A validation of cognitive biomarkers for proof-of-concept studies in surrogate populations: a three-centre double-blind placebo-controlled study in schizotypy

Ivan Koychev[1], Katrina McMullen[2], Jane Lees[1], Rukiya Dadhiwala[3], Lois Grayson[2,4], Charlotte Perry[4], Anne Schmechtig[2], James Walters[5], Kevin J. Craig[6], Gerard R. Dawson[6], Colin T. Dourish[6], Ulrich Ettinger[7], Lawrence Wilkinson[4,8], Steven Williams[2] , John Francis William Deakin[1] and Emma Barkus[9,10]

[1] Neuroscience and Psychiatry Unit, School of Community Based Medicine, The University of Manchester, Manchester, M13 9PT, UK

[2] Department of Neuroimaging, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK

[3] Sir Colin Campbell Building, Institute of Mental Health, Section of Forensic Mental Health, University of Nottingham Innovation Park, Triumph Road, Nottingham, NG7 2TU, UK

[4] School of Psychology, Neuroscience and Mental Health Research Institute, Cardiff University, Tower Building. Park Place, Cardiff, CF10 3AT, UK

[5] MRC Centre for Neuropsychiatric Genetics and Genomics, Neuroscience and Mental Health Research Institute, School of Psychology, Tower Building, Park Place, Cardiff University, Cardiff, CF10 3AT, UK

[6] P1vital, Department of Psychiatry, University of Oxford, Wameford Hospital, Oxford, OX3 7JX, UK

[7] Departments of Psychiatry and Psychology, Ludwig-Maximilians-University, Munich, 80336, Germany

[8] School of Medicine, Department of Psychological Medicine and Neurology, Neuroscience and Mental Health Research Institute, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Henry Wellcome Building, Heath Park, Cardiff, CF14 4XN, UK

[9] Department of Psychology, University of Wollongong, Wollongong, New South Wales, NSW 2522, Australia

[10] Department of Psychiatry, School of Community-Based Medicine, The University of Manchester, Manchester, M13 9PT, UK

Introduction

- Cognitive deficits are unaffected by currently available antipsychotics[1]
- The majority of novel drugs fail in Phase 2
- Need for proof-of-concept Phase 1 studies testing a molecule's chance for success[2]
- Schizotypy - a surrogate population of schizophrenia for the assessment of potential cognitive enhancers?

Question

Are cognitive biomarkers sensitive to the schizoypy phenotype and the effect of risperidone, amisulpride or nicotine?

Methods

Recruitment

- Three centres: Manchester, London and Cardiff
- Screening appointment: age 18-45; no history of mental health or major medical disorders; no substance dependence; less than 5 cigarettes per day;
- Randomisation appointment: 244 healthy volunteers scoring high (>41, HS) and average (21-36, AS) on the Schizotypal Personality Questionnaire (SPQ)[3]

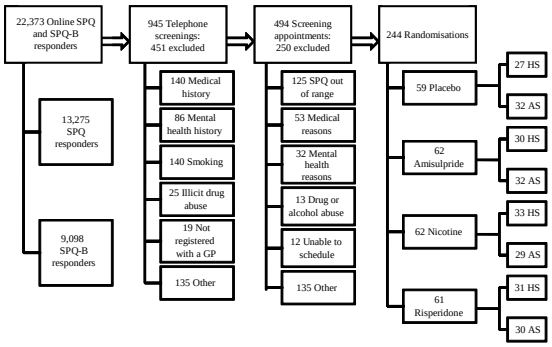
Procedures at randomisation

- HS and AS randomized separately to either
  i) Nicotine patch 7 mg and placebo capsule
  ii) Placebo patch and 2 mg risperidone capsule
  iii) Placebo patch and 400 mg amisulpride capsule
  iv) Placebo patch and placebo capsule
- Patch administered 4.5 hours before testing
- Capsule given 1.5 hours before testing
- During testing participants completed two working memory (N-back and Spatial Working memory) and one verbal fluency task as part of a larger battery

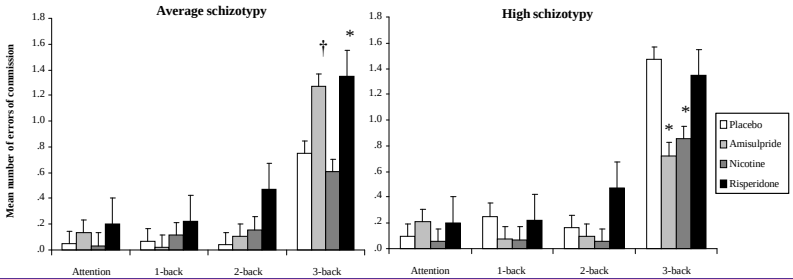
Statistical analysis

- ANOVA with factors of group, drug, sex and site
- Between-subject factor of difficulty
- Covariates: age, IQ, years of education, minutes since capsule

Recruitment breakdown



N-back working memory task: errors of commsion



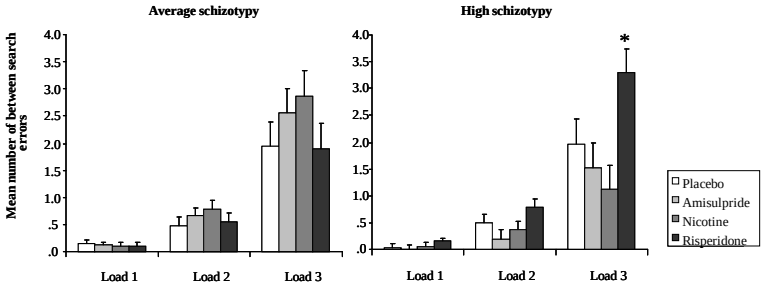
Main effects

- Task difficulty (p <.001)
- Schizotypy (p=.013) due to AS > HS
- Drug (p <.01) due to risperidone group worse than placebo

Schizotypy X Drug

- Interaction (p =.019)
- HS: improvement with amisulpride and nicotine vs. placebo
- AS: impairment under amisulpride and risperidone vs. placebo

Spatial Working Memory task: between search errors



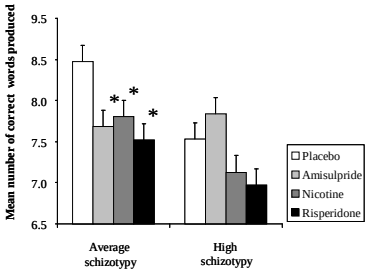
Main effects

- Task difficulty (p = .01)
- No overall main effect of schizotypy
- No main effect of schizotypy in placebo-treated participants
- No main effect of drug

Schizotypy X Drug

- Interaction (p <.01)
- HS: risperidone worsened performance vs. placebo
- AS: no difference between the treatment arms

Verbal fluency task: number of words



Main effects and interaction

- Trend for significance for schizotypy (p=.07) due to AS>HS
- Main effect of schizotypy in placebo group (AS >HS)
- Trend for significance for drug (p=.07) due to risperidone decreasing performance
- Trend for interaction (p=.06) due to all drugs worsened AS but not HS

Conclusions

1.Sensitivity to the schizotypy phenotype: N-back and VF tasks

➢ Early information processing deficits in schizotypy[4] could explain the effect on N-back but not SWM (encoding of 1 second vs. no time limit respecively)

2. Sensitivity to psychotropic action

➢ Reversal of the schizotypy effect with through amisulpride dopamine enhancement[5]: evidence for hypofrontality?

➢ Acute risperidone worsens cognitive performance

➢Nicotine: overall tendency to improve HS and impair AS (N-back and SWM)

3. No site effects

Proof-of-concept studies in schizotypy using cognitive biomarkers can guide drug development in Phase 1

Acknowledgments

This study was supported by the P1vital CNS Experimental Medicine Consortium (members AstraZeneca, GlaxoSmithKline, Lundbeck, Organon (a subsidiary of Merck) and Pfizer). Ivan Koychev has been awarded a Manchester Strategic PhD Studentship, sponsored by the University of Manchester and P1vital Ltd. The Manchester and Cardiff sites received facility and staff support by the Manchester and Cardiff Wellcome Trust Clinical Research Facilities respectively.

References

[1] Heinrichs, R. W. (2005). "The primacy of cognition in schizophrenia." Am Psychol 60(3): 229-42.
[2] Hurko, O. (2010). "Future drug discovery and development." Mol Genet Metab 100 Suppl 1: S92-6.
[3] Raine, A. (1991). "The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria." Schizophr Bull 17(4): 555-64.
[4] Koychev, I., W. El-Deredy, et al. (2010). "Visual information processing deficits as biomarkers of vulnerability to schizophrenia: an event-related potential study in schizotypy." Neuropsychologia 48(7): 2205-14.
[5] Schoemaker, H., Y. Claustre, et al. (1997). "Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity." J Pharmacol Exp Ther 280(1): 83-97.