# Effects of Risperidone, Amisulpride and Nicotine on Eye Movement Control and their Modulation by Schizotypy

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## Introduction

- The personality trait of schizotypy is a multidimensional continuous construct which has been hypothesized to reflect a subclinical level of schizophrenia and thus adds valuable insight into the aetiology, treatment and prevention of the disease[1].
- Similarities between schizotypy and schizophrenia have been identified on neuro-cognitive and neuronal levels. An overlap in treatment response characteristics has also been reported[2-4].
- Over the past years there has been increasing recognition of the lack of efficacy in the drug development for schizophrenia.
- Schizotypy offers a new perspective as a potential model system of drug development for schizophrenia.
- Eye movement measures have been proposed to be sensitive and specific translational neurophysiological indices of pharmacological effects and thus pose reliable biomarkers[5]. Eye movement deficits have also been proposed to mark the vulnerability to schizophrenia reporting impairments in patients, their relatives and related spectrum populations[6-7].
- Here we combine the model of psychometric schizotypy with the biomarker approach to enhance our understanding of drug response characteristics in the schizophrenia spectrum.

## Aims & Objectives

- To examine the effects of antipsychotics and nicotine on oculomotor performance and to investigate whether individuals with subclinical levels of schizophrenia-like symptoms (high schizotypy) show a differential profile of drug response to controls.

## Materials & Methods

- 240 healthy volunteers were recruited as part of a multicentre study (Manchester, Cardiff, London)

### Recruitment:

- Participants were asked to fill in an online version of Schizotypal Personality Questionnaire (SPQ), suitable participants repeated the SPQ under lab conditions and were divided into medium (between 21-36 -control group: MS) or high (≥40) scorers (HS).

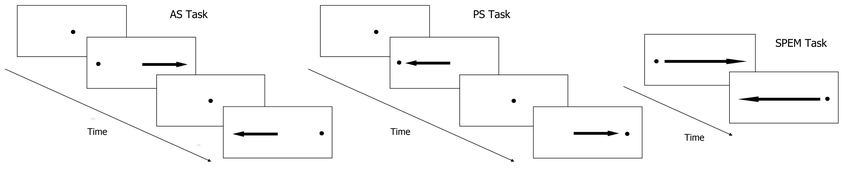
- Demographic data was collected and matched between the schizotypy groups (see Table 1).
- Standard screening methods and exclusion criteria for pharmacological studies were applied on screening and randomization day.

### Study design:

- Double-blind, randomised, placebo controlled, parallel study design with 4 study arms:
  - Placebo (PLA)
  - Risperidone- 2mg (RIS)
  - Amisulpride- 400mg (AMI)
  - Nicotine- 7mg (NIC)
- Focal imaging technology (Eyelink 1000 - SR Research Ltd., Toronto-Ottawa, Canada) with sampling rate of 1000Hz frequency was used to record eye tracking

### Tasks:

- Four possible peripheral positions of a black dot on white background (±7.25°,±14.5°) for the random duration of 1000-2000ms, 60 trials in total




### Dependent variables:

- Antisaccade (AS)/ Prosaccades (PS): directional error rate, latency, amplitude gain, peak velocity
- Smooth Pursuits task (SPEM): sinusoidal target velocities: 12°/s, 24°/s, 36°/s, 20 half-cycles: SPEM velocity gain, SPEM saccadic frequency

## Analyses

- AS/PS: Eye Link Data Viewer (SR Research Ltd., Mississauga, Ontario, Canada)
- SPEM: LabView (National Instruments Corporation)
- Statistical analysis was carried out using univariate/repeated measure ANOVA models in SPSS 15.0 (SPSS Inc., Chicago, IL, USA)
  - Within-subject factor: Saccade Task (AS, PS) or SPEM Task(3 velocities: 12°/s, 24°/s, 36°/s)
  - Between-subject factors: Site, Drug, Schizotypy Group, Gender
  - Covariates: Age, IQ, Time since dosing (included if significant)
- Post-hoc comparisons were performed using Bonferroni corrections

## Results

**Table 1: Descriptive statistics for demographic variables**

| | Schizotypy level | | Statistical Test |
|---|---|---|---|
| | Medium | High | |
| Age in Years | 23.56 (5.71) | 23.9 (5.31) | F [1,229]=0.21, p=0.64 |
| [range] | [18-42] | [18-44] | |
| IQ (NART score) | 113.38 (4.99) | 113.58 (5.17) | F[1,231]=0.08, p=0.77 |
| N male (%) | 59 (25) | 57 (24) | $X^2$=0.04, df=1, p=0.90 |
| N right-handed | 104 | 105 | $X^2$=2.8, df=1, p=0.25 |
| **Ethnicity (%)** | | | |
| Caucasian | 104 (45) | 89 (38) | $X^2$=6.24, df=1, p=0.10 |
| Asian | 10 (4) | 19 (8) | |
| Black | 2 (1) | 5 (2) | |
| Other | 1 (0.5) | 3 (1) | |
| *Note: Data represent means (SDs) by schizotypy group unless otherwise stated* | | | |

**Figure 1:**

This shows Antisaccade Error Rate by Schizotypy Group. Bars represent Means, whiskers represent 95% Confidence Interval for Mean.

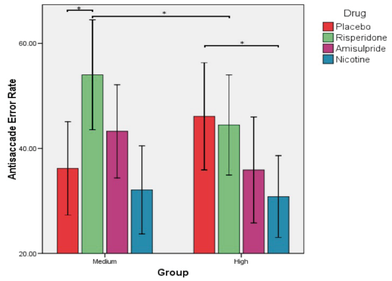
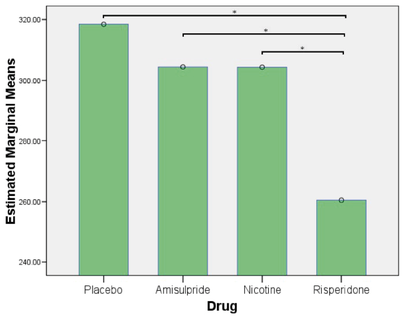



**Figure 2:**

This shows Estimated Marginal Means of Saccadic Peak Velocity by Drug Group irrespective of Schizotypy Level.




- For the antisaccade error rate a significant main effect of drug (F(3,179)=5.86, p<0.01) as well as a drug by group interaction (F(3,179)=2.97, p=0.03) was found indicating a trend that HS' performance was worse than MS on PLA but improved with both antipsychotics. Both groups profited from NIC (p=0.04). HS significantly improved in performance on NIC compared to PLA (p=0.02). In the MS group RIS significantly worsened performance compared to PLA (p=0.03). The MS group performed significantly worse on RIS compared to the HS group (p=0.04). See Figure1 for details.
- A main effect of task(F(1,183)=97.69, p<0.01) and drug(F(3,183)=12.06, p<0.01) was found for peak velocity with RIS impairing performance compared to PLA, AMS and NIC irrespective of schizotypy group (all p<0.01). See Figure2 for details.
- SPEM gain showed a main effect of task (F(2,350)=13.36, p<0.01) as well as a trend for a drug effect (F(3,175)=2.38, p=0.07) with RIS displaying the tendency to impair the ability to match eye velocity to target velocity compared to NIC (p=0.05).
- No main effect of schizotypy group was observed in this study. A main effect of site was found for AS error rate (F(2,179)=7.52, p<0.01) indicating lower error rates in Cardiff compared to Manchester and London. Also a significant effect of gender (F(1,175)=4.31, p=0.04) was found for SPEM gain with males performing significantly better than females.

## Discussion

- We were able to replicate previous findings of the cognitive enhancing effects of NIC on antisaccade performance[8].
- RIS caused a slowing of peak saccade velocity and an impairment in the ability to match eye velocity to target velocity during SPEM was found reflecting its sedative properties[9]
- For the key biomarker of antisaccade error rate there was a trend towards the expected modulation of drug effects by schizotypy status: RIS and AMI tended to disrupt saccade inhibition in AS but improve it in HS. The HS improved more on NIC indicating a higher sensitivity to the influence of cholinergic pharmaceuticals potentially remediating associated cognitive deficits in an imbalanced cholinergic system.

### Strengths:

- The schizotypy model has been found to be suitable for drug investigations. There are no overt symptoms and illness- or treatment-related confounds in this schizophrenia spectrum population allowing for confounder free interpretation of the results.
- Eye movement measures show a high sensitivity to pharmacological interventions. They can be measured objectively and they are easy to apply.

### Limitations:

- The single acute dose administration might not represent long term treatment responses.
- The inclusion of a low scoring schizotypy group may strengthen the effects of interest in future samples.
- The main effects of site and gender need to be taken into careful consideration when interpreting the results.

## Conclusion

**The findings of this study represent promising trends for future research investigating pharmacological influences on high risk and schizophrenia spectrum populations.**

## Acknowledgements

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