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

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Introduction

• Cognitive deficits are unaffected by currently available antipsychotics.
• The majority of novel drugs fail in Phase 2
• Need for proof-of-concept Phase 1 studies testing a molecule’s chance for success.

Schizotypy - a surrogate population of schizophrenia for the assessment of potential cognitive enhancers?

Question

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

Methods

• 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 10 cigarettes per day.
• Randomisation appointment: 244 healthy volunteers scoring high (≥45) HS and average (25-36) AS on the Schizotypal Personality Questionnaire (SPQ).

Procedures at randomisation

• HS and AS randomised separately to either
  - Nicotine patch 7 mg and placebo capsule
  - Placibo patch and 2 mg risperidone capsule
  - Placebo patch and 600 mg amantadine capsule
  - 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

• ANCOVA with factors of group, drug, sex and site.
• Between-subject factor of difficulty:
  - Covariates: age, IQ, years of education, minutes into session.

N-back working memory task: errors of omission

Spatial Working Memory task: between search errors

Verbal fluency task: number of words

Main effects

• Task difficulty (p < 0.001)
• Schizotypy (p=0.013) due to AS >> HS
• Drug (p=0.01) due to risperidone group worse than placebo

Schizotypy X Drug

• Interaction (p=0.019)
• HS: improvement with amisulpride and nicotine vs. placebo
• AS: impairment under amisulpride and risperidone vs. placebo

Conclusions

1. Sensitivity to the schizotypy phenotype: N-back and VF tasks
   - Early information processing deficits in schizotypy could explain the effect on N-back but not SWM (encoding of 1 second vs. no time limit respectively)
2. Sensitivity to psychotropic action
   - Reversal of the schizotypy effect with through amisulpride dopamine enhancement: 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

References


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