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Original data

Childhood trauma and altered response of retinal neurons as an early risk endophenotype of schizophrenia and mood disorder

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A R T I C L E I N F O

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A B S T R A C T

Background: Exposure to childhood trauma may cause several alterations in brain structure and connectivity in adult patients having a major psychiatric disorder. Recent reports have shown that adult patients and young healthy offspring of patients carry similar abnormal retinal response. Because the retina and the brain have the same embryonic origin, the retina gives access to living neuronal tissue that may capture the early neurobiological effect of trauma.
Objective: Evaluate the association between exposure to childhood trauma and anomalies in cone (photopic) and rod (scotopic) responses assessed by electroretinography (ERG) in children and adolescents at familial risk (FHRs) of psychosis or mood disorders.
Methods: ERG recordings (n=194) undertaken on 134 offspring (M_{age} of 1st recording=15.7, 49% females) enrolled in our longitudinal study and born to a parent having DSM-IV schizophrenia, bipolar disorder or major depressive disorder were analyzed using repeated measures linear mixed models and applying multiple comparisons. The scotopic and photopic a- and b-wave latencies and amplitudes were recorded. Five types of childhood trauma were assessed prospectively and retrospectively in FHRs: physical abuse, sexual abuse, emotional abuse, neglect and witnessing domestic violence.
Results: None of the ERG scotopic or photopic parameters were associated with the global measure of exposure to trauma. However, when analyzing the specific effect of each type of trauma, data suggested that physical abuse in girls would be significantly associated with a prolonged scotopic a-wave latency (p=0.024, ES=0.28) and a trend of association was observed with a prolonged photopic b-wave latency (p=0.099, ES=0.27).
Conclusion: Our study did not suggest a substantial effect of childhood trauma on previously reported ERG anomalies in the cone and rod response in youth at familial risk of psychosis or mood disorder. Only one type of trauma i.e., physical violence toward the child, could have a specific effect on the cone and rod prolonged latencies in girls. Methodological limitations are discussed for consideration in interpreting the findings.

Introduction

Childhood trauma, under the form of childhood maltreatment, has a potent and pervasive effect on the developmental origin and the clinical status of major psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder (Bailey et al., 2018; Berthelot et al., 2019; Berthelot et al., 2022; Teicher et al., 2022). More than 45% of these patients report having been exposed to childhood trauma (Varese et al., 2012; Palmier-Claus et al., 2016; Nelson et al., 2017; Stanton et al., 2020) and trauma exposed patients have an earlier age of onset, greater illness severity and a poorer response to treatment (Leverich and Post, 2006; Hovens et al., 2012; Cakir et al., 2016; Kocsis-Bogar et al., 2018; Kilian et al., 2020).

We have ourselves reported on the mechanisms through which

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childhood trauma may have a deleterious effect in the early risk trajectory heading to the development of a major affective or non-affective disorders (Berthelot et al., 2022). First, we showed that, in children and adolescents at familial risk (FHRs) of schizophrenia, bipolar and major depressive disorder, childhood trauma was associated with the presence of cognitive deficits (Berthelot et al., 2015) in domains that are also impaired in adult patients (Maziade et al., 2011). Second, trauma was found associated with the progressive accumulation of risk indicators in FHRs (Berthelot et al., 2022). Importantly, such an accumulation or aggregation of risk indicators was shown to have a greater predictivity of a later transition to illness than any individual risk indicator alone (Cannon et al., 2016; Carpenter, 2016; Paccalet et al., 2016; Demmin et al., 2018; Bernardin et al., 2020; Cosker et al., 2021).

Besides, a large body of data indicate that exposure to maltreatment would provoke neurobiological alterations in stress-susceptible brain regions such as the hypothalamic pituitary adrenal response or a decrease in the volume of the hippocampus (Riem et al., 2015; Samson et al., 2023). Although these hits on brain structures and connectivity are long lasting, the exact timing of the expression of these neurobiological scars are little-known and some studies suggest that many might not yet be apparent earlier in youth at risk (De Bellis et al., 2002; Riem et al., 2015; Ahmed-Leitao et al., 2016). Furthermore, data suggest that specific types of childhood maltreatment would produce alterations in specific regions of the adult patient's brain (Cassiers et al., 2018; Teicher et al., 2022). For example, domestic violence would be associated with reduced visual cortex gray matter (Tomoda et al., 2012) while subjects exposed to parental verbal abuse during childhood would develop alterations in neural pathways involved in language (Choi et al., 2009). In contrast, emotional abuse was found to be associated with cortical thinning in regions relevant to self-awareness and self-evaluation (Heim et al., 2013). Moreover, some neurobiological marks would not be the same in female as in male adult patients (Teicher et al., 2018; Teicher et al., 2022; Samson et al., 2023).

Anomalies in the physiological response of retinal cells may represent an informative target for investigating the neurobiological impact of childhood trauma since these anomalies have been reported by us and others in the three major psychiatric disorders (Hebert et al., 2015; Hebert et al., 2017; Demmin et al., 2018; Bernardin et al., 2020; Hebert et al., 2020; Cosker et al., 2021). More precisely, electroretinographic (ERG) studies have shown that retinal neurons such as the rods and the cones exhibit decreased amplitudes and prolonged latencies in response to light stimuli in schizophrenia and bipolar patients. Remarkably, these same ERG anomalies were observable in children and adolescents at familial risk of schizophrenia, bipolar disorder and major depressive disorder suggesting that they would have a developmental origin (Gagne et al., 2020). Since both adult patients and FHR display differences compared to normal controls, these retinal anomalies may represent early neurobiological marks of vulnerability of a child at risk. Moreover, since the retina and the brain have the same embryonic origin (Lavoie et al., 2014; Gagne et al., 2015; Silverstein et al., 2020), retinal anomalies would be a reflection or a signal of the brain dysfunctions involved in major psychiatric disorders (Silverstein et al., 2020).

Thus, a critical and relevant question raised by the above bodies of data is the extent to which exposure to childhood trauma, or the different types of traumas, can be responsible for these childhood retinal anomalies that are also present in adult patients affected by schizophrenia, bipolar disorder and major depressive disorder. Whereas mice studies have shown that laboratory procedures mimicking early maternal neglect induced anomalous rods and cones responses (Calanni et al., 2023) and diminished thickness of retina layers (Grigoruta et al., 2020), to our knowledge, the association between trauma and retinal anomalies has never been evaluated in human subjects. The *objective of the present paper* was to address that question by formulating a priori hypotheses based on the preceding bodies of data that if a relationship between trauma and early retinal anomalies were to be found, it would be specific to certain types of maltreatment and would also be specific to biological sex (assigned at birth).

Material and methods

Sample of offspring

The sample consisted of 134 FHRs, 69 biological boys and 65 biological girls, that included 59 singletons, 25 sibling pairs, 7 sibships of three children and 1 sibship of four children. All participants were white. The offspring inclusion criteria were having one parent affected by a DSM-IV schizophrenia, bipolar disorder, recurrent major depressive disorder (MDD) and being between 5 and 27 years old. The offspring exclusion criteria were: a DSM-5 diagnosis of schizophrenia, bipolar disorder, MDD or spectrum disorders, brain and metabolic disorders, known ocular pathology, myopia requiring a correction over 5 diopters, being pregnant, working night shifts, substance use in the two days preceding the ERG except for alcohol, caffeine and tobacco that were allowed respectively 24, 12 and 2 hours prior to ERG recording. Because the circadian rhythm impacts the ERG response, having travelled two time zones one month or less prior to the ERG was also an exclusion criterion (Lavoie et al., 2010). The inclusion and exclusion criteria were assessed during a clinical interview with the offspring and the parent when under the age of 18 years old and the review of medical records.

The average age of FHRs at first ERG evaluation was 15.7 years (SD=7.0), 79 FHRs had only one ERG recording, 50 FHRs had a second ERG evaluation at an average age of 18.25 years (SD=6.3) whereas 5 FHRs had a third ERG evaluation at an average age of 17.9 years (SD=7.0).

Out of the 134 FHRs, 50 were offspring of an affected parent who was a member of multigenerational kindreds densely affected by schizophrenia and bipolar disorder, a sample that has been the object of several previous reports (Maziade et al., 2005; Bureau et al., 2013; Boies et al., 2018; Bureau et al., 2023). The other 84 were offspring of an affected parent and were children referred for mental health care to the Centre intégré universitaire de santé et de services sociaux (CIUSSS) de la Capitale-Nationale, the health institution that covers under a universal health care system all child and family mental health services in the Quebec City area (population of 800,000), Canada. These offspring have also been the subjects of previous reports (Gagne et al., 2020; Berthelot et al., 2022). To examine a possible bias created by the two sampling sources, we looked at the distribution of each type of childhood trauma by sampling sources (See Table S1).

Signed consent was obtained from all participants or from the parents for participants under 18, as reviewed by our University Ethics Committee.

Measures

Clinical diagnoses of parents and offspring

As regards the parents, we administered a consensus best estimate lifetime diagnostic procedure based on multiple sources of information as previously described (Maziade et al., 1992; Maziade et al., 1995). The estimate procedure included the Structured Clinical Interview for DSM-IV disorders (SCID) (Spitzer et al., 1992), family interviews and review of all available medical records across lifetime according to a previous method showing reliability (Maziade et al., 1992; Maziade et al., 1995; Roy et al., 1997; Maziade et al., 2005). The public universal health care in Quebec makes easily available the out- and in-patient medical records across the patient's life. Based on this lifetime information, a DSM-IV diagnosis of schizophrenia spectrum disorder, bipolar disorder or major depressive disorder was made by a panel of experienced clinicians who reached a consensus. The case was rejected when there was an absence of consensus. *As regards the offspring,* the same methods were applied except for the administration of the *Kiddie-Schedule for Affective Disorders and Schizophrenia* (K-SADS) (Kaufman et al., 1997) with the parents of children under 18 in the presence of the child, or the SCID to offspring over 18 years old as we also have previously reported (Maziade et al., 2008; Maziade and Paccalet, 2013; Paccalet et al., 2016).

ERG recording

The recording procedure was the same as for adult patients (Hebert et al., 2015; Hebert et al., 2017; Hebert et al., 2020), as reported in our previous study on offspring (Gagne et al., 2020). Full-field cone and rod ERG, also respectively referred to as photopic and scotopic responses, was recorded using one of two Espion systems (E2 or E3) (Diagnosys, LLC, MA, USA) with DTL electrodes (Shieldex 33/9 Thread, Statex, Bremen, Germany) placed in the conjunctival sac. The analysis controlled for the use of E2 or E3. We did not dilate the eye as reported in previous studies (Gagne et al., 2010; Hébert et al., 2010; Hebert et al., 2015). Ground and reference electrodes (Grass gold cup electrodes filled with Grass EC2 electrode cream) were pasted on the forehead and external canthi (Hébert et al., 1995). Flashes and background were provided using a Color Dome ganzfeld (Diagnosys, LLC). Cone ERG: participants were submitted to a light adaption of 10 min at 80 cd·s/m2. A cone luminance-response function was achieved using increasing flash intensities ranging from 2.37 to 800 cd·s/m2 (i.e., −0.37 to 2.9 log units). Rod ERG: participants were dark-adapted for 30 min. Then a rod luminance-response function was achieved using green flashes of increasing intensities ranging from 0.001 to 1 cd·s/m2 (i.e., −3 to 0 log units).

ERG parameters measured

The typical ERG waveform is made of a negative component called the a-wave followed by a positive component called the b-wave. By convention, the b-wave amplitude is measured from the trough of the a-wave to the peak of the b-wave. The latency, also known as implicit time, is measured from the flash onset and corresponds to the time in milliseconds (ms) to reach the peak of the b-wave. Figure S1 shows the parameters measured from the ERG waveform. The following 8 ERG parameters were analyzed: cone a-wave amplitude, cone a-wave latency, rod a-wave amplitude and rod a-wave latency, cone b-wave amplitude, cone b-wave latency, rod b-wave amplitude and rod b-wave latency. Consistent with previous literature, the cone b-wave was measured at a fixed luminance of 7.5 cd·s/m2. For rod ERG, the b-wave was measured from the wave forms obtained at a fixed luminance of 1 cd·s/m2.

Childhood Trauma

Childhood trauma was assessed using a method described previously (Berthelot et al., 2022). Five types of childhood trauma were assessed: physical abuse, sexual abuse, emotional abuse, neglect (emotional and physical), and witnessing domestic violence. These categories of abuse and neglect are comparable to those reported in meta-analytic work on childhood trauma (Varese et al., 2012; Kraan et al., 2015) and in widely used instruments (Bernstein et al., 1994). The presence or absence of childhood trauma was rated year by year on a life chart inspired by the Post et al. (Post et al., 1988) method which allowed us to get a good estimate of each participant's age at first exposure to trauma. Ratings were made blind to the goals by a clinical PhD psychologist specialized in childhood trauma (NB) and a PhD student (JGB), using all information collected through two complementary sources: (1) a semi-structured interview developed to assess childhood trauma and having sound psychometric properties (Traumatic Event Screening Inventory (Strand et al., 2005; Choi et al., 2019)) administered to the offspring, one of their parents and relatives (when available), (2) the review of all medical records, clinical interviews and research briefs of the home visits by research assistants throughout the longitudinal follow-up. Discordances between raters were reviewed to obtain a consensus on the presence of trauma. Table S2 presents the number of boys and girls exposed to each type of childhood trauma.

Statistical Analysis

We analyzed 134 FHRs and focused our analysis on 194 ERG recordings assessed after the first trauma. We built eight repeated measures mixed models, one for each precedingly described ERG parameter used as the dependent variable. Biological sex, the Espion system (E2, E3), age and pupil size at ERG assessments were entered in the analyses as covariates. A sensitivity analysis was performed using the sample source as an additional covariate. The relatedness among subjects of a sibship was accounted for using a random effect and the correlation between ERG evaluations of a single FHR within a sibship was accounted for using a continuous autoregressive correlation structure of order 1. Parameters estimation was made using restricted maximum-likelihood.

Our dual objective was to look at 1) the effect of a global rating of exposure to trauma and 2) the effect of each of the 5 specific types of trauma. For the former a fixed effect was used for the presence or absence of at least one type of childhood trauma and for its interaction with sex. For the latter, a fixed effect was used for the presence or absence of each of the 5 types of childhood trauma that were all included in the models as well as an interaction with sex. For sexual abuse, no interaction with sex was used in the model as only one boy was exposed to sexual abuse in our sample. Accordingly, the effect of sexual abuse was estimated for girls and that single boy together.

Degrees of freedom were corrected using the Kenward-Roger method. P-values were adjusted for multiple comparisons under the same model using the single-step method (Hothorn et al., 2008). Model assumptions were all validated using residuals plots. Global likelihood ratio tests under maximum-likelihood were carried out to compare the full models to their reduced models using covariates only. Marginal R^2 were reported as we were interested in the proportion of variance explained by the fixed effects. Effect sizes were computed using the Cohen's D. Statistical Analyses were performed using the *nlme* V3.1–160, the *performance* V0.10.5 and the *multcomp* V1.4–20 packages of the *R* software V4.2.2 (Hothorn et al., 2008; Lüdecke et al., 2021; R Core Team, 2021; Pinheiro, 2023).

Results

We first looked at the association between the presence or absence of exposure to childhood trauma and ERG and no significant associations were observed (Table 1). Secondly, we looked at the associations between each of the five types of trauma entered in the models and the eight ERG variables. Table S3 and S4 respectively display the mean values of photopic and scotopic ERG variables for exposed and unexposed boys and girls to each type of childhood trauma. Effect sizes by sex of the association between each type of trauma and the ERG variables are shown in Fig. 1 with their corrected 95% confidence intervals. Table 2 presents the effect size exact numeric values and their corrected p-values, along with each model global likelihood ratio test p-value and marginal R^2. After corrections for the multiple tests among the five types of trauma in the models, exposure to only one type of trauma, *physical abuse*, kept a significant effect on a specific ERG parameter i.e., an increased scotopic a-wave latency among girls (β=0.89, p=0.024, ES=0.28, IC95%=[0.002; 0.55]). Another close-to-significance trend was observed in girls again with physical abuse that would be associated with an increased photopic b-wave latency (β=0.66, p=0.099, ES=0.27, IC95%=[−0.06; 0.60]).

The different types of trauma were found homogeneously distributed among the two sampling sources except for one type i.e., neglect that showed a trend toward significance of heterogeneity among the sampling sources (p= 0.06; Table S1). We nonetheless carried out a sensitive analysis using it as an additional covariate in our models. Results did not change using this approach, as shown in Tables S5 and S6.

Table 1
Effect sizes and one-sided p-value of the association by sex between the global rating of trauma exposure and ERG variables.

Sex	Trauma Exposure Effect Size (p-value)							
	Photopic a-wave Amplitude	Photopic a-wave Latency	Photopic b-wave Amplitude	Photopic b-wave Latency	Scotopic a-wave Amplitude	Scotopic a-wave Latency	Scotopic b-wave Amplitude	Scotopic b-wave Latency
Boys (n=69)	-0.083 (0.34)	-0.022 (0.82)	0.065 (0.92)	0.038 (0.60)	-0.032 (0.49)	0.017 (0.67)	0.11 (0.96)	0.023 (0.66)
Girls (n=65)	-0.014 (0.64)	0.078 (0.38)	-0.081 (0.40)	-0.0027 (0.75)	-0.12 (0.42)	0.11 (0.18)	0.037 (0.85)	0.039 (0.59)
Marginal R^2	0.047	0.18	0.096	0.13	0.11	0.096	0.38	0.034
Global test p-value	0.66	0.63	0.71	0.94	0.67	0.63	0.43	0.91

No association was found between trauma exposure and the ERG variables. Effect sizes were estimated in repeated measures mixed linear models corrected for the ERG Espion system (E2, E3), the age and the pupil size at ERG evaluations. p-values were adjusted for multiple comparisons using the single-step method. Latency and amplitude units were, respectively, milliseconds and microvolts. Global tests (likelihood ratio test) were carried out to compare the full models to their equivalent model using covariates only. Marginal R^2 were reported as we were more interested in the proportion of variance explained by the fixed effects.

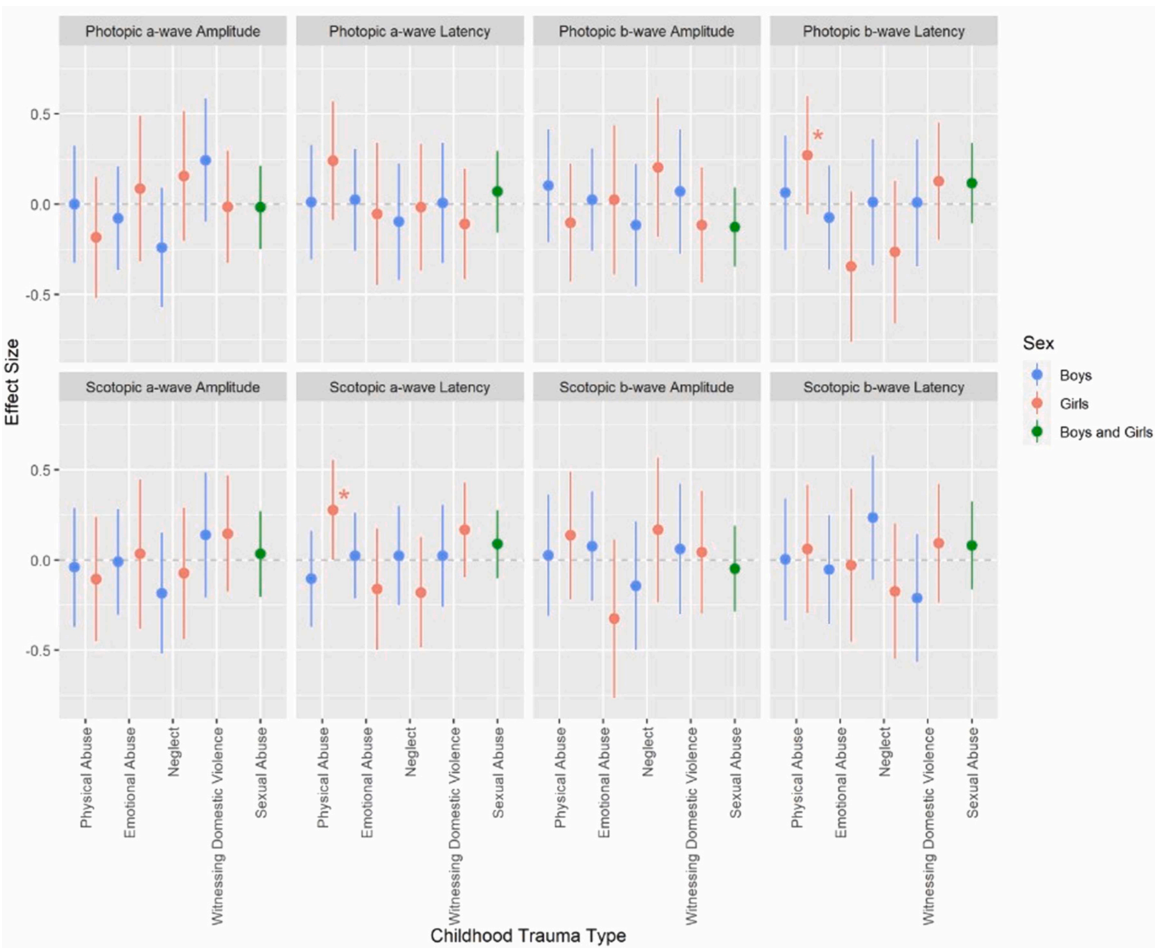

Fig. 1. Effect sizes and their 95% IC by sex of the association between each type of childhood trauma and ERG variable. * Physical Abuse was significantly associated with a prolongation of scotopic a-wave latency for girls (p=0.024, ES=0.28) and a trend was also observed for a prolongation of photopic b-wave latency (p=0.099, ES=0.27). In our sample of 69 boys and 65 girls, effect sizes were estimated in repeated measures mixed linear models corrected for the ERG Espion system (E2, E3), the age and the pupil size at ERG evaluations. Confidence intervals were adjusted for multiple comparisons using the single-step method. Latency and amplitude units were, respectively, milliseconds and microvolts. Regarding sexual abuse, the effect was estimated for boys and girls jointly as only one boy was exposed in our sample.

Discussion

To our knowledge this is the first study reporting on the relationship between childhood trauma and retinal dysfunctions in human subjects and, more specifically, in children and adolescents at familial risk of major psychiatric disorders. The present data suggest that there would be no substantial global effect of childhood trauma on dysfunctional retina response as an index of central neurobiological dysfunctions. However, our findings pointed to possible specific effects of a particular type of trauma. Physical abuse, contrary to the other four types of maltreatment (i.e., sexual abuse, emotional abuse, neglect and witnessing domestic violence) would be associated with prolonged latencies of both the cone and rod response to light stimuli as measured by electroretinography (ERG). This potential negative effect of physical abuse would be sex-specific as observed in girls only. Sex-specific differences in effect of trauma have also be found in adult samples (Cooke and Weathington, 2014; Helpman et al., 2017). Our finding necessarily needs replication even though our exploratory study used a very

Table 2
Effect sizes and one-sided p-value of the association by sex between each type of childhood trauma and ERG variable.

Childhood Trauma Type	Sex	Effect Size (p-value)							
		Photopic a-wave Amplitude	Photopic a-wave Latency	Photopic b-wave Amplitude	Photopic b-wave Latency	Scotopic a-wave Amplitude	Scotopic a-wave Latency	Scotopic b-wave Amplitude	Scotopic b-wave Latency
Physical Abuse	Boys	-0.0004 (1)	0.011 (1)	0.10 (1)	0.062 (0.98)	-0.041 (0.95)	-0.10 (1)	0.027 (1)	0.0028 (1)
	Girls	-0.18 (0.58)	0.24 (0.18)	-0.10 (0.88)	0.27 **(0.1)**	-0.11 (0.989)	0.28 **(0.024)**	0.14 (1)	0.061 (0.99)
Emotional Abuse	Boys	-0.079 (0.87)	0.023 (1)	0.024 (1)	-0.075 (1)	-0.0097 (1)	0.024 (1)	0.077 (1)	-0.052 (1)
	Girls	0.085 (1)	-0.055 (1)	0.024 (1)	-0.35 (1)	0.034 (1)	-0.16 (1)	-0.33 (0.17)	-0.028 (1)
Neglect	Boys	-0.24 (0.16)	-0.097 (1)	-0.12 (0.85)	0.011 (0.99)	-0.18 (0.56)	0.024 (1)	-0.14 (0.76)	0.24 (0.24)
	Girls	0.15 (1)	-0.018 (1)	0.20 (1)	-0.27 (1)	-0.073 (0.96)	-0.18 (1)	0.17 (0.31)	-0.17 (1)
Witnessing Domestic Violence	Boys	0.24 (1)	0.0066 (1)	0.070 (1)	0.0077 (1)	0.14 (1)	0.024 (1)	0.061 (1)	-0.21 (1)
	Girls	-0.016 (1)	-0.11 (1)	-0.12 (0.82)	0.13 (0.77)	0.15 (1)	0.17 (0.31)	0.043 (1)	0.093 (0.92)
Sexual Abuse	Boys and girls	-0.017 (1)	0.069 (0.91)	-0.13 (0.40)	0.12 (0.51)	0.034 (1)	0.070 (0.61)	-0.048 (0.98)	0.081 (0.87)
Marginal R^2		0.096	0.29	0.14	0.20	0.13	0.15	0.42	0.069
Global test p-value		0.33	0.56	0.54	0.11	0.81	0.46	0.16	0.54

Associations were found between the scotopic a-wave and photopic b-wave latency with physical abuse only and among girls. In our sample of 69 boys and 65 girls, effect sizes were estimated in repeated measures mixed linear models corrected for the ERG Espion system (E2, E3), the age and the pupil size at ERG evaluations. p-values were adjusted for multiple comparisons using the single-step method. Latency and amplitude units were, respectively, milliseconds and microvolts. Regarding sexual abuse, the effect was estimated for boys and girls jointly as only one boy was exposed in our sample. Global tests (likelihood ratio test) were carried out to compare the full models to their equivalent model using covariates only. Marginal R^2 were reported as we were more interested in the proportion of variance explained by the fixed effects.

conservative approach introducing the five maltreatment types in the same analysis and using stringent multiple comparison corrections.

Given the established relationship between exposure to childhood trauma and numerous brain alterations in adults having a major psychiatric disorder (Cancel et al., 2019; Teicher et al., 2022; Zovetti et al., 2022), it may appear intriguing that early developmental ERG anomalies characterizing FHRs (Gagne et al., 2020; Maziade et al., 2022) would not largely be associated with maltreatment in childhood, especially in boys. It must be however reminded that the CNS neurobiological correlates of ERG retinal anomalies or their potential environmental determinants are still generally unknown (see two recent reviews; (Bhatt et al., 2023; Constable et al., 2023). More research on that matter is certainly needed. In the same line of thought, previous reports have shown that the risk effect of childhood trauma on future transitions to a psychiatric illness would be mediated through a facilitating effect on the accumulation of risk indicators across the trajectory of male FHRs (Berthelot et al., 2022). It could also be mediated through its effect on the development of cognitive deficits early in the trajectory of FHR children and adolescents (Berthelot et al., 2015). Our findings suggest that these two negative impacts of trauma would not be mediated by ERG retinal dysfunctions in childhood as a proxy of a brain dysfunction.

Importantly, the observed absence of a strong association between trauma and retinal anomalies in FHRs may also be attributable to methodological properties. First, it is possible that trauma exerts an effect on other ERG parameters than those presently investigated.

For instance, mice studies found no association between maternal neglect and cones or rods amplitudes, but documented a relation with scotopic threshold response (STR) and photopic negative response (PhNR). Interestingly, group differences in visual evoked potential were also observed, suggesting altogether that the effect of trauma may be especially observed by looking at post-photoreceptor and post-bipolar cell activity including ganglion cell activity (Calanni et al., 2023). Knowing that (1) these parameters arise predominantly from the activity of ganglion cells, (2) the role of retinal ganglion cells dysfunctions in major psychiatric disorders (Kalenderoglu et al., 2016; Bernardin et al., 2020), (3) evidence that ganglion cells are highly sensitive to inflammation (Sivakumar et al., 2011), and (4) evidence that trauma may induce inflammation (Baumeister et al., 2016) future studies should include parameters assessing both the activity and structure of retinal ganglion cells. Retinal structures were never studied in human trauma, which could be made using technology like the Optical Coherence Tomography (OCT). Second, there is a possibility that the neurobiological mark of trauma on the retina is expressed only at an older age along the risk trajectory heading to a later transition to a psychotic or affective disorder. The exact sensitive period for the expression of these neurobiological scars are little-known and some studies indeed suggest that many may not emerge earlier in youth at risk but later in development (De Bellis et al., 2002; Riem et al., 2015; Ahmed-Leitao et al., 2016)

Regarding the observed sex difference, it is difficult at this time to describe precise mechanisms through which young girls exposed to physical violence would be more likely to develop prolonged latencies of response of retinal neurons which is a trait marker present in adult patients (Hebert et al., 2015; Hebert et al., 2017; Demmin et al., 2018; Bernardin et al., 2020; Hebert et al., 2020; Cosker et al., 2021), and also in young FHRs 10–15 years before the incidence of prodrome and psychiatric illness (Gagne et al., 2020; Maziade et al., 2022). However, other sex-specific pathways leading to a transition to a psychiatric illness have already been observed (Pruessner et al., 2019; Berthelot et al., 2022). In addition, our findings would be congruent with the extensive review of Teicher et al. that revealed numerous sex-specific brain alterations in adult schizophrenia patients who were exposed to childhood trauma (Teicher et al., 2018).

Our study has strengths and limitations. One strength is certainly the relatively large sample of young FHRs in which we had both reliable prospective assessments of childhood trauma and of electroretinographic recordings. A *first* limitation is that the sample was nonetheless relatively small in some comparisons such as the evaluation of the respective contributions of different types of trauma to ERG parameters and their interaction with sex. This raises the possibility of type II errors. *Second*, the assessment of trauma in this study was based on a categorical approach (exposed vs non-exposed), lacking indications of the gradient of severity. *Third*, our subjects were all white caucasians. FHRs of other races, especially those who lived in adverse environments relative to health (e.g., poverty, discrimination), might show a greater impact of trauma due to interactions with other variables. *Fourth*, our study did not include an age-matched group that was trauma-exposed but without a family history of serious mental illness to investigate potential differences in the association between trauma and ERG in absence of family history. *Finally*, we did not assess the subjective perception of stress following trauma which is known to impact the sequels of trauma on child development (Danese and Widom, 2020).

Conclusion

Although retinal ERG anomalies and trauma were developmentally contemporary across childhood and adolescence in our study, the findings would suggest an absence of a sizeable association between this serious environmental disturbance and the retinal endophenotype. The abnormal ERG response in FHRs and in adult patients most-likely have multi-causal determinants. Future basic and clinical research will certainly have to address the mechanisms underlying ERG anomalies given the increasing importance of the retina for the understanding of the illness pathophysiology, the early detection of vulnerable children and prevention.

CRediT authorship contribution statement

Nicolas Berthelot: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jasmin Ricard:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Michel Maziade:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Alexandre Bureau:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Eric Arseneault:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Julia Garon-Bissonnette:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Marie-Claude Boisvert:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Énora Fortin-Fabbro:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare that they have no conflict of interest, except for Maziade who is listed as co-inventor in a patent application (PCT/CA2014/050233) entitled "Use of electroretinography (ERG) for the assessment of psychiatric disorders" and holds shares in a start-up company (diaMentis) that commercializes the claims listed in the patent application

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bionps.2024.100095.

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