OPEN

Citation: Transl Psychiatry (2013) 3, e334; doi:10.1038/tp.2013.109

www.nature.com/tp

ORIGINAL ARTICLE

The effects of ketamine and risperidone on eye movement control in healthy volunteers

A Schmechtig[1], J Lees[2], A Perkins[1], A Altavilla[3], KJ Craig[4], GR Dawson[4], JF William Deakin[2], CT Dourish[4], LH Evans[3], I Koychev[2], K Weaver[1], R Smallman[2], J Walters[5], LS Wilkinson[3,5], R Morris[6], SCR Williams[1] and U Ettinger[7]

The non-competitive *N*-methyl-D-aspartate receptor antagonist ketamine leads to transient psychosis-like symptoms and impairments in oculomotor performance in healthy volunteers. This study examined whether the adverse effects of ketamine on oculomotor performance can be reversed by the atypical antipsychotic risperidone. In this randomized double-blind, placebo-controlled study, 72 healthy participants performed smooth pursuit eye movements (SPEM), prosaccades (PS) and antisaccades (AS) while being randomly assigned to one of four drug groups (intravenous 100 ng ml^{-1} ketamine, 2 mg oral risperidone, 100 ng ml^{-1} ketamine plus 2 mg oral risperidone, placebo). Drug administration did not lead to harmful adverse events. Ketamine increased saccadic frequency and decreased velocity gain of SPEM (all $P < 0.01$) but had no significant effects on PS or AS (all $P \geqslant 0.07$). An effect of risperidone was observed for amplitude gain and peak velocity of PS and AS, indicating hypometric gain and slower velocities compared with placebo (both $P \leqslant 0.04$). No ketamine by risperidone interactions were found (all $P \geqslant 0.26$). The results confirm that the administration of ketamine produces oculomotor performance deficits similar in part to those seen in schizophrenia. The atypical antipsychotic risperidone did not reverse ketamine-induced deteriorations. These findings do not support the cognitive enhancing potential of risperidone on oculomotor biomarkers in this model system of schizophrenia and point towards the importance of developing alternative performance-enhancing compounds to optimise pharmacological treatment of schizophrenia.

Translational Psychiatry (2013) **3,** e334; doi:10.1038/tp.2013.109; published online 10 December 2013

Keywords: glutamate; ketamine; risperidone; saccades; schizophrenia; smooth pursuit

INTRODUCTION

There is a continuing debate in schizophrenia research about the effectiveness of currently available antipsychotic drugs. This concerns, amongst other issues, the treatment of cognitive deficits; one of the core features of schizophrenia that has been suggested to be an important treatment target, which can predict functional outcome.[1] Hence, there is an increasing demand to develop new and more effective drugs to overcome observed treatment resistance and to improve deficits in different cognitive domains.[2]

One approach to achieve a better understanding of the underlying pathophysiological mechanisms is to investigate pharmacological model systems such as the amphetamine, phencyclidine or ketamine. Ketamine is a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors, which also has dopaminergic and serotonergic agonist properties.[3] The compound has become increasingly popular following the discovery that its administration can mimic key symptoms of schizophrenia.[4] Ketamine has been found to display a broad range of psychotomimetic effects in healthy volunteers and has also been reported to induce cognitive impairments similar to those seen in schizophrenia.[5] These include, for example, impairments on tasks that require executive functions, such as working memory[6,7] or the Wisconsin Card Sorting Test.[8] Together, these findings offer a promising perspective in which ketamine administration could represent a potential pharmacological model mimicking aspects of cognitive and frontal lobe functioning in schizophrenia.[2,8,9]

Pharmacological models are often investigated in combination with biomarkers as translational neurobehavioral indices of pharmacological effects.[10] Eye movements have been proposed to be especially promising biomarkers in drug development and the evaluation of treatment effects.[10,11] The use of eye movements in this approach is supported by findings that oculomotor performance is impaired in schizophrenia patients, schizotypal personality and in psychometric schizotypy, thus representing neural abnormalities underlying the schizophrenia spectrum.[12–16] The well-known neural correlates, high reliability and simple application of oculomotor paradigms make them ideally suited to study pharmacological effects in healthy volunteers and patient populations.[10] The most commonly studied procedures include prosaccades (PS), a simple measure of stimulus-driven overt attentional shifts, which often provides a useful baseline condition,[17] antisaccades (AS), a measure of the integrity of volitional control of behaviour (for review see Hutton and Ettinger 2006[13])

[1]Department of Neuroimaging, Institute of Psychiatry, King's College London, London, UK; [2]Neuroscience and Psychiatry Unit, School of Community Based Medicine, The University of Manchester, Manchester, UK; [3]School of Psychology, Cardiff University, Cardiff, UK; [4]P1vital Ltd, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK; [5]Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK; [6]Department of Psychology, Institute of Psychiatry, King's College London, London, UK and [7]Department of Psychology, University of Bonn, Bonn, Germany. Correspondence: Dr A Schmechtig, Department of Neuroimaging, CNS Building PO89, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK.
E-mail: anne.schmechtig@kcl.ac.uk
Received 26 April 2013; revised 15 October 2013; accepted 21 October 2013

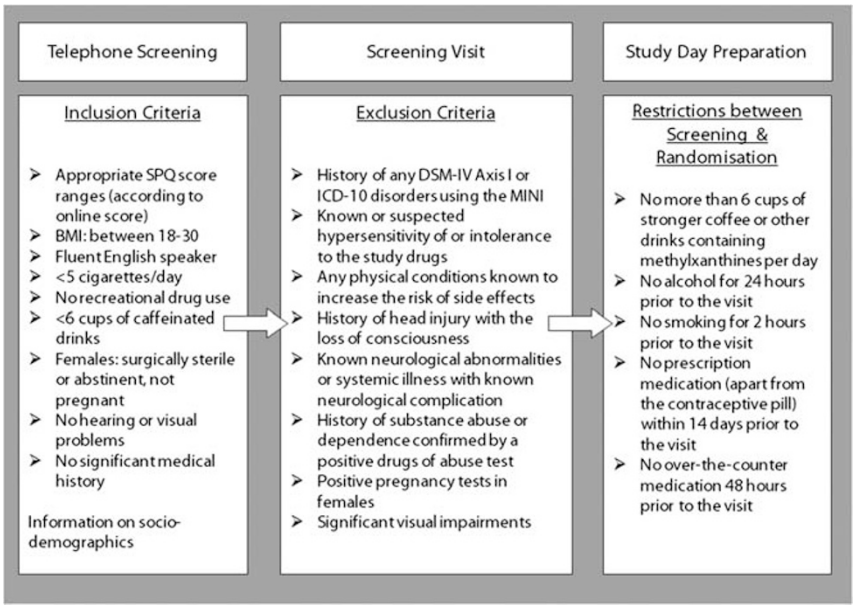

Figure 1. Inclusion and exclusion criteria. BMI, body mass index; DSM-IV, Diagnostic and Statistical Manual, Fourth Edition;[72] ICD-10, International Classification of Disease and Related Health Problems, 10th Revision;[73] MINI, Mini International Neuropsychiatric Interview;[74] SPQ, Schizotypal Personality Questionnaire.[30]

and smooth pursuit eye movements (SPEM), measuring attentional and motion processing functions.[18,19]

Some studies have explored the influence of ketamine on eye movement control in healthy volunteers and experimental animals.[20–24] These studies reported ketamine-induced SPEM impairments resembling those seen in schizophrenia with decreases in smooth pursuit gain,[22] impairments in eye acceleration[23] and an increase in saccadic frequency.[20,22] Results concerning AS suggest increased error rates following ketamine administration in monkeys[21] but not in humans.[22]

The aims of the present study were (1) to replicate the observation of eye movement deficits in the ketamine model and (2) to explore whether administration of the well-established antipsychotic risperidone can offer prophylaxis from the expected effects of ketamine. Atypical antipsychotics linked to 5-HT_{2A} receptors have been suggested to play a role in the NMDA receptor antagonist model[25,26] and ketamine has been reported to be a reliable assay to investigate pharmacological pre-treatment with risperidone on the neural level.[27] Enhancing effects of risperidone on eye movement control have been observed in schizophrenia patients,[28,29] making this compound a prime candidate for investigation in a pharmacological model of schizophrenia.

We hypothesised, based on the previous literature, that ketamine would lead to decreased velocity gain and increased saccadic frequency during SPEM compared with placebo. We additionally re-examined the effects of ketamine on AS performance and explored whether risperidone, a clinically effective atypical antipsychotic with beneficial effects on oculomotor performance in schizophrenia, would act prophylactically in attenuating ketamine-induced impairments.

MATERIALS AND METHODS

Subjects

A total of 72 volunteers were recruited as part of a multisite study (University of Manchester, Cardiff University, King's College London) from May 2010 to December 2010. Recruitment was performed through advertisements placed around the universities, the local communities and online. Volunteers were invited to fill in an online version of the Schizotypal Personality Questionnaire.[30] Given known associations between oculomotor performance and schizotypy,[31–33] participants were only invited if they had a score on the Schizotypal Personality Questionnaire between 8 and 36, representing the normal range on the Schizotypal Personality Questionnaire. Approval of the local ethics committee at each site was obtained and volunteers provided written informed consent before entering the study.

Screening procedure

A telephone interview was conducted with individuals who expressed interest in participating in the study. If all inclusion criteria were met, they were invited for a screening visit. On the screening visit, information was collected on age, gender, intelligent quotient assessed with the National Adult Reading Test (NART),[34] handedness and ethnicity. A medical screening was carried out including blood tests, vital sign checks, electrocardiographical recording and a physical examination by a study doctor confirming that all participants were fit for inclusion into the study. Suitable individuals were invited for the study day within 6 weeks of the screening visit. Figure 1 describes the eligibility criteria of the study in more detail.

On the study day, participants underwent pre-dose, drug metabolism and testing phases. More details about the study day procedures can be found in Figure 2.

Study design and implementation

The pharmacological part of the study employed a double-blind, randomised, placebo-controlled, parallel groups design. Equal numbers of participants were randomly assigned to one the following four study arms on the study day (that is, the ratio was 1:1:1:1):

Arm 1: Placebo capsule and saline infusion: PLA_SAL
Arm 2: Placebo capsule and ketamine infusion (100 ng ml^{-1}): PLA_KET
Arm 3: Risperidone capsule (2 mg) and saline infusion: RIS_SAL
Arm 4: Risperidone capsule (2 mg) and ketamine infusion (100 ng ml^{-1}): RIS_KET.

On the basis of similar studies[33,35] it was estimated that a sample size of 18 participants per study arm should be sufficient. Randomisation was computer generated. For each site, a pharmacist implemented an allocation schedule generated by P1vital. Adequate allocation concealment procedures were in place to avoid treatment effect biases. Researchers conducting the study were blinded and had no involvement in generating the randomisation schedule or allocating participants to the different drug arms.

All participants received a risperidone or placebo capsule 90 min before the start of the biomarker test battery based on previously reported

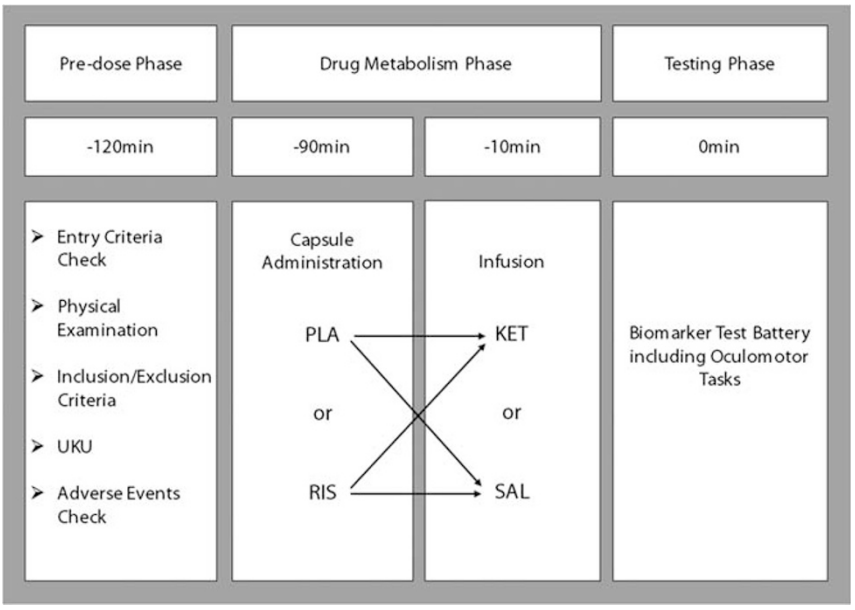

Figure 2. Overview of procedures on the study day. KET, ketamine; PLA, placebo; RIS, risperidone; SAL, saline; UKU, Udvalg for Kliniske Undersøgelser side effect rating scale.[75]

T_{Max}.[36–40] A subclinical dose range of risperidone was chosen on the basis of reported tolerability[41] and previously described study ranges.[42] Each participant also received an intravenous infusion of ketamine or saline, which began 10 min before the start of the biomarker test battery and was continuous for the duration of the battery.[4]

The ketamine solution was prepared by a pharmacist and consisted of a 2-mg ml^{-1} ketamine by 0.9% saline dilution supplied in a BD 50 ml Plastipak syringe. The targeted ketamine plasma concentration was 100 ng ml^{-1} for the active ketamine arms. A continuous infusion paradigm was carried out using a Graseby 3500 infusion pump (Smith Medical Int. Ltd, Luton, UK). The pump was programmed to a default ketamine concentration of 100 ng ml^{-1}. In order to determine the correct infusion rate, additional information on subjects' weight (in kg) and the confirmation of a 2-mg ml^{-1} ketamine solution was provided. Infusion procedures were conducted according to an infusion protocol based on the three-compartment model by Domino *et al.*[43]

Eye movements

Recording. The eye movement tasks were acquired as part of a biomarker test battery. Eye movements were recorded using a combined pupil and corneal reflection tracker at 1000 Hz sampling rate (Eyelink 1000, SR Research, Kanata, ON, Canada). Participants were seated 57 cm from a 17-in monitor with their head resting on a chinrest. The target was a 0.3° diameter black dot on a light grey background. A 9-point calibration was carried out before the beginning of each task. Practice trials were carried out before the PS and AS tasks. The order of tasks was PS, AS, SPEM for all subjects.

A PS trial started with the black dot in the central position of the screen (0°) for a random duration of 1000–2000 ms. The target then jumped to one of four possible peripheral positions (±7.25°, ±14.5°) where it remained for 1000 ms. There were 60 trials, with 15 for each location, arranged in pseudorandom order. Participants were instructed to follow the target as fast and accurately as possible.

The settings for the AS task were the same as for the PS task. However, participants were asked to look at the target while in the centre and to avoid looking at it when it jumped to the side. Instead, they were asked to look at the exact mirror image position of the peripheral target as fast and accurately as possible. The acquisition time for each of the two tasks was ~4 min.

In the SPEM task, the target moved horizontally across the screen (between ±14.5°) in a sinusoidal waveform at three different target velocities (0.25, 0.5 and 0.75 Hz), starting at −14.5°. For each of the target velocities, the target completed 10 full cycles. Participants were told to keep their eyes on the target as closely as possible. The durations of these tasks were 40, 20 and 13.3 s, respectively.

Analysis. The analysis of saccades and SPEM was carried out by a single rater blind to drug group.

PS and AS data were analysed using DataViewer software (SR Research). Inclusion of saccades was based on minimum amplitude (1°) and minimum latency (100 ms) criteria. Trials where a saccade or an eye blink occurred between 100 ms before and after target movement were excluded. Primary outcome measures for PS and AS tasks were as follows:

Directional error rate describes the percentage of error trials (that is, trials where the participant's first included saccade is away from (PS trials) or towards (AS trials) the target) over the total number of included trials (that is, error trials plus correct trials, excluding eye blink trials).

Latency is defined as the time (ms) from target appearance to initiation of the first directionally correct saccade in each trial (calculated as mean per subject).

Amplitude gain (percentage) was determined for the first directionally correct, included saccade in each trial. It was obtained by dividing saccade amplitude by target amplitude and multiplying the result by 100 (calculated as mean per subject).

Peak velocity (degree per second) was determined from the first directionally correct, included saccade in each trial (calculated as mean per subject).

SPEM analysis was carried out using purpose written routines in LabView (National Instruments Corporation, Austin, TX, USA). The following primary outcome measures were derived.

First, velocity gain was calculated by dividing mean eye velocity by target velocity for segments of pursuit in the central half of each ramp excluding saccades and eye blinks. Velocity gain scores of segments of pursuit for each target velocity were time weighted and subsequently averaged. Second, saccadic frequency ($N\,s^{-1}$) was measured across the entire pursuit task at each target velocity.

Questionnaires

As a secondary measure, after completing the oculomotor assessment (however, still during infusion), all participants were assessed on the Clinician Administered Dissociative States Scale (CADSS),[44] and the Brief Psychiatric Rating Scale Expanded Version,[45,46] by trained raters to investigate the range of pharmacologically induced psychotomimetic symptoms and side effects. Participants also completed the Launay–Slade Hallucinations Scale (LSHS)[47] to capture the presence of psychotic symptoms at the time of infusion.

Statistical analysis

Data pre-screening. Data pre-screening was carried out using SPSS 20.0 (http://www.ibm.com/spss). Demographic data were compared across

drug groups using univariate analyses of variance (ANOVA) for continuous variables such as age, years in full time education and NART.[34] For categorical data such as gender, handedness and ethnicity, χ^2-tests were performed to examine their distribution across drug and schizotypy groups. An outlier analysis and an analysis of normality were performed using frequency tables, box plots and Kolmogorov–Smirnov tests.

Data analysis. Inferential statistical analysis was carried out using SPSS 20.0. In all models, gender was included as a factor based on previous findings about gender-specific differences in ketamine challenge.[48]

For saccade latency, amplitude gain and peak velocity, a repeated measures ANOVA model was calculated including Task (AS, PS) as within-subject factor and Ketamine (ketamine or saline infusion), Risperidone (risperidone or placebo capsule) and Gender (male, female) as between-subject factors.

For AS error rate as well as correction rate, a univariate ANOVA model was carried out including Ketamine (ketamine or saline infusion), Risperidone (risperidone or placebo capsule) and Gender (male, female) as fixed factors. This was done because directional errors (and subsequent corrections) are rarely observed on the PS task.

For SPEM, velocity gain and saccadic frequency were investigated using separate repeated measures ANOVA with Velocity (14.5, 29 and 43.5 $^\circ s^{-1}$) as within-subject factor and Ketamine (ketamine or saline infusion), Risperidone (risperidone or placebo capsule) and Gender (male, female) as between-subject factors.

Questionnaires. Questionnaires and rating scales were analysed using non-parametric tests such as the Mann–Whitney test as they violated assumptions of normality and homogeneity of variances.[49]

RESULTS

Pre-screening

In total, 72 healthy participants (mean age = 22.51 years; s.d. = 4.17; 35 male/37 female) were randomly allocated to one of the four drug groups. Descriptive statistics of demographic variables are displayed by drug group in Table 1.

Pre-screening of the data revealed that the following variables were significantly skewed according to Kolmogorov–Smirnov statistics and subsequently transformed to obtain normality: AS and PS amplitude gain (both log transformed), SPEM velocity gain at 14.5, 29 s and 43.5° s^{-1} (all square transformed), age (log transformed).

Results for the main analysis

Descriptive statistics for oculomotor measures can be found in Table 2. Details of results (F, df, *P*) as well as a short description of the observed effects are summarised in Table 3.

Antisaccade error rate and correction rate. No significant main effects of ketamine or risperidone and no ketamine by risperidone interactions were observed for the AS error rate and correction rate.

Saccadic latency. A main effect of task was observed, indicating faster latencies for PS than AS. No other significant main effects or interactions were found.

Saccadic amplitude gain. Reduced amplitude gain was observed for risperidone-treated groups compared with the other groups. No other significant main effects or interactions were observed.

Saccadic peak velocity. A main effect of task was observed indicating faster peak velocities for PS compared with AS. Risperidone slowed peak velocity compared with placebo. A task by risperidone interaction was also found, indicating a higher sensitivity of the AS peak velocity compared with PS peak velocity to the influence of risperidone. No other significant main effects or interactions were observed.

Smooth pursuit saccadic frequency and velocity gain. Both SPEM velocity gain and saccadic frequency showed an effect of velocity with worse performance at faster velocities. In addition, the ketamine-treated groups showed worse performance on both SPEM velocity gain and saccadic frequency compared with placebo. A velocity by ketamine interaction was also observed for both SPEM measures, indicating a smaller difference between ketamine and placebo in saccadic gain and frequency for the fastest velocity.

Gender effects

For the AS error rate, a main effect of gender was found, with females displaying higher error rates than males. A trend for a ketamine by gender interaction was observed, indicating higher error rates in males but not females under the influence of ketamine.

For SPEM gain and saccadic frequency, an effect of gender was observed with men showing more accurate velocity gain performance and higher saccadic frequencies than women. A velocity by gender interaction was found for saccadic frequency, indicating performance differences for males and females in the two faster velocities but not for the slowest velocity.

Ketamine by risperidone interaction

None of the ketamine by risperidone interactions were found to be significant (all $P>0.26$).

Table 1. Descriptive statistics for demographic variables by drug

	Drug				*Statistical test*
	PLA_SAL, N = *19*	*PLA_KET*, N = *17*	*RIS_SAL*, N = *18*	*RIS_KET*, N = *18*	
Age in years	22.05 (3.22)	21.59 (1.94)	23.89 (5.37)	22.50 (5.12)	F (3,71) = 1.00, $P = 0.39$
NART score	116.90 (4.97)	114.39 (5.12)	116.18 (5.67)	114.76 (6.76)	F(3,71) = 0.79, $P = 0.50$
YoE	15.84 (1.26)	16.59 (2.06)	16.33 (1.71)	15.72 (1.87)	F(3,71) = 0.97, $P = 0.41$
SPQ	18.74 (7.18)	17.18 (7.29)	18.18 (8.16)	16.06 (6.31)	F(3,67) = 0.48, $P = 0.70$
Height in cm	171.42 (7.17)	173.64 (7.25)	173.39 (7.94)	170.5 (9.12)	F(3,71) = 0.66, $P = 0.58$
Weight in kg	71.16 (10.89)	67.23 (8.7)	69.1 (11.45)	71.39 (10.51)	F(3,71) = 0.61, $P = 0.61$
N male (%)	9 (12.50)	10 (13.90)	9 (12.50)	7 (9.70)	$\chi^2 = 1.42$, df = 3, $P = 0.70$
Ethnicity Caucasian (%)	17 (23.60)	15 (20.83)	16 (22.22)	17 (23.61)	$\chi^2 = 3.73$, df = 6, $P = 0.71$

Abbreviations: NART, National Adult Reading Test;[34] PLA_KET, placebo capsule and ketamine infusion; PLA_SAL, placebo capsule and saline infusion; RIS_KET, risperidone capsule and ketamine infusion; RIS_SAL, risperidone capsule and saline infusion; SPQ, Schizotypal Personality Questionnaire;[30] YoE, years spent in full time education. Data represent means (s.d.) unless otherwise stated.

Table 2. Descriptive statistics and effect sizes of oculomotor measures

	Drug group				*Effect size (Cohen's d)*	
	PLA_SAL, N = *19*	*PLA_KET*, N = *17*	*RIS_SAL*, N = *18*	*RIS_KET*, N = *18*	*PLA_SAL – PLA_KET*	*PLA_KET – RIS_KET*
AS						
Error rate (%)	41.83 (22.81)	45.73 (20.65)	47.58 (29.48)	45.28 (22.30)	0.18	0.02
Correction rate (%)	98.99 (2.77)	99.58 (1.22)	98.34 (3.20)	97.24 (4.33)	0.27	0.75
Latency (ms)	291.21 (48.07)	314.28 (52.34)	304.57 (47.51)	329.49 (69.07)	0.47	0.20
Amplitude gain (%)	101.16 (21.42)	114.89 (29.47)	98.68 (28.48)	119.15 (58.58)	0.55	0.09
Peak velocity (° s^{-1})	307.76 (73.41)	278.39 (50.53)	224.74 (47.24)	224.00 (61.06)	0.47	0.99
PS						
Latency (ms)	176.25 (18.51)	174.82 (21.02)	173.49 (17.13)	184.17 (26.43)	0.07	0.40
Amplitude gain (%)	106.04 (5.87)	104.83 (8.16)	94.57 (13.15)	93.60 (16.39)	0.18	0.88
Peak velocity (° s^{-1})	333.51 (54.99)	289.74 (44.72)	269.23 (46.54)	253.97 (61.22)	0.89	0.68
SPEM						
Velocity gain 14.5° s^{-1} (%)	90.96 (9.92)	77.76 (19.24)	91.41 (16.57)	68.81 (21.77)	0.90	0.45
Velocity gain 29° s^{-1} (%)	82.44 (16.01)	61.36 (26.30)	79.32 (21.75)	47.12 (27.15)	1.01	0.55
Velocity gain 43.5° s^{-1} (%)	62.51 (16.12)	39.58 (26.26)	57.70 (19.54)	24.18 (21.85)	1.06	0.66
Saccadic frequency 14.5° s^{-1} (N s^{-1})	0.94 (0.44)	1.40 (0.58)	0.65 (0.33)	1.42 (0.52)	0.93	0.04
Saccadic frequency 29° s^{-1} (N s^{-1})	1.55 (0.63)	2.01 (0.54)	1.47 (0.55)	1.83 (0.72)	0.80	0.29
Saccadic frequency 43.5° s^{-1} (N s^{-1})	2.27 (0.65)	2.39 (0.83)	2.18 (0.72)	1.92 (0.81)	0.17	0.59

Abbreviations: PLA_KET, placebo capsule and ketamine infusion; PLA_SAL, placebo capsule and saline infusion; RIS_KET, risperidone capsule and ketamine infusion; RIS_SAL, risperidone capsule and saline infusion. Data represent untransformed means (s.d.) of the eye movement measures by drug unless otherwise stated.

Questionnaire data

CADSS total scores and the subscales of amnesia, and derealisation were significantly higher in the ketamine-treated groups compared with the placebo groups (all $P < 0.01$). Ketamine did not have an influence on LSHS total scores ($P = 0.14$). No effect of risperidone was observed (all $P > 0.13$).

Effect sizes for the comparison of placebo/saline vs placebo/ketamine-treated groups as well as placebo/ketamine vs ketamine/risperidone-treated groups are displayed in Tables 2 and 4.

DISCUSSION

Summary of main findings

This study aimed to replicate the deteriorations in oculomotor performance following ketamine administration. It was also investigated, for the first time, whether the atypical antipsychotic risperidone would act prophylactically by attenuating the expected ketamine-induced deteriorations.

As hypothesised, a highly significant effect of ketamine was observed for both measures of SPEM performance, indicating a slowing of the eye in the pursuit of the target and higher saccadic frequencies.[20,22] However, ketamine did not have any main effects on the AS error rate, a performance measure known to be substantially impaireded in schizophrenia.[13] Ketamine also did not have any effects on other saccadic measures such as latency, gain or velocity.

Risperidone administration had a significant effect on saccadic amplitude gain, a measure of spatial accuracy. Participants in the risperidone-treated groups undershot the target more strongly compared to participants in the placebo groups. Risperidone also lead to a general slowing in saccadic peak velocity, a well-established biomarker of sedation,[11] consistent with a recent independent study of our group.[33]

None of the interactions between ketamine and risperidone were found to be significant. This indicates that risperidone did not attenuate any ketamine effects. Instead, as suggested by its main effects described above, this clinically effective antipsychotic led to further deteriorations in different parameters.

Ketamine and smooth pursuit

The observed effects of ketamine on SPEM performance are in line with previously reported findings of a decrease in pursuit gain and an increase in saccadic frequency following ketamine administration.[20,22]

A neural circuitry involving the cerebellum has been proposed to have a central role in integrating and coordinating SPEM and saccadic information. It could be argued that NMDA receptor blockage in areas involved in frontal-thalamic-cerebellar circuits such as frontal eye fields, thalamus and cerebellum[50] would be likely to cause disruption in SPEM.[22] The results of this study could indicate a shared cerebellar pathophysiology as a potential cause for SPEM impairments in schizophrenia and during ketamine challenge.[20] An involvement of a glutamatergic imbalance in cortical-subcortical-cerebellar circuits underlying the integrative theory of cognitive dysmetria may be assumed.[51]

It should, however, be noted that ketamine also has agonistic effects on the dopamine and serotonin systems.[3] Therefore, the observed effects on smooth pursuit could also be the result of more complex effects of ketamine on other neurotransmitter receptor sites within the above neural circuits.

The role of gender

Females displayed higher AS error rates and worse SPEM velocity gain compared with males in this study. Those results are comparable to previous findings of AS performance differences between men and women.[52] In prepulse inhibition, another sensitive neurophysiological schizophrenia spectrum marker, gender differences have also been observed with females in general displaying less prepulse inhibition and hence more 'psychosis-like' behaviour on this task.[53,54]

The trend for the interaction between ketamine and gender indicates that ketamine may have detrimental effects on performance in males but not in females. This is in line with previous reports of greater performance deterioration in cognitive tasks in males compared with females under the influence of ketamine.[55] Protective and neuromodulatory effects of oestrogen in females have been proposed to have a role.[48,56] The need to

Table 3. Overview of main effects and their interactions for pro- and antisaccades and smooth pursuit

Eye movements	*Effects*			
	Main effects	*F*	*p*	*Description*
Saccades				
AS error rate	Ketamine	$F(1,64) = 0.02$	$P = 0.88$	
	Risperidone	$F(1,64) = 0.22$	$P = 0.64$	
	Gender	$F(1,64) = 4.92$	$P = 0.03$	Higher error rates in females than in males.
	Ketamine by risperidone	$F(1,64) = 0.39$	$P = 0.53$	
	Ketamine by gender	$F(1,64) = 3.55$	$P = 0.06$	Trend for higher error rates in females compared with males under placebo. Higher error rates in males but not in females under the influence of ketamine.
	All other interactions		All $P \geqslant 0.08$	
AS correction rate	No main effects and no interactions		All $P \geqslant 0.07$	
Latency	Task	$F(1,63) = 439.10$	$P < 0.01$	Faster latencies for PS than AS.
	Ketamine	$F(1,63) = 3.21$	$P = 0.08$	
	Risperidone	$F(1,63) = 0.87$	$P = 0.35$	
	Gender	$F(1,63) = 1.44$	$P = 0.23$	
	Ketamine by risperidone	$F(1,63) = 0.05$	$P = 0.82$	
	All other interactions		$P \geqslant 0.48$	
Gain	Task	$F(1,63) = 0.59$	$P = 0.44$	
	Ketamine	$F(1,63) = 1.01$	$P = 0.32$	
	Risperidone	$F(1,63) = 4.22$	$P = 0.04$	Lower amplitude gain values for participants on risperidone compared with placebo.
	Gender	$F(1,63) = 0.23$	$P = 0.63$	
	Ketamine by risperidone	$F(1,63) = 0.06$	$P = 0.81$	
	All other interactions		$P \geqslant 0.11$	
Velocity	Task	$F(1,63) = 38.91$	$P < 0.01$	Faster peak velocities for PS compared with AS.
	Ketamine	$F(1,63) = 3.26$	$P = 0.08$	
	Risperidone	$F(1,63) = 22.04$	$P < 0.01$	Slowing of peak velocities under the influence of risperidone compared with placebo.
	Gender	$F(1,63) = 0.96$	$P = 0.33$	
	Ketamine by risperidone	$F(1,63) = 1.28$	$P = 0.26$	
	Task by risperidone	$F(1,63) = 4.86$	$P = 0.03$	AS peak velocity more sensitive to the influence of risperidone compared with prosaccade peak velocity.
	All other interactions		$P \geqslant 0.14$	
SPEM				
Gain	Velocity	$F(2,128) = 346.08$	$P < 0.01$	Lower velocity gain with faster velocities.
	Ketamine	$F(1,64) = 28.84$	$P < 0.01$	Lower velocity gain under the influence of ketamine compared with placebo.
	Risperidone	$F(1,64) = 1.37$	$P = 0.25$	
	Gender	$F(1,64) = 6.11$	$P = 0.02$	More accurate velocity gain performance in males compared with females.
	Ketamine by risperidone	$F(1,64) = 0.68$	$P = 0.41$	
	Velocity by ketamine	$F(2,128) = 3.22$	$P = 0.04$	Reduced influence of ketamine on velocity gain performance for the fastest velocity.
	All other interactions		$P \geqslant 0.13$	
Saccadic frequency	Velocity	$F(2,128) = 85.50$	$P < 0.01$	General increase in saccadic frequency with faster velocities.
	Ketamine	$F(1,64) = 9.18$	$P < 0.01$	Higher saccadic frequencies under the influence of ketamine compared with placebo.
	Risperidone	$F(1,64) = 1.96$	$P = 0.17$	
	Gender	$F(1,64) = 5.50$	$P = 0.02$	Higher saccadic frequencies in males compared with females.
	Ketamine by risperidone	$F(1,64) < 0.01$	$P = 0.95$	
	Velocity by ketamine	$F(2,128) = 7.59$	$P < 0.01$	Reduced influence of ketamine on saccadic frequency for the fastest velocity.
	Velocity by gender	$F(2,128) = 4.86$	$P < 0.01$	Performance differences for males and females in the two faster velocities, which was not observed for the slowest velocity.
	All other interactions		$P \geqslant 0.12$	

Abbreviations: AS, antisaccade; SPEM, smooth pursuit eye movements.

Table 4. Descriptive statistics and effect sizes of the questionnaire data

	Drug		*Statistical test*	*Drug*		*Statistical test*	*Effect size (Cohen's d)*	
	PLA_SAL, N = *19*	*PLA_KET*, N = *17*		*PLA_KET*, N = *17*	*RIS_KET*, N = *18*		*PLA_SAL – PLA_KET*	*PLA_KET – RIS_KET*
BPRS total	15.76	21.56	$U = 109.50$; $Z = 1.76$; $P = 0.04$	17.38	18.58	$U = 142.50$; $Z = -0.35$; $P = 0.36$	0.29	0.06
BPRS thinking disorder	15.24	22.15	$U = 99.50$; $Z = -2.24$; $P = 0.01$	17.82	18.17	$U = 150.00$; $Z = -0.10$; $P = 0.46$	0.37	0.02
BPRS withdrawal	14.79	22.65	$U = 91.00$; $Z = -2.60$; $P = 0.005$	16.68	19.25	$U = 130.50$; $Z = -0.76$; $P = 0.22$	0.43	0.13
BPRS anxiety	18.30	18.73	$U = 157.50$; $Z = -0.17$; $P = 0.45$	16.50	19.42	$U = 127.50$; $Z = -1.02$; $P = 0.15$	0.03	0.17
BPRS hostility	18.39	18.62	$U = 159.50$; $Z = -0.12$; $P = 0.45$	18.50	17.53	$U = 144.50$; $Z = -0.58$; $P = 0.28$	0.02	0.10
BPRS activity	16.74	20.47	$U = 128.00$; $Z = -1.19$; $P = 0.11$	18.15	17.86	$U = 150.50$; $Z = -0.09$; $P = 0.46$	0.20	0.02
CADSS total	13.18	24.44	$U = 60.50$; $Z = -3.31$; $P = 0.0005$	19.71	16.39	$U = 124.00$; $Z = -0.97$; $P = 0.16$	0.55	0.16
CADSS amnesia	13.66	23.91	$U = 69.50$; $Z = -3.19$; $P = 0.0005$	19.03	17.03	$U = 135.50$; $Z = -0.62$; $P = 0.27$	0.53	0.10
CADSS depersonalisation	16.50	20.73	$U = 123.50$; $Z = -1.53$; $P = 0.06$	18.44	17.58	$U = 145.50$; $Z = -0.29$; $P = 0.38$	0.26	0.05
CADSS derealisation	14.16	23.35	$U = 79.00$; $Z = -2.88$; $P = 0.002$	19.38	16.69	$U = 129.50$; $Z = -0.81$; $P = 0.21$	0.48	0.14
LSHS total	20.26	16.53	$U = 128.00$; $Z = -1.08$; $P = 0.14$	19.94	16.17	$U = 120.00$; $Z = -1.12$; $P = 0.13$	0.18	0.19

Abbreviations: BPRS-E, Brief Psychiatric Rating Scale Expanded Version;[45,46] CADSS, Clinician Administered Dissociative States Scale;[44] PLA_KET, placebo capsule and ketamine infusion; PLA_SAL, placebo capsule and saline infusion; RIS_KET, risperidone capsule and ketamine infusion;[44] LSHS: Launay–Slade Hallucinations Scale.[47] Threshold after Bonferroni correction: $P \leqslant 0.004$; data represent mean ranks of Mann–Whitney tests unless otherwise stated.

consider these gender differences and their interactions, especially when investigating pharmacological challenges and treatment effects should be highlighted for future studies.

Effects of risperidone

Successful attenuation of ketamine-induced deteriorations has been described for typical and atypical antipsychotics such as haloperidol, clozapine and olanzapine,[57,58] anti-epileptics such as lamotrigene and LY354740, a glutamate agonist.[59,60] Risperidone treatment has previously been shown to improve antisaccade performance in schizophrenia patients after switching from typical antipsychotics to risperidone and in antipsychotic naive first-episode patients.[28,29] In our study, risperidone did not reverse or attenuate ketamine-induced oculomotor impairments. In fact, further deterioration in performance was observed in participants receiving ketamine in combination with risperidone on some parameters (see effect sizes in Table 2). For the AS error rate, the most obvious reason for the lack of enhancing effects of risperidone in this study may be the observation that it was not affected by the ketamine challenge overall.

With regards to smooth pursuit performance, no beneficial effects of risperidone on ketamine-induced SPEM deficits were found. Some studies have investigated the effects of antipsychotics on SPEM in first episode and chronic schizophrenia patients (for review see Reilly *et al*.[10]). No treatment effect on predictive pursuit in first-episode patients[61,62] but a worsening in SPEM performance in antipsychotic-treated, chronic schizophrenia patients compared with non-treated chronic patients has been observed.[61] Hence patients' pursuit performance deficits seem to persist despite pharmacological treatment possibly even representing cumulative adverse effects of typical and atypical antipsychotics on the pursuit system.[10]

With regards to the present study, it should be pointed out that the acute administration design cannot be equated with long-term antipsychotic treatment studies of schizophrenia patients. Therefore, although a single dose of risperidone did not offer prophylaxis from the effects of ketamine in this study, reversal of negative effects may well have been seen with longer-term treatment with risperidone, as in the patient studies.[28,29] However, this was not possible in the present study.

Psychotomimetic effects of ketamine

In addition to oculomotor impairments, the infusion of ketamine also caused some symptom related effects in this study. Participants showed higher total scores on CADSS under the influence of ketamine. From the subscales, it could be observed that ketamine produced amnesia and derealisation. For further subscales, medium effect sizes could be observed (see Table 4 for details).

These psychotomimetic effects of ketamine have been described in the previous literature[5,63] and confirm the broad range of symptom dimension that can be induced by this pharmacological challenge, thereby validating the ketamine model of psychosis in this study.

Interestingly, risperidone did not attenuate these psychotomimetic effects of ketamine. We interpret this negative result as confirming our above argument that the beneficial effects of risperidone are not observed prophylactically after a one-off administration but likely require longer-term treatment to become apparent, at the clinical as well as the oculomotor level.

The predictive value of the ketamine model and oculomotor biomarkers

The acute administration of NMDA receptor antagonists has been found to affect a wide range of cognitive domains known to be disrupted in schizophrenia. On the basis of these and other findings, NMDA receptor antagonism has been proposed to represent a predictively valid model of cognitive dysfunction in schizophrenia[64] as well as a reliable model of neurotransmitter dysfunction in healthy volunteers.[65]

Here we observed that SPEM performance displays a remarkable sensitivity to the influence of ketamine. Hence, we propose that future studies should investigate alternative compounds such as metabotropic glutamate receptor agonists in order to attempt to reverse ketamine-induced SPEM impairments.[66] This approach offers a promising starting point to enhance the mechanistic understanding of glutamatergic agonists and potentially the development of a new generation of antipsychotic treatment for schizophrenia.

Ketamine, however, did not significantly influence the AS error rate, latency or amplitude gain, measures which are frequently observed to be impaired in schizophrenia.[67] It could be hypothesised that the observed impairments in schizophrenia patients might not be directly mediated by underlying glutamatergic pathophysiology but that dysregulations of other neurotransmitter systems, such as the dopaminergic system could be reflecting such impairments.[68]

Limitations

Certain limitations of our study have to be taken into consideration. First, our study may have benefitted from a within-subject design in which the oculomotor performance of each participant on placebo is compared with their performance on the study drug.[69] It should be noted, however, that the between-subjects design in our study circumvented problems of repeated measurement such as practise effects.[35,70] Second, no measures of plasma levels were obtained. However, testing times were arranged to account for absorption rates for risperidone[36,37] and the targeted ketamine concentration over an extended testing period.[4,71] A pre-planned randomisation schedule for the test battery was applied to account for interindividual variances in metabolism, peak plasma concentrations and fatigue. Finally, our study involved a one-off administration of risperidone only, which cannot be compared with the therapeutic effects of the drug in longer-term treatment of schizophrenia patients. Therefore, conclusions about the potential of the drug to reverse effects of ketamine administration remain speculative.[24]

Summary: ketamine challenge as a schizophrenia model

Overall, the ketamine challenge appears to represent an adequate pharmacological model to mimic several aspects of schizophrenia symptoms and their pathophysiology. However, based on the current study, the model is not fully comprehensive, as some oculomotor dysfunctions that are present in schizophrenia were not observed under the influence of ketamine. We confirmed that SPEM parameters are especially sensitive to ketamine administration, which could indicate that SPEM impairment in schizophrenia might be mediated by dysregulations of glutamatergic neurotransmission in frontal-thalamic-cerebellar circuits (but note the possible role of dopaminergic and serotonergic transmission mentioned above). Risperidone did not attenuate ketamine-induced deterioration, highlighting the need for the development of new compounds, for example, those targeting glutamatergic receptors. Finally, we interpret our results as a promising indicator that oculomotor measures could be used as valuable translational biomarkers in future pharmacological investigations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank the participating volunteers and all research staff and students who helped collecting the data. This study was supported by the P1vital CNS Experimental Medicine Consortium (members AstraZeneca, GlaxoSmithKline, Lundbeck, Organon (a subsidiary of Merck) and Pfizer). The PhD of Anne Schmechtig was partly funded by P1vital CNS Experimental Medicine Consortium. Ivan Koychev was awarded a Manchester Strategic PhD Studentship, sponsored by the University of Manchester and P1vital Ltd. John Francis William Deakin, Lawrence Wilkinson, Gerry Dawson and Colin Dourish own shares in P1vital Ltd. Kevin Craig is employed by and owns shares in Covance Inc. Lawrence Wilkinson is a member of the Wellcome Trust Investigator Funding Committee. Ulrich Ettinger acknowledges financial support from the Deutsche Forschungsgemeinschaft (Et 31/2–1). Steve Williams wishes to thank the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Kings College London for their on-going support of our translational imaging research programme. The experiments carried out in this study comply with the current laws of the country in which they were performed.

REFERENCES

1 Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry* 2006; **67**: e12.
2 Stone JM. Glutamatergic antipsychotic drugs: a new dawn in the treatment of schizophrenia? *Ther Adv Psychopharmacol* 2011; **1**: 5–18.
3 Kapur S, Seeman P. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. *Mol Psychiatry* 2002; **7**: 837–844.
4 Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD *et al.* Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994; **51**: 199–214.
5 Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. *Psychopharmacology (Berl)* 2003; **169**: 215–233.
6 Adler CM, Goldberg TE, Malhotra AK, Pickar D, Breier A. Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. *Biol Psychiatry* 1998; **43**: 811–816.
7 Lofwall MR, Griffiths RR, Mintzer MZ. Cognitive and subjective acute dose effects of intramuscular ketamine in healthy adults. *Exp Clin Psychopharmacol* 2006; **14** (4): 439–449.
8 Krystal JH, Bennett A, Abi-Saab D, Belger A, Karper LP, D'Souza DC *et al.* Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. *Biol Psychiatry* 2000; **47**: 137–143.
9 Koychev I, Barkus E, Ettinger U, Killcross S, Roiser JP, Wilkinson L *et al.* Evaluation of state and trait biomarkers in healthy volunteers for the development of novel drug treatments in schizophrenia. *J Psychopharmacol* 2011; **25**: 1207–1225.
10 Reilly JL, Lencer R, Bishop JR, Keedy S, Sweeney JA. Pharmacological treatment effects on eye movement control. *Brain Cogn* 2008; **68**: 415–435.
11 de Visser SJ, van der Post J, Pieters MS, Cohen AF, van Gerven JM. Biomarkers for the effects of antipsychotic drugs in healthy volunteers. *Br J Clin Pharmacol* 2001; **51**: 119–132.
12 Ettinger U, Picchioni M, Hall MH, Schulze K, Toulopoulou T, Landau S *et al.* Antisaccade performance in monozygotic twins discordant for schizophrenia: the Maudsley twin study. *American Journal of Psychiatry* 2006; **163**: 543–545.

13 Hutton SB, Ettinger U. The antisaccade task as a research tool in psychopathology: a critical review. *Psychophysiology* 2006; **43**: 302–213.
14 Levy DL, Sereno AB, Gooding DC, O'Driscoll GA. Eye tracking dysfunction in schizophrenia: characterization and pathophysiology. *Curr Top Behav Neurosci* 2010; **4**: 311–347.
15 Smyrnis N, Evdokimidis I, Mantas A, Kattoulas E, Stefanis NC, Constantinidis TS *et al.* Smooth pursuit eye movements in 1,087 men: effects of schizotypy, anxiety, and depression. *Exp Brain Res* 2007; **179**: 397–408.
16 Smyrnis N, Evdokimidis I, Stefanis NC, Avramopoulos D, Constantinidis TS, Stavropoulos A *et al.* Antisaccade performance of 1,273 men: effects of schizotypy, anxiety, and depression. *J Abnorm Psychol* 2003; **112**: 403–414.
17 Hutton SB. Cognitive control of saccadic eye movements. *Brain Cogn* 2008; **68**: 327–340.
18 Barnes GR. Cognitive processes involved in smooth pursuit eye movements. *Brain Cogn* 2008; **68**: 309–326.
19 Sharpe JA. Neurophysiology and neuroanatomy of smooth pursuit: lesion studies. *Brain Cogn* 2008; **68**: 241–254.
20 Avila MT, Weiler MA, Lahti AC, Tamminga CA, Thaker GK. Effects of ketamine on leading saccades during smooth-pursuit eye movements may implicate cerebellar dysfunction in schizophrenia. *Am J Psychiatry* 2002; **159**: 1490–1496.
21 Condy C, Wattiez N, Rivaud-Pechoux S, Gaymard B. Ketamine-induced distractibility: An oculomotor study in monkeys. *Biol Psychiatry* 2005; **57**: 366–372.
22 Radant AD, Bowdle TA, Cowley DS, Kharasch ED, Roy-Byrne PP. Does ketamine-mediated N-methyl-D-aspartate receptor antagonism cause schizophrenia-like oculomotor abnormalities? *Neuropsychopharmacology* 1998; **19**: 434–444.
23 Weiler MA, Thaker GK, Lahti AC, Tamminga CA. Ketamine effects on eye movements. *Neuropsychopharmacology* 2000; **23**: 645–653.
24 Morgan CJ, Huddy V, Lipton M, Curran HV, Joyce EM. Is persistent ketamine use a valid model of the cognitive and oculomotor deficits in schizophrenia? *Biol Psychiatry* 2009; **65**: 1099–1102.
25 Meltzer HY, Horiguchi M, Massey BW. The role of serotonin in the NMDA receptor antagonist models of psychosis and cognitive impairment. *Psychopharmacology (Berl)* 2011; **213**: 289–305.
26 Large CH. Do NMDA receptor antagonist models of schizophrenia predict the clinical efficacy of antipsychotic drugs? *J Psychopharmacol* 2007; **21**: 283–301.
27 Doyle OM, De Simoni S, Schwarz AJ, Brittain C, O'Daly OG, Williams SC *et al.* Quantifying the attenuation of the ketamine pharmacological magnetic resonance imaging response in humans: a validation using antipsychotic and glutamatergic agents. *J Pharmacol Exp Ther* 2013; **345**: 151–160.
28 Burke JG, Reveley MA. Improved antisaccade performance with risperidone in schizophrenia. *J Neurol Neurosurg Psychiatry* 2002; **72**: 449–454.
29 Harris MS, Reilly JL, Keshavan MS, Sweeney JA. Longitudinal studies of antisaccades in antipsychotic-naive first-episode schizophrenia. *Psychol Med* 2006; **36**: 485–494.
30 Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull* 1991; **17**: 555–564.
31 O'Driscoll GA, Lenzenweger MF, Holzman PS. Antisaccades and smooth pursuit eye tracking and schizotypy. *Arch Gen Psychiatry* 1998; **55**: 837–843.
32 Ettinger U, Kumari V, Crawford TJ, Flak V, Sharma T, Davis RE *et al.* Saccadic eye movements, schizotypy, and the role of neuroticism. *Biol Psychol* 2005; **68**: 61–78.
33 Schmechtig A, Lees J, Grayson L, Craig KJ, Dadhiwala R, Dawson GR *et al.* Effects of risperidone, amisulpride and nicotine on eye movement control and their modulation by schizotypy. *Psychopharmacology (Berl)* 2013; **227**: 331–345.
34 Nelson HE. *The National Adult Reading Test (NART).* NFER-Nelson: Windsor UK, 1982.
35 Ettinger U, Kumari V, Zachariah E, Galea A, Crawford TJ, Corr PJ *et al.* Effects of procyclidine on eye movements in schizophrenia. *Neuropsychopharmacology* 2003; **28**: 2199–2208.
36 Mannens G, Huang ML, Meuldermans W, Hendrickx J, Woestenborghs R, Heykants J. Absorption, metabolism, and excretion of risperidone in humans. *Drug Metab Dispos* 1993; **21**: 1134–1141.
37 Huang ML, Van Peer A, Woestenborghs R, De Coster R, Heykants J, Jansen AA *et al.* Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. *Clin Pharmacol Ther* 1993; **54**: 257–268.
38 Aman MG, Vinks AA, Remmerie B, Mannaert E, Ramadan Y, Masty J *et al.* Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. *Clin Ther* 2007; **29**: 1476–1486.
39 Zhou ZL, Li X, Peng HY, Yu XY, Yang M, Su FL *et al.* Multiple dose pharmacokinetics of risperidone and 9-hydroxyrisperidone in Chinese female patients with schizophrenia. *Acta Pharmacol Sin* 2006; **27**: 381–386.
40 van Schaick EA, Lechat P, Remmerie BM, Ko G, Lasseter KC, Mannaert E. Pharmacokinetic comparison of fast-disintegrating and conventional tablet formulations of risperidone in healthy volunteers. *Clin Ther* 2003; **25**: 1687–1699.
41 King DJ. Guidelines for the use of antipsychotic drug studies in healthy volunteers. *The BAP Consensus Group. J Psychopharmacol* 1997; **11**: 201–209.
42 Barrett SL, Bell R, Watson D, King DJ. Effects of amisulpride, risperidone and chlorpromazine on auditory and visual latent inhibition, prepulse inhibition, executive function and eye movements in healthy volunteers. *J Psychopharmacol* 2004; **18**: 156–172.
43 Domino EF, Zsigmond EK, Domino LE, Domino KE, Kothary SP, Domino SE. Plasma levels of ketamine and two of its metabolites in surgical patients using a gas chromatographic mass fragmentographic assay. *Anesth Analg* 1982; **61**: 87–92.
44 Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS *et al.* Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress* 1998; **11**: 125–136.
45 Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; **10**: 799–812.
46 Ventura MA, Green MF, Shaner A, Liberman RP. Training and quality assurance with the brief psychiatric rating scale: 'The drift buster'. *Int J Methods Psychiatric Res* 1993; **3**: 221–244.
47 Launay G, Slade P. The measurement of hallucinatory predisposition in male and female prisoners. *Personality and Individual Differences* 1981; **2**(3): 221–234.
48 Lees J, Hallak JE, Deakin JF, Dursun SM. Gender differences and the effects of ketamine in healthy volunteers. *J Psychopharmacol* 2004; **18**: 337–339.
49 Field A. *Discovering Statistics Using SPSS,* vol. 2nd. Sage Publications Inc, 2005.
50 Lencer R, Trillenberg P. Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain Cogn* 2008; **68**: 219–228.
51 Andreasen NC, Paradiso S, O'Leary DS. 'Cognitive dysmetria' as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull* 1998; **24**: 203–218.
52 Crawford TJ, Sharma T, Puri BK, Murray RM, Berridge DM, Lewis SW. Saccadic eye movements in families multiply affected with schizophrenia: the Maudsley Family Study. *Am J Psychiatry* 1998; **155**: 1703–1710.
53 Aasen I, Kolli L, Kumari V. Sex effects in prepulse inhibition and facilitation of the acoustic startle response: implications for pharmacological and treatment studies. *J Psychopharmacol* 2005; **19**: 39–45.
54 Kumari V, Aasen I, Sharma T. Sex differences in prepulse inhibition deficits in chronic schizophrenia. *Schizophr Res* 2004; **69**: 219–235.
55 Morgan CJ, Perry EB, Cho HS, Krystal JH, D'Souza DC. Greater vulnerability to the amnestic effects of ketamine in males. *Psychopharmacology (Berl)* 2006; **187**: 405–414.
56 Riecher-Rossler A. Oestrogen effects in schizophrenia and their potential therapeutic implications--review. *Arch Womens Ment Health* 2002; **5**: 111–118.
57 Breese GR, Knapp DJ, Moy SS. Integrative role for serotonergic and glutamatergic receptor mechanisms in the action of NMDA antagonists: potential relationships to antipsychotic drug actions on NMDA antagonist responsiveness. *Neurosci Biobehav Rev* 2002; **26**: 441–455.
58 Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D *et al.* Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology (Berl)* 1999; **145**: 193–204.
59 Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A *et al.* Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. *Arch Gen Psychiatry* 2000; **57**(3): 270–276.
60 Krystal JH, Abi-Saab W, Perry E, D'Souza DC, Liu N, Gueorguieva R *et al.* Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. *Psychopharmacology (Berl)* 2005; **179**: 303–309.
61 Hutton SB, Crawford TJ, Gibbins H, Cuthbert I, Barnes TR, Kennard C *et al.* Short and long term effects of antipsychotic medication on smooth pursuit eye tracking in schizophrenia. *Psychopharmacology (Berl)* 2001; **157**: 284–291.
62 Lencer R, Sprenger A, Harris MS, Reilly JL, Keshavan MS, Sweeney JA. Effects of second-generation antipsychotic medication on smooth pursuit performance in antipsychotic-naive schizophrenia. *Arch Gen Psychiatry* 2008; **65**: 1146–1154.
63 Deakin JF, Lees J, McKie S, Hallak JE, Williams SR, Dursun SM. Glutamate and the neural basis of the subjective effects of ketamine: a pharmaco-magnetic resonance imaging study. *Arch Gen Psychiatry* 2008; **65**: 154–164.
64 Gilmour G, Dix S, Fellini L, Gastambide F, Plath N, Steckler T *et al.* NMDA receptors, cognition and schizophrenia-testing the validity of the NMDA receptor hypofunction hypothesis. *Neuropharmacology* 2012; **62**: 1401–1412.
65 De Simoni S, Schwarz AJ, O'Daly OG, Marquand AF, Brittain C, Gonzales C *et al.* Test-retest reliability of the BOLD pharmacological MRI response to ketamine in healthy volunteers. *Neuroimage* 2013; **64**: 75–90.
66 Javitt DC. Glutamatergic theories of schizophrenia. *Isr J Psychiatry Relat Sci* 2010; **47**: 4–16.
67 Gooding DC, Basso MA. The tell-tale tasks: a review of saccadic research in psychiatric patient populations. *Brain Cogn* 2008; **68**: 371–390.
68 Allman AA, Benkelfat C, Durand F, Sibon I, Dagher A, Leyton M *et al.* Effect of D-amphetamine on inhibition and motor planning as a function of baseline performance. *Psychopharmacology (Berl)* 2010; **211**: 423–433.

69 Babin SL, Hood AJ, Wassef AA, Williams NG, Patel SS, Sereno AB. Effects of haloperidol on cognition in schizophrenia patients depend on baseline performance: a saccadic eye movement study. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35**: 1753–1764.
70 Green JF, King DJ, Trimble KM. Antisaccade and smooth pursuit eye movements in healthy subjects receiving sertraline and lorazepam. *J Psychopharmacol* 2000; **14**: 30–36.
71 Honey GD, O'Loughlin C, Turner DC, Pomarol-Clotet E, Corlett PR, Fletcher PC. The effects of a subpsychotic dose of ketamine on recognition and source memory for agency: implications for pharmacological modelling of core symptoms of schizophrenia. *Neuropsychopharmacology* 2006; **31**: 413–423.
72 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn (DSM-IV). American Psychiatric Association: Washington DC, USA, 1994.
73 World Health Organization. ICD-10. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization: Geneva, Switzerland, 1992.
74 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E *et al*. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** (Suppl 20): 22–33, quiz 34-57: 22-33.
75 Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987; **334**: 1–100.