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ORIGINAL INVESTIGATION

Effects of risperidone, amisulpride and nicotine on eye movement control and their modulation by schizotypy

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Abstract
Rationale The increasing demand to develop more efficient compounds to treat cognitive impairments in schizophrenia has led to the development of experimental model systems. One such model system combines the study of surrogate populations expressing high levels of schizotypy with oculomotor biomarkers.
Objectives We aimed (1) to replicate oculomotor deficits in a psychometric schizotypy sample and (2) to investigate whether the expected deficits can be remedied by compounds shown to ameliorate impairments in schizophrenia.
Methods In this randomized double-blind, placebo-controlled study 233 healthy participants performed prosaccade (PS), antisaccade (AS) and smooth pursuit eye movement (SPEM) tasks after being randomly assigned to one of four drug groups (nicotine, risperidone, amisulpride, placebo). Participants were classified into medium- and high-schizotypy groups based on their scores on the Schizotypal Personality Questionnaire (SPQ, Raine (Schizophr Bull 17:555–564, 1991)).
Results AS error rate showed a main effect of Drug ($p<0.01$), with nicotine improving performance, and a Drug by Schizotypy interaction ($p=0.04$), indicating higher error rates in medium schizotypes ($p=0.01$) but not high schizotypes under risperidone compared to placebo. High schizotypes had higher error rates than medium schizotypes under placebo

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(p=0.03). There was a main effect of Drug for saccadic peak velocity and SPEM velocity gain (both $p \leq 0.01$) indicating impaired performance with risperidone.
Conclusions We replicate the observation of AS impairments in high schizotypy under placebo and show that nicotine enhances performance irrespective of group status. Caution should be exerted in applying this model as no beneficial effects of antipsychotics were seen in high schizotypes.

Keywords Schizotypy · Schizophrenia · Antisaccades · Smooth pursuit · Biomarkers · Nicotine · Risperidone · Amisulpride

Introduction

Cognitive deficits such as impairments in executive function, attention and memory represent a core feature of schizophrenia and predict functional outcome and treatment adherence (Burton 2005; Green 2006; Green et al. 2000). Due to the mixed evidence of the beneficial effects of current pharmacological treatments to improve such impairments (Heinrichs 2005), there is an increasing demand to develop new and more efficient drugs targeting cognitive deficits. However, this process is costly and the success rates of developing novel pharmacological agents are low. One promising approach to establish more efficient and cheaper ways of developing and validating new targets is the use of experimental model systems in combination with the application of biomarkers (Koychev et al. 2012). Several pharmacological models such as the amphetamine or ketamine models have already been used in animals and humans (Farber 2003; Krystal et al. 2005). Another promising approach is the investigation of surrogate populations which are similar to schizophrenia without displaying the confounding factors associated with the illness. One such population is represented by participants with elevated scores on psychometric schizotypy (Koychev et al. 2012).

Schizotypy is a multidimensional construct that is closely linked to schizophrenia on phenomenological, genetic and neural levels (Meehl 1990; Rado 1953; Raine 2006). There is growing awareness that schizotypy as a continuously distributed trait can add valuable insights into the etiology, treatment and prevention of schizophrenia (Claridge 1997; Eysenck and Eysenck 1976; Raine 2006). Schizotypy scales such as the Schizotypal Personality Questionnaire (SPQ, Raine 1991) capture schizophrenia-related characteristics in the general population including cognitive–perceptual and interpersonal disturbances as well as disorganised behaviour and speech (Raine 2006) and thus tap clinically relevant features of schizotypal personality disorder (SPD, Raine 1991). Healthy volunteers with high levels of psychometric schizotypy show cognitive (Baruch et al. 1988; Beech et al. 1989; Gooding 1999; Gooding et al. 2006; Lenzenweger 1994; O'Driscoll et al. 1998), neuroanatomical (Ettinger et al. 2011; Moorhead et al. 2009) and neurophysiological (Aichert et al. 2012; Kumari et al. 2008) deficits similar to those seen in the full-blown clinical condition. In addition some studies investigated the link between schizotypy and drug use (e.g. Barkus and Lewis 2008; Herzig et al. 2010) and have reported associations between schizotypal traits and the consumption of substances such as cannabis, nicotine, alcohol and caffeine in healthy volunteers (Esterberg et al. 2009; Jones and Fernyhough 2009; Williams et al. 1996).

Importantly, there is also evidence of overlap between schizophrenia and schizotypy at the neurochemical level (Williams et al. 1997) and pharmacological treatment response. For example, schizotypy has been shown to modulate the cognitive effects of levodopa (Mohr et al. 2005) thus supporting the involvement of dopamine in schizotypy, which is compatible with a role of this neurotransmitter system in schizophrenia (Howes and Kapur 2009). Also, neuroleptic medication has been reported to reduce psychotic-like symptoms and symptom severity in SPD (Koenigsberg et al. 2003; O'Flynn et al. 2003) which suggests a similar drug response as in schizophrenia.

The use of biomarkers as translational neurobehavioral indices of pharmacological effects (Reilly et al. 2008) is also relevant to the schizotypy model. Eye movements have been proposed to be especially promising biomarkers in drug development and the evaluation of treatment effects (de Visser et al. 2001; Reilly et al. 2008). Their well-known neural correlates, high reliability and simple application makes them ideally suited to study pharmacological effects in healthy volunteers and patient populations (Reilly et al. 2008). The most commonly studied procedures include prosaccades (PS)—a simple measure of reflex-like behaviour which often represents a useful control condition to more complex tasks (Hutton 2008); antisaccades (AS)—a measure of the integrity of cognitive and neural mechanisms of volitional control of behaviour (for review see Hutton and Ettinger 2006); and smooth pursuit eye movements (SPEM), measuring processes such as attention, prediction as well as motion processing (Barnes 2008; Lencer and Trillenberg 2008; Sharpe 2008).

Oculomotor tasks may be particularly useful biomarkers in schizophrenia spectrum populations (Gooding and Basso 2008; Levy et al. 2010) because of their well-known impairments in the schizophrenia spectrum as well as previous evidence of drug effects in schizophrenia patients and healthy controls (Reilly et al. 2008). First, impairments such as increased error rates, increased latencies, reduced spatial accuracy and lower pursuit accuracy have been observed in schizophrenia patients (for review see Hutton and Ettinger 2006; O'Driscoll and Callahan 2008), their relatives (Calkins et al. 2008), SPD patients (Brenner et al. 2001;

Clementz et al. 1995; Lencz et al. 1993), and in psychometric schizotypy (Ettinger et al. 2005; Gooding 1999; Holahan and O'Driscoll 2005; O'Driscoll et al. 1998).

Second, several studies have investigated the effects of psychotropic drugs on oculomotor control in healthy volunteers and schizophrenia patients (for review see Reilly et al. 2008). Nicotine (NIC) improves AS and pursuit performance in healthy people and patients with schizophrenia (Depatie et al. 2002; Ettinger et al. 2009; Larrison et al. 2004; Reilly et al. 2008). Regarding antipsychotics, Barrett et al. (2004) reported increased AS error rates with chlorpromazine and risperidone (RIS) in healthy volunteers. Other studies in healthy volunteers have shown a slowing of peak saccade velocity, a measure of sedation, under the influence of typical (Barrett et al. 2004; Green and King 1998) and atypical antipsychotics (Barrett et al. 2004). Regarding SPEM, it should be noted that the literature on pharmacological influences remains somewhat heterogeneous, with mixed evidence for enhancement of SPEM performance under the influence of nicotine as well as heterogeneous findings regarding an increase in saccadic intrusions with antipsychotic treatment (for review see Reilly et al. 2008). Finally, improvements have been reported on the AS task under the influence of RIS in chronic schizophrenia patients after switching from typical antipsychotics to RIS (Burke and Reveley 2002) and in antipsychotic naïve first-episode patients (Harris et al. 2006).

Thus, whilst there have been numerous studies of pharmacological influences on oculomotor control (Ettinger and Kumari 2003; Reilly et al. 2008) and of the association between schizotypy and eye movements (Ettinger et al. 2005; Gooding 1999; O'Driscoll et al. 1998), drug effects in schizotypal populations are less well explored (Wonodi et al. 2006). Such an approach may help to enhance the understanding of schizotypy as a potential model system for future drug development (Koychev et al. 2011).

Accordingly, the goal of this study was to investigate pharmacological effects on cognition in the schizotypy model by applying oculomotor biomarkers. More specifically the aims were (1) to replicate the observation of oculomotor deficits in high psychometric schizotypy and (2) to investigate whether the expected deficits can be remedied using substances that are established treatments of schizophrenia (i.e. RIS and amisulpride (AMI), Leucht et al. 2009) and which hold the promise to improve cognitive impairments (i.e. NIC, Winterer 2010).

RIS and AMI were chosen because of their well established, safe and efficacious profiles in patients and healthy volunteers (Mauri et al. 2007; Rosenzweig et al. 2002). While RIS has been shown to improve oculomotor function in schizophrenia (Burke and Reveley 2002; Harris et al. 2006), presumably via high affinity for serotonergic and dopaminergic D2 receptors, AMI as a D2/D3 antagonist was included as it has a different receptor profile than RIS against which hypothesised beneficial effects of RIS could be compared. In addition NIC as a procholinergic cognitive enhancing compound targeting nicotinic acetylcholine receptors was chosen as cholinergic mechanisms are found to play an increasingly important role in the development of new treatment targets (Cincotta et al. 2008).

Our hypotheses were as follows:

1. NIC has been found to improve AS and SPEM performance in schizophrenia patients and healthy controls (Depatie et al. 2002; Ettinger et al. 2009; Larrison et al. 2004; Petrovsky et al. 2012; Reilly et al. 2008). It is hypothesised that NIC will improve oculomotor performance in this study irrespective of schizotypy group status.
2. RIS has been reported to improve AS performance in schizophrenia patients (Burke and Reveley 2002; Harris et al. 2006) but deteriorate it in control participants (Barrett et al. 2004). It is hypothesised that RIS displays advantageous effects in high schizotypes and disadvantageous effects in medium schizotypes for AS performance.
3. AMI is an atypical antipsychotic that has not shown any worsening effects on eye movements in controls (Barrett et al. 2004). It is a D2/D3 antagonist with a similar receptor profile to typical antipsychotics which have shown mixed effects on eye movements in schizophrenia (for review see Reilly et al. 2008). It is explored here for the first time whether there are any effects of AMI in schizotypal individuals. Neither improving nor worsening effects of AMI are expected for oculomotor performance.

Method

Subjects

A total of 244 healthy volunteers were recruited as part of a multi-site study (University of Manchester, Cardiff University, King's College London) through local and online advertisements. Initial recruitment was carried out via the internet, using the SPQ or SPQ-Brief (Raine 1991; Raine and Benishay 1995) (74/22 items, both with a YES/NO response format) as online screening tools. The SPQ which is based on the DSM-III-R criteria for SPD was deemed suitable to explore individual differences in schizotypal features in a healthy volunteer population. It was also used to identify subjects at risk for schizophrenia spectrum disorders, however without a diagnosis of SPD. Based on their online scores, volunteers with high (SPQ scores of ≥41 or SPQ-B scores of ≥15) and medium (SPQ scores between 21 and 36 or SPQ-B scores between 7 and 12) levels of schizotypy were contacted and invited for further screening. Volunteers were then asked to complete the full

SPQ again under controlled conditions and were excluded if they did not fit the predefined score ranges on the screening day. Based on the scores of the screening day, participants were divided into medium and high schizotypal scorers (see cut-offs above) with the medium-schizotypy group serving as a control group for the high schizotypals. This classification was based on previous observations of normal distributions of the SPQ scores in the general population (Avramopoulos et al. 2002; Fossati et al. 2007; Johns and van Os 2001) and previously reported cut-offs (Avramopoulos et al. 2002; Bora and Baysan 2009; Fossati et al. 2007; Raine 1991; Smyrnis et al. 2007) with high schizotypes being selected based on the 10 % upper cut-off reported by Raine (1991).

Screening procedure

A telephone interview was conducted with participants who completed the online questionnaire and displayed appropriate score ranges. If all inclusion criteria were met they were invited for a screening visit (Fig. 1). On the screening day, information was collected on age, gender, handedness, ethnicity and years spent in full-time education. An IQ estimate was obtained with the National Adult Reading Test (NART, Nelson and Willison 1991). A medical screening was carried out including blood tests, vital sign checks, ECG recording and a physical examination by a study doctor confirming that all participants were fit for inclusion into the study.

Approval of the local ethics committee was obtained for this study and volunteers provided written informed consent. The testing day took place within 6 weeks of the screening visit. Participants were reimbursed with £130 for their time and inconvenience.

Study design

The pharmacological part of the study employed a double-blind, randomized, placebo-controlled, parallel group design. Equal numbers of participants were randomly assigned to one of four study arms (i.e. the ratio 1:1:1:1). The active compounds were 2 mg RIS, 400 mg AMI, and 7 mg NIC. RIS and AMI were administered orally and NIC was administered via a patch. A placebo (PLA) condition was also employed (see Fig. 2).

Subclinical dose ranges were in accordance with the recommendation of the Consensus Statement of the British Association for Psychopharmacology for acute pharmacological challenges in healthy volunteers (King 1997). They were chosen on the basis of their reported tolerability (Curran and Perry 2001; Mauri et al. 2007; McKeage and Plosker 2004) and previously described study ranges (Artaloytia et al. 2006; Barrett et al. 2004; Depatie et al. 2002; Sherr et al. 2002). No blood samples for pharmacokinetics were obtained, however testing times were arranged to account for known peak plasma concentration of the applied compounds. To keep the study blind, a PLA capsule and/or a PLA patch was administered to all study participants.

Study day preparation

Prior to the study day visit participants were asked to follow certain restrictions. These are described in Fig. 1.

Study day procedure

The study day began at a fixed time of the day and consisted of a pre-dose phase, drug metabolism phase, and the oculomotor assessment (Fig. 2). Two participants were tested in

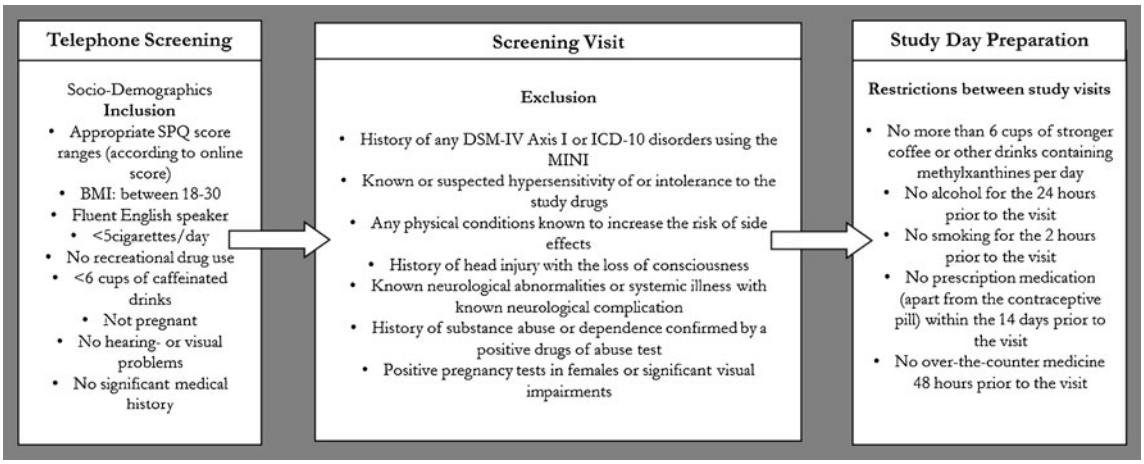

Fig. 1 Inclusion and exclusion criteria for the study. Note: Abbreviations: *SPQ* Schizotypal Personality Questionnaire (Raine 1991), *DSM-IV* Diagnostic and Statistical Manual, Fourth Edition (American Psychiatric 1994), *ICD-10* International Classification of Disease and Related Health Problems, 10th Revision (World Health Organisation 1992), *MINI* Mini International Neuropsychiatric Interview (Sheehan et al. 1998)

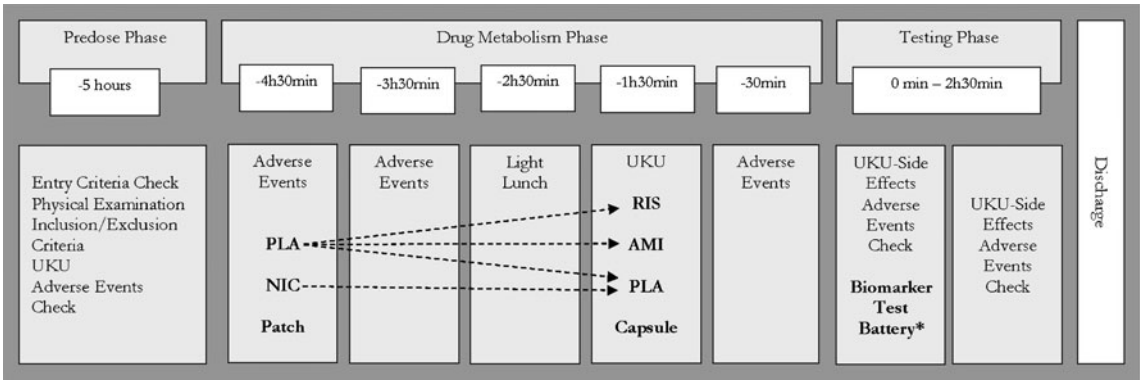

Fig. 2 Timeline of the study procedure on the randomization day. Note: Abbreviations: *UKU* Udvalg for Kliniske Undersøgelser side effect rating scale (Lingjaerde et al. 1987); *Eye movement tasks were part of a biomarker test battery

one randomization day. The pre-dose phase was to complete pre-examination and check inclusion/exclusion criteria. After successful entry criteria checks, participants underwent standardized pre-dose medical procedures. A NIC or PLA patch was applied to the upper arm 4.5 h prior to the testing. A capsule containing RIS, AMI or PLA was administered with water 1.5 h prior to the testing. Fixed drug administration times were chosen to account for peak absorption rates of the drugs (Mannens et al. 1993; Rosenzweig et al. 2002).

The oculomotor assessment, which took 10–15 min to complete, was part of a task battery with its position in the battery being arranged at random to control for systematic time effects such as variances in metabolism, peak plasma concentrations and fatigue. Participants stayed under constant observation throughout the study day.

Eye movements

Recording

Eye movements were recorded at 1,000 Hz sampling rate (Eyelink 1000, SR Research Ltd., Kanata Ontario, 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 nine-point calibration was carried out before the beginning of each task. Practice trials were carried out before the PS and AS tasks.

A PS trial started with the black dot in the central position of the screen (0°) for a random duration of 1,000–2,000 ms. The target then jumped to one of four possible peripheral positions (±7.25°, ±14.5°) for 1,000 ms. Each of the possible locations was used 15 times in a random order resulting in 60 trials in total. Participants were instructed to look at the target while it was in the central position and to follow it as fast and accurately as possible when it jumped to one of the peripheral positions.

The settings for the AS task were the same as for the PS task. Participants were asked to look at the target whilst in the centre and to look at the exact mirror image position as fast and accurately as possible when the target jumped to either side.

In the SPEM task, the target moved horizontally across the screen (from −14.5° to +14.5°) in a sinusoidal waveform at three different target velocities (0.25, 0.50 and 0.75 Hz), starting at −14.5°. For each of the target velocities, the target completed ten full cycles. Participants were told to keep their eyes on the target as closely as possible.

Analysis

PS and AS data were analysed using EyeLink DataViewer software (SR Research Ltd.) by a single rater blind to drug and schizotypy group. Saccades were of minimum amplitude (1°) and minimum latency (100 ms). Based on the previous literature the following primary endpoints were chosen due to their consistently described impairments within the schizophrenia spectrum (Gooding and Basso 2008; O'Driscoll and Callahan 2008) and their sensitivity to pharmacological influences (Reilly et al. 2008).

Directional error rate	describes the percentage of error trials (i.e., trials where the participant's first saccade is away from [PS trials] or towards [AS trials] the target) over the total number of valid trials (i.e. 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.
Amplitude gain (percentage)	as a measure of spatial accuracy was determined by the primary saccade amplitude divided by target amplitude multiplied by 100 where the amplitude was calculated for the

	first directionally correct saccade in a correct trial.
Peak velocity (degree per second)	was automatically determined from the first directionally correct saccade after 100 ms of target movement

SPEM analysis was carried out by a single rater blind to drug and schizotypy group using purpose written routines in LabView (National Instruments Corporation, Austin, Texas, USA). Two dependent variables were derived.

First, the time-weighted average *velocity gain* was calculated by dividing mean eye velocity by target velocity. The analysis included sections of pursuit in the central half of each ramp excluding saccades and eye blinks. Velocity gain scores for each section of pursuit without saccades or blinks were time-weighted and subsequently averaged. Additionally, the mean proportion of time contributing to velocity gain was calculated.

Second, *saccadic frequency* (in N/second) for each velocity was measured across the entire pursuit task at each velocity.

Statistical analysis

Data pre-screening

Data pre-screening was carried out using SPSS 15.0. Demographic data were compared across the drug and schizotypy groups using univariate analyses of variance (ANOVA) for continuous variables such as age, years in full-time education and NART-R (Nelson and Willison 1991). For categorical data such as gender, handedness and ethnicity, chi-square 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 also carried out using SPSS 20.0. For AS and PS variables (except directional error rate, see below) the model was a repeated measure ANOVA design in which Task (AS, PS) served as within-subject factor, Drug (RIS, AMI, NIC, PLA) and Schizotypy (medium, high) as between-subject factors. Age and IQ were initially included as covariates. Additionally, to acknowledge the pharmacodynamic effects of the different compounds, time since dosing (in minutes) was included as a covariate.

Due to extremely low variance in PS error rate (only two participants made any directional errors on this task), AS error rate was examined using a separate univariate ANOVA including Drug (RIS, AMI, NIC, PLA) and Schizotypy (medium, high) as fixed factors and Age, IQ and time since dosing as covariates.

For SPEM, the dependent variables of velocity gain and saccadic frequency variables were investigated using separate repeated measures ANOVA with Velocity (0.25, 0.50 and 0.75 Hz) as within-subject factor and, Drug (RIS, AMI, NIC, PLA) and Schizotypy (medium, high) as between-subject factors. Age, IQ and time since dosing were included as covariates into the model.

For both AS/PS and SPEM, covariates which did not contribute significantly to the statistical models were excluded from analysis.

After calculating these initial models, subsequent ANOVA models were carried out for any significant drug effects and their interactions to separately compare each type of compound (NIC; RIS and AMI) to PLA. Subsequent pairwise comparisons for all significant effects were performed using Bonferroni corrections.

Results

The final sample consisted of 233 participants with an average age of 23.73 years (SD=5.51) and included 116 (49.8 %) males. Data from seven participants had to be excluded due to poor calibration. In addition four participants discontinued the study due to adverse reactions during the testing. Descriptive statistics of demographic variables are displayed by drug group in Table 1. No associations between schizotypy group and age, IQ, gender, handedness or ethnicity were found (all $p>0.10$). The SPQ and SPQ-B showed high retest reliabilities between online and test conditions (SPQ: $r_S=0.73$, $p<0.01$; SPQ-B: $r_S=0.69$, $p<0.01$).

Pre-screening of the dataset was carried out to ensure that assumptions and criteria for statistical analysis of the data were met. Some dependent variables were skewed and subsequently square (SPEM velocity gain at 0.25 Hz), square root (AS error rate) or log (AS latency) transformed to obtain normality according to Kolmogorov–Smirnov statistics. In order to include related dependent variables into repeated measure ANOVA models they were transformed accordingly (SPEM velocity gain at 0.50 and 0.75 Hz square transformed, PS latency log transformed). Table 2 displays untransformed means and standard deviations of the eye movement measures by Schizotypy and Drug. As "time since dosing" was significantly different between drug groups (see Table 1), it was initially included as a covariate into all ANOVA models. Age (for PS/AS latency, SPEM gain,) and IQ (for AS error rate, SPEM gain, SPEM saccadic frequency) were also included as covariates as they contributed significantly to these ANOVA models.

Table 1 Descriptive statistics for demographic variables by drug group

	Drug group				Statistical Test
	RIS	AMI	NIC	PLA	
Sample size					
London	19	20	21	21	χ^2=0.66, *df*=6, *p*=0.99
Manchester	24	26	23	22	
Cardiff	12	16	15	14	
N right-handed	47 (22.5)	58 (27.7)	53 (25.3)	51 (24.4)	χ^2=7.72, *df*=6, *p*=0.26
N male (%)	27 (23.3)	30 (25.9)	30 (25.9)	29 (25.0)	χ^2=0.11, *df*=3, *p*=0.99
Ethnicity (%)					
Caucasian	47 (24.3)	50 (25.9)	48 (24.9)	48 (24.9)	χ^2=12.13, *df*=9, *p*=0.21
Asian	6 (20.7)	10 (34.5)	10 (34.5)	3 (10.3)	
Black	2 (28.6)	1 (14.3)	1 (14.3)	3 (42.8)	
Other	0	1 (25.0)	0	3 (75.0)	
Age in years	23.65 (5.31)	23.97 (6.39)	23.52 (5.25)	23.75 (5.01)	*F*[3,229]=0.07, *p*=0.98
[range]	18–44	18–42	18–42	18–40	
IQ (NART score)	113.63 (4.46)	113.14 (5.20)	113.07 (5.11)	114.13 (5.48)	*F*[3,229]=0.55, *p*=0.65
SPQ					
Medium	28.19 (4.80)	28.72 (4.57)	30.11 (4.66)	27.74 (4.06)	*F*[3,113]=1.46, *p*=0.23
High	49.82 (5.14)	50.40 (6.08)	49.81 (5.24)	50.15 (6.24)	*F*[3,112]=0.07, *p*=0.97
Time since dosing in minutes	149.65 (35.15)	136.10 (34.12)	152.14 (35.72)	149.86 (31.75)	*F*[3,229]=2.74, *p*=0.04

Data represents means (proportions) for categorical data and means (SD) for continuous data unless otherwise stated

RIS risperidone, *AMI* amisulpride, *NIC* nicotine, *PLA* placebo, NART National Adult Reading Test (Nelson 1982), *SPQ* Schizotypal Personality Questionnaire (Raine 1991)

AS directional error rate

AS error rate showed a significant main effect of Drug (F[3,219]=5.99, p<0.01) as well as a significant Drug by Schizotypy interaction (F[3, 219]=2.77, p=0.04). In the first post-hoc ANOVA model NIC was compared to PLA. There was a main effect of Drug (F[1,111]=5.87, p=0.02) but no Drug by Schizotypy interaction (p=0.18) indicating that NIC is associated with fewer errors than PLA irrespective of schizotypy group (Fig. 3). In the second post-hoc ANOVA model both antipsychotics (RIS and AMS) were compared to PLA. No main effect of Drug (p=0.17) but a Drug by Schizotypy interaction was observed (F[2,163]=4.15, p=0.02). Medium schizotypes displayed higher error rates in the RIS condition compared to PLA (p<0.01). High schizotypes did not show significant differences between antipsychotics and PLA (all p >0.32). In post-hoc pairwise comparisons the two groups differed significantly from each other in their performance on PLA (p=0.03). The groups did not differ in their performance on RIS (p=0.10) or AMI (p=0.33). The results are displayed in Fig. 3. No significant main effect of Schizotypy group was found (p=0.78).

Latency

There was a main effect of Task (F[1, 223]=211.35, p< 0.01) indicating longer latencies for AS than PS (p<0.01). Neither significant effect of Drug or Schizotypy nor their interactions was observed (all p>0.78).

Amplitude gain

A significant effect of Task was observed (F[1,220]=10.38, p<0.01) indicating smaller gain values for AS than PS. Neither significant effect of Drug or Schizotypy nor their interactions were observed (all p>0.21).

Peak velocity

There was a significant main effect of Task (F[1,223]= 117.84, p<0.01) indicating slower peak velocity for AS than PS (p<0.01). A significant main effect of Drug was observed (F[3,223]=15.08, p<0.01). RIS significantly reduced peak velocity compared to PLA and AMI and NIC (all p<0.01) (Fig. 4). No main effect of Schizotypy or Drug by Schizotypy interaction was observed (all p>0.39).

Smooth pursuit–gain

A main effect of Drug was observed (F[2,212]=4.31, p< 0.01) with RIS showing reduced velocity gain compared to NIC (p=0.01). No main effect of Schizotypy or Drug by Schizotypy interaction was observed (all p>0.81).

Table 2 Descriptive statistics for schizotypy by drug group

Schizotypy group									
		Medium				High			
		RIS	AMI	NIC	PLA	RIS	AMI	NIC	PLA
AS	Error rate (%)	54.02 (25.93)	43.25 (24.58)	32.09 (21.17)	36.18 (24.21)	44.46 (24.61)	35.89 (27.06)	31.81 (21.61)	46.10 (25.28)
	Correction rate (%)	96.06 (7.15)	98.18 (3.95)	97.18 (4.95)	97.24 (5.51)	97.88 (3.76)	97.94 (5.14)	98.45 (5.16)	99.01 (1.92)
	Latency (ms)	326.56 (110.92)	307.84 (48.18)	301.67 (64.65)	296.46 (53.77)	302.80 (35.82)	306.93 (59.11)	290.51 (39.23)	314.86 (74.01)
	Velocity gain (%)	101.59 (30.43)	103.03 (22.95)	98.93 (23.55)	101.22 (23.15)	101.28 (27.49)	98.33 (29.37)	101.56 (23.49)	99.02 (24.90)
	Peak velocity (°/s)	243.94 (67.98)	292.95 (69.99)	279.31 (63.05)	302.31 (70.85)	228.59 (62.39)	290.25 (63.68)	295.65 (58.03)	299.53 (62.06)
PS	Error rate (%)	-	1.92[a]	-	4.08[a]	-	-	-	-
	Correction rate (%)	-	100[a]	-	50[a]	-	-	-	-
	Latency (ms)	175.07 (25.27)	177.82 (20.50)	178.60 (21.88)	175.7 (21.65)	177.31 (25.44)	179.44 (23.91)	180.88 (22.21)	176.44 (20.49)
	Velocity gain (%)	94.26 (11.71)	105.24 (7.85)	105.16 (7.67)	103.75 (9.89)	93.96 (9.76)	102.30 (6.91)	103.86 (9.02)	105.92 (8.91)
	Peak velocity (°/s)	282.81 (56.76)	325.87 (48.20)	312.12 (45.97)	333.91 (50.56)	164.82 (50.31)	316.01 (53.15)	326.15 (50.08)	344.75 (57.92)
SPEM	Velocity gain 0.25 Hz (%)	87.81 (9.17)	90.89 (10.36)	92.36 (8.21)	89.90 (10.19)	82.43 (18.72)	90.64 (12.97)	93.27 (6.60)	91.56 (8.68)
	Velocity gain 0.50 Hz (%)	78.22 (15.60)	80.69 (15.24)	83.07 (12.20)	78.86 (15.86)	71.71 (22.51)	81.28 (18.69)	82.87 (15.51)	82.83 (14.35)
	Velocity gain 0.75 Hz (%)	60.23 (16.83)	64.13 (21.38)	67.05 (20.85)	61.12 (23.21)	51.97 (27.99)	64.01 (20.52)	68.79 (22.78)	67.29 (20.13)
	Saccadic frequency 0.25 Hz (N/s)	0.76 (0.36)	0.82 (0.41)	0.81 (0.39)	0.89 (0.39)	0.90 (0.43)	0.82 (0.38)	0.74 (0.32)	0.73 (0.35)
	Saccadic frequency 0.50 Hz (N/s)	1.51 (0.48)	1.46 (0.44)	1.56 (0.36)	1.48 (0.38)	1.53 (0.49)	1.59 (0.34)	1.41 (0.37)	1.55 (0.49)
	Saccadic frequency 0.75 Hz (N/s)	2.16 (0.69)	2.27 (0.63)	2.44 (0.59)	2.17 (0.64)	2.23 (0.74)	2.34 (0.61)	2.09 (0.61)	2.48 (0.66)

Data represents untransformed means (standard deviation) unless otherwise stated

RIS risperidone, *AMI* amisulpride, *NIC* nicotine, *PLA* placebo, *AS* antisaccade task, *PS* prosaccade task, *SPEM* smooth pursuit

[a] Original data of two participants who performed errors on prosaccade task

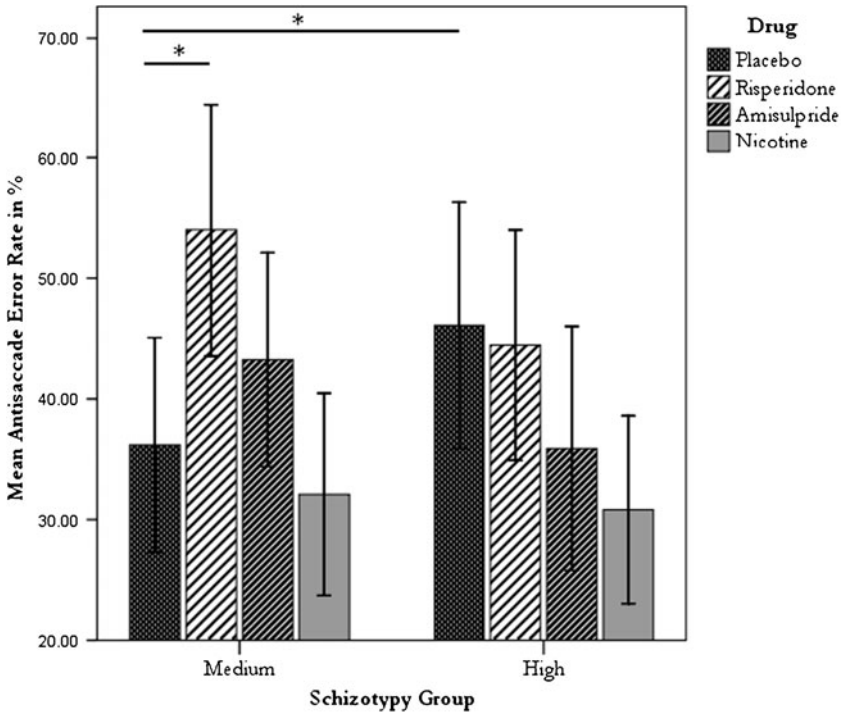

Fig. 3 Drug response by schizotypy group for mean antisaccade error rate. Note: *significant drug effect ($p<0.05$); *error bars* represent 95 % confidence intervals

Smooth pursuit–saccadic frequency

No main effects of Drug or Schizotypy or their interaction were found (all $p>0.10$).

Discussion

This multi-centre study aimed to replicate the observation of oculomotor deficits in a high-schizotypy sample and investigated whether such deficits can be ameliorated by compounds with proven pro-cognitive effects in schizophrenia. High schizotypes had worse antisaccade (but not SPEM) performance than medium schizotypes under placebo. Cognitive enhancing effects of nicotine on antisaccade performance, as they have been reported for schizophrenia patients and healthy volunteers, were observed irrespective of schizotypy group status. However, no effects of nicotine on SPEM were observed. Importantly, differences in response to antipsychotic treatment with risperidone between medium- and

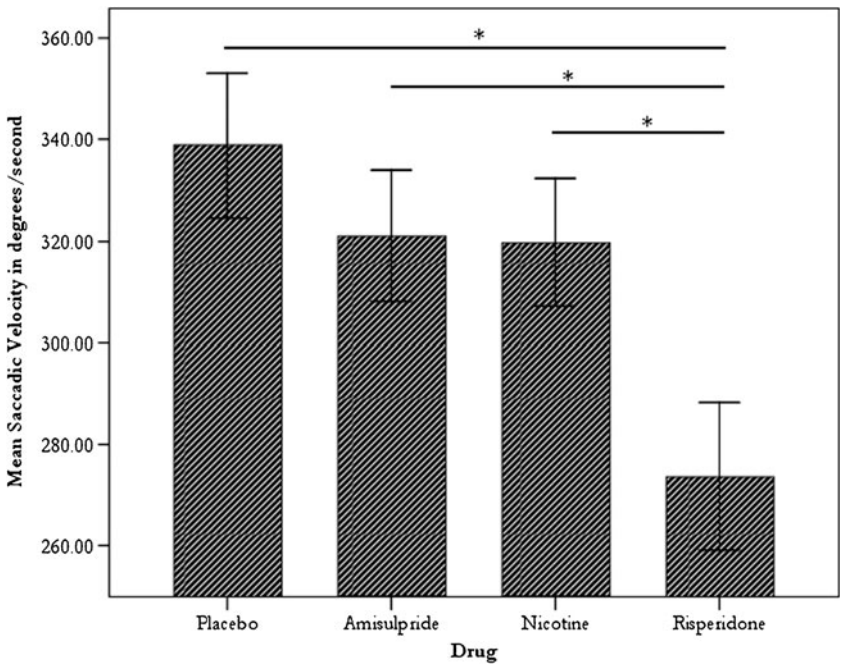

Fig. 4 Mean saccadic velocity by drug group. Note: *significant drug effect ($p<0.01$); *error bars* represent 95 % confidence intervals

high-schizotypy groups were observed for the antisaccade error rate. Risperidone also had a sedative effect in both groups.

Main findings

The first main finding concerns the beneficial effects of nicotine on antisaccade errors irrespective of schizotypy group. We replicated widely reported findings that this cholinergic agonist reduces antisaccade error rates in healthy volunteers (Depatie et al. 2002; Larrison et al. 2004; Rycroft et al. 2006). The fact that this effect is observed in schizophrenia patients and controls (Depatie et al. 2002; Larrison et al. 2004; Rycroft et al. 2006) and, in our study, in people with high and medium levels of schizotypy, suggests that nicotine is a general cognitive enhancer that acts on this task without specificity to schizophrenia spectrum traits. This conclusion is compatible with studies showing cognitive improvements through nicotine in a diversity of patient populations, ranging from younger people with ADHD (Potter and Newhouse 2008) to older people with mild cognitive impairment (Newhouse et al. 2012) and Parkinson's disease (Thiriez et al. 2011). However, unlike previous studies (Depatie et al. 2002), we did not observe any effects of nicotine on SPEM.

The second main finding concerns the effects of schizotypy. As expected (Ettinger et al. 2005; Holahan and O'Driscoll 2005), the high- and medium-schizotypy groups differed significantly in their error rates on placebo with high schizotypes displaying more antisaccade errors. It was also found that medium schizotypes showed significantly higher antisaccade error rates on risperidone compared to placebo. However, contrary to our hypothesis, the antisaccade error rate was *not* lower in high schizotypes under the influence of risperidone compared to placebo. Unexpected was also the failure to find a difference between high and medium schizotypes on SPEM under placebo.

Antisaccade *impairments* under the influence of risperidone in healthy volunteers have previously been reported by Barrett et al. (2004). Our results are compatible with their findings, given that the medium-schizotypy group displayed impaired performance with risperidone. On the other hand, *improvements* in antisaccade performance have been reported in first-episode antipsychotic-naïve schizophrenia patients treated with risperidone and in chronic patients after switching from typical antipsychotics to risperidone (Burke and Reveley 2002; Harris et al. 2006). However, neither of the antipsychotics showed beneficial effects in our high-schizotypy group.

The observed difference in treatment response between high and medium schizotypes could open new opportunities to investigate pharmacological responses in surrogate populations. A candidate for the pharmacological mechanisms underlying these effects is dopamine. In addition to evidence for the involvement of other neurotransmitter systems dopamine plays an essential role in the effects of antipsychotic compounds in the treatment of schizophrenia (Kapur and Seeman 2001). Schizotypy has previously been associated with dopamine functioning (Abi-Dargham et al. 2004; Mohr et al. 2004; Williams et al. 1997; Woodward et al. 2011). Also antisaccade task performance has been reported to be associated with DA administration (Hood et al. 2007). It may be concluded from our findings that the administration of atypical antipsychotic medication with affinity to D2/D3 receptor binding moved medium (but not high) schizotypes beyond their optimal dopamine level, resulting in the observed performance impairment.

Any implications for the high-schizotypy group should be carefully considered. The altered pharmacological response in high schizotypes compared to controls could reflect either (1) a differential tolerance of this group to dopamine antagonists (Carpenter 2011) or (2) compensatory or protective mechanisms in this acute pharmacological challenge (Mohr et al. 2004). To further explore the nature of the observed response differences in association to protective factors, compensatory mechanisms and resilience of such spectrum populations will be an important step forward in future investigations. From our results, it could be concluded that the antisaccade biomarker has some potential to capture the effects of subclinical alterations in dopamine signalling in a psychosis prone population (Williams et al. 1997).

Pharmacology, neural mechanisms, and cognition

The antisaccade task requires inhibitory as well as monitoring processes (Hutton and Ettinger 2006) and has been found to involve fronto-parieto-subcortical networks (for review, see Hutton and Ettinger 2006; McDowell et al. 2008; Sweeney et al. 2007). The dorsolateral prefrontal cortex plays a particularly prominent role in the inhibition of directional errors in this task (Pierrot-Deseilligny et al. 2003). In this study, risperidone impaired antisaccade performance in medium schizotypes while sparing it in high schizotypes. It could be hypothesised that risperidone disrupts a balanced neuronal prefrontal system in medium schizotypes. As no impairments are observed for high schizotypes, it could be assumed that risperidone influences underlying prefrontal cortical areas to an intermediate degree between the observed impairment of medium schizotypes and improvements in schizophrenia patients when performing cognitive tasks (Surguladze et al. 2007).

For nicotine, effects of enhanced neural efficiency in task relevant areas and strengthened deactivations in the default-mode network have been observed (Ettinger et al. 2009; Newhouse et al. 2011).

Concerning smooth pursuit eye movements, most studies of nicotine effects on pursuit performance in patients and controls show improvement (Depatie et al. 2002; Olincy et al. 1998, 2003; Sherr et al. 2002), although there is also evidence of deterioration (Sibony et al. 1988; Thaker et al. 1991). Here, we were not able to report any effects of nicotine on smooth pursuit, a measure of attention, prediction, anticipation and motion processing, in line with reports of Avila et al. (2003) who did not find any nicotine effects among healthy non-smokers. Nicotine is a cholinergic agonist that is known to improve cognition (Kumari and Postma 2005) and it has been found to play a role in the release of dopamine in all major dopaminergic systems in the brain including mesolimbic, mesocortical and nigrostriatal pathways (Janhunen and Ahtee 2007). Dopamine release in the stratum, for example, could play a role; however, the exact neuropharmacological mechanisms responsible for our findings remain to be investigated further.

We also observed effects of risperidone suggestive of sedation. Risperidone reduced peak saccade velocity, an objective and widely used, brainstem mediated measure of sedation (de Visser et al. 2001), and impaired the ability to match eye velocity to target velocity during smooth pursuit eye movements. Other studies have also observed sedative effects of risperidone on eye movements in healthy volunteers (Barrett et al. 2004) and first-episode schizophrenia patients (Lencer et al. 2008; Sweeney et al. 1997). Interestingly, these sedative effects were not observed for amisulpride. This finding may be of importance for future studies investigating the effects of both antipsychotics on cognition.

Consistent with findings of Barrett et al. (2004), no significant influences of amisulpride on any eye movement measures were observed in this study. Neither sedative effects nor any influence on cognitive processes that are captured by oculomotor tasks such as attention, inhibition or motion processing could be observed. In a previous study a single dose 400 mg of amisulpride was not found to influence cognitive measures (Ramaekers et al. 1999). However, when given repeatedly amisulpride induced significant impairments in several cognitive tests (Ramaekers et al. 1999). Considering the pharmacokinetic profile and the poor blood–brain barrier penetration (see Natesan et al. 2008), it could be assumed that when frequently given in higher doses, amisulpride displays sedative effects in healthy volunteers and psychometric schizotypy (Rosenzweig et al. 2002).

Oculomotor biomarkers and schizotypy as a model system in drug development

Over the past few decades, schizotypy research has provided significant contributions to the understanding of the schizophrenia pathophysiology (Claridge 1997; Eysenck and Eysenck 1976; Meehl 1989; Rado 1953). Associations of psychometric schizotypy with brain structure (Ettinger et al. 2011), function (Aichert et al. 2012; Mohanty et al. 2005) and cognition (Barkus et al. 2010; Beech et al. 1989; Ettinger et al. 2005; Gooding et al. 2006; Migo et al. 2006; Völter et al. 2012) qualitatively similar to the deficits seen in schizophrenia, have been reported. There is also important evidence of associations between pharmacological influences on cognition and schizotypy (Evans et al. 2005; Mohr et al. 2004, 2005; Williams et al. 1997). Here, we were able to show that psychometric schizotypy represents a predictor of response to risperidone. This finding provides further evidence of a putatively shared neurobiology with schizophrenia when considering the aforementioned tolerance to D2 antagonists (Carpenter 2011). However, the high-schizotypy group fell short of providing a model system in which oculomotor biomarker performance improved with antipsychotics. Schizotypy has in the past been examined as an experimental model to contribute to the understanding of pharmacological mechanisms within the schizophrenia spectrum (Williams et al. 1997). Together with the present results, we conclude that there is some evidence that the schizotypy model represents an interesting approach for explaining inter-individual variance in antipsychotic response. Caution, however, needs to be exerted in studies aimed at antipsychotic drug development and the validation of established antipsychotic compounds, given the failure of our high-schizotypy group to improve with either antipsychotic. Additionally, antisaccade performance was found to improve with nicotine equally in both groups. Within this context, there are, of course, several advantages of studying schizotypy as a schizophrenia spectrum population. Schizotypal personality is a reliably measured trait and recruitment of schizotypes provides a cost- and time-effective alternative to patient studies. There are also advantages of using oculomotor biomarkers. First, biomarkers in general offer the opportunity to break down the heterogeneous and highly complex disorder of schizophrenia into simpler objectively measurable markers of neurophysiological abnormalities to investigate the efficacy of antipsychotic treatments on cognition and brain function (Migo et al. 2011). Second, oculomotor measures in particular have been found to be temporally stable and sensitive biomarkers for the investigation of specific compounds (Reilly et al. 2008; Thaker 2007). Third, eye movements have well studied neural correlates (McDowell et al. 2008) allowing for follow-up studies of antipsychotic influences on specific brain regions within the schizophrenia spectrum in pharmacological magnetic resonance imaging studies. Finally, the consistencies between our results and previous studies investigating pharmacological influences of atypical antipsychotics in healthy volunteers, risk populations or patients support the validity of eye movement measures as biomarkers to enhance the understanding in schizophrenia drug discovery and compound development.

Limitations and outlook

Certain limitations of our study have to be taken into consideration. First, based on the acute single dose administration design, our findings may not necessarily generalize to long-term treatment effects. Second, due to the strict exclusion criteria of the study, it could be argued that a particularly high functioning group of high schizotypes was included in our sample, thus not necessarily representing the full spectrum of the trait. Third, the study focused on the investigation of total SPQ scores to capture the overall schizotypy construct rather than exploring subscale scores of positive or negative symptom dimensions. It would have been instructive to investigate nicotine and antipsychotic effects in separate groups of positive and negative schizotypes, given that these facets of schizotypy show differential profiles of cognitive impairment (Holahan and O'Driscoll 2005; Suhr and Spitznagel 2001). However, to put this criticism in perspective it should be mentioned that a high score on the SPQ has been reported to be representative of high scores across all dimensions (Barkus et al. 2010). Finally, the inclusion of a low-schizotypy group would have further enriched our study. The current approach has been found to be sensitive to detect oculomotor performance differences in this and previous studies (Gooding 1999; O'Driscoll et al. 1998). However, the inclusion of a low-schizotypy group would have further improved our understanding about modulatory effects of drug administration on eye movement control in a wider spectrum of psychometric schizotypy.

Conclusion

In this study, we replicated observations of antisaccade impairments in high schizotypy under placebo and showed that both high and medium schizotypes improve with nicotine. The differences in response to risperidone between the two groups for antisaccade performance could reflect subclinical alterations in dopamine signalling, providing further evidence of a putatively shared neurobiology between schizotypy and schizophrenia. The experimental schizotypy model may thus represent an interesting approach for exploring inter-individual variance in antipsychotic response. On the basis of this study we argue, however, that caution needs to be exerted in studies aimed at antipsychotic drug development and the validation of established antipsychotic compounds, given that oculomotor biomarker performance in the high-schizotypy sample in this study did not show selective improvements with antipsychotics. This could, of course, imply a limitation either of the schizotypy model or the particular tasks employed in this study or both.

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The experiments carried out in this study comply with the current laws of the country in which they were performed

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