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Saccadic distractibility is elevated in schizophrenia patients, but not in their unaffected relatives

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ABSTRACT

Background. Saccadic distractibility, as measured by the antisaccade task, has attracted attention as a putative endophenotypic marker for schizophrenia. Some studies have suggested that this measure is elevated in the unaffected relatives of schizophrenia patients. However, recent studies have called this into question and the topic remains controversial.

Method. Saccadic distractibility was measured in 53 patients with DSM-IV schizophrenia, 80 unaffected first-degree relatives and 41 unaffected controls.

Results. Schizophrenia patients performed worse than relatives and controls combined ($p < 0.00001$), but relatives did not differ significantly from controls. Performance in multiply affected families was no worse than that in singly affected families. Relatives with a high presumed genetic risk for schizophrenia performed no worse than other relatives. The performance of the patients did not predict that of their relatives.

Conclusions. These results demonstrate that saccadic distractibility is strongly associated with disease status but not with genetic loading for schizophrenia. We conclude that saccadic distractibility is unlikely to be useful as an endophenotypic marker in schizophrenia.

INTRODUCTION

Family, twin and adoption studies have indicated that operationally defined schizophrenia has a heritability of over 0.8 (Cardno *et al.* 1999). However, the non-Mendelian segregation within families and the disparate linkage findings suggest that schizophrenia is a complex, polygenic disorder (Gottesman & Shields, 1982). Genetic transmission in schizophrenia is likely to be further complicated by epistasis (Wade, 2001) (non-additive interactions between genes), pleiotropy (Hodgkin, 1998) (a single gene determining two or more characteristics), incomplete penetrance (Levinson *et al.* 1996), interactions with environmental factors (Van Os & Sham,

2002), and the probable aetiological heterogeneity of the clinically defined disorder (Cardno & Gottesman, 2000).

One approach to overcoming these problems is the use of intermediate phenotypes, or biological markers. These are anatomical, physiological or biochemical variables that segregate with genetic risk for the disorder, and which are assumed to have a simpler genetic architecture than the disorder itself (Weinberger, 2002), with a more proximal relationship to the underlying genes. It is hoped that the use of biological markers will identify more homogeneous groups of subjects within the broader clinically defined phenotype, and thus lead to improved success in the search for susceptibility genes.

The necessary criteria for a biological marker were set out by Wickham & Murray (1997).

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The most important criterion, and the one that has received the most research attention, is an increased prevalence of the marker in the unaffected relatives of affected subjects. Several putative biological markers have been studied, including structural brain changes (McDonald *et al.* 2004), endogenous event-related potentials (Bramon *et al.* 2004) and performance on a variety of neuropsychological tasks (Touloupoulou *et al.* 2003).

The study of eye-movement abnormalities as potential biological markers for schizophrenia dates back to the 1970s (Holzman *et al.* 1974). Initially research focused on abnormalities of smooth pursuit eye movements, but recently, the study of saccadic eye movements has attracted attention, particularly the antisaccade task.

The antisaccade task

The standard antisaccade task (Hallett, 1978) begins with the subject fixating on a central illuminated target. The target then moves rapidly to a peripheral location, and the subject is required to inhibit his/her reflexive saccade (in pursuit of the target) and to generate, instead, a saccade in the opposite direction, which is termed an antisaccade. A saccadic distractibility error is recorded if a subject fails to inhibit the reflexive saccade in the direction of the target. Saccadic distractibility is usually expressed as the percentage of trials in which the initial eye movement was towards the stimulus. Variations of the task include a gap or overlap (McDowell & Clementz, 1997) between the offset of the central stimulus and the onset of the peripheral stimulus.

Every published study to date examining the antisaccade task in schizophrenia and its variants has demonstrated that schizophrenia patients perform more poorly than control subjects in suppressing reflexive saccades, regardless of variations in the paradigm (Levy *et al.* 2004). By contrast, studies that have examined the ability of schizophrenia patients to perform simple reflexive saccades have found that their performance is within the normal range (Crawford *et al.* 1995a).

Several studies have examined the prevalence of saccadic distractibility errors in unaffected relatives of patients with schizophrenia, including one study by our research group

(Crawford *et al.* 1998). Some studies have shown evidence of elevated rates of saccadic distractibility errors in well relatives compared to control populations (Curtis *et al.* 2001; Karoumi *et al.* 2001) but others have either found non-significant differences, or have not presented a statistical test comparing well relatives with controls (Thaker *et al.* 1996, 2000; Katsanis *et al.* 1997; Crawford *et al.* 1998; Brownstein *et al.* 2003). Two recent meta-analyses have investigated the presence of abnormalities in the unaffected relatives of schizophrenia patients. Calkins and colleagues (2004) demonstrated that when all studies are combined, relatives perform worse than controls. However, Levy *et al.* (2004) showed that studies which applied more stringent exclusion criteria to controls than to relatives reported large effect sizes, whereas those with symmetrical criteria showed small and non-significant differences.

As well as being over-expressed in the well relatives of patients, biological markers should correlate with the likelihood of carrying susceptibility genes, both between and within families. Thus, members of multiply affected families are hypothesized to have poorer eye tracking than members of singly affected families (Lewis *et al.* 1987). This hypothesis has previously been tested in a small study by Ross *et al.* (1998), with negative results.

A further prediction is that within multiply affected families, relatives who appear to be 'carriers' of the genetic risk for schizophrenia have worse performance than other members of multiply affected families. An example of such a 'presumed obligate carrier' would be a man whose daughter and brother both had schizophrenia, but who was not affected himself. Ross *et al.* (1998) found that these 'presumed obligate carriers' had worse performance than other well relatives.

To summarize, previous research has demonstrated that schizophrenia patients perform worse than control subjects on the antisaccade task, but the crucial question as to whether this trait is related to genetic risk for schizophrenia, thus warranting further investigation as a putative biological marker for schizophrenia, remains controversial (Brownstein *et al.* 2003). We therefore examined antisaccades in both schizophrenia patients and their relatives from

both singly and multiply affected families. Our hypotheses were as follows:

(1) Schizophrenia patients will perform worse than their unaffected relatives and normal controls.

(2) Unaffected first-degree relatives of patients will perform worse than normal controls.

(3) Patients from multiply affected families will perform worse than those from singly affected families.

(4) Relatives from multiply affected families will perform worse than those from singly affected families.

(5) Among the relatives from multiply affected families, presumed obligate carriers will perform worse than the remainder.

(6) Relatives of patients who perform poorly will have worse performance than relatives of patients who perform well.

METHOD

The study was conducted as part of the Maudsley Family Study (McDonald *et al.* 2004), a larger investigation of biological markers in schizophrenia patients and their relatives. There is no overlap between the data presented here and the data previously reported by Crawford *et al.* (1998).

Subjects

All subjects were Caucasians, aged 16–69 years, whose first language was English. Exclusion criteria were substance or alcohol dependence in the previous year, or a lifetime history of significant head injury or organic brain disease. Subjects gave informed written consent for their participation. The study was approved by the local Ethical Committee.

The study groups are represented diagrammatically in Fig. 1. A total of 53 patients fulfilling DSM-IV (APA, 1994) criteria for schizophrenia ($n=47$), schizoaffective disorder ($n=5$) or schizophreniform disorder ($n=1$) were included in the study. Patients were divided into two groups on the basis of family history: (a) multiply affected, where the proband had at least one first- or second-degree relative with schizophrenia or other psychotic disorder, and (b) 'singly affected', where the proband had no family history of schizophrenia or other

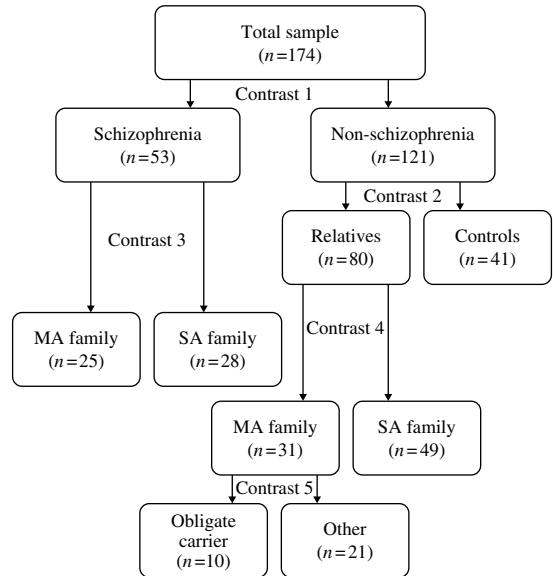


FIG. 1. Composition of subject groups and contrasts. MA, multiply affected; SA, singly affected.

psychotic disorder as far as third-degree relatives. Patients were recruited either in response to advertisements through voluntary organizations or by direct referral from their treating clinicians. Due to the comparative rarity of multiply affected families, these were specifically targeted when advertising the study.

All available first-degree relatives were screened for mental health problems. Any who were suspected of psychotic symptoms were interviewed using the Schedule for Affective Disorders and Schizophrenia – Lifetime version (SADS-L; Endicott & Spitzer, 1978), and were reassigned to the Patient category if they fulfilled diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder. However, those with a lifetime history of a non-psychotic DSM-IV disorder were not excluded. The relatives from multiply affected families included 10 parents who were classified as 'presumed obligate carriers', on the basis that (a) they also had a sibling or parent affected and (b) transmission of liability was apparently unilineal within that family.

Forty-one control subjects were recruited from the local community via newspaper advertisements and from hospital and university staff. None of the control subjects had a personal or family history of schizophrenia or other

Table 1. Lifetime DSM-IV diagnoses and demographic details in the six groups

Group	Schizophrenia	Schizophreniform disorder	Schizoaffective disorder	MD	Other DSM-IV diagnosis	No disorder	Age (yr)		Education (yr)		Gender (% males)
							Mean	S.D.	Mean	S.D.	
Sz, MA family	22	1	2				36.4	11.5	14.1	3.9	69.6
Sz, SA family	25		3				32.7	8.8	13.6	2.2	66.7
Obligate carrier				2	1	7	54.0	3.7	14.0	3.3	30.0
Relative, MA family				5	2	14	42.6	14.4	14.3	3.0	45.5
Relative, SA family				6	1	42	50.1	14.1	13.8	2.8	32.7
Control				4		37	41.9	14.7	13.7	3.5	41.5
<i>F</i>							9.9		0.2		
χ^2											18.8
<i>p</i>							<0.001		n.s.		<0.01

MD, Major depression; Sz, schizophrenia; MA, multiply affected; SA, singly affected.

psychotic disorder. A lifetime personal or family history of other psychiatric disorders was not an exclusion criterion. Therefore, unlike many previous studies, having a relative with schizophrenia (or other psychotic disorder), was the only criterion that distinguished between unaffected relatives and controls. The diagnoses in the six groups are shown in Table 1.

Clinical assessment

Patients, relatives, and controls were assessed using the same clinical scales in face-to-face interviews. Diagnoses were made using the SADS-L and family history was assessed using the Family Interview for Genetic Studies (Nurnberger *et al.* 1994). Additional information regarding the timing and nature of psychopathology was collected for all participants allowing DSM-IV diagnoses to be made. Clinical information was always supplemented with collateral histories with informants, and from medical notes where available.

Eye-movement assessment

The antisaccade task was conducted using the AmTech ET3 eye-tracking system (AmTech GmbH, Weinheim, Germany). A Dell Optiplex 560/L computer (Dell Inc., Round Rock, TX, USA) was used to control the apparatus, and to record eye movements, using AmTech ET3 software. Eye movements were detected by means of an infra-red reflection oculograph, with eye position sampled at 200 Hz. The stimuli consisted of a central LED, with peripheral LEDs at 15° horizontally, mounted on a board, 180 cm away from the subject's eyes. Eye-movement recordings were later analysed using AmTech Eyemap version 2.0, by a trained

rater (H.S.) who was blind to diagnosis or subject group.

The tests were carried out as the last of a battery of eye-movement tasks, including smooth pursuit and prosaccade tasks. The subjects were seated in a darkened room, and were requested not to move their head, which rested on an adjustable frame. At the start of each trial, the central LED was illuminated. After 800 ms, the central LED was extinguished and simultaneously, one of the peripheral targets ($\pm 15^\circ$ eccentricity) was illuminated for 3 s (accompanied by an audible signal) and then returned to the centre. The subjects were instructed to fixate on the central target until it moved to the peripheral position, and then to direct their gaze as quickly and accurately as possible to its mirror position (of equal distance from, but in the opposite direction to, the peripheral target). Blinks and other artefacts were identified by inspection of the trace, and removed from the analysis. A saccade was defined as a deflection of $\geq 2.5^\circ$. Any initial saccade (discounting the first 80 ms) towards the peripheral target was scored as a distractibility error. Where this was followed by a saccade in the correct direction, the latter was termed a corrective saccade. The number of corrected distractibility errors divided by the number of analysable trials gave the distractibility error score. As well as the distractibility error score, the mean latency of each type of saccade (antisaccade, corrective saccade, and distractibility error) was measured for each subject.

Each participant completed a set of 12 practice trials to ensure that they understood the test instructions. Subjects with an error rate of

over 50% on the practice battery were given a further explanation of the task, followed by a second practice battery, with a maximum of two practice batteries. Subjects then completed two sets of 12 experimental trials, during which the position of the stimulus was varied pseudo-randomly throughout the set to prevent predictive saccades, in the order LRRLLRLLRRL.

Statistical analyses

Statistical analyses were conducted using SPSS version 10.1 (SPSS Inc., Chicago, IL, USA) and STATA version 7.0 (StataCorp., College Station, TX, USA). Age and years of education were compared between groups using analysis of variance (ANOVA), and gender using the χ^2 statistic.

Since members of a family are likely to share both genes and environment, observations from within the same family should not be assumed to be independent, particularly for a putative genetic marker. We therefore used multilevel modelling to take account of the non-independence of observations within families using the 'robust cluster' option in STATA. The rationale for its use in studies of this type is discussed more fully by Rabe-Hesketh *et al.* (2001).

Age and gender were entered as covariates. In order to allow the calculation of adjusted means, we used a linear regression equation without a constant, and centred the age variable around the overall mean. Gender was coded such that female was the reference category. The regression coefficients for the dummy group variables therefore represented the group means, adjusted to the mean age of the sample and to female gender (Table 2).

We made comparisons between combinations of groups in an orthogonal design, according to the diagram in Fig. 1. The comparisons corresponded to our hypotheses, as stated above, and were as follows: test 1, schizophrenia patients *versus* all other groups; test 2, relatives *versus* controls; test 3, schizophrenia patients from multiply affected *versus* singly affected families; test 4, relatives from multiply affected *versus* singly affected families; test 5, presumed obligate carriers *versus* other relatives from multiply affected families.

The hypothesis that the performance of patients would predict that of their relatives was tested in our sample by dividing the patients

Table 2. Raw and adjusted means for saccadic distractibility by group

Group	Mean saccadic distractibility (%)	95% CI	s.d.	Mean adjusted for age and gender
Sz, MA family	41.7	30.8–52.6	29.0	47.7
Sz, SA family	48.5	38.0–59.1	28.2	55.5
Obligate carrier	29.2	18.5–39.8	17.5	30.2
Relative, MA family	18.6	13.4–23.9	12.9	22.6
Relative, SA family	29.4	24.4–34.4	19.4	31.0
Control	26.6	20.5–32.6	19.4	30.7

Sz, Schizophrenia; MA, multiply affected; SA, singly affected. 95% confidence intervals (CI) are shown. The means adjusted for age and gender are the regression coefficients for the dummy group variables in the regression. They are based on the mean age of the entire sample, and female gender.

into 'good' and 'poor' groups, using a cut-off score of the mean error score in controls + 1 s.d., and then comparing the performance in the relatives of each group using Student's *t* test.

RESULTS

Demographic details

The demographic details of the groups are shown in Table 1.

The schizophrenia patients had a mean length of illness of 12.5 years (s.d. = 10.6). The groups were well matched for years of education, but there were significant group differences for age [$F=9.9$ (5 d.f.), $p<0.001$] and gender [$\chi^2=18.77$ (5 d.f.), $p<0.01$], and these variables were, therefore, included in the regression equation.

Neither age (Pearson's $r=-0.13$, $p=\text{n.s.}$) nor gender ($t=-0.337$, $p=\text{n.s.}$) was associated with saccadic distractibility score in the whole sample, although saccadic distractibility was significantly correlated with length of illness ($r=0.37$, $p<0.01$). However, some studies have found that the relationship between age and saccadic distractibility may be different in patients and controls (Crawford *et al.* 1998), indicating that simply controlling for age across the entire sample may not be appropriate. We therefore tested for different effects of age in different groups by using group dummy variables to generate age x group interaction terms and testing for differences between their regression coefficients. There were no significant differences ($F=1.82$, $p=0.13$). We are, therefore, satisfied that it was appropriate to control for age over the whole sample.

Table 3. Comparisons of group means for saccadic distractibility

Hypothesis	Test group(s)	ADE score	Comparison group(s)	ADE score	F(1, 98)	p
1	Schizophrenia	45.3	All others	26.6	32.3	<0.00001
2	All relatives	26.6	Controls	26.6	0.51	N.S.
3	Sz, MA families	41.7	Sz, SA families	48.5	1.03	N.S.
4	Relatives, MA families	22.0	Relatives, SA families	29.4	1.48	N.S.
5	Obligate carriers	29.2	Other relatives, MA families	18.6	1.43	N.S.

ADE, Antisaccade distractibility error; Sz, Schizophrenia; MA, multiply affected; SA, singly affected.

Table 4. Other measures: latencies

	Schizophrenia, MA families		Schizophrenia, SA families		Obligate carriers		Relatives, other MA families		Relatives, SA families		Controls	
	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.
ADE latency (ms)	305.0	54.0	298.4	35.4	311.2	58.3	277.9	85.8	316.8	52.4	302.2	83.7
Antisaccade latency (ms)	417.2	171.0	394.8	133.3	418.2	65.4	406.7	55.7	445.2	79.6	400.0	84.6
ADEs corrected (%)	87.2	24.6	93.1	17.0	100	—	90.3	30.1	96.8	14.6	95.2	16.7

MA, multiply affected; SA, singly affected. ADE, Antisaccade distractibility error.

The raw and adjusted means for the six groups are shown in Table 2.

The results of the Wald tests for orthogonal comparisons between group means are shown in Table 3. Hypothesis (1), that schizophrenia patients would differ from all other groups, was supported. Hypotheses (2)–(5), which predicted differences between relatives and controls, and between relatives and patients with different presumed genetic loading, were all rejected.

Division of the schizophrenia patients in to good and poor performers resulted in two approximately equal groups of good ($n=27$) and poor ($n=26$) performers. There was no statistical difference in the error scores of relatives of good performers ($n=51$, mean error score = 27.2) and relatives of poor performers ($n=29$, mean error score = 24.8, $t=0.534$, $p=0.595$).

Other measures

Regression analyses similar to those described above were conducted for other measures. There were no significant group differences for latency of either correct or incorrect saccades, or the proportion of antisaccade errors that were corrected (Table 4).

DISCUSSION

As in all previous studies, schizophrenia patients performed significantly worse than relatives and control subjects. However, we found no evidence that such performance indicates a genetic vulnerability to schizophrenia: unaffected relatives performed no worse than control subjects, and there was no significant difference between members of singly or multiply affected families, nor between obligate carriers and other relatives from multiply affected families. While these results do not preclude a genetic influence on the antisaccade task, they do not support a strong genetic overlap with schizophrenia.

Our results raise two important questions:

(a) Why are our results not in agreement with some previous studies, which showed differences between relatives and control subjects?

(b) If we are correct in concluding that saccadic distractibility is not a genetic marker for schizophrenia, then why is it elevated in schizophrenia?

(a) Why are our results not in agreement with previous studies?

Before answering the first question, it should be noted that few studies have conclusively

demonstrated differences in saccadic distractibility between relatives and controls (Levy *et al.* 2004). Many studies (Clementz *et al.* 1994; Thaker *et al.* 1996; Katsanis *et al.* 1997; Crawford *et al.* 1998; Ross *et al.* 1998; McDowell *et al.* 1999), have, however, shown non-significant trends for relatives to perform more poorly than control subjects, whilst our data showed an opposite trend.

Task parameters

Although the large difference in ADE score between our patients and the rest of the sample demonstrates that methodology of the study was sufficient to detect highly significant group differences, the task parameters that we used may not have been optimal for detecting differences between groups. McDowell and others have investigated the effects of manipulations of stimulus parameters on antisaccade performance. In one study (McDowell *et al.* 1999), patients and relatives could be better distinguished from controls using a 16° stimulus eccentricity than 8°. At 15°, our study should, therefore, be well placed to detect group differences. The same group (McDowell & Clementz, 1997) have also investigated the effect of introducing an overlap between the illumination of the central cue and the peripheral target. They found that a better separation between groups was achieved in the 'overlap' condition than in the standard version of the task. It is thus possible that, had we used the overlap condition, a difference would then have emerged between relatives and controls. Our study used 24 trials per subject, whereas some have used more (Thaker *et al.* 1996, 2000; McDowell & Clementz, 1997; Karoumi *et al.* 2001). However, the meta-analysis by Levy *et al.* (2004) demonstrated that the number of trials did not influence the effect size.

Unlike most previous studies, we employed an objective definition of a saccade, and used a blinded rater. Both of these factors were designed to eliminate observer bias.

Selection of relatives and controls

Saccadic distractibility has a poor specificity for schizophrenia, with increased rates in unipolar depression (Sweeney *et al.* 1998), bipolar affective disorder (Serenio & Holzman, 1995; Tien *et al.* 1996; Katsanis *et al.* 1997) and

obsessive-compulsive disorder (Tien *et al.* 1992; Rosenberg *et al.* 1997). It follows that, if they are to be comparable, relative and control groups must be subject to the same exclusion criteria with respect to psychiatric morbidity and differ only with regard to family history of schizophrenia. However, in some studies, controls were included only if they had a negative personal and family history of any psychiatric disorder, whereas this restriction was not applied to relatives. In one study, for example Katsanis *et al.* (1997), about one third of 'well' relatives had a psychiatric disorder. These relatives were compared to control subjects with no lifetime history of any psychiatric disorder. Since the lifetime population prevalence of psychiatric disorders is estimated at over 1 in 4 (Goldberg, 1991) such 'normal' controls are not typical of the general population, and should not be compared with relatives who have significant levels of morbidity. This issue has recently been explored by Levy *et al.* (2004) in a meta-analysis, which demonstrated that whereas studies with asymmetrical exclusion criteria tended to demonstrate large significant differences between relatives and controls, those with symmetrical criteria showed smaller, usually non-significant, effects.

In the present study, the only criterion that distinguished the relative and control group was the presence of psychosis in a first-degree relative.

The performance of our control sample (26.6% error rate) is comparable to that of previous studies (Brownstein *et al.* 2003). To simulate the use of super-normal controls, we excluded the four control subjects who had a psychiatric history, but this did not change our results. Nevertheless, our data did not allow us to identify control subjects with a family history of psychiatric disorders, so the effects of this could not be tested.

Statistical analysis

Our analysis differed from most previous studies in two main respects. First, we used robust standard errors, taking into account non-independence of observations from within the same family. Second, we controlled for age and gender. Previous studies have demonstrated an increase in saccadic distractibility with normal ageing (Sweeney *et al.* 2001), and Crawford

et al. (1998) found that females performed worse than males in a similar sample of schizophrenia subjects, their healthy first-degree relatives, and normal controls.

Publication bias

The tendency of authors, journals and reviewers to favour positive results has been well documented. Furthermore, with some notable exceptions (Brownstein *et al.* 2003), the published studies that have failed to show statistically significant differences between relatives and control subjects have not always made this clear. We are aware of other negative findings that have not been published (P. Clissa and A. Jablensky, personal communication).

Lack of power

Our sample size was clearly adequate to demonstrate highly significant differences between schizophrenia and non-schizophrenia subjects. Although the contrast between schizophrenia and non-schizophrenia subjects had somewhat greater power than the contrast between unaffected relatives and controls, our data indicate that if the first-degree relatives of schizophrenia patients do have a deficit in saccadic distractibility, it is very small compared to the deficit in patients.

(b) If saccadic distractibility is not a genetic marker for schizophrenia, then why is it elevated in schizophrenia?

Marker of environmental risk factors

A number of early and late environmental risk factors for schizophrenia have been identified, including pregnancy and birth complications, winter birth and drug misuse (Murray & Fearon, 1999). Saccadic distractibility could be a marker for one or more of these risk factors.

Marker of the neuropathology of schizophrenia

Saccadic distractibility may be a marker of a neuropathological process in schizophrenia. Brain lesion and electrophysiological studies of the antisaccade task have implicated a large number of brain areas, particularly the prefrontal cortex (Everling & Fischer, 1998). Functional MRI studies suggest that prefrontal activity is increased in normal, but not in

schizophrenia, subjects during antisaccade tasks (McDowell *et al.* 2002). Furthermore, several studies have found correlations between antisaccade distractibility error score and the Wisconsin Card Sorting Test, an established test of frontal lobe dysfunction (Milner & Petrides, 1996), in both normal and schizophrenic individuals (Rosse *et al.* 1993; Crawford *et al.* 1995*a, b*, 1996; Tien *et al.* 1996; Radant *et al.* 1997; Karoumi *et al.* 1998).

Direct effect of antipsychotic drugs

Although abnormalities have been observed in neuroleptic-naïve schizophrenia patients (Hutton *et al.* 1998), an effect of medication on antisaccade errors cannot be ruled out. Crawford *et al.* (1995*b*) found that neuroleptic-treated patients produced more saccadic distractibility errors than untreated patients. Karoumi *et al.* (2001) noted a positive correlation between antipsychotic dose (measured in chlorpromazine dose equivalents) and distractibility error rate (Spearman's $\rho = 0.48$, $p < 0.05$). In our sample, however, there was no correlation between saccadic distractibility and current antipsychotic dose, measured in chlorpromazine equivalents ($r = -0.153$, $p = \text{N.S.}$).

Chronic effect of medication usage

Chronic effects of antipsychotics would not necessarily be detected by examining current drug dose. Thaker *et al.* (1989) demonstrated a two-fold excess of saccadic distractibility errors in schizophrenia patients with tardive dyskinesia (TD), compared with those without TD. In our own sample, saccadic distractibility was significantly correlated with length of illness ($r = 0.37$, $p < 0.01$) but not with age ($r = 0.18$, $p = \text{N.S.}$) in schizophrenia subjects, a finding that is compatible with an effect of chronic medication or disease progression.

Marker of neurodegeneration or neuroplasticity

Although there is no conclusive evidence at present of neurodegeneration in schizophrenia (Allin & Murray, 2002), there have recently been some suggestions of a progression of brain abnormalities in schizophrenia, possibly as a result of neuroplasticity (Weinberger & McClure, 2002). Our finding of a correlation between saccadic distractibility and length

of illness is consistent with such an interpretation.

Poor understanding of the task

The schizophrenia patients may have had a worse comprehension of the task than other groups, due, perhaps, to the presence of psychotic symptoms. However, distractibility errors were followed by a corrective saccade in around 90% of instances, with no significant difference between schizophrenia subjects and other groups (see Table 4). Furthermore, we took steps to minimize any such effect by re-explaining the task if the proportion of errors exceeded 50% in the practice trial.

Part of a generalized neuropsychological deficit

In a separate study using an overlapping sample, we have found substantial correlations between ADE score and both pre-morbid and current IQ, verbal memory and associative learning, most of which were not present in relatives or control subjects (Zanelli *et al.* unpublished observations). This suggests that, whatever the cause of these antisaccade errors in schizophrenia subjects, they are likely to represent part of a more generalized deficit.

Weaknesses of the study

As in most investigations of this type, the patients in this study may have a higher level of functioning than most schizophrenia subjects, as they were all well enough to travel to the study centre and participate willingly. Our groups were not well matched for age and gender, although we did not attempt to match them, preferring to control for these statistically in the analysis.

CONCLUSIONS

Schizophrenia patients perform poorly on the antisaccade task, compared to their unaffected relatives and controls, and the abnormality appears to worsen with length of illness. However, our data do not provide support for the hypotheses that the unaffected relatives of patients have impaired performance, nor that performance reflects genetic loading, either between or within families. These results challenge the validity of saccadic distractibility as a putative genetic marker of schizophrenia.

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DECLARATION OF INTEREST

None.

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