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A validation of cognitive biomarkers for the early identification of cognitive enhancing agents in schizotypy: A three-center double-blind placebo-controlled study

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Abstract

A number of compounds aimed at improving cognition in schizophrenia have failed to demonstrate efficacy in Phase 2 clinical trials. Translational studies using biomarkers in surrogate populations, such as schizotypy, could be used to assess the efficacy of novel compounds. In this study, we aimed to validate the sensitivity and inter-site reliability of cognitive biomarkers (working memory (N-back), spatial working memory (SWM) and verbal fluency (VF) tasks) to detect the schizotypy phenotype and its reversal by psychotropic drugs. Healthy volunteers scoring high or average on a schizotypal personality measure (122 in each group) were randomized to receive a single dose of risperidone, amisulpride, nicotine or placebo in a double-blind, between-subject design. We found evidence for a poorer performance on N-back and VF tasks in the high schizotypy group, replicating previous research. This effect was counteracted by amisulpride on N-back: it improved working memory in high schizotypy group but impaired the controls. A similar pattern was seen in SWM and VF. We interpret this finding in the light of the dopamine enhancing action of amisulpride when given in low doses. In contrast, risperidone impaired both groups and nicotine had a beneficial effect for the low baseline performers only. These effects were consistent across sites. These data demonstrates the utility of biomarkers in detecting the effect of schizotypy and its reversal by drugs that enhance dopamine and cholinergic function. Studies using similar design could help the early assessment of potential of compounds designed to improve cognition in schizophrenia.

1. Introduction

Cognitive deficits in schizophrenia are evident in nearly all individuals diagnosed with schizophrenia and the most common cognitive impairments are those of attention, memory and executive functions. Average cognitive impairments for patients with schizophrenia in these cognitive domains often reach two standard deviations below that of healthy matched volunteers (Saykin et al., 1991; Heinrichs and Zakzanis, 1998). These deficits are a core feature of schizophrenia (Green, 2006) that predict functional outcome (Green et al., 2000; Hofer et al., 2005; Milev et al., 2005) and treatment adherence (Burton, 2005). These deficits are present before the onset of the disorder (Erlenmeyer-Kimling et al., 2000) and are relatively stable over time (Albus et al., 2002). Currently available therapies offer at best marginal improvement (Heinrichs, 2005) and development of novel agents specifically to ameliorate cognitive deficits in schizophrenia is a recognized unmet need (Nuechterlein et al., 2008).

In the last two decades technological advances, notably genome sequencing, combinatorial chemistry and high-throughput screening, led to rapid expansion of potential drug targets for cognition. As a result, a number of theoretically sound compounds have emerged from the animal models as safe and effective (Gray and Roth, 2007). However, the clinical success rate has been dwindling, as most novel compounds fail at the initial tests of efficacy in human disease, phase 2 clinical trials (Hurko, 2010). This trend has exposed drawbacks of animal models of mental illness: despite capturing certain aspects of the condition, they do not predict efficacy. In addition, the noisiness of the traditional clinical end-points in psychiatry is likely to have contributed to the rejection of otherwise promising compounds.

The use of biomarkers and surrogate end points to detect efficacy early in development has been proposed as a way of reducing the risk of failure in clinical development (Hurko, 2009). The aim is to give a compound every chance to succeed, for example by selecting only a subgroup of patients that is more likely to respond or by recruiting groups of individuals that have only limited symptom profile but lack the confounds associated with patient research (surrogate populations). These "proof-of-concept" studies precede the costly Phase 2 clinical trials which use more rigid diagnostic criteria, heterogeneous populations and traditional clinical end-points. Their principal goal is to single out the compounds that are unlikely to be effective in humans and thus inform decision making.

In the case of schizophrenia, such early assessment of drug efficacy could be accomplished using cognitive biomarkers in surrogate populations such as high schizotypes. These individuals have personality traits corresponding to the different schizophrenia psychopathology and also exhibit a profile of attenuated cognitive deficits (Raine, 2006). This overlapping symptom profile, as well as evidence highlighting the common genetic and neurobiological basis of schizophrenia and schizotypy (Siever et al., 2002) support theories that see the two conditions as the two extreme ends of a spectrum of disorders (Meehl, 1989; Tsuang et al., 2002; Lenzenweger, 2006). Despite these similarities, schizotypal individuals have by and large been spared psychotic episodes, repeated hospitalizations and chronic antipsychotic treatment (Raine et al., 1995). Importantly for cognition research, IQ levels and education levels are largely normal (Raine, 2006) and their cooperation with the study procedures is not hampered by profound psychotic and negative symptoms. In contrast, a large proportion of the schizophrenia patients have decreased IQ levels which predict negative symptoms and cognitive impairment (Leeson et al., 2009) thus possibly confounding the core cognitive deficit.

The development of validated cognitive biomarkers for the use in clinical trials in schizophrenia has been at the forefront of several high profile joint initiatives between

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industry and academia. The most prominent project is MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia (Nuechterlein et al., 2008; Keefe et al., 2010)) which aimed to identify and validate a neuropsychological battery that can be used to objectively measure the effect of cognitive enhancers in schizophrenia. The process yielded seven separate cognitive domains that represented fundamental dimensions of the cognitive impairment in schizophrenia (Nuechterlein et al., 2004) and performance on the derived neuropsychological battery has been piloted in clinical trials as standardised measure of cognitive enhancement (Harvey et al., 2011). These cognitive domains and the corresponding neuropsychochological tests are therefore particularly well suited to enhance translation between schizotypy and schizophrenia samples.

In this experiment, we aimed to validate the use of cognitive biomarkers for the detection of cognition enhancing drug action in schizotypy samples. We used an online schizotypy questionnaire (Schizotypal Personality Questionnaire, (Raine, 1991)) to screen a large number of healthy volunteers and identify volunteers with elevated schizotypal traits. Our choice of recruitment method was based on; i) data demonstrating that the SPQ identifies reliably a sample with a high prevalence of schizotypal personality disorder (Raine, 1991; Kremen et al., 1998); ii) extensive literature on cognitive abnormalities in among individuals with elevated schizotypal personality traits (Park and McTigue, 1997; Mitropoulou et al., 2002; Matheson and Langdon, 2008).

Three centers in the UK administered three cognitive tasks (two probing working memory and one testing speed of processing) to volunteers with extremely high and average SPQ scores and challenged their performance with three psychopharmacological agents in a double-blind randomized design. Working memory and speed of processing are two of the seven separable cognitive domains identified by the MATRICS consensus meeting as providing reliably separation between patients with schizophrenia and controls (Kern et al., 2011). Additionally, schizotypal individuals have been shown to be consistently impaired in these domains (Siever et al., 2002).

There have been several reports of trials aimed at improving cognition in schizotypy. Most notably, one study found that 30 mg of oral amphetamine improved working memory performance in SPD but not in non-schizophrenia related personality disorders (Kirrane et al., 2000). Additionally, a longitudinal trial by McClure et al. (2010) using a combined D1/D2 receptor agonist (pergolide) reported improvement of cognition. In both cases the individuals with the greatest baseline impairment benefited the most. These effects were attributed to the stimulation of prefrontal D1 receptors which have been shown to regulate working memory (Williams and Goldman-Rakic, 1995). The agents used in the present study were amisulpride (D2/D3 receptor antagonist that has dose-dependent differential effects on dopamine neurotransmission — inhibition in high doses and enhancement in low doses), risperidone (full dopamine D2 antagonist, inhibitor of dopamine neurotransmission), as well as a patch of nicotine (cholinergic agonist). Amisulpride and risperidone were chosen on the basis of reports of modest cognitive enhancement in schizophrenia patients when treated with atypical antipsychotics (Purdon et al., 2000). To minimize side-effects in healthy volunteers amisulpride and risperidone were given in doses at the lower end of clinical effectiveness (2 mg and 400 mg respectively). Nicotine was included as a putative cognition enhancer and the mode of administration (transdermal patch) and the dose (7 mg) were selected on the basis of published results (White and Levin, 2004) and on the advice of Dr. Gersham Dent (AstraZeneca) who had recently concluded a trial investigating the effects of nicotine on cognition in healthy volunteers.

We laid out the following criteria for successful validation:

1. The biomarkers detect cognitive deficits in the schizotypy group.
2. The effect of schizotypy is reversed by antipsychotic and/or nicotine administration.
3. The observed effects are reliable across several sites.

2. Experimental procedures

2.1. Subjects and study criteria

Subjects were recruited from three sites in the United Kingdom: Manchester, London and Cardiff via an online questionnaire measuring schizotypy (Schizotypal Personality Questionnaire in its short (SPQ-B, (Raine et al., 1995)) and full version (SPQ, Raine, 1991)). Participants were screened via telephone interview to exclude relevant mental health and medical conditions. The volunteers that passed the telephone screening were invited for a screening appointment. At the screening, participants provided written consent and completed the full version of the SPQ again. Respondents with scores >1 standard deviations above the mean were classified as high schizotypes (HS) and invited to participate in the study (that is scores >41). Respondents with scores falling within ±0.5 standard deviations of the mean were classified as average schizotypes (AS) and could be invited to participate in the study (that is scores from 21 to 36 inclusive). This was based on a previously collected sample of approximately 790 participants where we found that these cut off led to separation between the groups. These data have been published elsewhere (Barkus and Lewis, 2008). Male and female participants, aged 18–45 years, fluent English speakers, and physically healthy (BMI, blood pressure, ECG, blood biochemistry and ECG all within normal range) were included in the sample. The lack of relevant medical history was confirmed by letter from GP. The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to screen for psychiatric disorders. All MINI raters attended a training event prior to the initiation of the study to ensure reliability of the screening procedures. On the screening and day of testing participants had to provide a clear screen for alcohol (alcohol breath test), illicit drug use (urine dipstick) and pregnancy (urine dipstick). Other exclusion criteria were: known or suspected intolerance or allergy to the study drugs, smoking more than 5 cigarettes per day, consumption of more than 8 standard caffeinated drinks per day, history of migraines, significant visual or hearing impairment, participation in any other drug trial in the 84 days before the randomization visit, prescribed medication 14 days prior to or over the counter medicine 48 h before the randomization. Additionally participants were asked not to consume caffeinated drinks on the randomization day.

13,275 people completed the full version of the online SPQ and a further 9098 filled out the short version, SPQ-B (SPQ mean: 22.2, SD: 13.8; SPQB mean: 8.6, SD: 4.8). 949 high and average scoring individuals underwent telephone screening and 451 were excluded at this stage. Of the 498 people that attended a screening appointment, 250 were excluded. Half of those exclusions were due to participants failing to replicate an acceptable score on the SPQ questionnaire (21–36 or >41) which they completed at the onset

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of the screening appointment. Data on the reasons for exclusions at each stage are presented in Fig. 1. The randomised sample consisted of 248 participants.

2.2. Randomisation day procedures

High and average schizotypy individuals were separately randomized to one of four treatment arms: nicotine (7 mg nicotine patch and placebo capsule), amisulpride (placebo patch and 400 mg amisulpride capsule), risperidone (placebo patch and 2 mg risperidone capsule) or placebo arm (placebo patch and placebo capsule). The patch (nicotine or placebo) was applied first and the capsule (amisulpride, risperidone or placebo) was administered 3 h later. The treatments were randomized by an independent pharmacy and both the research and the medical staff were blind to drug status.

A set of neuropsychological tests was completed 4.5 h after the application of the patch and 1.5 h after administration of the drug capsule. The timing was chosen to allow the drugs to reach peak plasma concentrations by the time of the cognitive testing. This paper presents the results of tests in the MATRICS domains of working memory (N-back), verbal fluency (VF) and spatial working memory (SWM). The order of the tasks was randomized for each participant. Vital signs were assessed regularly to check for adverse reactions to the treatments.

248 participants attended the randomization visits at the three sites (99 in Manchester, 83 in London and 66 in Cardiff). 4 participants (3 HS in Cardiff and 1 HS in Manchester) did not complete the randomisation due to non-serious and short-lasting side effects (nausea, headache) that prevented them from completing the neuropsychological battery. The number of successfully randomised participants was 244. In total, 72 adverse events were reported by 58 of the 244 participants randomised into the study. The most common adverse events were drowsiness/tiredness (14), headache (13), nausea (11), flu-like symptoms (10) and dizziness (8). The least common adverse events reported include feeling faint/fainting (1), tachycardia (1), irritation to nicotine patch (1) and erthyma nodosum (1).

There was no main effect of site on the SPQ scores of the successfully randomised high and average schizotypy groups. The successfully randomised high and average schizotypy groups consisted of 122 participants each. 59 were randomized on placebo, 62 on amisulpride, 62 on nicotine and 61 on risperidone (Fig. 1). All participants were followed-up in 3 to 5 days after the randomization visit to inquire about side effects. No serious adverse effects were reported. The demographic data for the randomised participants is presented in Table 1.

2.3. Task description

2.3.1. Working memory (N-back) task

A series of alphabet letters were presented one at a time on a color monitor. Participants were instructed not to respond until they saw the same letter twice following one another. The task had three levels of difficulty according to the number of letters in between the two matching letters. In the 1-back test the two letters followed each other immediately. In the 2-back test the target letters were separated by one letter and in the three back two letters separated the target letters. Thus participants had to hold in mind one, two or

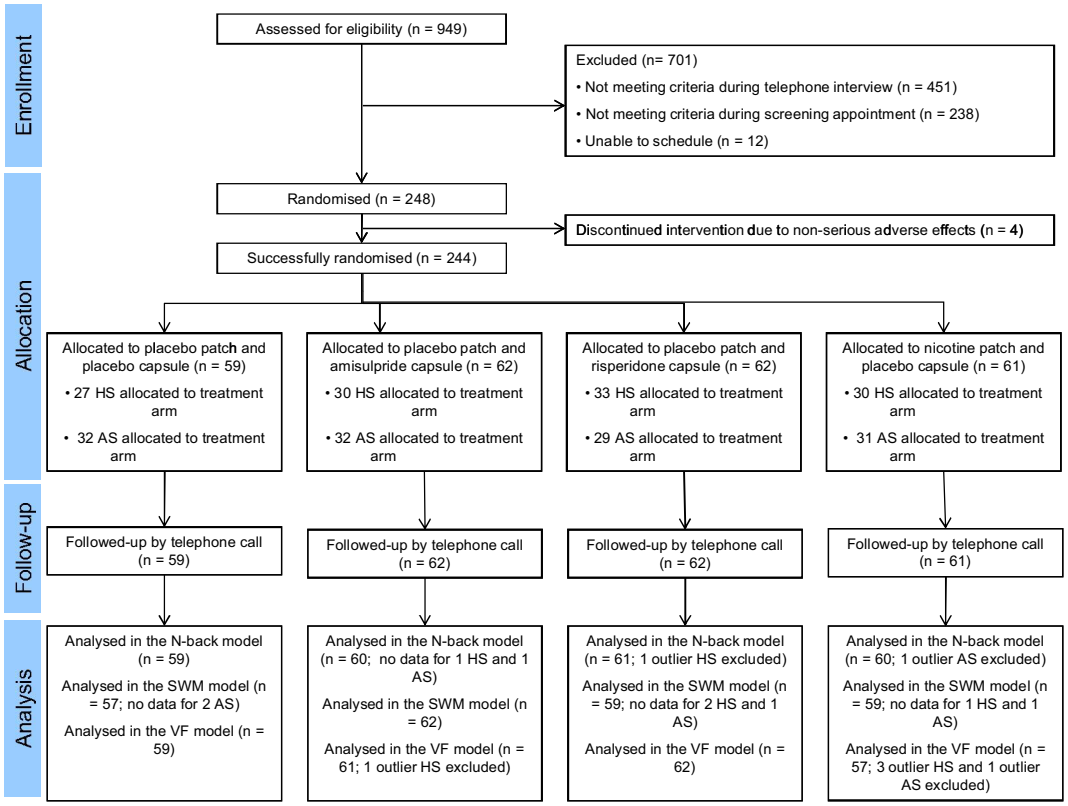

Figure 1 Flow-chart of participants screened, allocated to treatment, followed-up and analyzed. Out of the 949 participants who were screened for eligibility, 701 were excluded. 248 were allocated to a treatment arm with 4 participants discontinued due to non-serious and short-lasting side effects (nausea, headache). All participants in the four treatment arms were followed-up in 3–5 days to check for side effects. Outliers and participants with missing data were excluded from the analysis for each cognitive task, as described in the Experimental procedures section. Abbreviations: HS — high schizotypy group; AS — Average schizotypy group.

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Table 1 Demographics of randomised study participants.

Demographics	Average schizotypy group (mean ± SD)	High schizotypy group (mean ± SD)	Significance
Age	23.5 ± 5.6	23.7 ± 5.3	$p = .70$
NART	113.6 ± 4.9	113.6 ± 5.2	$p = .96$
Years of education	15.5 ± 2.0	16.1 ± 2.2	$p = .05$
Sex	61	62 female	$\chi^2 = .90$
Family history of mental health disorders in first-degree relatives	20	29	$\chi^2 = .13$
Family history of psychosis	3	3	$\chi^2 = .98$
Family history of manic disorders	1	5	$\chi^2 = .01$
Family history of anxiety disorders	1	7	$\chi^2 = .03$

three letters. Consequently, the 1-back test exerted the lowest load on working memory and the 3-back task the highest. Participants completed three blocks of tests with increasing working memory load: 1-back, 2-back and 3-back on each block. There were also baseline blocks to control for attending to the task where participants simply needed to respond when they saw the letter 'X'.

2.3.2. Spatial working memory (SWM) task

Treasure chests were presented on a computer screen. The participants were instructed to search for coins in the treasure chests. Only one of the chests contained a coin at any one time and once it had been found it moved to a treasure chest that it had not been present in during the trial. The participants completed trials with 4, 6 and 8 chests and 4 repetitions of each set. A practice trial with only 3 treasure chests was completed to ensure the understanding of the task.

2.3.3. Verbal fluency (VF) task

Speed of information processing was probed by recording letter and category VF and word production during a succession of one minute periods. For the letter VF test participants were asked to verbally report as many words as they could beginning with the letters F, A and S. The experimenter wrote down the words produced. In the category VF test the categories used were vegetables and animals. In the third condition, category swap, participants were then asked to switch between two categories (fruit and furniture) during the same one minute period.

2.3.4. IQ

IQ was determined using the National Adult Reading Test (Nelson and O'Connell, 1991), a reading-based estimate of premorbid intelligence. We collected this data to check the group have comparable IQ and as a potential covariate of performance. The participant was asked to pronounce irregularly spelt words from a standardized written list. The scores were determined on the basis of the number of correctly pronounced words.

3. Statistical analysis

3.1. Outcome variables

The dependent variables in the N-back task were percentage correct, errors of commission and the reaction times of correct and incorrect responses for each of the four levels of the task (attention, 1-back, 2-back, 3-back). In the SWM task, 3 outcome measures were extracted for each set of trials: time to complete, within and between search errors. For all conditions of the VF task the following measures were calculated: mean number of correct words, set and repetition errors. Additionally, for the category swap, the number of correct transitions was calculated.

3.2. Statistical procedures

Before analysis, the data was checked for outliers. For the N-back task, the criterion for outlier was response at both the attention and 3-back level outside the 95% confidence interval. Participants that had below 20% accuracy on the 3-back level were also excluded from the analysis. For the VF task, participants were classed as outliers if their numbers of either set or repetition errors on the FAS condition were outside the 95% confidence interval. For the SWM task, outliers were identified by visual inspection of boxplots and the extreme values tables produced from SPSS. The dependent variables were entered into a repeated-measures ANOVA (with the exception of set errors, repetition errors and number of correct transitions of the VF task which were entered into univariate ANOVAs) with between subject factors of group, drug, sex and site. The within-subject factor was level of difficulty or condition of the task. Covariates added into the model were IQ, age and time since dosing. Covariates that were found to be non-significant were removed from the model for each variable. In case of a main effect of level of difficulty, polynomial contrasts were run to determine the character of the relationship. Significant effects of drug were investigated by pairwise contrasts of the treatment arms. The effect of schizotypy was examined both in the ANOVAs and separately in the placebo-treated groups. Schizotypy group by drug interactions were explored by three way interactions between schizotypy, drug and level of difficulty of the task. Significant interactions were followed by univariate ANOVAs on the identified level of difficulty in the two schizotypy groups separately. In case of significant main effect of drug in these analyses, post-hoc comparisons of the study drugs versus placebo were then used to explore the effect of each drug in the two schizotypy groups. Also, to test the hypothesis that amisulpride affected the two schizotypy groups differentially, we performed the ANOVA analyses on the level of the task where the interaction between group, drug and task level occurred including the amisulpride and placebo treatment arms only. Since this is an exploratory study with multiple endpoints, no correction for multiple testing was made on any of the analyses.

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Additionally, in order to determine whether one of the three factors of the SPQ (disorganised, interpersonal and cognitive-perceptual) was more strongly related to cognitive impairment we correlated the performance on the cognitive tasks of the placebo-treated groups with the scores on the three subscales. We report the correlations in Pearson's coefficients.

3.3. Ethical approval

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by The North West Research Ethics Committee (REC Ref: 08/H1010/2).

4. Results

4.1. N-back

4.1.1. Subjects

For 2 participants there was no data on the N-back test available (1 AS on amisulpride and 1 HS on amisulpride). 2 participants (1 HS (risperidone) and 1 AS (nicotine)) were excluded based on the criteria for outliers. The final sample consisted of 240 participants, 120 high and 120 average schizotypes. The two schizotypy groups used in the N-back analysis did not differ in terms of age, IQ and sex. The HS group had significantly more years of education however ($p=.04$).

4.1.2. Main effects

The performance in both groups decreased with increasing task difficulty ($F(3, 573)=6.383$, $p<.001$) in a linear fashion ($F(1, 191)=7.527$, $p<.01$). The main effect of schizotypy was not significant in the main repeated measures ANOVA in the percentage correct and errors of commission models (Table 2). However in the placebo treated arm it reached significance for errors of commission with the HS group making more errors than the AS group ($F(1, 46)=6.628$, $p=.01$, Table 3). The main effect of drug was significant for errors of commission ($F(3, 191)=4.010$, $p<.01$, Table 2) which was due to risperidone worsening the performance in comparison with all other treatment arms ($p=.06$ vs. placebo, $p=.021$ vs. amisulpride and $p=.001$ vs. nicotine). Risperidone also increased the latency of the correct responses ($F(3, 189)=7.804$, $p<.001$) and the latency of the errors of commission ($F(3, 190)=8.428$, $p<.001$).

4.1.3. Interactions

A significant drug, schizotypy and WM load interaction was evident on the measure of errors of commission ($F(9, 573)=2.489$, $p<.01$, Table 2). 3-back was confirmed as the level of this interaction by visual inspection of the histograms (Fig. 2). Univariate ANOVA with a dependent variable of errors of commission at 3-back was performed separately for each schizotypy group to explore this effect. Pairwise comparisons in the HS group demonstrated that amisulpride and nicotine improved the performance against placebo, the latter significantly ($p=.02$), the former at a trend level of significance ($p=.06$). In contrast, in the controls, risperidone and amisulpride both worsened the performance, $p=.04$ and $p=.08$ respectively (Fig. 2).

To confirm the differential effect of amisulpride on the two groups, we performed a post-hoc test, where only the placebo

Table 2 Summary of the schizotypy and drug main effects, as well as the schizotypy×drug interaction from the main ANOVA model. The schizotypy×drug interaction at 3-back of the N-back and Load 3 of the SWM is also included.

Measure	Main effect	F	p value	Partial Eta^2
N-back				
Percentage correct	Schizotypy	.031	.86	.000
	Drug	1.893	.13	.029
	Schizotypy×drug	.592	.62	.009
	Schizotypy×drug 3-back	1.815	.15	.028
Errors of commission	Schizotypy	.189	.66	.001
	Drug	**4.010**	**.01**	**.059**
	Schizotypy×drug	**2.502**	**.06**	**.038**
	Schizotypy×drug 3-back	**3.317**	**.02**	**.050**
SWM				
Within search errors	Schizotypy	.027	.87	.000
	Drug	1.092	.35	.017
	Schizotypy×drug	.268	.85	.004
	Schizotypy×drug load 3	.420	.74	.007
Between search errors	Schizotypy	1.636	.20	.009
	Drug	.935	.43	.015
	Schizotypy×drug	**4.123**	**<.01**	**.062**
	Schizotypy×drug load 3	**4.551**	**<.01**	**.068**
VF task				
Correct words	Schizotypy	3.673	.06	.019
	Drug	**2.371**	**.07**	**.036**
	Schizotypy×drug	1.650	.179	.026
Correct transitions	Schizotypy	**5.665**	**<.01**	**.029**
	Drug	**4.294**	**<.01**	**.064**
	Schizotypy×drug	1.260	.29	.020

Comparisons with p values of less than .1 highlighted in bold.

Table 3 Summary of the main effects of schizotypy in the models of the placebo-treated groups.

Measure	F	p value	Eta^2
N-back task			
Percentage correct	2.421	.13	.050
Errors of commission	**6.628**	**.01**	**.126**
Latency of correct responses	1.101	.30	.024
Latency errors of errors of commission	.916	.34	.019
SWM task			
Within search errors	.010	.92	.000
Between search errors	.001	.97	.000
VF task			
Correct words	**6.063**	**.02**	**.116**
Correct transitions	**5.213**	**.03**	**.100**

Comparisons with p values of less than .1 highlighted in bold.

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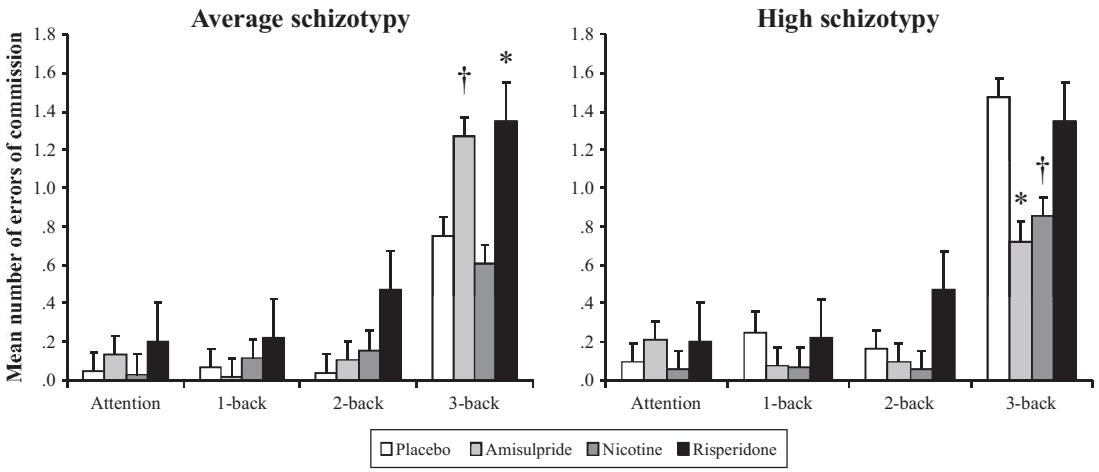

Figure 2 Effect of study drugs on the mean number of errors of commission in the N-back task. Load of the task on the horizontal axis, mean number of errors of commission on the vertical one. High schizotypy group (HS) on the left hand side and average schizotypy (AS) on the right. At 3-back risperidone and amisulpride worsened performance in AS (significantly and at trend respectively) while the HS group benefited from treatment with amisulpride and nicotine (significantly and at trend respectively). *=$p \leq .05$, †=$.05 < p < .10$.

and amisulpride treated groups were retained in the univariate ANOVA. The outcome measure was errors of commission at the 3-back level. The interaction between schizotypy and drug was highly significant in this analysis ($F(1, 96) = 7.827$, $p < .01$).

4.1.4. Effects of covariates, site and sex

IQ was a significant factor for the measure of errors of commission ($F(1, 191) = 5.717$, $p = .02$) but not in the percentage correct model. IQ and time since dosing were significant covariates in the latency of correct responses ($F(1, 190) = 5.080$, $p = .03$ and $F(1, 190) = 8.603$, $p < .01$, respectively). There were no significant effects of site or sex on the measures of N-back performance, nor did sex interact with schizotypy.

4.2. Spatial working memory

4.2.1. Subjects

For 7 subjects, no data on SWM was available (3 HS (1 on nicotine and 2 on risperidone) and 4 AS (2 on placebo, 1 on nicotine and 1 on risperidone)). The final sample consisted of 237 subjects, 118 HS and 119 AS. The two schizotypy groups used were well matched in terms of age, IQ and sex, but the HS group had significantly more years of education ($p = .031$).

4.2.2. Main effects

The performance on the task as measured by the number of between search errors decreased with difficulty ($F(2, 376) = 4.527$, $p = .01$) and the relationship was linear ($F(1, 188) = 5.490$, $p = .02$). There were no main effects of schizotypy in respect to the main repeated measures analysis and in the placebo-treated arm for any of the outcome variables (Tables 2 and 3). There were no main effects of drug for any of the outcome variables (Table 2).

4.2.3. Interactions

The drug × schizotypy and drug × schizotypy × load interactions were both significant ($F(3, 188) = 4.123$, $p < .01$ and $F(6, 376) = 4.257$, $p < .001$ respectively, Table 2). Inspection of the histograms (Fig. 3) confirmed that the level of this interaction was at load 3 of the task. To explore this effect we performed univariate ANOVAs within each schizotypy group. In the HS group, risperidone worsened the performance significantly in comparison with placebo ($p = .05$) (Fig. 3). No difference was found between the treatment arms in the AS group.

To test the hypothesized differential effect of amisulpride, we repeated the same univariate ANOVA analyses in the groups treated with placebo and amisulpride only. The interaction between drug and schizotypy was not significant in this case ($F(1, 94) = 1.683$, $p = .2$).

4.2.4. Effect of covariates, site and sex

IQ was a significant factor for the measure of between search errors only ($F(1, 188) = 6.860$, $p = .01$). Age was a significant factor for the measure of time to complete only ($F(1, 185) = 5.893$, $p = .02$). The factor of site approached significance for the between search errors measure ($F(2, 188) = 2.712$, $p = .07$). This was due to the participants in Cardiff performing the task better than the ones in Manchester ($p = .08$) and London ($p = .03$). The main effect of sex was not significant nor did it interact with Schizotypy.

4.3. Verbal fluency task

4.3.1. Subjects

5 participants were excluded from the analysis due to being outliers on the number of errors on the FAS task (4 HS (3 on nicotine, 1 on amisulpride) and 1 AS (nicotine)). The final sample consisted of 117 HS and 120 AS participants. The two groups did not differ in terms of age and IQ. The HS group had higher number of years of full-time education at a trend for significance ($p = .08$).

4.3.2. Main effects

In the main ANOVA model Schizotypy approached and reached significance in respect to the number of produced words and correct transitions in the category swap task respectively, the high schizotypes performing worse than the controls ($F(1, 188) = 3.673$, $p = .06$ and $F(1, 189) = 5.665$, $p < .01$, respectively — Table 2). This trend was sustained in the placebo-

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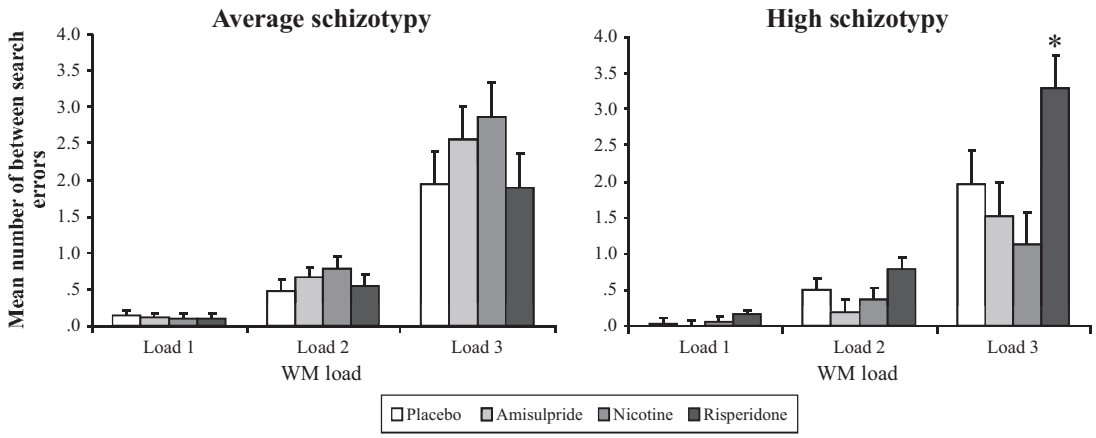

Figure 3 Effect of study drugs on the mean between search errors on the SWM task. Load of the task of the horizontal axis, mean number of between search errors on the vertical one. High schizotypy group (HS) on the left hand side, average schizotypy (AS) on the right. At Load 3 risperidone significantly impaired HS but not AS. *=p≤.05.

treated groups where the effect was significant (F(1, 46)=6.063, p=.02 and F(1, 47)=5.213, p=.03, respectively — Table 3). The main effect of drug approached and reached significance in respect to the number of correct words and correct transition models respectively (F(3, 188)=2.371, p=.07 and F(3, 189)=4.294, p<.01, respectively — Table 2). Pairwise comparisons showed that the effect was due to risperidone worsening performance in comparison with placebo (p=.01 and p<.01 for the two models respectively, Fig. 4).

4.3.3. Interactions

The correct word model revealed an interaction between drug, schizotypy and task condition that approached significance (F(6, 376)=2.023, p=.06, Table 2). Visual inspection of the histograms presented in Fig. 4 indicated that the level of the interaction is the category swap level. A univariate ANOVA on this level was performed for the two schizotypy groups separately. In the controls, all study drugs led to worsening of the performance (p=.01, p=.04 and p<.01 for amisulpride, nicotine and risperidone respectively). No significant difference between the treatment arms were observed in the HS group.

To test the hypothesized differential effect of amisulpride on the two schizotypy groups, we performed the univariate ANOVA in the category swap condition for the placebo and amisulpride treated groups only. This analysis revealed a significant drug and schizotypy interaction (F(1, 95)=4.574, p=.04), indicating that while amisulpride improved the performance in the HS group, it had the opposite effect in the AS controls (Fig. 4).

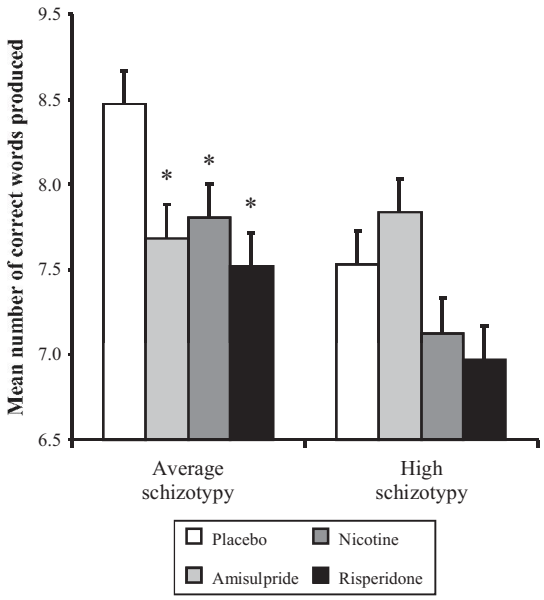

Figure 4 Effect of study drugs on the mean produced words on the VF task. The two study groups on the horizontal axis, number of words produced on the vertical one. All study drugs worsened performance in AS, no statistically significant difference between the treatment arms in HS. *=p≤.05.

4.3.4. Effect of covariates and site

IQ was a significant covariate for the number of correct words (F(1, 188)=17.508, p<.001). There were no significant effects of site on the number of correctly produced words or on the number of errors. There was a main effects of sex in the category swap model (F(1, 188)=18.963, p<.001). This was due to female participants performing better than males. There was no interaction between sex and schizotypy group.

4.3.5. Correlation of SPQ subscales with performance

The correlations of the three subscales revealed that the disorganisation subscale correlated negatively with performance on the 3-back percentage correct measure of the N-back task (r=−.3, p=.02), the time to complete for load 3 on the SWM (r=−.3, p=.02) and number of correct transitions measure of the VF task (r=−.2, p=.7). Time to complete load 3 correlated positively with the cognitive-perceptual subscale.

5. Discussion

In this double-blind placebo-controlled study we aimed to validate the use of cognitive biomarkers to detect drug action in schizotypy. We laid out three validation criteria:

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the biomarkers should be sensitive to the schizotypy phenotype; this effect of schizotypy should be reversed by some or all of the drug challenges; the first two criteria should be consistent across different sites. In this section we will discuss the results of the study in respect to each of those in turn.

5.1. Criterion 1: sensitivity of the biomarkers to the schizotypy phenotype

Two of the tasks satisfied this requirement. On the N-back task, the placebo treated HS group performed worse than the controls in respect to the errors of commission measure of the 3-back. That there was no schizotypy effect in percentage correct model implies that while high schizotypes had intact recall they were more likely to respond when they shouldn't have. This was probably not a simple impulsivity problem as similar effect should have been evident in the attention blocks of the N-back. Instead, the schizotypy group may have been more reliant on familiarity than recollection-based judgments. Such gist-based strategy would explain the combination of high number of correct hits and errors of commission. Similar preference of familiarity-based over source information strategies have repeatedly been reported in schizophrenia patients (Moritz et al., 2006; Thoma et al., 2006; Mammarella et al., 2010) and it probably reflects a source monitoring deficit.

This central executive impairment in consistent with results from a recently published study on a subgroup of the same sample where we again found evidence of behavioral and neurophysiological abnormalities during a working memory task (Koychev et al., 2010). Working memory deficits are one of the most widely replicated findings in both schizotypy and schizophrenia and are considered a neurocognitive hallmark of the schizophrenia spectrum (Lee and Park, 2005; Raine, 2006). The performance in high schizotypes generally tends to be intermediate between that of healthy controls and schizophrenia patients (Trestman et al., 1995).

The speed of information processing task (VF), the HS group had a significantly lower number of words on the category switch condition, but not on the FAS or category naming. This indicates that the detected abnormality is not due to verbal fluency impairment, but rather a central executive mechanism related to working memory (mental manipulation and inhibition of irrelevant cues). Hence, both biomarkers appear to be sensitive to the effect of schizotypy on executive function in its working memory (source monitoring) and inhibitory domains.

The findings of deficits in working memory on the N-back task but not the SWM task could be attributed to the key differences that exist between the two working memory tasks. In the former the presentation of each stimulus was very brief (1 s) while in the latter it was unlimited. Previous research has already indicated that schizophrenia patients require longer stimulus presentations to achieve stable working memory representations (Hartman et al., 2003; Fuller et al., 2005, 2009). Also, ample evidence has now accumulated pointing out abnormalities in the earliest stages of information processing that in turn drive higher-order cognitive impairment (Butler et al., 2007; Haenschel et al., 2007). In addition, the cognitive abnormalities in patients can sometimes be reduced by increasing the duration of the encoding phase of the tasks (Tek et al., 2002; Lencz et al., 2003). In the previously mentioned study on a subsample of the HS, we found that they showed abnormal WM performance on a working memory task that allowed only brief encoding but intact performance in cognitive tasks with unlimited stimulus presentation (Koychev et al., 2010). This data indicates that early information processing is a key component in the pathogenesis of the schizophrenia spectrum cognitive abnormalities. The practical implication is that these abnormalities will be more easily demonstrable using tasks that allow only brief stimulus encoding, as suggested by the result from our study.

Additionally, the correlations between the SPQ subscales and performance on the tasks suggested that it was mainly the disorganisation dimension of schizotypy that negatively correlated with cognitive performance. This is in line with theories that distinguish between neurodevelopmental and pseudoschizotypy (Raine, 2006). Neurodevelopmental schizotypy is hypothesised to be closely related to the genetic risk for schizophrenia (Calkins et al., 2004), is relatively stable longitudinally and features mostly negative schizotypal symptoms (disorganisational and interpersonal schizotypal traits), as well as cognitive impairment (Chen et al., 1997). In contrast, pseudoschizotypy is considered to be unrelated to genetic liability and is instead mostly due to psychosocial adversity. It is characterized by predominantly cognitive-perceptual symptoms and has been shown to be associated with weaker cognitive deficits (Chen et al., 1997). Therefore these results reinforce the concept that the neurobiological links between schizotypy and schizophrenia may more consistent in those schizotypal individuals who exhibit higher disorganisational schizotypal traits.

5.2. Criterion 2: reversal of the effect of schizotypy by drug challenge

All drug challenges induced effects that were detectable using the proposed biomarkers, but amisulpride provided the clearest tendency to reverse the effect of schizotypy. In the HS group it reduced the number of errors of commission on the N-back task but worsened the performance in the AS group (Fig. 2). In the SWM task the same effect was evident in respect to the between-search errors, but this effect did not reach significance (Fig. 3). In VF the AS produced significantly more words than the HS in the category switch task when placebo treated. AS participants treated with amisulpride produced significantly fewer correct words whereas performance improved non-significantly in the HS (Fig. 4). A direct comparison between the amisulpride and placebo treated groups revealed that amisulpride had differential effect on the two schizotypy groups. These effects of amisulpride could be explained by data that shows that when given in low doses (less than 10 mg/kg) it blocks the presynaptic dopamine receptors and enhances dopamine neurotransmission (Schoemaker et al., 1997). This is compatible with the results of a study that found improvement of working memory performance in schizotypal personality disorder (SPD) after acute amphetamine administration (Kirrane et al., 2000). The benefit of dopamine enhancing agents in schizotypy is not limited to acute challenges, as a

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recently published study also found improvement in the cognitive function of SPD patients after 4-week treatment with pergolide, a combined D1 and D2 receptor agonist (McClure et al., 2010). Further, dopamine agonist challenges in humans and primates improve cognition, but only in those with low baseline performance (Barch, 2004). These findings fit in well with the idea that the relationship between dopamine and executive function is best described by a U-shaped curve (Barch, 2004). According to this theory, hypodopaminergic states of the prefrontal cortex (e.g. schizophrenia spectrum disorders) improve with enhancement of dopamine function, while people that have already optimal dopamine function are worsened by these challenges.

In contrast to amisulpride, risperidone worsened spatial working memory in HS and verbal fluency performance of the AS group or did not otherwise benefit the performance. These findings are consistent with previously published effects of high potency D2 antagonists in healthy volunteers (Luciana et al., 1998; Honey et al., 1999; Mehta et al., 1999). The observed effect of risperidone could have also been due at least partly to its sedative effects (Miller, 2004). In support of this interpretation, an increase of the latency of the responses in the N-back task was found in the participants taking risperidone. These sedative effects have been attributed to H1-receptor affinity (Richelson and Souder, 2000).

Nicotine had mixed effects on cognition. However, it showed an overall tendency to improve the HS group and to impair the AS one. In the N-back working memory task it reduced the number of errors of commission in the HS group but had no effect on the AS performance. In VF however, nicotine did not improve performance in the HS group but impaired the AS control group. This suggests that the two tasks engage different cognitive mechanisms. The beneficial effect of nicotine on the N-back task could reflect its well-known ability to improve attention (Newhouse et al., 2004). This may have interfered with the requirement for inhibition in the category swap condition of VF.

5.3. Criterion 3: site-independence of criterions 1 and 2

There were no differences between the sites in respect to the main effect of schizotypy, drug or their interaction. The only interaction between schizotypy group and site that approached significance was found in the SWM task on the measure of between search errors. We consider this to be a random finding.

6. Limitations

Several limitations of this study exist. First and foremost, an inherent problem with validating biomarkers is the lack of drugs known to reliably improve cognition in schizophrenia. Consequently there is currently no criterion treatment against which biomarkers, surrogate populations and novel treatments can be validated.

Another consideration is that the choice of schizotypy groups could have lessened the main effect of schizotypy. Firstly, we used a self-reported schizotypy measure (Raine, 1991; Raine et al., 1994) which may have missed certain domains of the schizotypal psychopathology (such as circumstantial thinking and speech, constricted affect, odd behavior and appearance). These may be evident in a clinical interview but often remain unrecognized by the schizotypal individuals (Compton and Chien, 2008). As a result, it may be that the HS group did not fully capture the extreme of the schizotypy spectrum. Secondly, the HS group included only individuals who were non- or light-smokers (less than 5 cigarettes per day) and had no history or presence of substance abuse. Given the link between schizotypy and increased incidence of substance abuse and smoking (Esterberg et al., 2007; Barkus and Murray, 2010) it could be argued that our high schizotypy sample may be particularly high functioning. On a similar note, the HS group had more years of education relative to the AS control group. Thirdly, we also excluded people with concurrent past or present Axis I disorders, including depression. Since depression is common in schizotypal personality the high schizotypy sample may not have been representative. However, we wished to avoid the effects of current or past symptoms of depression on performance. Finally, the use of an average scoring schizotypy control group rather than low scoring one could also have led to lessening of the effect of schizotypy. Despite these considerations regarding our choice of schizotypy groups, two of the tasks demonstrated the anticipated effect of schizotypy. We interpret this as further evidence for the validity of these cognitive biomarkers.

Since the statistically significant effects were not corrected for multiple comparisons and the control group was average rather than low scorers, further studies are required to validate these biomarkers in high schizotypy against a low scoring control sample.

Other valid limitations of the study are the absence of a stimulant medication (e.g. methylphenidate), the single administration, and the single dose per drug. Retrospectively, using a more potent stimulant medication would have probably led to more pronounced differential effects, similar to the ones observed with amisulpride. The usage of several agents in this design limited the feasibility of longitudinal or variations in the administered doses. Future studies using fewer agents could use such designs to further clarify the results obtained in this pilot study.

It is also worth pointing out that while the high schizotypy group had higher incidence of family history of mental health disorders than the average schizotypy controls this did not reach statistical significance. Moreover, the two groups had equal number of first-degree relatives with schizophrenia (3 vs. 3). Significant differences were obtained only in respect to anxiety disorders while the difference in bipolar disorder relatives was significant at trend. These findings go against the body of evidence indicating higher level of schizotypal personality traits in relatives of schizophrenia patients (Raine, 2006) and question the relevance of results obtained in schizotypy samples to the schizophrenia neurobiology. However, the validity of this conclusion is limited by our method of data collection which relied on asking the participants the question 'Has anyone in your immediate relatives been diagnosed with a mental illness?'. The decision not to use a standardised family history method (such as the FH-RDC, (Andreasen et al., 1977)) or family study method was made in order to limit the duration of the screening appointment. Given that

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standardised family history methods have also been shown to have only modest validity (Hardt and Franke, 2007), we speculate that the incidence of schizophrenia cases among the HS group might have been underreported due to the low reliability of the method employed. Therefore the results give some tentative support for higher incidence of mental health disorders in the HS group but our methods have limited power to detect the incidence of schizophrenia cases among high schizotypy scorers and the negative result should be treated with caution.

One unexpected finding was the higher number of years of education in HS compared to AS. One way of interpreting this result is that the interpersonal deficits in HS were requiring them to complete higher levels of education in order to be competitive in terms of employment. Additionally, the same personality traits may be forcing the HS into career paths with lower interpersonal contact which however require longer education. Another possibility is that the subtle cognitive deficit makes education more difficult for the HS and they therefore need longer time to attain the same educational level as the AS.

In summary this double-blind three-center study showed that biomarker measures of WM can reliably detect the schizotypy phenotype and are also sensitive to the action of psychopharmacological agents, such as amisulpride, risperidone and nicotine. The experiment's large sample size and the consistency of the effects across the different sites strengthen the validity and reliability of these conclusions. The reversal of the schizotypy effect by amisulpride adds further weight to claims that suboptimal prefrontal cortex dopamine neurotransmission is at the core of the schizophrenia spectrum disorders. These results support the use of cognitive biomarkers and surrogate populations such as schizotypy in translational studies aimed at early assessment of the efficacy of cognition enhancing agents in schizophrenia.

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Contributors

Ivan Koychev collected and analyzed study data, as well as wrote the first draft of the article. Emma McMullen collected and analyzed study data. Jane Lees, Rukiya Dadhiwala, Lois Grayson, Charlotte Perry, Anne Schmechtig and James Walters collected data. Kevin J. Craig, Gerard R. Dawson, Colin T. Dourish, Ulrich Ettinger, Lawrence Wilkinson, Steven Williams, and John Francis William Deakin participated in the study design. Emma Barkus analyzed study data and contributed to the first draft of the article.

Conflict of interest

Ivan Koychev has been awarded a Manchester Strategic PhD Studentship, sponsored by the University of Manchester and P1vital Ltd. The PhD projects of Katrina McMullen and Anne Schmechtig have been partly funded by P1vital Ltd. Lois Grayson's salary as a postdoctoral research associate at Cardiff University was entirely funded by P1vital Ltd. Ulrich Ettinger is supported by the Deutsche Forschungsgemeinschaft (Et 31/2-1). Dr. Walters was supported by a Welsh Assembly/MRC Clinical Research Training Fellowship and NARSAD Young Investigator Award. Lawrence Wilkinson declares consultancy work for for the MRC (Non-clinical Fellowship Panel) and Welcome Trust (Neuroscience and Mental Health Funding Committee). John Francis William Deakin has been supported by the Manchester Biomedical Research Centre. John Francis William Deakin has carried out paid consultancy work and speaking engagements for Servier, Merck Sharpe and Dohme, Astrazeneca, Janssen, Eli Lilly. The fees are paid to the University of Manchester to reimburse them for the time taken. John Francis William Deakin, Lawrence Wilkinson, Gerry Dawson, Colin Dourish and Kevin Craig own shares in P1vital Ltd. Emma Barkus acknowledges the support of a Young Investigator Award from NARSAD.

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