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Smooth pursuit and antisaccade eye movements in siblings discordant for schizophrenia

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Abstract

Smooth pursuit eye movement (SPEM) and antisaccade deficits have been proposed as endophenotypes in the search for schizophrenia genes. We assessed these measures in 24 schizophrenia patients, 24 of their healthy siblings, and 24 healthy controls closely matched to the siblings. Between-group differences were assessed using a random effects regression model taking into account the relatedness between patients and siblings. Patients showed reduced SPEM gain, increased frequency of saccades during pursuit, increased antisaccade error rate, and reduced antisaccade gain compared to controls. Siblings performed intermediate, i.e. between patients and controls, on most measures, but were particularly characterised by reduced antisaccade gain. SPEM gain at one target velocity was significantly correlated between patients and siblings, highlighting the necessity of taking into account within-family correlations in the statistical analysis of between-group differences. It is concluded that subtle SPEM and antisaccade deficits are observed in clinically unaffected siblings of schizophrenia patients; these deficits may be useful markers of genetic liability to schizophrenia.

Keywords: Schizophrenia; Endophenotype; Genetics; Smooth pursuit eye movements; Antisaccade; First-degree relatives

1. Introduction

Smooth pursuit eye movement (SPEM) and antisaccade deficits have been studied as schizophrenia endophenotypes (Calkins & Iacono, 2000). An endophenotype is a circumscribed behavioural or biological marker thought to represent more closely the action of a disease gene than the clinical phenotype (Leboyer et al., 1998). This strategy may be profitable in schizophrenia research given the genetic, clinical, and neurobiological heterogeneity of the disorder. An important validity criterion of an endophenotype is its observation not only in the patient group, but also in their unaffected relatives.

Supporting this hypothesis, a number of studies have demonstrated impaired SPEM and antisaccades in schizophrenia patients and their relatives. Impaired SPEM occurs in about 50–80% of schizophrenia patients and 30–40% of their first-degree relatives, compared to about 8% of healthy individuals (Lencer et al., 2003; Levy et al., 1993). SPEM impairments show concordance in monozygotic twins discordant for schizophrenia (Holzman et al., 1980; but see Litman et al., 1997) and have been linked to frontal cortex dysfunction in

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patients (MacAvoy & Bruce, 1995) and their relatives (O'Driscoll et al., 1999). Preliminary evidence links the deficit to a locus on chromosome 6p (Arolt et al., 1999).

Schizophrenia patients also display an increased antisaccade error rate, possibly linked to prefrontal dysfunction (McDowell & Clementz, 2001). Several studies have demonstrated this deficit in relatives of schizophrenia patients (Curtis et al., 2001; Karoumi et al., 2001; Katsanis et al., 1997), particularly those from multiplex schizophrenia families (McDowell et al., 1999). However, there is evidence showing no significant impairments (Crawford et al., 1998; Thaker et al., 1996) or only in relatives with schizophrenia spectrum symptoms (Thaker et al., 2000) or family history of schizophrenia (Ross et al., 1998).

One methodological concern of some previous studies is the inclusion of relatives with psychiatric symptoms (Clementz et al., 1994). Given the observation of oculomotor impairments in various neuropsychiatric disorders (Everling & Fischer, 1998) and in schizotypal personality (O'Driscoll et al., 1998) asymmetrical inclusion criteria (i.e. relatives *with* psychiatric symptoms and controls *without* such symptoms) may lead to spuriously increased endophenotype frequency among relatives and should be avoided.

A second issue concerns the genetic relatedness of patients and their first-degree relatives, which is likely to lead to correlated scores on biological and behavioural measures (Plomin et al., 2000). The use of analysis of variance (ANOVA) is, therefore, inappropriate in statistical analyses involving these groups, as the assumption of independence of observations is violated. To overcome this problem, a random effects linear regression model has been outlined that controls for effects of relatedness (Rabe-Hesketh et al., 2001).

A third methodological point concerns the recruitment of parents into the samples of schizophrenia patients' relatives. Inclusion of older relatives may be problematic beyond the introduction of age differences as it may cloud performance deficits of relatives (Faraone et al., 1996).

In this study we investigated siblings discordant for schizophrenia, taking into consideration these issues. SPEM and antisaccade, as well as visual fixation and prosaccade, tasks were applied to 24 patients with schizophrenia, 24 of their healthy siblings, and 24 healthy controls. We used tightly matched patient–sibling–control triplets and appropriate statistical analysis methods. The inclusion of siblings and controls without psychiatric illness allowed the isolation of the variable of interest, namely the genetic relatedness to someone with schizophrenia, in the absence of other, potentially confounding, variables. Siblings' SPEM and antisaccade performance levels were predicted to fall in between those of patients and controls.

2. Method

2.1. Participants

Twenty-four clinically stable outpatients with schizophrenia (mean age = 30.71, S.D. = 5.84; 13 males), 24 of their full biological siblings (one sibling for every patient) (mean age = 28.63, S.D. = 6.41; seven males) and 24 healthy controls (mean age = 28.50, S.D. = 5.99; seven males) took part. In each group 16 participants were Caucasian, six were Afro-Caribbean, and two were Asian. The study was approved by the Bethlem and Maudsley Ethical Committee (Research). All participants provided written informed consent.

Diagnoses were established using the Structured Clinical interview for DSM-IV Axis I disorders (First et al., 1996b). Patients and siblings with a history of alcohol or drug dependence in the past year or a lifetime history of 5 years of alcohol or drug abuse/dependence, head injury with cognitive sequelae or loss of consciousness exceeding five minutes, history of neurological disorder or medical illness associated with significant neurocognitive impairment were excluded. Patients' duration of illness ranged from 2 to 20 years (mean = 7.08, S.D. = 5.36; median = 5; interquartile range = 3–10). Nineteen patients were on atypical antipsychotics, four were on typical antipsychotics, and one patient was untreated.

Siblings were within 5 years of the patient's age (sibling range: 16–40 years; patient range: 16–45 years). Siblings were excluded if they had a DSM-IV Axis I disorder, or Axis II schizotypal personality disorder (First et al., 1996a). Controls were screened according to the same criteria as siblings, with the additional requirement that they did not have a first-degree relative with a history of psychosis (Family Interview for Genetic Studies) (Gershon & Guroff, 1984). Controls were individually matched to a sibling on age (±5 years), sex, years of education (±2 years), ethnicity, and handedness, yielding patient–sibling–control triplets.

Patients' current symptoms were rated using the Positive and Negative Syndrome Scales (PANSS) (Kay et al., 1987). Schizotypal symptoms were assessed in siblings and controls using the Structured Interview for Schizotypy (SIS) (Kendler et al., 1989).

3. Eye movement paradigms

Light-emitting diodes (AMTech Digital LED Bar 96; AMTech GmbH, Weinheim, Germany) were presented at 200 cm distance from participants (visual angle 0.15°) in a quiet, darkened room. Head movements were minimised using a chinrest.

3.1. Smooth pursuit

Trapezoidal constant-velocity smooth pursuit tasks at 10°/s (13 half-cycles) and 24°/s (14 half-cycles) were used, in order to assess pursuit function at slow and fast velocities. At the end of each ramp (±15°) the target remained stationary for 300–1000 ms. Instructions were to follow the target as closely as possible.

3.2. Fixation

The target was presented in the central position and at ±15° (15 s each). Participants were instructed to keep their eyes on the target.

3.3. Antisaccade

A standard no-gap, non-overlap antisaccade task was applied. A trial involved a 1000 ms central fixation and a 1000 ms peripheral location (±15°). Four practice trials and two blocks of eight trials each were performed with an equal number of right and left targets in a fixed, quasi-random sequence. Participants were instructed to focus on the target while in the centre and quickly redirect their gaze to the mirror image location of the target as soon as it moved to the side. Emphasis was thus placed on (1) the inhibition of a reflexive saccade and (2) the rapid initiation of a saccade (3) to a location exactly opposite the target.

3.4. Prosaccade

Two blocks of 12 no-gap, non-overlap prosaccade trials (500 ms central fixation, 500 ms peripheral target at ±5°, ±10°, or ±15°) were performed. Each target location was used four times. Instructions were to follow the target as closely as possible.

4. Eye movement recording and analysis

Eye movements were recorded using infrared oculography (IRIS 6500; Skalar Medical BV, Delft, The Netherlands) (Reulen et al., 1988). Sampling frequency was 500 Hz. After calibration recordings from the left eye were analysed using interactive software (EYEMAP 2.1; AMTech GmbH). Smooth pursuit at both velocities from one patient and one sibling, smooth pursuit at 24°/s from one sibling, and prosaccades from one patient were unavailable due to computer storage errors.

4.1. Smooth pursuit

Saccadic frequency (N/s) and velocity gain were measured. Criteria for detection of anticipatory (AS) and catch-up saccades (CUS) using an interactive routine in EYEMAP were minimum velocity = 30°/s and minimum amplitude = 1.5°. An AS is an intrusive saccade taking the eye ahead of the target, thereby increasing position error, followed either by postsaccadic slowing or a back-up saccade of smaller amplitude (Ross et al., 1999). Inclusion of AS was not restricted to large saccades (Ross et al., 1999). CUS are saccades in target direction initiated while the eye is behind the target, thereby decreasing position error. Back-up saccades and square wave jerks occurred infrequently in all groups and were omitted from the analyses. Previous studies have shown that these saccades are not systematically affected in the schizophrenia spectrum (Lencer et al., 2000).

To calculate gain, saccades and eye-blinks were removed. A five-point central averaging filter was then applied twice. The first and last quarters of each ramp were removed to avoid pursuit initiation and slowing at target turnarounds. Gain was calculated from remaining sections by dividing mean eye velocity by target velocity. Scores were time-weighted and averaged (Lencer et al., 2000; Abel et al., 1991).

4.2. Fixation

The frequency of saccades (N/sec) during fixation was calculated.

4.3. Antisaccade and prosaccade

Saccades were identified using above velocity and amplitude criteria as well as a minimum latency of 100 ms and were classified as prosaccade, antisaccade, antisaccade error, or antisaccade corrective saccade. Prosaccade and antisaccade gain reflects primary saccade amplitude divided by target amplitude multiplied by 100. Perfect gain thus results in scores of 100% for prosaccades and −100% for antisaccades. An antisaccade error was counted when the first saccade was made towards the target. Antisaccade error rate was the percentage of error trials over the total number of valid trials. Latency was the time (ms) between target presentation and saccade initiation. Corrective saccades were saccades in opposite target direction following an antisaccade error. Average correction rates for patients (79.23%; S.D. = 32.28), siblings (97.10%; S.D. = 10.84), and controls (96.37%; S.D. = 11.56) were similar to those reported previously and suggest that participants understood and were willing to follow the task instructions (McDowell & Clementz, 1997).

5. Statistical analysis

Sex differences on oculomotor variables were investigated in each group using multivariate analysis of

variance (MANOVA). Pearson correlations were obtained between age and oculomotor variables in each group.

The genetic relatedness between patients and siblings and the likely within-family correlations violate ANOVA's assumption of independent observations. Therefore, group differences on oculomotor variables, age, and years of education were analysed using a random effects regression model (Rabe-Hesketh et al., 2001) in Stata 7.0. The model uses group (patient, sibling, control) as independent variable and each oculomotor variable as dependent variable. A random effect is introduced into the regression equation, which takes on a different value for each patient–sibling–control triplet, thereby allowing for correlations within triplets due to relatedness and individual matching. In addition to maximising statistical power compared with ANOVA, this model is advantageous over *t*-tests in (1) providing an overall test statistic, (2) allowing the inclusion of covariates, and (3) maximising power by excluding missing values on a casewise, not pairwise, basis.

Effect sizes were calculated according to the formula $(\mu_1-\mu_2)$ / SD_{diff} where μ_1 = mean of group 1, μ_2 = mean of group 2, and SD_{diff} = standard deviation of the difference scores (Cohen, 1988). Effect sizes were corrected for genetic relatedness by using the SD of the difference scores as the denominator. Effects of target velocity on SPEM variables and velocity-by-group interactions were tested using the patient–sibling–control triplets as "subjects" in repeated measures ANOVAs; group and velocity were used as within-triplet factors.

To explore effects of relatedness on eye movements, Pearson correlations were run for SPEM variables and antisaccade error rate within patient-sibling pairs. Pearson correlations were also run between oculomotor and clinical variables (PANSS and SIS).

6. Results

6.1. Effects of age, sex, and SPEM target velocity

Female patients had increased prosaccade latency [$F(1, 22) = 4.66$; $P = 0.04$] in comparison to male patients (all remaining $P > 0.06$). As no other variables showed sex effects, males and females were combined in each group and sex was used as covariate only for prosaccade latency. Groups did not differ in years of education (Wald $\chi^2 = 2.79$; df = 2; $P = 0.25$) but differed in age (Wald $\chi^2 = 15.87$; df = 2; $P = 0.0004$): patients were significantly older than siblings ($z = -3.34$; $P < 0.001$) and controls ($z = -3.34$; $P < 0.001$), who did not differ from each other ($z = 0.20$; $P = 0.84$). Age was correlated among patients with prosaccade latency ($r = 0.45$, $P = 0.03$) and among controls with CUS frequency at 10°/s ($r = -0.55$, $P = 0.005$). Therefore, age was covaried for in analyses involving these variables.

There were main effects of target velocity on SPEM gain [$F(1,21) = 16.99$; $P < 0.001$] and AS [$F(1,21) = 67.03$; $P < 0.001$] and CUS frequency [$F(1,21) = 258.82$; $p < 0.001$] but no group-by-velocity interactions (all $F < 1.55$; all $P > 0.22$).

6.2. Group comparisons

Descriptive statistics and effect sizes for group differences are given in Table 1. Results of the regression model are summarised in Table 2.

6.2.1. Patients vs. controls

Patients performed worse than controls on all variables, significantly ($P < 0.05$) or at trend level (P between 0.05 and 0.1), except the frequency of saccades during fixation ($P = 0.39$).

6.2.2. Patients vs. siblings

Compared with siblings, patients had reduced SPEM gain at 24°/s ($P = 0.02$), an increased CUS frequency at 10°/s ($P = 0.006$) and, nonsignificantly, at 24°/s ($P = 0.06$), increased antisaccade ($P = 0.06$) and prosaccade latency ($P = 0.02$), and a significantly increased antisaccade error rate ($P < 0.001$).

6.2.3. Siblings vs. controls

Compared with controls, siblings had significantly reduced SPEM gain at 10°/s ($P = 0.003$), an increased AS frequency at 10°/s ($P = 0.04$) and, nonsignificantly, at 24°/s ($P = 0.07$), a slightly increased CUS frequency at 10°/s ($P = 0.08$), significantly reduced antisaccade gain ($p = 0.03$), and a non-significantly increased antisaccade error rate ($p = 0.08$).

6.3. Effects of relatedness on SPEM and antisaccade performance

SPEM gain at 10°/s was significantly correlated within patient–sibling pairs ($r = 0.44$; $P = 0.04$). All other correlations were nonsignificant (all $r < 0.29$; all $P > 0.19$).

6.4. Interrelationships between oculomotor and clinical variables

Increased positive symptoms were associated with reduced SPEM gain at 24°/s among patients ($r = -0.43$; $P = 0.04$). Higher levels of general psychopathology were associated with greater CUS frequency at 10°/s ($r = 0.65$; $P = 0.001$) and at 24°/s ($r = 0.43$; $P = 0.04$) as well as reduced SPEM gain at 24°/s ($r = -0.47$; $P = 0.02$). Reduced prosaccade gain was associated with increased positive ($r = -0.44$; $P = 0.03$) and negative

Table 1
Descriptive statistics and effect sizes of oculomotor variables

	Mean (S.D.)			Effect size		
	Patients ($N=24$)	Siblings ($N=24$)	Controls ($N=24$)	P–C	S–C	P–S
SPEM gain 10°/s	85.26 (10.13)[a]	88.41 (12.52)[a]	96.26 (6.03)	−0.94	−0.56	−0.26
SPEM gain 24°/s	76.54 (16.45)[a]	86.14 (12.92)[b]	88.21 (12.83)	−0.52	−0.12	−0.42
Anticipatory saccades 10°/s	0.31 (0.04)[a]	0.28 (0.04)[a]	0.17 (0.02)	0.53	0.46	0.15
Anticipatory saccades 24°/s	0.62 (0.06)[a]	0.56 (0.06)[b]	0.43 (0.05)	0.56	0.36	0.20
Catch-up saccades 10°/s	0.21 (0.03)[a]	0.12 (0.02)[a]	0.05 (0.02)	0.87	0.45	0.48
Catch-up saccades 24°/s	0.98 (0.10)[a]	0.79 (0.06)[b]	0.67 (0.05)	0.60	0.30	0.37
Fixation	0.05 (0.01)	0.07 (0.02)	0.04 (0.01)	0.07	0.22	−0.17
Antisaccade gain	−87.75 (31.23)	−85.63 (18.53)	−99.61 (20.33)	0.33	0.59	−0.06
Antisaccade latency	369.53 (215.60)	299.35 (54.99)	282.22 (48.31)	0.41	0.35	0.30
Antisaccade error rate	45.89 (25.09)	24.27 (17.42)	15.04 (11.53)	1.09	0.49	0.73
Prosaccade gain	87.28 (16.61)[a]	92.40 (14.92)	93.98 (9.84)	−0.40	−0.10	−0.29
Prosaccade latency	200.22 (58.59)[a]	179.53 (21.65)	181.94 (25.50)	0.29	−0.08	0.33

SPEM, smooth pursuit eye movements; P, patients; S, siblings; C, controls.
[a] $N=23$.
[b] $N=22$.

Table 2
Results of the group comparisons for oculomotor variables

	Overall Group Effect		Patients–Controls		Patients–Siblings		Siblings–Controls	
	Wald χ^2 (df = 2)	P	z	P	z	P	z	P
SPEM gain 10°/s	18.16	<0.0001	4.13	<0.001	1.18	0.24	−2.94	0.003
SPEM gain 24°/s	8.96	0.01	2.82	0.005	2.27	0.02	−0.49	0.62
Anticipatory saccades 10°/s	8.31	0.02	−2.77	0.06	−0.70	0.48	2.06	0.04
Anticipatory saccades 24°/s	7.43	0.02	−2.66	0.008	−0.82	0.41	1.80	0.07
Catch-up saccades 10°/s[a]	20.42	<0.0001	−4.49	<0.001	−2.73	0.006	1.78	0.08
Catch-up saccades 24°/s	10.05	0.007	−3.15	0.002	−1.88	0.06	1.22	0.22
Fixation	1.56	0.46	0.85	0.39	1.22	0.22	0.37	0.73
Antisaccade gain	5.51	0.06	−1.83	0.07	0.33	0.74	2.19	0.03
Antisaccade latency	5.93	0.05	−2.30	0.02	−1.85	0.06	0.46	0.65
Antisaccade error rate	35.65	<0.0001	−5.82	<0.001	−4.08	<0.001	1.74	0.08
Prosaccade gain	3.73	0.16	1.86	0.06	1.41	0.16	−0.46	0.65
Prosaccade latency[b]	6.28	0.04	−2.08	0.04	−2.32	0.02	−0.25	0.80

Overall group effects and contrasts are generated by the random effects regression model (Rabe-Hesketh et al., 2001).
[a] With age as covariate.
[b] With age and sex as covariates.

($r=-0.44$; $P=0.03$) symptoms. There was a trend for a correlation between saccade frequency during fixation and general psychopathology ($r=0.39$; $P=0.06$). Duration of illness was correlated with prosaccade latency ($r=0.52$; $P=0.01$). When this correlation was rerun covarying for age ($r=0.33$; $P=0.13$) or age and sex ($r=0.34$; $P=0.13$), it became nonsignificant, suggesting an influence of age on this relationship. No significant correlations between oculomotor measures and SIS were found in siblings or controls (all $P>0.10$).

7. Discussion

Deficits in oculomotor function among schizophrenia patients replicated previous evidence, showing reduced smooth pursuit gain and an increased frequency of saccades during pursuit (Levy et al., 1993) as well as an increased antisaccade error rate (Clementz, 1998). Additionally, patients had reduced antisaccade gain (Karoumi et al., 1998; McDowell et al., 1999) and increased prosaccade latency (Mackert & Flechtner, 1989), but normal visual fixation (Kissler & Clementz, 1998).

Of particular interest to the endophenotype hypothesis was the comparison of siblings of schizophrenia patients and controls. As predicted, siblings' performance was intermediate on most measures. Significant differences were found on SPEM gain and anticipatory saccade frequency at 10°/s. The latter finding is noteworthy given evidence that the small anticipatory saccade, termed "leading saccade", may be a particularly promising schizophrenia endophenotype (Ross et al., 2002). Our results, however, are only in part compar-

able to those of Ross et al., as we did not distinguish between small and large intrusive saccades.

While siblings showed normal prosaccades and fixation, their antisaccade performance was characterised by reduced gain and mildly increased error rate. Previous studies have generated inconsistent findings on whether first-degree relatives of schizophrenia patients show significant increases in antisaccade error. The difference observed here fell short of the conventional level of statistical significance. Cohen's effect size for this difference (0.49) was "medium", falling well within the range of those reported previously (Clementz et al., 1994: 0.44; Crawford et al., 1998: 0.23; Curtis et al., 2001: 0.68; Karoumi et al., 2001: 0.8; McDowell et al., 1999: 0.50–3.75; Thaker et al., 1996: 0.02 for subjects without spectrum diagnoses, 0.41 for subjects with spectrum diagnoses; Thaker et al., 2000: −0.15 and 0.72).

Taken together, first-degree relatives of schizophrenia patients appear to have perhaps moderate antisaccade error rate impairments. Differences between studies might relate to various factors, such as recruitment of psychiatrically affected relatives and/or controls, levels of schizotypy amongst relatives and controls, and differences in task specifications (such as gap, overlap, or non-overlap tasks, or near and far peripheral targets) known to affect performance levels and between-group differences (McDowell et al., 1999; Klein et al., 2000; McDowell & Clementz, 1997).

A noteworthy finding is that of siblings' reduced antisaccade gain, similar to deficits observed in patients in this and previous studies (McDowell et al., 1999; Karoumi et al., 1998; Ross et al., 1998). Antisaccade spatial accuracy measures sensorimotor coordinate transformations that occur between sensory input and motor output (Krappmann et al., 1998), possibly involving parietal and prefrontal cortex (Pierrot-Deseilligny et al., 1995). It remains to be investigated whether this measure will serve as a useful endophenotype. The finding of preserved prosaccade accuracy of relatives in this and previous studies (Crawford et al., 1998; Curtis et al., 2001; Karoumi et al., 2001) suggests intact programming and execution of saccadic motor commands when there is minimal requirement of spatial remapping.

A number of methodological issues positively distinguish this study from previous family studies. First, siblings and controls were tightly matched on a number of important variables, such as age, sex, years of education, ethnicity, and handedness.

Second, in contrast to some previous studies, siblings *and* controls were free of DSM-IV Axis I disorders and Axis II schizophrenia spectrum disorders, allowing the isolation of the variable of interest, namely the genetic relationship with a schizophrenia patient, in the absence of effects of psychiatric symptoms or treatment. Our observations thus confirm that eye movement deficits represent, in part, the effects of genetic liability for schizophrenia. However, given associations of oculomotor impairments with levels of schizophrenia (spectrum) symptoms among patients, their relatives, and healthy individuals (Levy et al., 1993; Thaker et al., 1996, 2000; O'Driscoll et al., 1998), as well as the observation of increased levels of such symptoms among first-degree relatives (Kendler et al., 1995), it is possible that these siblings' deficits somewhat underestimate the true level of deficit in the total population of first-degree relatives of schizophrenia patients. On the basis of these associations it may also be speculated that the expression of schizophrenia spectrum symptoms and oculomotor deficits share, in part, underlying neural mechanisms. Support for this hypothesis comes from evidence linking frontal lobe dysfunction to SPEM impairments *and* negative, or deficit, symptoms (Ross, 2000).

Third, the choice of statistical analysis of between-group differences was based on the assumption that the genetic relatedness of patients and siblings violated the assumptions of ANOVA concerning independent observations. Relatives were expected to attract similar, i.e. statistically correlated, scores. Evidence of this relatedness was obtained for smooth pursuit gain. This finding highlights the familial contribution to smooth pursuit variance and underscores the need to consider effects of familial relatedness in the statistical analysis of between-group differences. The reason why within-family correlations did not attain statistical significance for other variables is unclear but could be due to the relatively small sample size or the absence of psychiatric symptoms in the siblings.

One limitation of this study concerns the sample size. Although of sufficient power to replicate well-established performance patterns among patients, larger samples are needed to conclusively assess the validity of any putative endophenotype. In this context it should be noted that statistically nonsignificant deficits in the siblings may be due to lack of statistical power, possibly representing Type II errors. Finally, including only one sibling per family may have allowed for the possibility of sampling bias, limiting the generalisability of the present findings.

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