impairments has been identified as a promising area for both clinical (Green et al. 2009) and pre-clinical (Siegel et al. 2013) research into schizophrenia. Perception may thus be a valid target for future treatment of the diseases I have mentioned, and may assist in understanding how disease pathology results in functional deficits. Furthermore, it

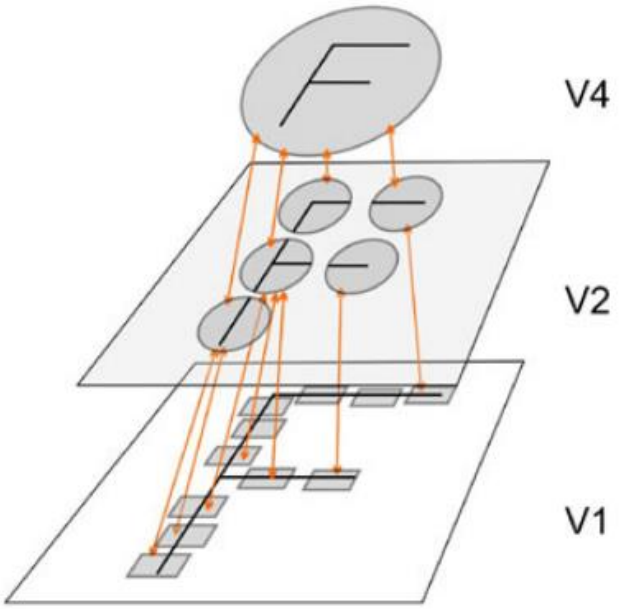


Fig.1 – Hierarchal organisation of the visual cortex; feedforward projections propagate simple features upwards, where they conjugate onto neurones which are tuned to more complex features. Though in this example it is the resolution of a single object by contrast borders, the same principles apply to more abstract measures of grouping (adapted from Roelfsema&Houtkamp 2011).

may be a useful biomarker to help diagnose neurological diseases in their early stages. For example it has been shown that deficits in early visual processing correlate with disease progression in Alzheimer's patients (Uhlhaas et al. 2008).

Deficits in perception arise when the basic function of the visual system, to transform an initial retinal input into distinct coherent images and scenes, is disrupted. Basic properties of visual information – shape, movement, colour, relative distance and spatial location, etc. – must be generated and processed from simple 2D inputs. Visual integration is an ascending process through the visual cortex, whereby neurones in lower-level areas (V1) coding for simple features (ie. contrast, orientation) are integrated into neurones in higher areas (V2-V4) coding for larger and more complex features (see fig.1), which when finally resolved are considered distinctly salient objects (Caplovitz et al. 2008; Connor et al. 2007; Palmer et al. 2003; Wagemans et al. 2012). This process relies on competitive inhibition as 'stronger' visual elements are amplified and inhibit nearby neurones (Wyatte et al. 2012), with the visual cortex relying on an excitation/inhibition balance to maintain equilibrium and normal sensory processing (Marino et al. 2005). A major part of this perceptual organization is grouping, the process by which similar visual elements following particular principles are grouped together (see fig.2 for examples) to allow a visual scene to become more salient. It is these processes that are thought to be disturbed in neurological disorders which feature disrupted perceptual processes. For example, V2-V4 of the visual cortex has been demonstrated to have reduced activation when schizophrenic patients perform a perceptual integration task (Silverstein et al. 2009). As well as upwards neural organisation, aspects of grouping also require recurrent top-down connections, which can 'label' neurones that respond to features of the same object (Roelfsema & Houtkamp 2011; Sillito et al. 2006). The feedforward and feedback mechanisms of sensory processing I have described have some analogy to the bottom-up and top-down theories of psychosis, whereby hallucinations and delusions are theorised to occur either through unrestricted, unfiltered sensory input, or from over-compensated recurrent feedback that does not match with expected incoming signal (Corlett et al. 2009).

The specific perceptual organisation principle that I will be investigating is grouping by proximity. This allows an easily-quantified scale of visual stimuli (see fig.3) – meaning that the differences between the images (distance ratio) allow them to be easily graphed. Rats were

trained to discriminate between rows of dots which were aligned either horizontally or vertically, with the perception of this alignment being dependent on the process of grouping. Once the animals had learned to discriminate between the two images, varying horizontal/vertical distance ratios were used; the most difficult stimuli to discriminate had a ratio close to 1, whereas the highest-signal image had a ratio of 2.76 (see fig.4). Stimuli were calculated to ascend in steps of 0.04 log10 [ratio]. Previous research has demonstrated that such a proximity grouping task is sensitive to pharmacological manipulation (Talpos et al. 2015b – please note that the memantine study therein was performed by myself, and relies on the same data as that presented in this thesis).

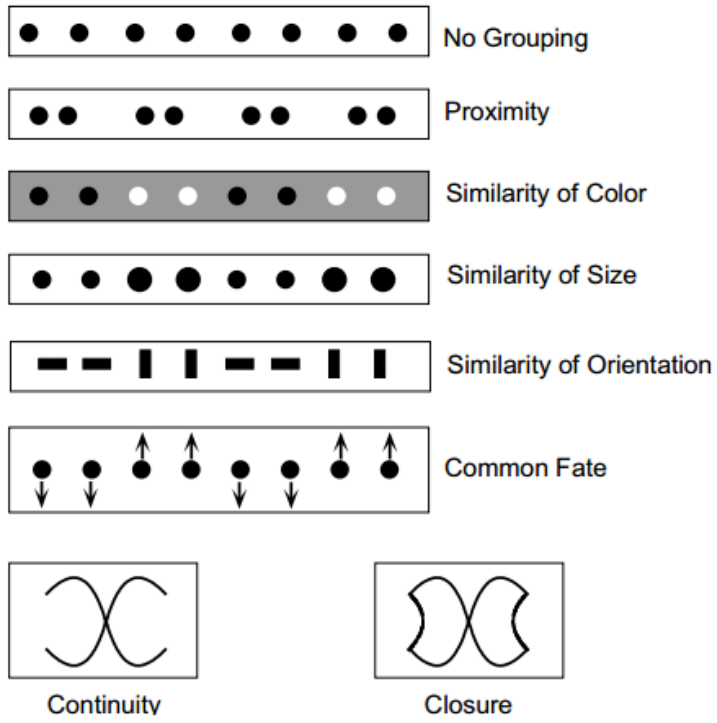


Fig.2 – examples of classical grouping principles. Elements related by a particular factor are grouped together perceptually (adapted from Palmer et al. 2003).

The study of perceptual symptoms ameliorates some of the difficulties of modelling schizophrenia in animals. These are chiefly that there is a lack of convincing evidence that non-primates suffer from identifiable mental illnesses, and the problem of studying a cognitive disorder in creatures much less cognitively developed than humans. Visuospatial disruptions can be more easily measured than, for example, thought disorganization or delusions. Despite this, little research has been conducted on perceptual measures in animal models. I have focused on pharmacological models over other mechanisms such as neonatal brain lesions and genetic modifications, which arguably show better validity in some measures (Lipska & Weinberger 2000), because of the ease and reversibility of acute drug administration allowed a

broader investigation than surgical or transgenic methods. Furthermore, pharmacological models can be directly tested clinically in humans for translational verification, something that is practically impossible with genetic or surgical studies.

Observations that certain classes of drugs exacerbated symptoms of schizophrenia and induced psychotic-like symptoms in healthy subjects helped lead to the development of theories of the molecular biology of schizophrenia; NMDA antagonists (PCP and ketamine), dopamine releasing agents (amphetamine and cocaine), and 5HT-2A agonists (LSD). Drugs in these classes are often used as pharmacological tools in animal models of psychosis and schizophrenia (Marcotte et al. 2001; Lipska& Weinberger 2000).

Similarities observed between both positive and negative symptoms of schizophrenia and the effects of NMDA antagonists such as ketamine and PCP (Javitt & Zukin 1991; Lahti et al. 1995) contributed to the development of the NMDA downregulation theory of schizophrenia (Olney & Farber 1995). These drugs are now often used as pharmacological models of psychosis (Sams-Dodd 1996; Newcomer et al. 1999). In particular, chronic administration of NMDA antagonists can lead to long-lasting effects on cognition similar to those seen with schizophrenia, even after the drug has been eliminated from the body. A comprehensive overview of this and other associations of NMDA antagonists with cognition and schizophrenia are beyond the scope of this thesis - see Gilmour et al. 2012 for review.

Previous research has demonstrated that ketamine can disrupt perceptual organization in both humans (Uhlhaas et al. 2007) and rats (Kurylo & Gazes 2008), with the disruption in humans mimicking deficits found in schizophrenic subjects (Silverstein et al. 2011). My work built on Talpos et al. 2015, where ketamine was shown to disrupt perceptual grouping by proximity, and MK801 and PCP to potentially impair performance on the task in a mechanism unrelated to grouping. I investigated memantine (used for treatment of Alzheimer's disease), NVP-AAM077 (partially selective for NR2A-subunit-containing NMDA receptors (Frizelle et al. 2006); more specific ligands unavailable), and CP-101,606 (selective for NR2B-subunit-containing NMDA receptors (Brimecombe et al. 1997)). The aim was to investigate whether inhibition of a specific subunit would result in the grouping deficit seen with ketamine in Talpos et al. 2015. Previous research has demonstrated pro-cognitive effects of NR2A and NR2B-selective antagonists (Gilmour et al. 2009; Dix et al. 2010; Smith et al. 2011). Furthermore, NR2A-containing NMDA receptors are thought to be associated with the process of LTP (long-term

potentiation), and NR2B with LTD (long-term depression) (Liu et al. 2004; Massey et al. 2004), with this modulation of plasticity potentially being involved with altered cognitive function. In addition, I was curious to see if a commonly-used therapeutic (memantine) exhibited effects on visual perception across a wide dose-range.

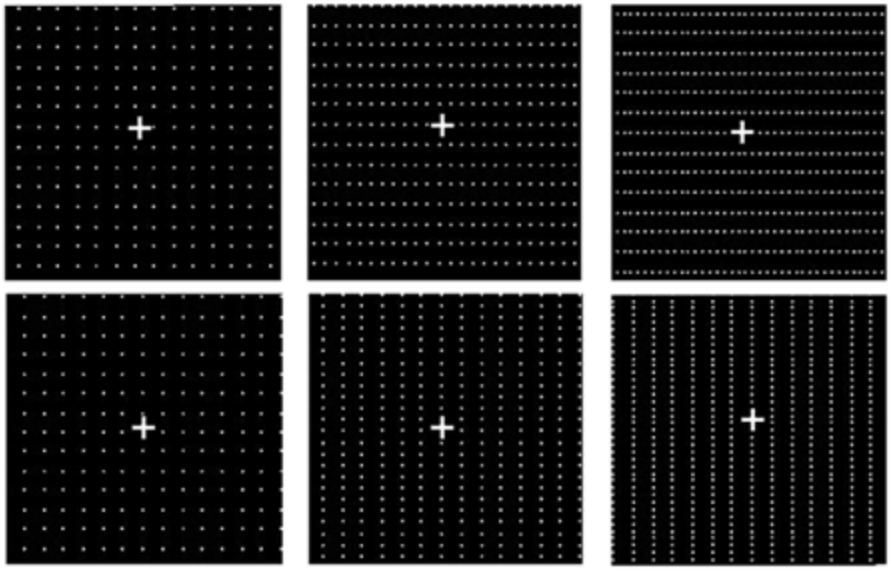


Fig.3 – From left to right; examples of the hardest (0.01), medium (0.24), and easiest (0.44) stimuli pairs used (note that + was always centered in stimuli used, here may be off-center due to formatting).

The development of the serotonergic theory of schizophrenia lead from both the discovery of serotonin as a neurotransmitter, and the profound effect of the drug LSD on mood, thought, and sensory perception (Geyer & Vollenweider 2008 for review). Such 5HT-2A agonists induce phenomenological effects, such as 'visual restructuralisation' and 'ego dissolution' which are not dissimilar to those seen in schizophrenic patients (Gouzoulis-Mayfrank et al. 1998). The NMDA and 5HT-2A theories of schizophrenia overlap, with NMDA antagonists though to indirectly affect signalling properties of 5HT-2A/mGlu2 receptor complex-expressing pyramidal neurones which are necessary for the psychedelic and pro-psychotic effect of drugs such as LSD and psilocybin (Gonzalez-Maeso&Sealfon 2009; Gonzales-Maeso et al. 2008; Moreno et al. 2011). The amelioration of positive symptoms through antagonism of 5HT-2A is thought to contribute to the efficacy of atypical antipsychotic drugs (Horacek et al.

Log Ratio	Ratio
0.01	1.03
0.04	1.1
0.08	1.2
0.12	1.32
0.16	1.44
0.2	1.58
0.24	1.74
0.28	1.91
0.32	2.09
0.36	2.29
0.4	2.51
0.44	2.76
0.77	5.9

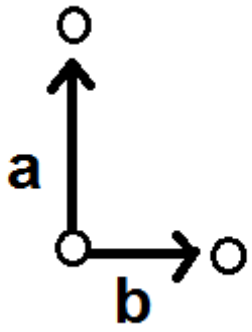


Fig.4 – Table of ratios of the stimulus levels used. In 'Horizontal' stimuli, values were calculated with [a/b]; in 'Vertical' stimuli, with [b/a].

2006), and a variety of serotonergic psychedelics have been used to model psychosis (Hanks & Gonzalez-Maeso 2012; Marona-Lewicka et al. 2011). Serotonergic projections have also been shown to innervate the visual cortex (Kosofky et al. 1984; Morrison et al. 1982) with the 5HT-2A receptor to be found in high density in the region (Adams et al. 2004) indicating a potential modulatory effect of the serotonergic system on perception.

A prominent feature of serotonergic psychedelics are geometric hallucinations. It has been previously suggested that the cryoarchitecture of the visual cortex contributes to the nature of the geometric patterns characteristic of these drugs (Bressloff et al. 2002; Veltz et al. 2014). 5HT-2A agonists, through a mechanism involving simulation of asynchronous glutamate release, may increase recurrent excitation and amplify feedback loops (Aghajanian & Marek 1999). The overamplified processing of sensory information may be what leads to the visual hallucinations associated with 5HT-2A agonists. These same underlying processes are those necessary for perceptual organisation and ascending sensory information (Hupe et al. 1998; Shao and Burkhalter 1996). I thus hypothesised that disinhibited feedback loops in bottom-up sensory input caused by 5HT-2A agonists would likewise amplify grouping processes. To test the theory that 5HT-2A activation will increase grouping ability, I used the drugs psilocybin and ketanserin, respective agonists and antagonists at the receptor. Psilocybin has been used as an acute serotonergic model of psychosis (Geyer & Vollenweider 2008; Hanks & Gonzalez-Maeso 2013), and in addition as a therapeutic for neuropsychiatric disorders such as alcohol dependence and depression (Tyls et al. 2013) which is why I chose to use it in my study over other commonly-used research tools such as DOI (Canal & Morgan 2012).

The hyperdopaminergic theory of schizophrenia has been historically the most pervasive, having been tied to the development of classical antipsychotic drugs (see Davis et al. 1991 for review). Dopamine-releasing drugs such as amphetamine are associated with ‘stimulant psychosis’ at high doses (Curran et al. 2004), and have been used historically to model schizophrenia (Bell 1965; Snyder 1973), though recent analysis has questioned the validity of such methods (Lipska & Weinberger 2000). The hyperdopaminergic state is thought to result in aberrant assignment of salience, which leads to delusions when focused internally and perceptual disruptions when applied to sensory information (Kapur 2003). Thus I tested D-amphetamine (the more active isomer of amphetamine), haloperidol, and methylphenidate. I predicted that, similar to how schizophrenic patients display impairments in perceptual

organisation, the psychotomimetic D-amphetamine would impair grouping performance on the task.

Haloperidol, an atypical antipsychotic, is a commonly prescribed drug to treat schizophrenia, and was thus selected to be tested for further investigation into the effects of therapeutic dopaminergic drugs on perception. In an ideal world, my hypothesis would have been that the drug has no effect on perception, or even produces an enhancement of grouping ability as a potential adjunct explanation for its efficacy as an antipsychotic; however, these drugs are known for their varied and diffuse cognitive impairments (an analysis of which is beyond the scope of this introduction), so conversely it would not have been surprising to produce a deficit in accuracy.

Methylphenidate (commonly known as Ritalin), a drug with amphetamine-like effects but different mechanism of action (norepinephrine-dopamine reuptake inhibitor), was also investigated. Clinically, it is used for similar reasons to D-amphetamine; primarily ADHD, though similar profiles mean both can be used for disorders such as narcolepsy. Both drugs have shown similar cognitive effects on a variety of operant tasks (Mayorga et al. 2000).Though not as closely associated with psychosis as amphetamine, methylphenidate has been shown to exacerbate positive symptoms of schizophrenia, and has abuse potential that may lead to paranoia and other psychosis-associated side effects (Spensley & Rockwell 1972).

The drugs I have mentioned are all associated, directly or indirectly, with the symptoms or treatment of schizophrenia and psychosis. Though the effect of such drugs (and others) on cognitive functions such as working memory and attention are relatively well studied, little pre-clinical research on the way they modulate perceptual processing has been conducted (Carpenter & Koenig 2008; Dudchenko et al. 2013). It is for this reason that I investigated the effects of certain drugs associated with and used as models of psychosis on perceptual grouping ability, a measure known to be impaired in human schizophrenia patients.

To analyse the accuracy data produced in this experiment, I utilised mixed effects logistic regression models. These can analyse significance of interaction (where the shape of the curves is changed, to imply intersection) and main effect (where the curve is shifted in parallel) between treatment and visual stimuli. An interaction between dose and stimuli would imply a specific effect of drug on perceptual grouping, whereas a main effect implies an effect on visual cognition that is non-specific to grouping. Secondary measures such as latencies and number of trials completed were also recorded and analysed with ANOVAs and T-tests.

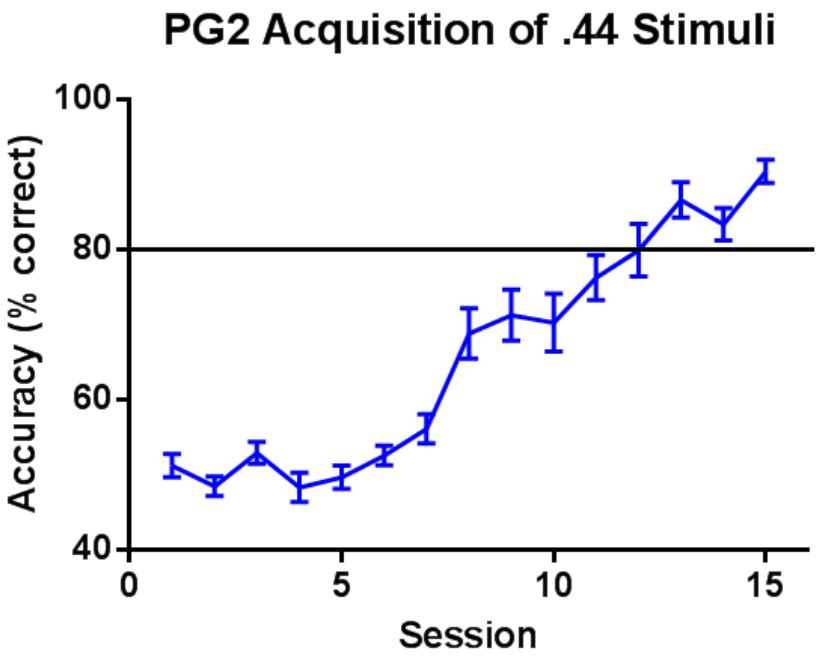


Fig.5– Graph displaying mean accuracy of group of animals (n = 22) learning to discriminate between horizontal and vertical stimulus at 0.44 level (errorbars = SE)

Materials and Methods

Subjects

All animals were treated in accordance with the European Ethics Committee (decree 86/609/CEE), the Animal Welfare Act (7 USC 2131) and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioural Research (National Research Council 2003). The study protocol was approved by the local animal experimental ethical committee at Janssen Research &Development (Beerse, Belgium).

Male Lister-hooded rats (Harlan, Netherlands, 200-240g on arrival) were used for the studies. These were divided into two groups of 24 – rats in the first group (PG1) were approximately 12 months old at start, whereas rats in the second group (PG2) were ordered at the beginning of the study. Drug tests were performed on only one of these groups. All animals were group housed (4 rats each) in individually-ventilated cages (approx. 48cm L x 37cm W x 22cm H; temperature maintained at 22°C, humidity 55%) on a 12 hour normal light/dark cycle. Animals were provided with in-cage enrichment consisting of red plastic tunnels and chew blocks. Each rat was fed approximately 15g of food per day (Purina standard rat chow) to maintain them at 85-90% free-feeding weight, and had free access to water at all times except during testing.

Treatment (mg/kg)	Mean Latencies (log10 (ms)				Trials		75%
	Response	SE	Collection	SE	Completed	SE	Stimuli
Memantine							
VEH	3.403	0.017	3.123	0.015	95.455	0.376	0.108
0.3	3.397	0.017	3.106	0.014	95.591	0.409	0.121
1	3.382	0.017	*3.094	0.013	94.864	0.893	0.121
3	3.451	0.024	#3.099	0.016	93.318	1.894	0.120
10	***4.062	0.040	***3.300	0.020	***48.954	4.325	0.270
NVP-AAM077							
VEH	3.400	0.014376	3.132	0.010	103.682	0.274	0.171
5	3.438	0.011953	3.143	0.021	103.818	0.125	0.206
10	***3.598	0.040362	***3.181	0.013	*94.409	4.176	0.113
20	***3.857	0.050393	***3.229	0.018	***62.682	7.028	0.141
CP-101,606							
VEH	3.422	0.011	3.136	0.009	104.000	0.000	0.140
1	3.406	0.015	*3.114	0.009	104.000	0.000	0.143
3	*3.386	0.013	***3.097	0.011	104.000	0.000	0.177
10	#3.395	0.014	***3.078	0.010	103.909	0.063	0.244
D-Amphetamine							
VEH	3.433	0.016	3.122	0.016	99.105	1.661	0.118
0.25	***3.351	0.021	3.106	0.016	98.105	2.586	0.136
0.5	***3.328	0.021	3.146	0.038	90.421	6.515	0.178
0.75	***3.355	0.021	3.144	0.019	**75.211	7.325	0.197
Methylphenidate							
VEH	3.428	0.020	3.105	0.015	103.684	0.316	0.126
1	3.427	0.017	3.107	0.014	103.684	0.316	0.127
3	#3.396	0.019	3.101	0.017	104.000	0.000	0.132
10	***3.367	0.018	3.107	0.021	102.053	1.339	0.168
Haloperidol							
VEH	3.455	0.018	3.115	0.015	103.263	0.737	0.113
0.01	3.502	0.023	3.128	0.018	102.263	1.629	0.129
0.02	***3.615	0.026	***3.174	0.019	*98.368	2.177	0.125
0.04	***3.808	0.036	***3.247	0.022	***67.368	6.400	0.161
Psilocybin							
VEH	3.400	0.013	3.162	0.038	95.286	4.144	0.130
0.3	#3.476	0.019	3.199	0.033	89.381	5.430	0.119
1	***3.623	0.025	3.240	0.024	*77.905	4.633	0.081
3	***3.881	0.044	***3.338	0.040	***40.810	4.921	0.072
Ketanserin							
VEH	3.442	0.015	3.152	0.011	104.000	0.000	0.165
0.3	3.468	0.018	3.165	0.011	103.727	0.230	0.125
1	3.464	0.018	3.165	0.008	103.773	0.197	0.135
3	3.473	0.017	*3.174	0.009	103.364	0.444	0.112

Fig.6 – Effects of compounds on secondary measures (for visual representation, see fig.7 and 8). The presence of an asterisk indicates significance; #p<0.1, *p<0.05, **p<0.01, ***p<0.001. Estimated 75% accuracy ratio is included for illustrative purposes.

Apparatus

All work was performed using modified Med Associates operant chambers (Med Associates Inc., Fairfax, Vermont; 33.5 cm H × 32.5 cm W × 40 cm L).One side of the chamber was equipped with a tone generator, a house light, and a food pellet receptacle (containing a reward light and an infra-red nose-poke detector) connected to a pellet dispenser. The opposite wall was replaced with a touch-sensitive infrared system paired with a computer monitor (26cm H x 36cm W). This monitor was partially covered with a metal 'mask' with two windows, restricting response to the areas upon the screen where images would appear. To slow the response of tested animals, and thus facilitate training and accuracy (Bussey et al. 2008), a counterweighted steel flap (5cm x 36cm) was placed in front of the screen. All operant chambers were housed within sound-attenuated boxes (60cm x 74cm x 60cm), fitted with a small ventilation fan. Screens and operant box functions were controlled by K-limbic software (K Limbic, Sawbridgeworth, UK).

Compounds

Compounds were administered either via subcutaneous (D-Amphetamine, haloperidol, methylphenidate, ketanserin, CP-101,606) or intraperitoneal (memantine, psilocybin, NVP-AAM077) injection in physiological saline solution (with the exception of CP-101,606, which was dissolved in 10% lactate + 5% glucose) at volumes of 1ml/kg for s.c. and 10ml/kg for i.p. route. Administration regimens (administration time and dose) were based on historical data and published accounts in other operant tasks. Memantine, D-Amphetamine –administered 60 minutes prior to start of task; haloperidol, psilocybin, ketanserin, CP-101,606, NVP-AAM077-30 minutes; methylphenidate - 20 minutes. Each compound was tested using a within-subject design, with all subjects receiving all doses of each compound, based on a randomized latin square design. Drugs were administered on Tuesdays and Fridays, to allow several days for washout between tests, in a window between 13:00 and 15:00 when possible. Memantine was administered at 0.3, 1.0, 3.0, 10.0 mg/kg (Talpos et al. 2012) , D-Amphetamine at 0.25, 0.50, 0.75 mg/kg (Talpos et al. 2014), Psilocybin at 0.3, 1.0, 3.0 mg/kg, Haloperidol at 0.01, 0.02, 0.04 mg/kg (Talpos et al. 2015a), Methylphenidate at 1, 3, 10 mg/kg (Robinson 2012), Ketanserin at 0.3, 1.0, 3.0 mg/kg, CP-101,606 at 1, 3, 10mg/kg, and NVP-AAM077 at 5, 10, 20mg/kg (Kumar

et al. 2015). Compounds were sourced from Sequoia Research Products (memantine, NVP-AAM077, CP-101,606), THC Pharm (psilocybin), Certa S.A. (D-amphetamine), or synthesised internally (ketanserin, methylphenidate, and haloperidol).

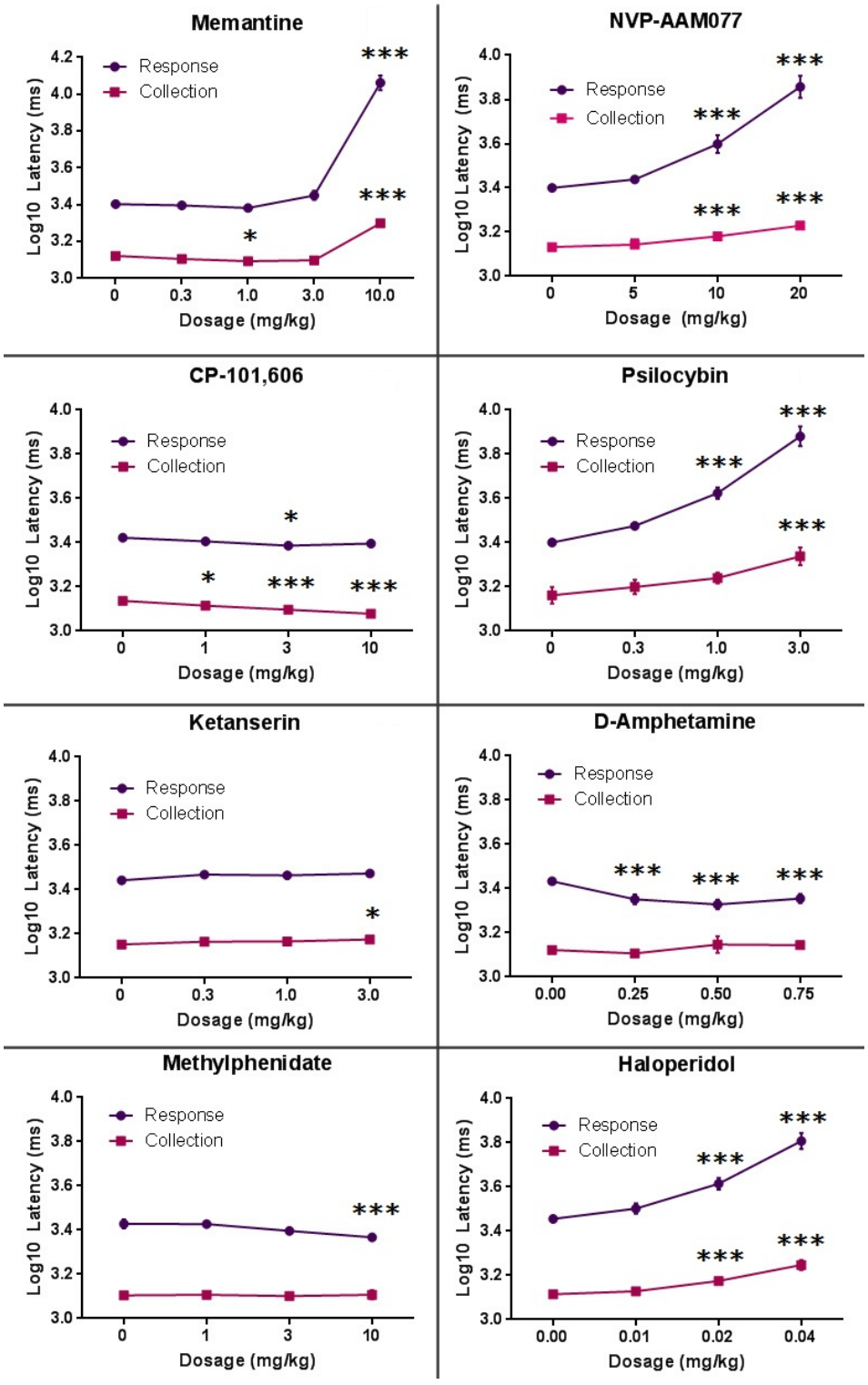


Fig.7 – Effects of compounds on latencies. Response refers to the time between trial starting and a screen-touch by the rat, and Collection refers to the time between screen-touch and collection of food pellet from receptacle. Errorbars = SEM.

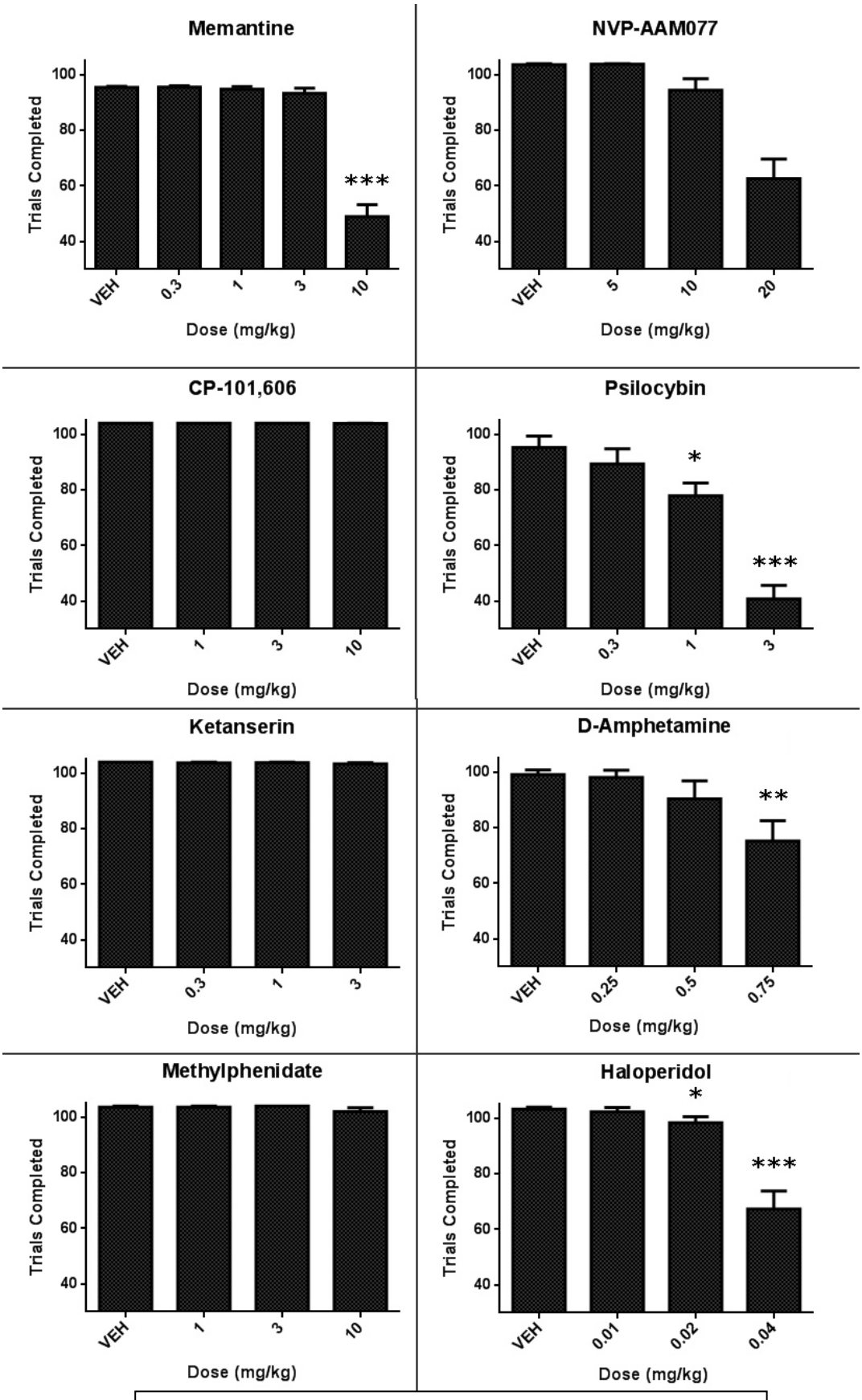


Fig.8 – Effect of compounds on number of trials completed (maximum = 104, except for Memantine where it = 96). Errobars = SEM.

Pre-Training

Rats were initially acclimatized to the operant chambers by placing them inside while the fans were running for approximately 45 minutes. A peanut butter and reward pellet (45mg, sucrose-based) mixture was placed on the screen, steel flap, and mask, in order to facilitate exploration of screen area. This was necessary to encourage interaction with the screen for future task acquisition. Once animals had acclimatized –determined by having consumed all peanut butter across various screen locations - they were moved onto tone training. This entailed a reward pellet being released into the pellet receptacle in conjunction with the sounding of the reward tone and the activation of the pellet receptacle light. Once the pellet was collected (detected by an infrared beam within the magazine), the light would turn off, and after 10s another pellet would be delivered with tone and light activation. This was done in order to train animals to associate sounding of the tone and the illumination of the food magazine with the delivery of a pellet. The session ended after the delivery of 60 pellets or after 45 minutes had passed, whichever came first. Animals proceeded to the next stage of training once they had completed 60 trials for two consecutive sessions.

The next stage of pre-training involved the rats learning to associate touching the screen with the delivery of a food reward. Initially, three large white boxes (covering most of the screen) were displayed. Touching any part of any of these images resulted in the images being removed from the screen, the reward tone sounding and a food pellet being dispensed. Once the pellet was collected, a 5-second 'inter-trial-interval' (ITI) occurred, and the next trial was initiated. As in previous pre-training, animals moved onto the next stage of training once they had achieved 60 completed trials on two consecutive sessions.

The final pre-training phase was similar to the previous one, except only one of the three white boxes on the screen was displayed, with the location changing randomly after each trial. This was done to ensure that rats learned to respond to presented stimuli, and not a particular spatial location on the screen. Once again animals were required to complete 60 trials within 45 min on two consecutive sessions to reach criteria for training on the perceptual grouping visual discrimination.

Visual Stimuli

This task consisted of a visual discrimination (discussed in detail later) in which subjects were required choose one of two stimuli to earn a food pellet. The stimuli consisted of dot lattices, which weremore strongly aligned either horizontally or vertically. This is defined by the ratio of distance between horizontal and vertical dots. At lower ratios, the alignment is weaker and the stimuli are harder to discriminate. The stimuli were expressed as Log10[ratio] (see fig.4), ascending in regular steps from 0.01(hardest) to 0.44 (easiest). One 'very easy' stimuli with a ratio of 5.9 (0.77 in log10 units) was also included as part of the task following its use in the perceptual grouping protocol of Kurylo & Gazes 2008, though it was omitted from further statistical analysis and curve-fitting on learning that inclusion would skew results toward this 'high-influence point'.

Perceptual Grouping Task Training

Rats were initially trained on stimuli with the penultimate greatest ratio (0.44), in order to acquire either a horizontal or vertical preference. Half of the rats were trained to select horizontal, and half vertical. Stimulus pairs were displayed in the two windows of the mask, with location randomized across trials within a session. On selection of the correct stimulus, rats were rewarded with a foot pellet. If the incorrect stimulus was selected, all lights were extinguished for 10s, before the image was re-displayed and trial repeated until the correct stimulus was selected. These repeated 'correction trials' did not count towards the total number of trials completed, nor were they included in accuracy measurements and analysis. To reach criterion in this stage of training (and to proceed to the next stage), animals had to complete a minimum of 72 trials within 45 minutes, as well as an average of at least 80% trials correct over 3 days. This was achieved in all animals over a period of 15 sessions (see fig.5 for mean acquisition of PG2 group).

The final stage of training was to ensure they could perform the discrimination task with the modified, more perceptually-ambiguous stimuli. During the session, all 12 levels of difficulty were presented 8 times in a randomized order (96 total trials), with a session lasting for 45 minutes (but terminating early in the case of all trials being completed). Rats were given at

least five sessions of training before being moved onto drug testing, to ensure that rats were able to complete the task with stable performance and a stimuli-dependent accuracy. This final training was identical to the protocol used during pharmacological testing.

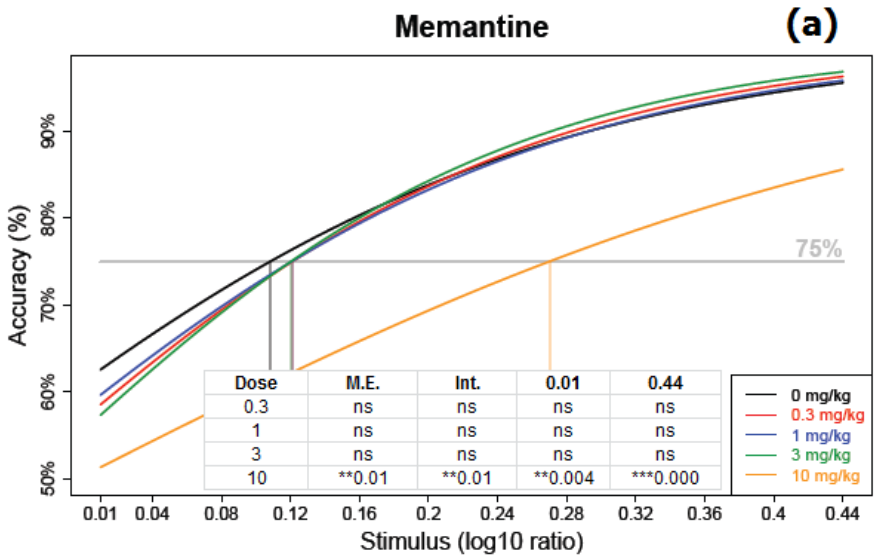
Statistics

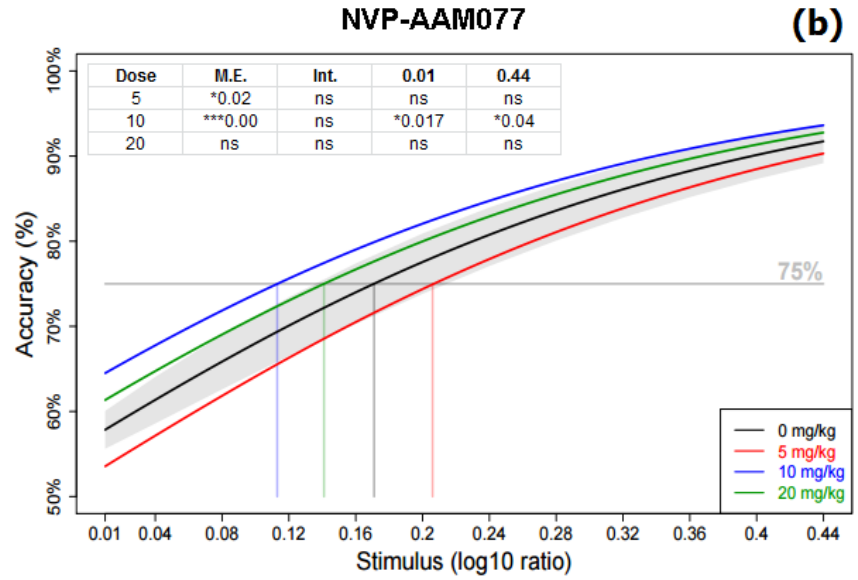
Operant boxes were controlled, and raw data generated, via K-Limbic (Conclusive Solutions, Sawbridge, UK) and then further formatted with Microsoft Excel 2010. Secondary measures - number of trials completed, and response & food pellet collection latencies were analysed with Statistica (Version 10; StatsSoft). Accuracy across levels 0.01 – 0.44 was investigated using R.

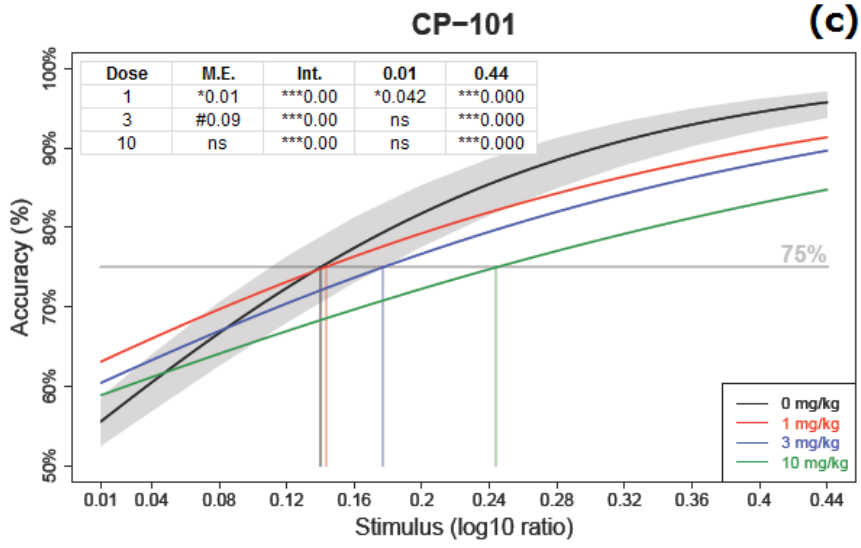
To test for effects of drug treatments on latencies (response and collection), all data were transformed into log10 (latency (ms)). This was to ensure that means were not skewed by excessively large latencies (where, for example, an animal had simply got distracted for a long time). Repeated measures ANOVA, with a post hoc analysis of Dunnett's T-test against vehicle, were performed.

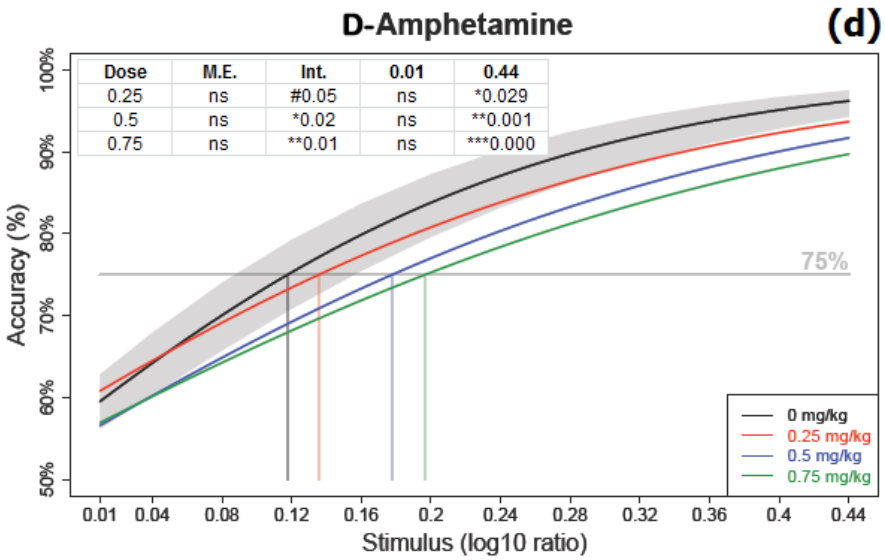
The number of completed trials were analysed with T-test – this was done as, in some tests, there was not enough variance to perform ANOVA's.

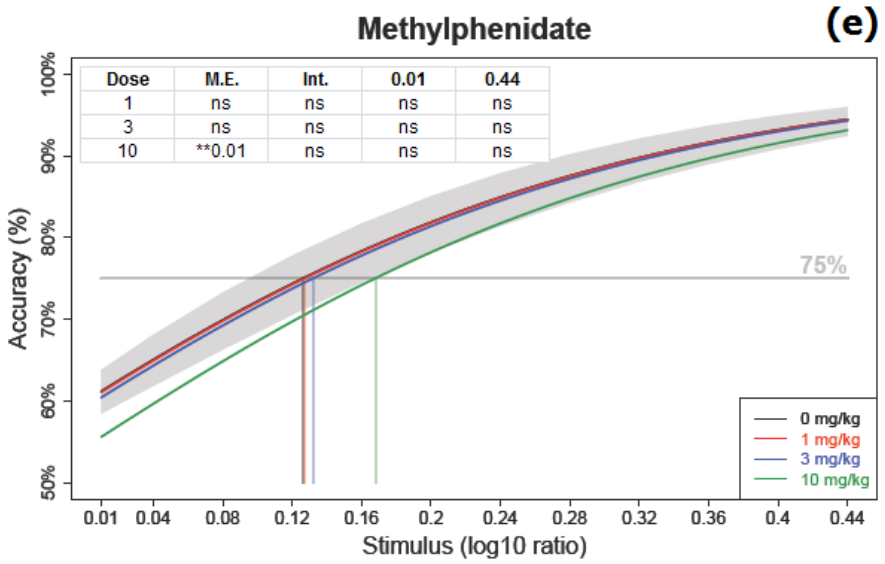
For analysis of accuracy (% correct), a mixed effects logistic regression model was utilized. This approach was based on four-parameter logistic regression models used in bio-assays. The advantages of this model over an ANOVA are that it is more powerful and accounts for the variance structure of percentage-based data. Furthermore, it allows the clear ascending hierarchy (0.01 having the lowest expected outcome, and 0.44 having the highest) to be considered. This allowed both the 'main effect' (if there was an overall increase/decrease in accuracy across all levels), and 'interactive effect' (whether there was an interaction between stimulus level and dose, ie. if the curves were non-parallel) of treatment to be analysed. Though the 0.77 ratio was included in test suites, it was omitted from further analysis due to it acting as a high-influence point and skewing the X-axis. Due to the complexity of this statistical approach, it was conducted by an external statistician. Details of the advantages of this approach are detailed in (Zhao et al. 2001), and a more in-depth description of the model can be found in (Talpos et al. 2015).

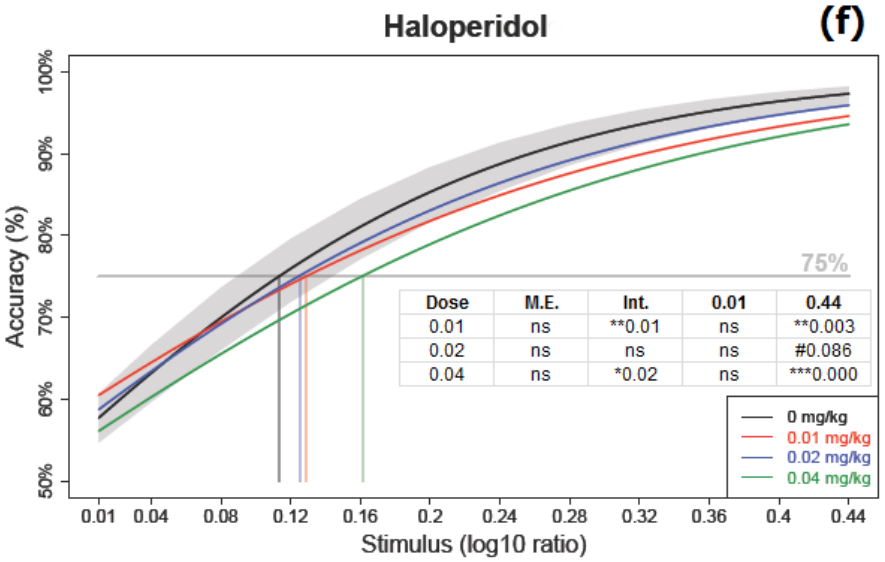

Memantine
(a)
Accuracy (%)
90%
80%
70%
60%
50%
75%
Dose | M.E. | Int. | 0.01 | 0.44
0.3 | ns | ns | ns | ns
1 | ns | ns | ns | ns
3 | ns | ns | ns | ns
10 | **0.01 | **0.01 | **0.004 | ***0.000
0 mg/kg
0.3 mg/kg
1 mg/kg
3 mg/kg
10 mg/kg
0.01 0.04 0.08 0.12 0.16 0.2 0.24 0.28 0.32 0.36 0.4 0.44
Stimulus (log10 ratio)


NVP-AAM077
(b)
Accuracy (%)
100%
90%
80%
70%
60%
50%
75%
Dose | M.E. | Int. | 0.01 | 0.44
5 | *0.02 | ns | ns | ns
10 | ***0.00 | ns | *0.017 | *0.04
20 | ns | ns | ns | ns
0 mg/kg
5 mg/kg
10 mg/kg
20 mg/kg
0.01 0.04 0.08 0.12 0.16 0.2 0.24 0.28 0.32 0.36 0.4 0.44
Stimulus (log10 ratio)


CP−101
(c)
Accuracy (%)
100%
90%
80%
70%
60%
50%
75%
Dose | M.E. | Int. | 0.01 | 0.44
1 | *0.01 | ***0.00 | *0.042 | ***0.000
3 | #0.09 | ***0.00 | ns | ***0.000
10 | ns | ***0.00 | ns | ***0.000
0 mg/kg
1 mg/kg
3 mg/kg
10 mg/kg
0.01 0.04 0.08 0.12 0.16 0.2 0.24 0.28 0.32 0.36 0.4 0.44
Stimulus (log10 ratio)


D-Amphetamine
(d)
Dose | M.E. | Int. | 0.01 | 0.44
0.25 | ns | #0.05 | ns | *0.029
0.5 | ns | *0.02 | ns | **0.001
0.75 | ns | **0.01 | ns | ***0.000
Accuracy (%)
100%
90%
80%
70%
60%
50%
75%
0 mg/kg
0.25 mg/kg
0.5 mg/kg
0.75 mg/kg
0.01 0.04 0.08 0.12 0.16 0.2 0.24 0.28 0.32 0.36 0.4 0.44
Stimulus (log10 ratio)


Methylphenidate
(e)
Dose | M.E. | Int. | 0.01 | 0.44
1 | ns | ns | ns | ns
3 | ns | ns | ns | ns
10 | **0.01 | ns | ns | ns
Accuracy (%)
100%
90%
80%
70%
60%
50%
75%
0 mg/kg
1 mg/kg
3 mg/kg
10 mg/kg
0.01 0.04 0.08 0.12 0.16 0.2 0.24 0.28 0.32 0.36 0.4 0.44
Stimulus (log10 ratio)


Haloperidol
(f)
Dose | M.E. | Int. | 0.01 | 0.44
0.01 | ns | **0.01 | ns | **0.003
0.02 | ns | ns | ns | #0.086
0.04 | ns | *0.02 | ns | ***0.000
Accuracy (%)
100%
90%
80%
70%
60%
50%
75%
0 mg/kg
0.01 mg/kg
0.02 mg/kg
0.04 mg/kg
0.01 0.04 0.08 0.12 0.16 0.2 0.24 0.28 0.32 0.36 0.4 0.44
Stimulus (log10 ratio)

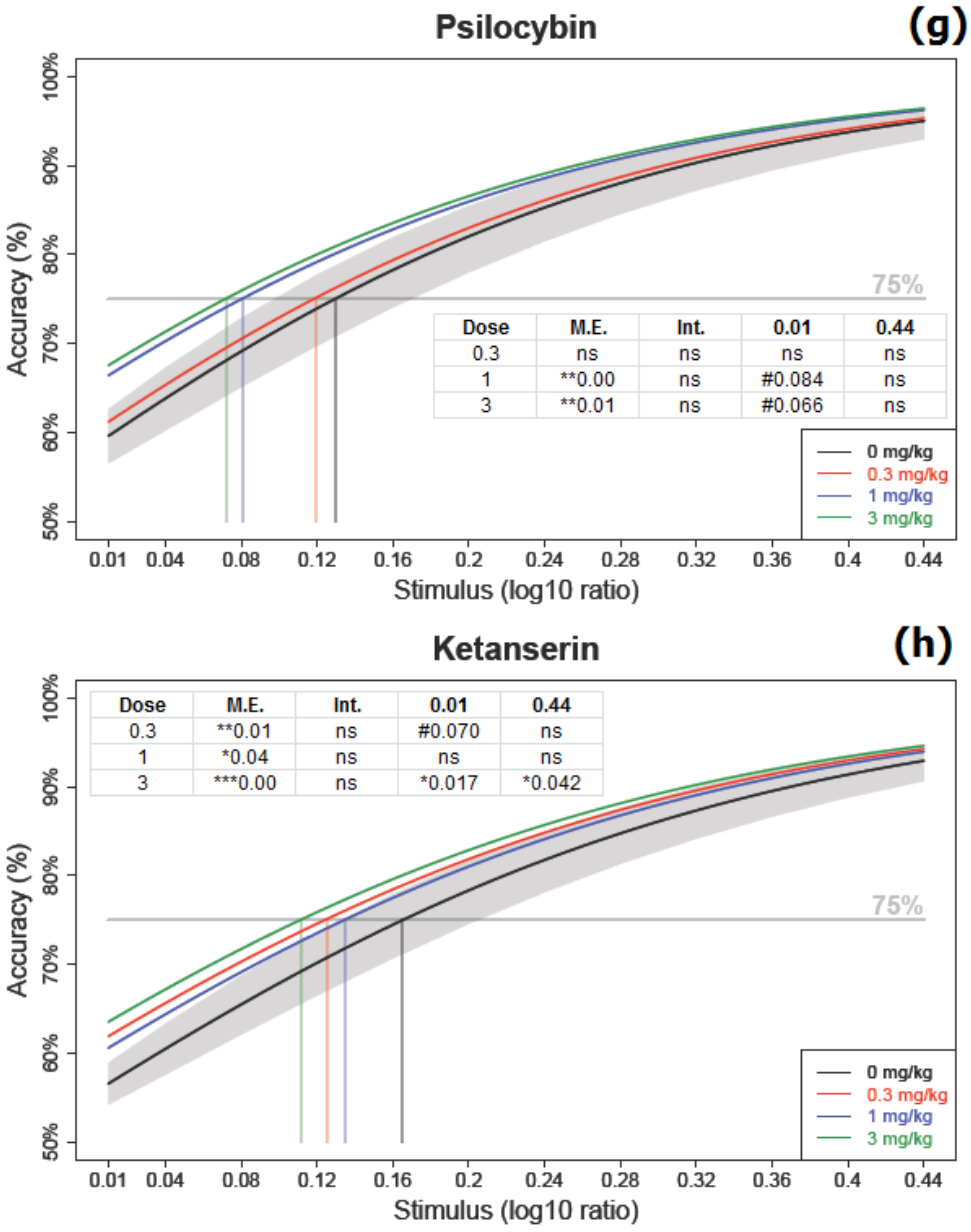


Fig.9 – Effects of drugs on task accuracy. Tables highlight presence of significant effects of 'main effects' (ME) and 'interactive effects' (Int.) between compounds and stimulus. Effects of compounds on accuracy at 0.01 and 0.44 (minimum and maximum) ratios are also highlighted. Vertical lines represent stimulus ratio needed to induce 75% accuracy under different drug conditions.

Results

Memantine

No effect was observed on either main effects or interactions between memantine treatment and difficulty, except with the 10mg/kg condition ($p<0.01$ for both). Significant differences from vehicle were also found at the 0.01 ($p<0.01$) and 0.44 ($p<0.001$) stimulus level (see fig.9a).

The significant effects on secondary measures were similarly restricted to the 10mg/kg condition, reducing trials completed by almost 50% ($p<0.001$), and increasing mean response time to over 10 seconds ($p<0.001$). A highly significant increase in collection latency was found at 10mg/kg ($p<0.001$), and a small but significant decrease at 1mg/kg ($p<0.05$) (see fig.6).

NVP-AAM077

Administration of NVP-AAM077 did not result in any interactive effects. However, significance was observed in the main effect, in a U-shaped dose-response; 5 mg/kg decreased accuracy ($p<0.05$), whereas 10 mg/kg ($p<0.001$) and 20 mg/kg (n.s.) increased it. This dose-response was also evident in contrasts at 0.01 and 0.44 levels, with 10 mg/kg the only dose reaching significance ($p<0.05$) (see fig.9b).

The effect of treatment on secondary measures followed a much more linear pattern. Both response and collection latencies were increased at 10 and 20 mg/kg ($p<0.001$). Number of trials completed was also only affected at these higher doses ($p<0.05$ and $p<0.001$ respectively) (see fig.6)

CP-101,606

CP-101,606 treatment resulted in a significant main effect of treatment only at 1mg/kg ($p<0.05$) (despite this dose causing very little shift in the ratio at which 75% accuracy was achieved), but highly significant ($p<0.001$ for all) interactions of level and dose were found. This was exemplified by the increased accuracy at the 0.01 level for all treatments (though the

1mg/kg dose was the only one that presented significance ($p<0.05$)), and highly significant decreased accuracy at the 0.44 level ($p<0.001$ for all treatments) (see fig.9c).

No effect was observed on number of trials completed. However, CP-101 significantly decreased response latency at the 3mg/kg treatment ($p<0.05$), and collection latency at all treatments ($p<0.001$ for 3mg/kg and 10mg/kg, $p<0.01$ for 1mg/kg) against vehicle (see fig.6).

Psilocybin

Psilocybin administration resulted in an overall increase in accuracy, with the main effect reaching significance at the 1 mg/kg and 3 mg/kg doses ($p<0.01$) (see fig.9g). No interactive significance was observed, though the difference in accuracy was more prominent at the 0.01 'hard' level than the 0.44 'easy' level ($p<0.1$ for 1 mg/kg and 3 mg/kg).

Latencies were visibly increased on a dose-dependent scale, reaching significance for response latencies at the 1 mg/kg and 3 mg/kg doses ($p<0.001$) and at the 3 mg/kg dose for collection latencies ($p<0.001$) (see fig.7). Trials completed were likewise impaired at the 1 mg/kg dose ($p<0.05$), and by over 50% at 3 mg/kg ($p<0.001$) (see fig.8).

Ketanserin

Significant main effects, signifying an overall increase in accuracy, were observed at all doses of ketanserin ($p<0.01$, $p<0.05$, $p<0.001$ respectively with ascending dose). The level at which 75% accuracy is achieved can thus be seen to shift downwards – though it should be noted that for the vehicle condition, the ratio is visibly higher than in other experiments (above 0.16, whereas vehicle in other tests stayed between 0.12 and 0.16, see fig.9h). No significance was observed in regard to interactive effects.

Secondary measures were mostly unaffected by ketanserin treatment; the exception being that at the highest dose, collection latency was slightly increased ($p<0.05$) (see fig.7).

D-Amphetamine

D-Amphetamine had no main effect of treatment on accuracy (though produced a visible shift in the level at which 75% accuracy was obtained, see fig.9d), but a significant interaction of level and dose was found at 0.50 mg/kg ($p<0.05$) and 0.75 mg/kg ($p<0.01$) doses. There was no significant difference in accuracy at the 0.01 level, though significant decreases in accuracy were observed at the 0.44 level with all treatments ($p<0.05$, $p<0.01$, $p<0.001$ for 0.25, 0.50 and 0.75 mg/kg respectively) (see fig.9d).

Trials completed decreased as dose increased, though this was only significant at the 0.75 mg/kg treatment ($p<0.01$). Collection latencies were mostly unaltered, with no treatment reaching significance, though the slight decrease in response latencies was highly significant at all doses ($p<0.001$) (see fig.6).

Methylphenidate

Methylphenidate had minimal effects on accuracy, with no significant interactive effects at any dose. A parallel decrease in accuracy was found at the highest dose ($p<0.01$), however (see fig.9e).

Trials completed and collection latencies were unaffected, but response latencies decreased slightly with dose, reaching significance at the 10 mg/kg treatment ($p<0.001$) (see fig.6).

Haloperidol

Treatment with haloperidol presented no significant main effects at any dose, but had interactive effects at the 0.01 mg/kg ($p<0.01$) and the 0.04 mg/kg ($p<0.05$) doses. These results are reflected in the effects on accuracy at the 0.44 level, with significant decreases occurring at 0.01 mg/kg ($p<0.01$) and 0.04mg /kg ($p<0.001$), and near-significant at 0.02 mg/kg ($p<0.1$). At the 0.01 level, slight increases in accuracy are seen at all but the highest dose, though this does not reach significance (see fig.9f).

Haloperidol significantly increased both collection and response latencies at 0.02 and 0.04 mg/kg ($p<0.001$) (see fig.7). Likewise, the number of trials completed decreased as dose increased, with significance emerging at 0.02 mg/kg ($p<0.05$) and 0.04 mg/kg ($p<0.001$) (see fig.8).

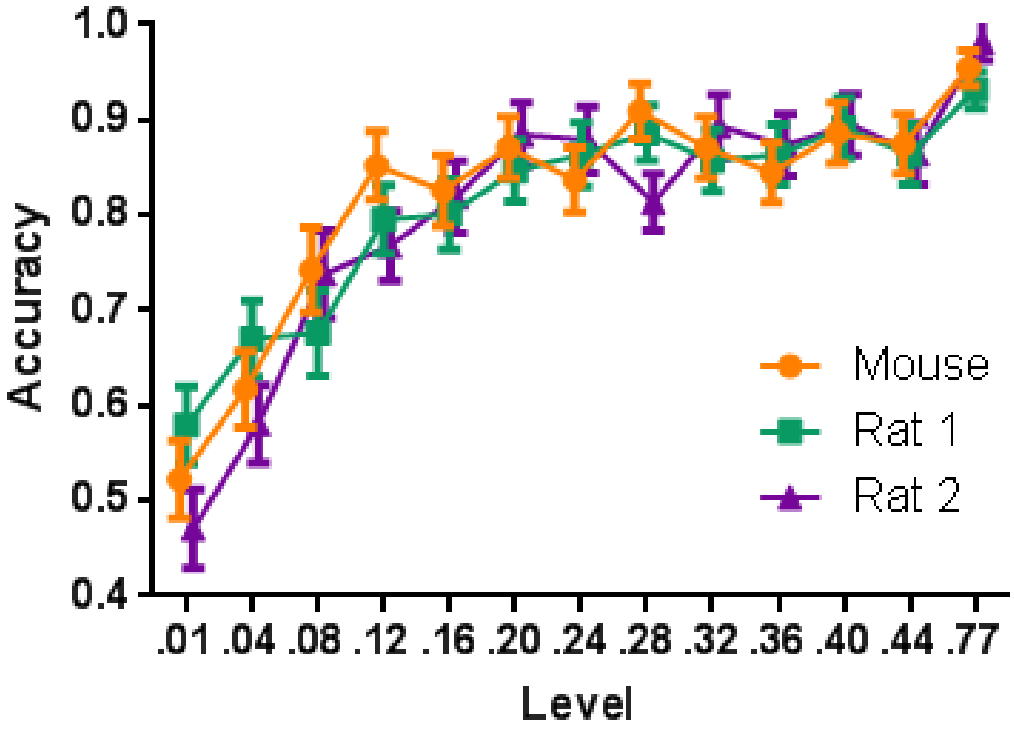


Fig.10 – Accuracy on the PG task of different groups of animals. Animals in Rat1 (PG1) were approximately 10 months older than animals in Rat2 (PG2). Data was acquired through one session for rats, and two sessions for mice (due to halved number of trials per session for mouse group). No significance was found at any level between any group using a repeated-measures ANOVA and an SNK post-hoc. Errorbars = SEM, n=22 for each group.

Discussion

NMDA antagonists

Three NMDA antagonists were tested: memantine, NVP-AAM077 (NR2A-selective) and CP-101,606 (NR2B-selective).

Memantine, a therapeutic agent commonly used in the treatment of Alzheimer's disease, was the first drug tested, as effects may have had relevance for human patient populations. At most doses tested memantine had negligible effects on both accuracy and secondary measures. However, the highest dose was an exception; compared to other doses, subjects completed half the number of trials with mean response latency increased to over 10 seconds, suggesting severe non-specific cognitive impairments. Unusually, significance was observed with both main effect and interactions at the maximum dose, and significant contrasts at both the easiest and hardest levels. These broad-range impairments make it difficult to determine if the interactive significance indicating a grouping deficit is biologically relevant or merely an artefact of non-specific cognitive impairment. While a comparison of human and rat pharmacokinetics is beyond the scope of this thesis, the maximum recommended daily dose of memantine in humans is 20mg p.o., compared to the 10mg/kg used in this study; the lack of effects at all but the highest dose suggests that perceptual effects are unlikely to occur at therapeutic doses.

The NR2A-partially-selective compound NVP-AAM077 and the NR2B-selective compound CP-101,606 were tested to investigate the potential pharmacodynamic cause of the differential effects on perception revealed by the Talpos' study. No research has previously investigated the effects of subunit-selective compounds on perceptual organization; however various differential effects on cognition have been demonstrated (Brigman et al. 2013; Kumar et al. 2015). Though too broad to summarise here, results seemed to show that antagonism of specific subunits resulted in pro-cognitive effects in some tasks, and deficits in others. In particular, antagonism at GluN2B showed improved performance on a number of tasks (Gilmour et al. 2009; Dix et al. 2010; Smith et al. 2011). I therefore expected differential effects of NR2A and NR2B antagonism on grouping, with binding at one particular subunit resulting in the deficit in grouping seen with ketamine administration (Kurylo & Gazes 2008; Ward et al.

2013; Talpos et al. 2015b), and the other having no effect on grouping to match results seen with other NMDA antagonists (Talpos et al. 2015b).

No significant effect on interaction was found with the NR2A antagonist NVP-AAM077, indicating no effect on grouping due to lack of stimuli-specificity, though a U-shaped dose-response was observed on overall accuracy. 5mg/kg treatment resulted in a significant decrease in task accuracy, while 10 mg/kg resulted in significant increases in accuracy; meanwhile 20 mg/kg showed no significant change. This unusual response, restricted to the main effect, is not dissimilar to the results seen with MK801 and PCP in Talpos et al. 2015b. However, the linear effect of dose on latencies and trials completed indicates a psychomotor alteration more similar to ketamine than MK801 and PCP. It has been previously demonstrated that PCP and MK801 have a small effect on visual discrimination ability (Talpos et al. 2012), and little or no effect on perceptual grouping (Talpos et al. 2015b). However, both NVP-AAM077 and CP-101,606 have previously been demonstrated to have no effect on visual discrimination ability (Talpos et al. 2009), and thus the enhancement seen with NVP-AAM077 may represent modulation of a cognitive mechanism that is distinct from both perceptual grouping and discrimination.

CP-101,606 resulted in significant interactive effects at all doses. There is a visible increase in accuracy at low-ratio conditions and impairment at 'easier' stimuli at all doses; though the overall effect tends towards impairment as the dose increases, there is an increase in accuracy at the lower signal levels at all doses. The notable absence of effects on secondary measures indicates a lack of non-selective cognitive and motor impairments (though latencies decreased slightly at higher doses, indicating a slight psychomotor disinhibition), which may be associated with the lack of NR2B expression in the cerebellum **(**Wang et al 1995). This result is very similar to that seen with ketamine in Talpos et al. 2015b, which was also determined to impair grouping while having little or no visuospatial disruption (Talpos et al. 2009, Talpos et al. 2014), indicating NR2B in the mechanism by which ketamine produced the disruption.

It seems likely from these results that blocking NR2B-containing NMDA receptors produces a specific impairment of perceptual grouping, whereas antagonism of NR2A-containing NMDA receptors results in a non-specific enhancement of visual perception distinct from both grouping and discrimination. However, other NMDA antagonists such as ketamine, MK801, PCP and memantine do not appear to display selectivity for any particular subunit (Paoletti &

Neyton 2007). One confounding factor may be NVP-AAM077's lack of specificity – though selective for the NR2A subunit, it also does have affinity for NR2B (Neyton & Paoletti 2006) as well as NR2C and NR2D –containing receptors (Feng et al. 2004 **–** note that NVP is referred to as PEAQX).The mechanisms of antagonism also vary; ketamine, MK801 and PCP act as channel blockers, NVP-AAM077 acts as a competitive antagonist, and CP-101,606 as a negative allosteric modulator. These different mechanisms of antagonism may affect the way in which perception is affected. Electrophysiological studies using NVP-AAM077 and CP-101,606 have indicated that LTP is primarily dependent on the NR2A receptor and LTD on the NR2B receptor (Liu et al. 2004; Massey et al. 2004). Though much research on synaptic plasticity has been conducted in the visual cortex, the differential effects of LTP and LTD on visual cognition are little investigated. My research indicates that the effects (and absence thereof) on perceptual grouping by NR2A and NR2B selective drugs could be associated with differential effects on LTP and LTD, as well as net excitation and inhibition (Talpos et al. 2015b).

CP-101,606's clear disruption of perceptual grouping ability indicates that it is potentially a better pharmacological model for the perceptual effects of psychosis than the more commonly used MK801 and PCP, which previous research has shown to have minimal effect on perceptual organisation (Talpos et al. 2015b). The lack of psychomotor impairment may also mean it is superior to ketamine; one potential avenue of research would be to investigate and compare the effects of [sub-]chronic dosing regimens which are used in pharmacological models of schizophrenia (Becker et al. 2006; Goetghebeur & Dias 2008). Other investigations should focus on translatability factors, such as comparing results to see if the deficit is similar to that expressed by schizophrenic patients, and testing the drug in human measures of perception.

5HT-2A receptor ligands

Two 5HT-2A receptor ligands were tested: psilocybin and ketanserin.

With psilocybin, I predicted an increased accuracy on the task, and was partially correct; it did indeed increase in a dose-dependent manner with psilocybin administration. This was particularly interesting at the easiest difficulties, where an increase of 5% to 95% accuracy represented half of the maximum possible increase before the 100% ceiling. This increase in ability appears to be dose-dependent, though the increase between 0.3 and 1.0 mg/kg is

greater than other consecutive doses. However as the statistical significance was restricted to a main effect, it cannot be inferred that the increase in task accuracy was the result of a specific improvement in grouping ability. In much the same way that a non-selective decrease in accuracy would imply a generalised cognitive impairment, the parallel increase in grouping accuracy seen with psilocybin administration may be the result of a non-selective cognitive enhancement. One possible explanation would be that the motor impairment that lead to an increase in latencies also allowed more time to process the stimuli, in much the same way that slowing response by adding a flap to touch has been shown to increase accuracy on operant tasks (Bussey et al. 2008). It may also be that psilocybin enhances visual discrimination ability through a mechanism that is not specific to grouping.

A study of ketanserin, a 5HT-2A antagonist, followed. This drug has been previously demonstrated to attenuate both visual disturbances and 'Altered State of Consciousness rating scale' scores induced by psilocybin (Vollenweider et al. 1998). Thus, I expected psilocybin and ketanserin test outcomes to be opposing. As can be seen in fig.9g+h, this was not the case. Instead, ketanserin dose-dependently increased accuracy as a main effect with no significance on interaction, similar to the results seen with psilocybin. Other than the S-shaped dose/response (0.3 mg/kg showed a greater effect on accuracy than 1.0 mg/kg), the effect of the drugs on task performance were remarkably similar.

Without further investigation, it is difficult to speculate on a pharmacodynamic mechanism that would result in such non-opposing effects of antagonistic drugs. Rigorous counterbalancing and test day spacing should have averted the possibility of rebound and withdrawal effects, and unlike psilocybin ketanserin showed almost no effect on latencies, so increased accuracy cannot be as a result of it allowing more time to process the visual signal. One potential pharmacodynamic explanation may be the drugs non-selective nature; psilocin (the active metabolite of psilocybin) binds the 5HT-1A receptor (Passie et al. 2002). Additionally, psilocin's partial agonism at 5HT-2A may have disrupted some sort of intrinsic activity at the receptor in a way similar to ketanserin's antagonism. Psilocin has been demonstrated to modulate concentrations of 5HT and dopamine in various cortical areas (Sakashita et al. 2015), and psychedelic serotonergic drugs have been shown to require interactions with mGlu2/3 (Gonzalez-Maeso et al. 2008; Moreno et al. 2011) and CB1 (Mato et al. 2007) receptors. 5HT-2A receptors are very widely distributed in the brain (Adams et al.

2004), so it is possible that the disrupted processes which lead to altered task performance are not even localized to the visual cortex – one must infer that perceptual effects mediated by 5HT-2A ligands through cognitive assays, rather than imaging studies.

It may be fallacious to expect linear on/off dynamics correlating with pharmacology; any movement from the optimal equilibrium can be considered aberrant, with upwards or downwards direction equally representing a disruption. The 5HT-2A ligands I have tested may be disrupting glutamatergic signalling, and in such complex dynamic balances as those encountered in the sensory system even small aberrations in the excitation/inhibition balance may have unpredictable effects (Vreeswijk & Sompolinsky 1996). Further investigations into the exact role and nature of the 5HT-2A receptor and its effect on visual cognition are warranted. In particular, verification of the effects on visual discrimination on a protocol such as that in Talpos et al. 2011 may elucidate my study results.

Dopaminergics

Three dopaminergic drugs were tested: D-amphetamine, methylphenidate, and haloperidol.

D-amphetamine dose-dependently caused a significant interactive impairment in accuracy, in absence of a main effect. The impairment was most prominent on easy stimuli, with the lowest dose actually slightly increasing accuracy at the hardest level. D-amphetamine also decreased response latencies (in line with its profile as a psychomotor stimulant) which may have amplified impairment on the task due to decreased attention and processing time; however, previous research on amphetamines effect on attention-based tasks have actually demonstrated an increase in accuracy accompanied by decreased response times (Bizarro et al. 2004). This suggests that perceptual grouping is specifically affected by the drug, which is in line with the prediction that a pro-psychotic drug such as D-amphetamine would impair perceptual abilities similar to the impaired visual organisation expressed in schizophrenia.

Due to the relatively non-selective pharmacodynamic mechanisms of D-amphetamine (which to summarise, lead to increased synaptic dopamine and norepinephrine concentrations) it is difficult to say which (if any) specific receptor and pathway is associated with this alteration in grouping. The dopaminergic system is closely associated with schizophrenia, with

amphetamine specifically thought to mimic over-expressed top-down processing (Corlett et al. 2009); it is possible that pathways in areas such as the prefrontal cortex may contribute to perceptual abnormalities via D1-mediated backprojections (Noudoost & Moore 2011). Furthermore, dopamine has been demonstrated to modulate retinal function (Witkovsky 2004), leading to the possibility that alterations in visual function may not even be constrained cortically. Similar to the dopaminergic system, norepinephrine pathways project widely throughout the brain, including into the visual cortex (Pourtois et al., 2012; Markovic et al. 2014), and the neurotransmitter is associated with neuroplasticity (Brocher et al. 1992). Though these backprojections are most closely associated with emotional salience and arousal (Bradley et al. 2003), their potential influence in an affectively-neutral task such as the one I have been investigating cannot entirely be disregarded. These distributed and often vague effects associated with D-amphetamine make it difficult to pinpoint a particular mechanism that would lead to impairment in perceptual grouping. Nevertheless, this confirmation that a specific perceptual deficit is elicited by a drug that has long been associated with psychosis should prove as a useful reference.

The next drug to be tested was methylphenidate. Its effect on perceptual grouping was mostly benign; no interactive effects were seen with any treatment, though an impairment in the form of a main effect was found at the highest dose. Likewise significant effects on response latency were found only at the highest dose. This lack of effect on perception, and the lack of precipitated psychomotor effects at all but the highest dose confirm that despite similar properties to D-amphetamine, methylphenidate has a lower propensity for psychotic and schizophrenia-associated perceptual effects.

Haloperidol revealed an unusual profile of effects on perceptual abilities. The effects on accuracy followed a U-shaped dose-response curve; interactive effects were found at the 0.01 and 0.04 mg/kg doses, but not at 0.02 mg/kg. This was also evident in the 0.44 contrasts, with 0.01 and 0.04 but not 0.02 mg/kg showing significant differences. This non-linear response may be due to the mixed pharmacological profile of haloperidol; of which the primary mechanisms of action are thought to be based on D2 and 5HT-2A receptor antagonism. Though non-significant, a small increase in accuracy was observed at the harder levels with the lower doses of haloperidol, supporting the suggestion of my previous investigations of psilocybin and ketanserin that binding at 2A increases accuracy on the task. One interesting observation is the

visible similarity between D-amphetamine and haloperidol – though the drugs are not pharmacological opposites, their effects with regard to psychosis can be considered opposing. These paradoxical results lead to the potentially troubling implication that observations of perceptual deficits in schizophrenic patients may be confounded by antipsychotic medication. Though previous research into perceptual deficits in schizophrenics has indicated no effect of medication dose on task performance (as reviewed in Silverstein & Keane 2011), this finding of antipsychotic-induced perceptual impairment n healthy animals may yet indicate an overlooked side effect of these drugs.

Conclusion

Aberrant perceptual organisation ability is a key characteristic of schizophrenia, and it must be considered when designing animal models of the disease. Having demonstrated that grouping is disrupted by D-amphetamine, haloperidol, and CP-101,606 on my protocol, the next step would be to create an analogous proximity grouping task for humans. If it can be demonstrated that schizophrenia patients display similar deficits to those induced by the drugs I have tested, the translatable validity of my findings would be greatly increased.

With regards to further pre-clinical research, there are several key areas that may be explored. These are primarily related to the paradoxical findings found with the pharmacologically opposing drugs psilocybin and ketanserin, and the therapeutically opposing drugs D-amphetamine and haloperidol. Testing the 5HT-2A drugs on a visual discrimination task would clarify whether increased task accuracy was due to an enhancement of such ability, or if it was the result of disruption of another process in the visual sensory pathway. Similarly, the effects on accuracy caused by NVP-AAM077 could not be due to either grouping or visual discrimination ability (Talpos et al. 2009), so further research is necessary to fully understand the cognitive profile of this drug. Further pharmacological studies targeting both 5HT-2A and D1/D2 receptors should also shed light on the reasons for such unexpected similar effects on grouping as were encountered with D-amphetamine and haloperidol. The paradoxical result found with these drugs is of particular relevance for clinical studies of perceptual deficits in schizophrenic populations, as they may represent a potential confound in patients medicated with atypical antipsychotics such as haloperidol.

One theory could be that pharmacodynamic interactions with a specific receptor are less important than the equilibrium of intrinsic activity and excitation/inhibition balance that is being disrupted by a foreign ligand binding. Optimal sensory processing in the visual cortex relies on maintaining an excitation/inhibition balance in order for relevant visual elements to be further processed and for irrelevant noise to be filtered out (Wyatte et al. 2012), and has been theorised to be directly involved with the process of grouping (Talpos et al. 2015b). Whereas glutamatergic drugs such as NVP-AAM077 and CP-101,606 may disrupt this directly, it is possible that drugs binding the 5HT-2A receptor are indirectly modulating this equilibrium (Aghajanian & Marek 1999). Attempting to predict whether grouping accuracy will increase or

decrease may be less relevant than one might assume, as either direction represents impairment relative to the 'normal' level of performance. Indeed, it may be that such seemingly paradoxical results are a feature, rather than an anomalous artefact, of disrupting particular aspects of visual processing pharmacologically. Further experimentation is required to take this speculation any further. The cholinergic and cannabinoid systems are two areas unexplored in this study, and have drugs which are associated with psychosis-like effects (for example, THC (Semple et al. 2005) and scopolamine (Cairncross 1983)) that may be investigated with this task to test this hypothesis.

Much previous research has demonstrated that sensory processing in the visual cortex is dependent on both bottom-up and top-down pathways (Grossberg & Williamson 2001; Hupe et al. 1998; Rauss et al. 2011**;** Kastner et al. 2001; Petro et al. 2014; Palmer et al. 2003; Roelfsema & Houtkamp 2011; McMains & Kastner 2010; McMains & Kastner 2011). Both directions are involved in maintaining the excitation/inhibition balance in the visual cortex which I have previously discussed (Shao and Burkhalter 1996; Zhang et al. 2014). Perceptual abnormalities encountered in schizophrenia are likewise classified as either bottom-up or top-down aberrations (Aleman et al. 2003; Corlett et al. 2009). My research and results do not differentiate the processes causing the increase or decrease of accuracy on the grouping task; accuracy changes may be related to decreased relative noise through enhanced contrast in competitive interactions in the visual cortex, or an enhanced signal through top-down amplification of early neural coding, or a number of other possibilities. Though some research has experimentally investigated the effects of top-down modulation on visual processing (McAlonan et al. 2008; Bradley et al. 2003; Noudoost & Moore 2011), specific pharmacological interactions are largely uninvestigated. Future investigations may try to connect theorised affinities of specific drugs to bottom-up/top-down processes to measureable effects on visual processing.

Though not covered in this thesis, I have also shown that mice can learn to complete the grouping task with performance analogous to that of rats (see fig.10). This opens the door to research into transgenic models of disease and perception, with particular relevance to autism-spectrum disorders and Alzheimer's disease.

Finally, one new direction of research that may contribute to understanding the mechanisms of perceptual grouping in animals is imaging and electrophysiology. Though it has been assumed

throughout my investigation that this protocol tests “grouping”, and that grouping occurs as an ascending process through the visual cortex, there is yet to be any definitive research to confirm this. Accordingly this work would benefit from research to prove the construct validity of this task, as well as the grouping phenomena in the rodent. A potential method to do this would entail a c-fos study to investigate the difference in selective activation of of the visual cortex between, for example, a perceptual grouping and a standard visual discrimination task (which is assumed not to require the visual cortex). Even more detailed work may involve single-cell recording within the visual cortex to investigate at which precise layer proximity grouping occurs, and whether it is the same for all levels of difficulty.

My study has focussed on clinically-relevant drugs, many of which have complex and non-selective effects. Further investigation into the specific neuropharmacological mechanisms of grouping may require a more targeted approach, such as agonists that target the norepinephrine and dopamine receptors specific to subtype, as well as reuptake inhibitors and other modulators. In particular, a more selective pharmacological approach may help in verifying the cause of the paradoxically-similar outcomes seen with D-amphetamine and haloperidol. I hope I have shown that proximity grouping is a valid mechanism to evaluate perceptual disruption in the rodent, and that that individual drugs have patterns of disruption that can be assayed on this protocol. Future work should elaborate this through pharmacology in both rodent and human to increase translatability and predictive validity, as well as to further reveal the underlying mechanisms of perceptual grouping.

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