Simple Viewing Tests Can Detect Eye Movement Abnormalities That Distinguish Schizophrenia Cases from Controls with Exceptional Accuracy

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Background: We have investigated which eye-movement tests alone and combined can best discriminate schizophrenia cases from control subjects and their predictive validity.

Methods: A training set of 88 schizophrenia cases and 88 controls had a range of eye movements recorded; the predictive validity of the tests was then examined on eye-movement data from 34 9-month retest cases and controls, and from 36 novel schizophrenia cases and 52 control subjects. Eye movements were recorded during smooth pursuit, fixation stability, and free-viewing tasks. Group differences on performance measures were examined by univariate and multivariate analyses. Model fitting was used to compare regression, boosted tree, and probabilistic neural network approaches.

Results: As a group, schizophrenia cases differed from control subjects on almost all eye-movement tests, including horizontal and Lissajous pursuit, visual scanpath, and fixation stability; fixation dispersal during free viewing was the best single discriminator. Effects were stable over time, and independent of sex, medication, or cigarette smoking. A boosted tree model achieved perfect separation of the 88 training cases from 88 control subjects; its predictive validity on retest assessments and novel cases and control subjects was 87.8%. However, when we examined the whole data set of 298 assessments, a cross-validated probabilistic neural network model was superior and could discriminate all cases from controls with near perfect accuracy at 98.3%.

Conclusions: Simple viewing patterns can detect eye-movement abnormalities that can discriminate schizophrenia cases from control subjects with exceptional accuracy.

Key Words: Classification, eye-movement phenotype, neural network, predictive model, risk marker, schizophrenia

Although Diefendorf and Dodge in 1908 (1) reported that abnormal eye movements were present in a proportion of unmedicated psychotic patients, only limited analyses of the multiple and subtle variations embedded in the many components that define eye-tracking performance in schizophrenia have been performed to date.

Indeed there has been a general lack of success in identifying stable trait markers associated with schizophrenia that can accurately delineate cases from control subjects; this includes studies using both composite and multivariate analysis of phenotypic abnormalities associated with schizophrenia. The literature is extensive and outside the scope of this article (see Supplement 1).

Regarding smooth pursuit, there is overwhelming evidence that schizophrenia probands and their biological family members have a deficit in accurate smooth pursuit (2–15). The incidence reported in probands also shows wide variation from as low as 12% (5) and as high as 95% (16). When the sensitivity reported in cases is high, it is usually accompanied by high rates in controls with as many as 19% of volunteers also having difficulty producing accurate pursuit (17–19).

Fixation/gaze maintenance on a single target is unsteady in schizophrenia (12,20–23). First-degree relatives of probands are also deficient in fixation maintenance (24). There have, however, been negative studies (25).

Free-viewing scanpaths formed in schizophrenia are also abnormal. Most studies have found eye movements are frequently confined to a limited area of the stimulus or are concentrated on selected features, and scanning is atypical in contextual perception (26,27), recognition (28–30), search (31,32), and free-viewing tasks (33,34). So far, restricted and atypical scanning are also found in relatives (35,35–37) and siblings (37,38). No incidence rates for abnormal fixation in scanning tasks have yet been reported in schizophrenia.

We examined a large group of schizophrenia cases and controls using a combination of picture free-viewing, smooth pursuit tracking, and steady fixation tasks. Highly accurate classifier models were built using their eye-movement performance measures. We tested these models using data from nine month retests and a new set of cases and controls and found them to be robust. When the data from all 298 assessments were used to train a network model, predicted classification accuracy was 98.3%.

Methods and Materials

Participants

Schizophrenia patients ($n = 88$) meeting DSM-IV criteria were recruited from ongoing research programmes. Detailed medical and psychiatric histories were collected for each person. Diagnoses were confirmed using case note review and the Structured Clinical Interview for DSM-IV (SCID) (39). A small number of patients ($n = 7$) were unable to complete the interview and SCID was completed by interrogating case notes alone. Operational criteria (OPCRIT)-generated diagnoses (40) were also obtained for all patients. There

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was good agreement on ratings performed by physicians and trained psychologists (Cohen's $\kappa = .8$). Patients were tested at the Ludwig-Maximilians-University of Munich and at three psychiatric health care research sites in Scotland. Schizophrenia cases were mostly outpatients, and all were in a stable clinical state at time of testing. Positive and Negative Syndrome Scale was obtained for 62 of the 88 cases: positive score Median (95% confidence interval [CI]) = 29 (25–32), negative = 22 (19–25), general = 48 (41–55.8), total = 98.5 (87–109). Six patients were receiving no antipsychotic medication at time of testing. Others received first-generation antipsychotics only ($n = 11$), second-generation antipsychotics only ($n = 64$), or a combination of the two ($n = 6$). Pharmacology was unavailable for one patient. Median chlorpromazine-equivalent dosage for those receiving antipsychotic medication was 350 mg per day (mean = 455.0, SD = 374.1 mg). A number of patients were also receiving antidepressants ($n = 25$), hypnotics ($n = 6$), anxiolytics ($n = 12$), mood stabilizers ($n = 3$), and anticholinergic medication ($n = 9$). Patients were excluded if they had a history of head injury or neurological disease(s).

The control group ($n = 88$) included mentally healthy, nonclinical individuals recruited from the volunteer panel at the University of Aberdeen and public advertisements. Exclusion criteria comprised responses to semistructured questions about history of drug or alcohol abuse or dependence within 6 months before testing, major head trauma involving loss of consciousness for more than 5 minutes, epilepsy or other neurological dysfunction, first-degree family history of psychosis, or unusable eye-movement data.

Groups were matched on age (Table 1 and Supplement 1). There were more males in the patient group than the control group [$\chi^2(1) = 14.22$, $p < .001$, $\varphi = .28$]. Participants had normal or corrected-to-normal vision.

Other Groups Tested

Retest Group. Schizophrenia ($n = 26$) and control subjects ($n = 8$) were retested after a 9-month interval [schizophrenia mean (SD) = 258 (121) days, control = 316 (149) days; $t(32) = 1.125$, $p = .269$].

Novel Groups. These groups included new schizophrenia ($n = 36$) and control ($n = 13$) subjects matched on age with training-set age and a group of younger controls ($n = 39$). The usual exclusion criteria applied (Table 2).

The study underwent academic and clinical ethical reviews in Scotland and Germany and was conducted in accordance with the Declaration of Helsinki.

Eye Movement Recordings

Infrared eye-movement recording was performed using head-mounted EyeLinkI (SMI, Berlin, Germany; 250 Hz) for 88% of participants or EyeLink1000 (SR Research, Ontario, Canada; 500 Hz) with a remote camera and head/chin rest. There were no obvious differences in data quality yielded by either device. Calibrations were performed using a 3 × 3 fixation matrix. Drift correction was applied throughout. Eye position was sampled binocularly (or monocularly if circumstances dictated) at a spatial resolution of .01° or greater.

Stimuli were presented on a 19-inch (48 cm) display viewed from 70 cm and subtended 28.1h × 21.4 v degrees of visual angle. Short breaks were permitted between tests. Smooth pursuit involved tracking a .5° circular target for 20 sec as it moved sinusoidally on the horizontal meridian (.4 Hz) or in Lissajous patterns (in horizontal and vertical space; .2 or .4 Hz). Free-viewing scanpaths were produced in response to 56 color images (8-sec each). Images included luminance-balanced natural and manmade environments showing information at different spatial scales; everyday objects and food in sparse and cluttered scenes; expressive, neutral, and occluded faces; animals; and unfamiliar computer-generated images (fractal patterns, gray-scale "pink noise"). We used a fixation stability test as a proxy for saccadic inhibition (Supplement 1), and because everyone was able to complete this task, data were available from all participants. Individuals were required to maintain steady gaze

Table 1. Participants

Variable	Schizophrenia Median[a] or Mean (SD)	Healthy Control Median[a] or Mean (SD)	χ^2 or $F(1,df)$[b] Value	*p* Value
Training Set				
n	88	88		
Sex, F:M	30:58	55:33	14.22[c]	<.001
Age, years	44.5 (10.1)	42.5 (12.3)	1.45 (174)	.347
Education, median, years	8–11	12–15	37.02 (173)	<.001
Illness age-of-onset, years	26.7 (8.1)			
Illness duration, years	16.9 (10.5)			
CPZe, mg/day	453.2 (372.2)			
Nicotine intake per day[d]	12.9 (16.5)	1.9 (5.5)	37.44 (171)	<.001
Nicotine recent, min since[e]	16.9 (28.9)	24.2 (126.7)	.34 (172)	<.001
Caffeine intake, cups/day[f]	4.9 (1.1)	3.5 (.49)	4.20 (174)	.497
Caffeine recent, min since[g]	364.8 (766.3)	255.4 (470.7)	1.23 (166)	.288
HADS (anxiety)	10.5 (5.9)	4.7 (2.7)	39.16 (130)	<.001
HADS (depression)	6.3 (4.0)	2.1 (2.2)	38.20 (83)	<.001

CPZe, neuroleptic chlorpromazine-equivalent dosage; HADS, Hamilton Anxiety and Depression Scale.

[a]Education was bracketed <8 years, 8–11 years, 12–15 years, >15 years. Controls typically spent 2 to 3 years longer than patients in full-time education. Median coded range is shown.

[b]*F* value based on univariate analysis of variance using ranked data if nonnormally distributed.

[c]Pearson χ^2 test.

[d]Nicotine general intake was coded as multiples of 10 per day.

[e]Nicotine recent intake to within 15-min periods.

[f]Caffeine general intake was coded as multiples of 5 cups per day.

[g]Caffeine recent consumption to within 15-min periods.