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The Electroretinogram as a Potential Biomarker of Psychosis in Children at Familial Risk

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We previously proposed the electroretinogram (ERG) as a promising biomarker of major psychiatric disorders such as schizophrenia (SZ) and bipolar disorder (BP), given that we found anomalies in the ERG parameters of patients with these diagnoses as well as in their children who are at high risk (HR) of developing such disorders. The aim of the present study is to investigate the usefulness of the ERG for individual detection, among HR children, of an ERG profile resembling that of a SZ patient, as this may indicate a stronger likelihood of transition to psychosis. Using a logistic regression model previously derived from the ERG assessments of SZ patients and control (CT) subjects, individual risk scores were obtained for 61 HR and 80 CT youth. Those with a very high individual risk score were classified as "schizophrenia-like" (*SZ-like*). We found that the HR subjects were 3.5 times more likely to be classified as *SZ-like* than the CT subjects (95% CI [1.1–11.8]). Furthermore, among the HR subjects, we studied the relationship between the *SZ-like* classification and psychotic-like experiences and found that HR subjects classified as *SZ-like* were 2.7 times more likely than all remaining HR subjects to have experienced psychotic-like symptoms (95% CI [1.3–4.6]), and 6.8 times more likely than those with a very low individual risk score (95% CI [1.4–40.4]). Our results suggest that a model previously derived from ERG data on SZ patients could be a potential tool for early detection of the susceptibility to a psychotic-like disorder among familial HR children.

Key words: familial high risk/individualized risk/validation/schizophrenia/bipolar disorder/prediction

Introduction

Over the past few years, researchers have been searching for biomarkers that could help diagnose psychiatric disorders, detect early onset, and predict transition to psychosis.[1] Biomarkers such as inflammatory markers,[2] neuroimaging,[3–5] or eye movements[6] have been proposed for these purposes. A biological diagnostic-aid tool could help to identify subjects most at risk of developing psychosis in order to prevent or delay onset of the disease with early treatment and intervention, thus improving patients' outcome and response to treatment.[7] In the present study, we are interested in the validation of the electroretinogram (ERG) as a non-invasive, rapidly acquired and objective biological tool capable of providing an individual estimate of the risk of developing psychosis for a subject at familial risk.

One of the major challenges in the search for a neurobiological marker has been the need for non-invasive techniques to investigate the living brain in humans. However, the retina has already been identified as an accessible part of the brain, and retinal functions can be safely investigated using an ERG. In Hébert et al,[8] we showed that a large sample of 150 subjects with schizophrenia (SZ) significantly differed from 200 healthy control (CT) subjects on several ERG parameters, on which basis we derived a logistic model that calculates, for a new subject, the risk score of having an ERG profile resembling that of an SZ patient. These findings supported the idea that the ERG could be used as a diagnostic aid, as suggested by Silverstein et al.[9] In previous studies, we also reported that the ERG parameters of unaffected and non-medicated children with a parent affected by SZ or bipolar disorder (BP) significantly differed, on average, from the ERG parameters of young CT subjects.[10,11] Family studies have clearly demonstrated that these youth are at high risk (HR) of developing SZ or BP, but fortunately, only a fraction will actually develop a psychiatric disorder.[12] Interestingly, based on this

hypothesis, Peredo et al[13,14] detected subgroups of familial HR subjects showing control-like (*CT-like*) cognitive and ERG profiles.

In research aiming to characterize HR subjects, analyses are often based on group comparisons, thus the conclusions apply to HR subjects as a group.[10,14,15] Other studies have considered individual prediction models, which would offer the advantage of helping clinicians to provide personalized prevention and intervention in clinical practice.[16] Some of these studies have used promising multi-domain risk calculators to detect individual risk of transition to psychosis.[16–19] However, a multi-domain approach requires a great deal of information in order to obtain individual risk scores. A few other approaches have been proposed that use only one domain to calculate risks, such as the "simple personalized risk calculator" derived from combinations of items from the Structured Interview for Prodromal Symptoms.[20] Our approach, based on ERG results, aimed to test the extent to which a single objective biomarker may be predictive. One of the strengths of this approach is that it uses knowledge gained from the ERG measurements of 150 patients with SZ to assess individual risk of transition to psychosis for young HR subjects.

Benefiting from our prediction model based on patients,[8] the main objective of the present study is to recognize, in children at familial risk of SZ or BP, those whose ERG profiles are thus classified as schizophrenia-like (*SZ-like*), assuming that this may pinpoint children most at risk of developing psychosis. We hypothesized that: (1) The HR group will have a higher proportion of subjects whose ERG profile is classified as *SZ-like* compared to the CT group; and (2) HR subjects classified as *SZ-like* will have experienced PLEs in a higher proportion than HR subjects classified as *CT-like*. Validation of these two hypotheses would support the ERG as a potential biomarker for estimating individual risk of transition to psychosis and thus, as a tool aiding early detection in familial HR subjects.

Methods

Sample Characteristics

As shown in Figure 2 in Gagné et al[10] the ERG profiles of patients with SZ and BP are the most distant from those of CT subjects. Drawing from the population of Eastern Québec (Canada), we recruited a sample of 61 children with a parent who had received a definite diagnosis of either SZ (HR-SZ: 16%) or BP (HR-BP: 84%). The clinical diagnoses of the parents were confirmed by reviewing their medical records according to the DSM-IV. All 61 HR participants were evaluated for psychotic-like experiences (see below for definition) and were between 6 and 24 years old at their ERG evaluation, 24 years remaining below the age of onset of SZ and BP. We used the same set of exclusion criteria as Peredo et al.[13,14] Note that siblings were not excluded, as long as each child met the criteria.

A reference group of 80 healthy young individuals was also recruited from the same population in Eastern Quebec, via ads in local newspapers. Exclusion criteria were the same as for HR participants with the addition of having received any axis I DSM-IV diagnosis or having a first-degree positive family history of SZ or BP spectrum. Note that none of these controls had been used to derive the ERG model in the previous Hébert et al[8] study involving SZ patients.

Study Design and Assessments

This follow-up cohort study was approved by the Neuroscience and Mental Health Research Ethics Committee of the CIUSSS-Capitale Nationale. A signed informed consent was obtained from all adult participants or from parents when children were under 18 years of age.

Electroretinogram

We employed the methodology and protocol described in Hébert et al.[8] Briefly, ERG full-field cone and rod ERGs were performed with the Espion (E2) system (Diagnosys LLC, Lowell, MA) and obtained in non-dilated eyes using DTL electrodes (Shieldex 33/9 Thread, Statex, Bremen, Germany) secured deep in the conjunctival sac. For the cones ERG, following 10 min of light adaptation to an 80 cd/m^2 background provided by a Ganzfeld color dome, a luminance response function (LRF) was generated using 13 white flash luminances ranging from 0.42 to 800 cd.s/m^2 (i.e., 20.37 to 2.9 log units). For the rod ERG, following 30 minutes of dark adaptation, an LRF was achieved using 13 green (peak: 509 nm) flash luminances ranging from 0.001 to 1 cd.s/m^2 (i.e., 23 to 0 log units). We used cone responses obtained at a fixed intensity of 7.5 cd.m^2/s and at Vmax (for definition see Hébert et al[8]) and rod responses obtained at 0.1 cd.m^2/s (pure rods) and 1 cd.m^2/s (mixed rod-cone response). The typical ERG waveform comprises a negative component called the a-wave followed by a positive component called the b-wave. By convention, two dimensions are used to define these two components, namely the amplitude and latency. Considering that no clear a-wave is observed for the pure rod response, this yielded 14 parameters (8 for the cones, plus 6 for the rods).

Definition of ERG Classification

In Hébert et al,[8] we showed that subjects with schizophrenia differed from healthy controls on several ERG parameters. A multiple stepwise logistic regression was performed comparing the 150 SZ patients to the 200 healthy CT subjects in order to obtain the subset of ERG measurements that best estimated the probability of being a SZ patient, controlling for gender, age at ERG assessment and pupil size. Table 1 shows the logistic regression coefficients (β) for the six ERG variables and covariates

retained in the model. For each new subject with ERG measurements, the following logit-transformed probability of this logistic regression model estimates the probability of their being classified as *SZ-like*:

$$\exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_6 x_6 + \beta_7 z_1 + \beta_8 z_2 + \beta_9 z_3) / [1 + \exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_9 z_3)]).$$

This probability represents the individualized risk score.

Each familial HR and young CT subject was classified according to their individualized risk score. HR and CT subjects with an ERG profile yielding a risk score of 0.90 or greater were classified as *SZ-like*, and were compared to the remaining subjects, i.e., those classified as *CT-like*. Then, subjects classified as *SZ-like* were compared to those with an ERG profile yielding a risk score below 0.10, a range referred to as *very low-risk*.

Psychotic-like Experiences

Psychotic-like experiences were assessed using direct semi-structured interviews with the HR youths and their parents, as adapted from the Dunedin Study interview protocol,[21] the DIS-C[22] and the questionnaire used by Laurens et al.[23] The nine core items focused on three key domains: perceptual abnormalities (visual and auditory hallucinations), delusions (persecutory, suspiciousness, reading thoughts, ideas of reference, control, grandiosity) and bizarre behavior. The corresponding questions are provided in Supplementary File 1. The interviewers probed to rule out symptoms with plausible explanations. In a second step, an experienced clinical neuropsychologist reviewed all of the narratives to classify each experience as either 0: absent of PLE; 1: likely a PLE; or 2: definite PLE. For the present study, the last two levels were combined to create a dichotomous outcome.

Age at Last Clinical Evaluation

Over the last 15 years, we recruited HR children, assessed their ERG and collected their clinical data related to psychotic-like experiences. In order to avoid any bias arising from an older age at the last clinical evaluation among subjects classified as *SZ-like*, thus increasing their risk of having experienced psychotic-like symptoms, subject age at last clinical evaluation was controlled for in subsequent analyses.

Statistical Analysis

All statistical analyses were performed using SAS/STAT software v. 9.4 (SAS Institute Inc., Cary, NC, USA). First, for each of the 61 HR and 80 young CT subjects, the Hébert et al[8] ERG logistic model shown in table 1 was used to obtain the individual risk scores of having an ERG profile resembling that of an SZ patient. This was achieved using the LOGISTIC procedure with the option *inmodel* and the *score* statement. Then, according to their risk score, all HR and young CT subjects were individually classified as *SZ-like* or *CT-like*. The percentage of subjects classified as *SZ-like* was compared between the groups of 61 HR and 80 CT using a one-sided chi-square test. The corresponding relative risk (RR) with a 95% confidence interval (CI) was also computed. A one-sided *P*-value was used, given that we expected the HR group to have a higher proportion of subjects classified as *SZ-like*. The HR and CT groups were also analyzed according to 0.95 and 0.85 risk score cut-off points to assess the sensitivity of our results to the choice of cut-off value. All subsequent analyses were performed with a cut-off value of 0.90. Chi-square and t-tests were performed between HR and CT groups to detect potential confounding variables listed in table 2, and a one-sided test compared their mean risk score. RRs were adjusted for confounding variables

Table 1. Parameter Estimates of the Logistic Regression Model From Hébert et al.[8] Derived from ERG Data on Patients with Schizophrenia (SZ).

Name of variable	Variable in regression model	Logistic regression coefficient (β)
Intercept	x_0	−24.53
Cone b-W Lat (Vmax)	x_1	1.04
Rod a-W Lat (Mixed)	x_2	−0.60
Cone a-W Lat (Vmax)	x_3	−0.61
Cone a-W Amp (Fixed)	x_4	−0.11
Rod b-W Amp (Mixed)	x_5	−0.01
Cone b-W Lat (Fixed)	x_6	0.67
Gender (female)	z_1	−0.25
Age at ERG assessment (years)	z_2	−0.03
Pupil size (mm)	z_3	−0.06

Note: a-W, a-Wave; *b-W*, b-Wave; *Amp*, amplitude; *Lat*, latency.This Model was Used to Calculate the Probability of Having an *SZ-like* ERG Profile, i.e., the Individualized Risk Score, and was Based on ERG Measurements, Controlling for Gender, Age at ERG Assessment and Pupil Size. For Each of the 61 Children at Risk and 80 Control Subjects in the Present Study, This Risk Score was Obtained with the Following Equation: $\exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_6 x_6 + \beta_7 z_1 + \beta_8 z_2 + \beta_9 z_3)/[1+\exp(\beta_0 + \beta_1 z_1 + \cdots + \beta_9 z_3)]$.

Table 2. Comparison of Sociodemographic and Clinical Characteristics Between 61 Children at High Risk (HR) and 80 Control (CT) Subjects

Sociodemographic and clinical characteristics	HR subjects $N = 61$	CT subjects $N = 80$	P-value[a]
Gender			
Number of males (%)	30 (49%)	40 (50%)	0.92
Age at ERG assessment in years			
Mean (SD) [Range]	15.7 (5.1) [6.2–24.8]	15.5 (5.0) [6.1–24.9]	0.80
Pupil size in *mm*.			
Mean (SD) [Range]	4.6 (1.0) [2.0–8.0]	4.5 (0.9) [1.0–7.0]	0.68
Smoking status[b]			
Number of smokers (%)	8 (15%)	3 (5%)	0.07
Alcohol use[b]			
Yes (%)	20 (38%)	18 (30%)	0.35
Drug use[b]			
Yes (%)	4 (8%)	3 (5%)	0.56
Medication use[c]			
Yes (%)	16 (36%)	0 (0%)	**<0.0001**

[a] HR and CT subjects were compared using a two-sided *t-test* for age and pupil size and a two-sided *chi-square* for gender, smoking status and alcohol, drug or medication use.
[b] Sample sizes differ from those of the full sample: $N_{HR} = 52$; $N_{CT} = 60$.
[c] Medication includes psychostimulants, antipsychotics, antidepressants and benzodiazepines.

using a generalized linear model with the GENMOD procedure, a *log* link and a *binomial* distribution.

The second objective of assessing the relationship between ERG profiles and presence of PLEs was investigated among the HR subjects. First, HR subjects classified as *SZ-like* were compared to HR subjects classified as *CT-like*, and then to those classified as *very low-risk*. This yielded 2 two-way frequency tables for which RRs were estimated with corresponding 95% CIs. One-sided *P*-values were used, given that HR subjects classified as *SZ-like* were expected to have a higher likelihood of having experienced psychotic-like symptoms than subjects classified as *CT-like*, and then those classified as *very low-risk*.

Lastly, to control for age at last clinical evaluation, RRs and significance levels were reassessed through a generalized linear model with the GENMOD procedure and a *log* link. This time, a modified Poisson distribution was used instead of the binomial, due to convergence problems that had occurred with the latter. To estimate robust error variance, the *repeated* statement was used, with subjects as identifier, and an unstructured correlation matrix (option *type* = *unstr*).[24] Hence, the presence of PLEs among HR subjects was predicted using the ERG classification as a dichotomous predictor variable, defined first by classifying HR subjects as *SZ-like* or not (model 1) and then defined by classifying HR subjects as *SZ-like* or as *very low-risk* (model 2), while controlling for age at last clinical evaluation. Relative risks were obtained by calculating the exponential of the beta estimate.

Results

HR and CT individuals had very similar sociodemographic and clinical characteristics, as described in table 2. Both groups were about 50% male and around 15 years old at ERG assessment. The proportions of smoking status and alcohol or drug use were similar between groups (*P*-values = 0.07, 0.35, and 0.56 respectively), but more HR subjects than CT subjects took medication (psychostimulants, antipsychotics, antidepressants or benzodiazepines; 36% vs 0%; *P*-value <0.0001). The distributions of individualized risk scores for the HR and CT groups are represented in boxplots in figure 1. Risk scores varied from 0.0 to 1.0 for each group but were, on average, higher in the HR group (0.52 for HR vs 0.38 for CT; *P*-value = 0.005).

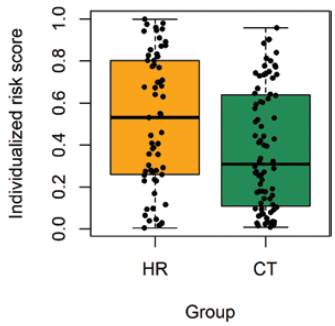

Fig. 1. Distributions of individualized risk scores of being classified as *SZ-like* according to the electroretinogram profile of subjects from the high risk (HR) and control (CT) groups, respectively. Risk scores are obtained through the logistic regression adjusted for schizophrenia patients published in Hébert et al.[8]

When comparing HR to CT children regarding their ERG classification defined according to the 0.90 cut-off value, analysis revealed that HR subjects were 3.5 times more likely to be classified as *SZ-like* than CT subjects

(95% CI [1.1, 11.8], *P*-value = 0.02). Indeed, 13% of HR subjects were classified as *SZ-like*, compared to only 4% of CT subjects. The RR of being classified as *SZ-like* was 4.0 using the 0.85 cut-off point (20% in HR vs. 5% in CT; *P*-value = 0.003) and reached 6.6 using the 0.95 cut-off point (8.20 % in HR vs 1.25% in CT; *P*-value = 0.02). Although all three cut-off points provided significant results, the cut-off value of 0.90 was selected for pursuing subsequent analyses given that it provided the most conservative result. When medication use was added as a covariate, the RR increased from 3.5 to 4.1.

Table 3 shows the proportion of HR subjects in each ERG classification that had experienced PLEs. The risk of having experienced psychotic-like symptoms was 2.7 times more likely among subjects classified as *SZ-like* than among those classified as *CT-like* (75% vs 28%, respectively; *P*-value = 0.005). Moreover, the risk of having experienced psychotic-like symptoms was 6.8 times more likely among subjects classified as *SZ-like* than among those classified as *very low-risk* (75% vs 11%, respectively; *P*-value = 0.004).

Table 4 shows the RR estimates corresponding to the two comparisons above, adjusted for age at last clinical evaluation. The adjusted RR was estimated as 2.6 when comparing subjects classified as *SZ-like* to those classified as *CT-like* (model 1; *P*-value = 0.005), while the adjusted RR reached 7 when subjects classified as *SZ-like* were compared to those classified as *very low-risk* (model 2; *P*-value = 0.03). Moreover, there were no significant changes in the RRs when we individually controlled for sociodemographic and clinical variables (see table 2). Lastly, the percentage of HR-SZ classified as *SZ-like* (10%) was comparable (*P*-value = 0.8) to that of HR-BP (14%).

Discussion

The originality of this study is to use the ERG regression model derived from SZ patients in Hébert et al[8] to determine how much the ERG profile of an HR or CT subject resembled that of an SZ patient. As hypothesized, we found that, based on their ERG profile, HR subjects were 3.5 times more likely than CT subjects to be classified as *SZ-like* (risk score > 0.9). In addition, although a higher proportion of HR subjects than of CT subjects took medication, when we controlled for this factor, the RR slightly increased to 4.1, suggesting that medication was not a confounding variable but rather a factor that could have normalized the ERG among HR subjects. No other sociodemographic or clinical characteristics differed between the HR and CT groups (table 2), thus none of these characteristics were considered to be confounding variables.

Our second objective aimed to address the fact that only some children with a familial risk will develop a psychiatric disorder.[12] Knowing that not all HR subjects will eventually transition to psychosis, we wished to verify the hypothesis that the ERG could identify those whose developmental trajectory would most likely lead to psychosis. We thus expected that HR subjects classified as *SZ-like* would be more likely to have experienced PLEs than the remaining HR subjects. Indeed, this study confirmed that subjects classified as *SZ-like* were 2.7 times more likely to have experienced PLEs than all remaining HR subjects, and 6.8 times more likely than those classified as *very low-risk*.

Given that our sample of 61 HR subjects combined 10 HR-SZ and 51 HR-BP, we verified whether family type was related to ERG classification and found no relationship. This could be due to the fact that the risk score assesses the probability of psychosis, which can also be part of bipolar disorder and is, once again, consistent with what was observed in Hébert et al[11] and Gagné et al.[10] We also verified whether age at last clinical evaluation could be a confounding factor. This was not at all the case since, after controlling for age at last

Table 3. Relationship Between ERG Classification and Psychotic-like Experiences Among the 61 Children at High Risk (HR).

		Psychotic-like experience			
ERG classification	*N*	Presence (%)	Absence (%)	Relative Risk[b] [95% CI]	*P*-value[c]
First comparison:	**61**			**2.7** [1.3-4.6]	0.005
SZ-like	8	6 (75.0)	2 (25.0)		
CT-like	53	15 (28.3)	38 (71.7)		
Second comparison:	**17**			**6.8** [1.4-40.4]	0.004
SZ-like	8	6 (75.0)	2 (25.0)		
Very low-risk	9	1 (11.1)	8 (88.9)		

Note: Subjects Classified as 'Schizophrenia-Like' (*SZ-like*), i.e., Those with an ERG Profile Yielding a Risk Score[a] of 0.90 or Greater ($n = 8$), were First Compared to Subjects Classified as 'Control-Like' (*CT-like*), i.e., Those with an ERG Profile Yielding a Risk Score of Less than 0.90 ($n = 53$), and Then to a Subgroup of HR Subjects Classified as *Very Low-Risk*, i.e., Those with an ERG Profile Yielding a Risk Score of 0.10 or Less ($n = 9$).

[a] Individual risk score obtained according to the ERG logistic model of Hébert et al.[9]

[b] Risk of having psychotic-like experiences among HR subjects classified as *SZ-like* over risk of those classified as *CT-like* (first comparison), and then over risk of those classified as *very low risk* (second comparison).

[c] Based on a one-sided *chi-square* test, given that relative risks greater than 1 were expected.

Table 4. Poisson Regression Modeling of the Risk of Psychotic-Like Experiences as Predicted by ERG Classification, While Controlling for Age at Last Clinical Evaluation.

Variable	*N*	β Estimate (se)	Relative risk[a]	*P*-value[b]
Model 1	**61**			
ERG classification[c]		0.96 (0.37)	**2.6**	0.005
Age at last clinical evaluation		−0.06 (0.02)	0.9	0.009
Model 2	**17**			
ERG classification[d]		1.95 (1.04)	**7.0**	0.03
Age at last clinical evaluation		0.01 (0.04)	-	0.73

Note: Model 1 was Performed on the 61 HR Subjects Classified as 'Schizophrenia-Like' (*SZ-like*) ($n = 8$) or as 'Control-Like' (*CT-like*) ($n = 53$), Whereas Model 2 was Performed on the 17 Subjects Classified as *SZ-like* ($n = 8$) or as *Very Low-Risk* ($n = 9$), as Defined in table 3.

[a] Exponential of the β estimate: risk of having PLE among subjects classified as *SZ-like* over risk of subjects classified as *CT-like* (Model 1) or over risk of subjects classified as *very low-risk* (Model 2).

[b] The *P*-values corresponding to the *classification* variables are one-sided given that relative risks greater than 1 were expected.

[c] The dichotomous *classification* variable in Model 1 is defined by classifying subjects as *SZ-like* or *CT-like*.

[d] The dichotomous *classification* variable in Model 2 is defined by classifying subjects as *SZ-like* or *very low-risk*.

clinical evaluation in Poisson regression models (table 4), the adjusted RRs remained significant and were very similar to those obtained in table 3 when no covariate was used. As for smoking, only 2 of the 8 subjects classified as *SZ-like* had a positive smoking status, therefore excluding smoking as a potential confounding factor in our results. However, given that a link between smoking and ERG had previously been reported,[9] future research should take this factor into account.

These results validated our second hypothesis, according to which HR subjects classified as *SZ-like* would be more likely to have experienced lifetime psychotic-like symptoms, even after controlling for age at last clinical assessment. This would suggest that, by calculating individual risks in familial HR subjects using the ERG logistic model, one could identify those with an increased likelihood of a developmental trajectory towards a psychosis. One of the advantages of a biomarker such as the ERG is that, although it is based on a single assessment, it involves multiple ERG indicators which strengthens its predictive and construct validity.

One significant limitation of our study is that our eligibility criteria limited our sample to 61 HR subjects who had both ERG and clinical assessments, which resulted in only 8 HR subjects being classified as *SZ-like*. Therefore, replications of our findings with larger samples will be necessary. Another limitation was that our clinical outcome for subjects was having experienced PLEs rather than a complete conversion to psychosis. We are aware that PLEs are not necessarily specific to SZ and that *SZ-like* ERG profiles may also be predictive of the trajectory of a broader psychiatric-like disorder, in a similar manner as clinical high risk of psychosis (CHR-P) syndrome can lead to psychosis or a broader disorder. Greater sensitivity might also be obtained by a more comprehensive assessment of the PLEs by adding sensory, perceptual or cognitive symptoms. Also, we cannot exclude the possibility that the schizophrenia risk based on ERG increases as the subject approaches the full expression of psychosis and that, therefore, the RR of the present study would be underestimated. Moreover, given that the conversion rate to psychosis in a familial HR sample like ours is lower than that of CHR-P samples, the predictive validity of ERG findings needs to be separately determined for samples that are defined using different criteria, as well as in larger samples of HR subjects with SZ parents, who would ideally be followed until the age of transition to psychosis. In addition, the ERG prediction algorithm, based on our previous study of 150 SZ patients, needs further refinement in larger and more varied patient samples for generalization.

The ERG is a non-invasive, safe, objective and accessible test that has already shown its potential to become an aid to diagnosis for several psychiatric illnesses[8,9,25] and neurological conditions, such as multiple sclerosis or Parkinson's disease.[26] The strength of the present study is that it relied on knowledge previously gained from a study of SZ patients[8] to derive individualized risk scores, which allowed identification of subjects having a *SZ-like* ERG profile. Our data suggest that this *SZ-like* ERG was more often found among HR than CT youths. Moreover, HR subjects classified as *SZ-like* were more likely to have experienced PLEs than those classified as *CT-like*. These two findings reinforce the ERG as a potential biomarker contributing to individualized prediction and early detection of the risk of transition to psychosis among children at familial risk, contributing highly translational findings to clinical practice, as previously recognized by Silverstein et al.[27]

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin Open* online.

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References

1. Weickert CS, Weickert TW, Pillai A, Buckley PF. Biomarkers in schizophrenia: a brief conceptual consideration. *Dis Markers*. 2013;35(1):3–9.
2. Khoury R, Nasrallah HA. Inflammatory biomarkers in individuals at clinical high risk for psychosis (CHR-P): state or trait? *Schizophr Res*. 2018;199:31–38.
3. Armio RL, Laurikainen H, Ilonen T, *et al.* Amygdala subnucleus volumes in psychosis high-risk state and first-episode psychosis: amygdala subnuclei and psychosis. *Schizophr Res*. 2020;215:284–292.
4. Decross SN, Farabaugh AH, Holmes AJ, *et al.* Increased amygdala-visual cortex connectivity in youth with persecutory ideation. *Psychol Med*. 2019;50(2): 273–283.
5. Karcher NR, Hua JPY, Kerns JG. Probabilistic category learning and striatal functional activation in psychosis risk. *Schizophr Bull*. 2019;45(2):396–404.
6. Obyedkov I, Skuhareuskaya M, Skugarevsky O, *et al.* Saccadic eye movements in different dimensions of schizophrenia and in clinical high-risk state for psychosis. *BMC Psychiatry*. 2019;19(1):1–10.
7. Van Der Gaag M, Smit F, Bechdolf A, *et al.* Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. *Schizophr Res*. 2013;149(1–3):56–62.
8. Hébert M, Mérette C, Gagné AM, *et al.* The electroretinogram may differentiate schizophrenia from bipolar disorder. *Biol Psychiatry*. 2020;87(3):263–270.
9. Silverstein SM, Fradkin SI, Demmin DL. Schizophrenia and the retina: towards a 2020 perspective. *Schizophr Res*. 2020;219:84–94.
10. Gagné AM, Moreau I, St-Amour I, Marquet P, Maziade M. Retinal function anomalies in young offspring at genetic risk of schizophrenia and mood disorder: the meaning for the illness pathophysiology. *Schizophr Res*. 2020;219:19–24.
11. Hébert M, Gagné AM, Paradis ME, *et al.* Retinal response to light in young nonaffected offspring at high genetic risk of neuropsychiatric brain disorders. *Biol Psychiatry*. 2010;67(3):270–274.
12. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr Bull*. 2014;40(1):28–38.
13. Peredo R, Jomphe V, Maziade M, Paccalet T, Merette C. Cluster analysis identifies two cognitive profiles among offspring of patients with a major psychiatric disorder: the healthy and impaired profiles. *J Child Adolesc Psychiatry*. 2018;2(2):6–11.
14. Peredo R, Gagné AM, Gilbert E, Hébert M, Maziade M, Mérette C. Electroretinography may reveal cognitive impairment among a cohort of subjects at risk of a major psychiatric disorder. *Psychiatry Res*. 2020;291(April):113227.
15. de Wit S, Ziermans TB, Nieuwenhuis M, *et al.* Individual prediction of long-term outcome in adolescents at ultra-high risk for psychosis: applying machine learning techniques to brain imaging data. *Hum Brain Mapp*. 2017;38(2):704–714.
16. Zarogianni E, Storkey AJ, Johnstone EC, Owens DGC, Lawrie SM. Improved individualized prediction of schizophrenia in subjects at familial high risk, based on neuroanatomical data, schizotypal and neurocognitive features. *Schizophr Res*. 2017;181:6–12.
17. Fernandes BS, Karmakar C, Tamouza R, *et al.* Precision psychiatry with immunological and cognitive biomarkers: a multi-domain prediction for the diagnosis of bipolar disorder or schizophrenia using machine learning. *Transl Psychiatry*. 2020;10(1):1–13.
18. Cannon TD, Yu C, Addington J, *et al.* An individualized risk calculator for research in prodromal psychosis. *Am J Psychiatry*. 2016;173(10):980–988.
19. Paccalet T, Gilbert E, Berthelot N, *et al.* Liability indicators aggregate many years before transition to illness in offspring descending from kindreds affected by schizophrenia or bipolar disorder. *Schizophr Res*. 2016;175(1–3):186–192.
20. Zhang T, Xu L, Tang Y, *et al.* Prediction of psychosis in prodrome: development and validation of a simple, personalized risk calculator. *Psychol Med*. 2019;49(12):1990–1998.
21. Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch Gen Psychiatry*. 2000;57(11):1053–1058.
22. Costello A, Edelbrock C, Kalas R, Kessler M, Klaric S. *Diagnostic Interview Schedule for Children: Child Version*. Rockville, MD: National Institute of Mental Health; 1982.
23. Laurens KR, Hodgins S, Maughan B, Murray RM, Rutter ML, Taylor EA. Community screening for psychotic-like experiences and other putative antecedents of schizophrenia in children aged 9-12 years. *Schizophr Res*. 2007;90(1–3):130–146.
24. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702–706.

25. Youssef P, Nath S, Chaimowitz GA, Prat SS. Electroretinography in psychiatry: a systematic literature review. *Eur Psychiatry*. 2019;62:97–106.
26. Silverstein SM, Demmin DL, Schallek JB, Fradkin SI. Measures of retinal structure and function as biomarkers in neurology and psychiatry. *Biomarkers Neuropsychiatry*. 2020;2(May):100018.
27. Silverstein SM, Thompson JL. Progress, possibilities, and pitfalls in electroretinography research in psychiatry. *Biol Psychiatry*. 2020;87(3):202–203.