Progress in Neuropsychopharmacology & Biological Psychiatry 127 (2023) 110807

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Evaluation of electroretinography (ERG) parameters as a biomarker for ADHD☆

Marc-André Dubois [a,c], Charles-Antoine Pelletier [a], Chantal Mérette [a,d], Valérie Jomphe [a], Rose Turgeon [a], Richard E. Bélanger [e,f], Simon Grondin [c], Marc Hébert [a,b,*]

[a] CERVO Brain Research Centre, Centre Intégré Universitaire de Santé et des Services Sociaux de la Capitale Nationale, Quebec, QC, Canada
[b] Department of Ophthalmology and Otorhinolaryngology – Head and Neck Surgery, Faculty of Medicine, Université Laval, Quebec, QC, Canada
[c] School of Psychology, Faculty of Social Sciences, Université Laval, Quebec, QC, Canada
[d] Department of Psychiatry and Neurosciences, Faculty of Medicine, Université Laval, Quebec, QC, Canada
[e] CHU de Québec Research Centre, Quebec, QC, Canada
[f] Department of Pediatrics, Faculty of Medicine, Université Laval, Quebec, QC, Canada

ARTICLE INFO

Keywords:
Biomarker
Attention-deficit/hyperactivity disorder (ADHD)
Electroretinogram (ERG)
Retina
Diagnostic

ABSTRACT

Background: The retina is recognized as an accessible part of the brain due to their common embryonic origin. The electroretinogram (ERG) has proven to be a valuable tool for detecting schizophrenia and bipolarity. We therefore investigated its ability to detect ADHD.
Methods: The cone and rod luminance response functions of the ERG were recorded in 26 ADHD subjects (17 women and 9 men) and 25 controls (16 women and 9 men).
Results: No significant differences were found between the mixed groups, but sexual dysmorphia was observed in the significant results. In males, a significant prolonged cone a-wave latency was observed in the ADHD group. In females, we observed a significant decrease in the cone a- and b-wave amplitudes and a trend for a prolonged cone b-wave latency as well as a higher scotopic mixed rod-cone a-wave in the ADHD group.
Conclusion: The data obtained in this study show the potential of the ERG to detect ADHD, warranting further large-scale studies.

1. Introduction

Worldwide, attention deficit hyperactivity disorder (ADHD) affects approximately 7.2% of children (Thomas et al., 2015). However, data reported in the literature vary widely. For instance, in the United States, ADHD is estimated to affect 9.4% of children between the ages of 2 and 17 (Danielson et al., 2018) when the European rates are closer to 3–5% (Kooij et al., 2019). Interestingly, it is argued that the USA rate is closer to 8.7% in South Carolina (Wolraich et al., 2014) and climbs to 15.5% in North Carolina (Rowland et al., 2015), despite being two geographically and culturally similar states.

The observed variability in rates reported highlights the difficulties of studying the true prevalence of ADHD with a high level of confidence. This is mainly due to the fact that diagnosis relies primarily on subjective, self-reported information (Gualtieri and Johnson, 2005). The fact that objective physiological data to support the diagnosis are still lacking makes the path to a solid diagnosis fraught with pitfalls, as secondary gains, comorbidity, and differential diagnoses can bias the assessment process, leading to misdiagnosis (Cumyn et al., 2009; French et al., 2020; Kessler et al., 2006; Woolterton, 2005). Such issues surround the debate about ADHD being either over diagnosed or underdiagnosed (Ginsberg et al., 2014; Prasad et al., 2019; Sayal et al., 2018; Sciutto and Eisenberg, 2007; Thomas et al., 2015). The discovery of specific biomarkers for ADHD would improve the current situation by providing an additional tool for health care practitioners evaluation, and for patients during their clinical journey.

One of the leads guiding the search for such a biomarker is the presence of abnormalities in brain dopamine among people with ADHD. In fact, ADHD has been associated with an increase in the amount of the dopamine transporter (DAT), responsible for dopamine reuptake (Fusar-Poli et al., 2012). For instance, some studies showed a dopaminergic decrease in the striatum ranging from 17% to 70% (Cheon et al., 2003;

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
* Corresponding author at: CERVO Brain Research Centre, 2601 d'Estimauville, Quebec City, QC G1J 2G3, Canada.
E-mail address: marc.hebert@fmed.ulaval.ca (M. Hébert).

https://doi.org/10.1016/j.pnpbp.2023.110807
Received 30 January 2023; Received in revised form 19 May 2023; Accepted 1 June 2023
Available online 7 June 2023
0278-5846/

Dougherty et al., 1999; Dresel et al., 2000; Jucaite et al., 2005; Spencer et al., 2005; van Dyck et al., 2002). In addition, volumetric (Castellanos et al., 2002) and functional magnetic resonance imaging (Bush et al., 2005) studies have shown differences in cerebral volume and functional activation in the prefrontal cortex, basal ganglia, anterior cingulate cortex and cerebellum, regions known to be related to dopamine and being involved in ADHD symptomatology (Arnsten et al., 2010; Poelmans et al., 2011; Vaidya, 2011). For those reasons, the most common medications used to treat ADHD symptoms target overactive brain dopamine transporters in order to increase the level of dopamine available (Rubia et al., 2014).

Interestingly, dopamine is reported to be the major catecholamine present in the retina of most vertebrate species (Reis et al., 2007). Over the years, the retina has been recognized as an approachable part of the brain. This idea is supported by the fact that the development of the retina begins in the embryonic phase, during which it developed from the same cells as the rest of the brain (Dowling, 2012). Since we know that some dopaminergic systems are already developed at this stage (Reis et al., 2007), some hypothesized that if the dopaminergic abnormalities associated with neurodevelopmental disorders are already there, it is possible to detect a remnant of these abnormalities within the retina later in life (Dowling, 2012; Hébert et al., 2020). One study even showed that brain dopaminergic variations can impact ERG recordings in mice, even though no dopaminergic abnormalities were found in their dissected retinas (Lavoie et al., 2014). Today, the retina is probably the most promising and best-studied alternative site of investigation in the field of mental health (MacCormick et al., 2015; Youssef et al., 2019). The retina can be studied directly via the bioelectric response of its cells using electroretinography (ERG).

The typical ERG response is composed of a first negative component called the a-wave, followed by a larger positive component called the b-wave. Another parameter, which occurs after the b-wave, can be optimized with a red stimulus over a blue background, namely the photopic negative response (PhNR). The a-wave corresponds to the photoreceptor's hyperpolarization, the b-wave to the ON-bipolar cells depolarization and the PhNR to the ganglion cells activity. These ERG parameters are characterized by their amplitudes (μv) and their latencies (ms) (Hébert and Lachapelle, 2003). Two distinct recording conditions can be used to isolate the activity of the different photoreceptors. The photopic condition (daytime vision) provides a cones response. The scotopic condition (nighttime vision) allows to obtain the pure rod responses (using low intensity flashes that fall below the cone threshold) as well as the mixed rod-cone response (using flashes of sufficiently high intensity to activate both photoreceptors). In addition, the use of multiple flash intensities provides a luminance-response function (LRF), which is used to observe the dynamics of the retinal response over a wider spectrum.

Several studies have detected anomalies in ERGs parameters in patients with various mental disorders often associated with cerebral dopaminergic dysfunctions (Ayano, 2016; Money and Stanwood, 2013; Nakamura et al., 2020). In schizophrenia (SZ), Warner et al. (1999) were the first to find rod and cone ERG anomalies. This finding, originally based on a small sample (9 SZ), was later confirmed by studies based on larger samples (Balogh et al., 2008; Bernardin et al., 2020; Demmin et al., 2018; Hébert et al., 2015, 2020). In addition, Demmin et al., 2018 also reported a decreased PhNR in SZ. Interestingly, ERG anomalies similar to those observed in the largest schizophrenia study ($N = 150$) to date (Hébert et al., 2020), but less pronounced, were reported in 90 subjects with autism spectrum disorder (Constable et al., 2020), also hypothesized to be related to dopaminergic dysfunctions (Pavăl, 2017).

Given previous ERG findings in psychiatric disorders that, like ADHD, are likely related to dopaminergic dysfunctions, the purpose of this research is to provide preliminary insight into the potential of ERG parameters to detect retinal differences in subjects with ADHD compared with control subjects.

2. Methods

2.1. Sample characteristics

Our sample consisted of an experimental group of 26 subjects with a diagnosis of ADHD (17 women [27.1 ± 4.7 years]; 9 men [27.6 ± 4.7 years]) and a control group of 25 subjects (16 women [27.1 ± 4.7 years]; 9 men [28.1 ± 4.8 years]), matched as closely as possible for age and sex, and recruited over a 6-month period. From now on, the term "sex" refers to the sex assigned at birth. The samples were largely composed of subjects with a university academic level. Posters, emails, and social media posts were used to reach the target audience, but word-of-mouth was mostly sufficient to reach our initial goal of 50 subjects. All subjects gave their voluntary and informed consent when signing the informative and agreement form previously approved by the CIUSSS-CN Neurosciences and Mental Health Institutional Ethics Committee.

To be eligible for the study, subjects in the experimental group had to be diagnosed with ADHD by a qualified professional (physician or psychologist). Control subjects had to complete the ASRS-5 tool validated in French (Baggio et al., 2020) to verify that they were not likely to have ADHD by answering the six questions using a 5-point Likert-type scale (0 = never and 4 = often). This tool shows a specificity of 91.9% and a sensitivity of 84.3% (Baggio et al., 2020). The exclusion criterion was a score > 13 (out of 24) on the ASRS-5, based on Baggio et al. (2020). Above this threshold, the possibility of having undiagnosed ADHD was considered too high and the applicant was not accepted for the project, although none reached this threshold (mean = 7.3 ± 2.5 out of 24).

Exclusion criteria for all applicants were: the presence of a diagnosis of a major neuropsychiatric disorder (e.g., schizophrenia, bipolar disorder, etc.), the presence of an ocular condition (glaucoma, cataract, macular degeneration, high myopia [correction greater than −5 diopters]), the presence of any medical condition that does not allow the procedure to be completed (i.e., intellectual disability, acute substance intoxication or withdrawal, consultation for head injury or traumatic brain injury within the last three months), presence of a serious brain or metabolic disease (Parkinson's disease, Alzheimer's disease, epilepsy, stroke, heart disease, diabetes, thyroid disorder, renal failure, cancer, or any other condition reported by the subject and susceptible to impact the ERG recording). Other exclusion criteria were hormone therapy, being pregnant or breastfeeding, working on night shifts, or having travelled outside the country for more than two time zones in the past month. Cannabis, tobacco, or alcohol use were not considered in the exclusion criterion but was documented. The use of any other medication was excluded, except for those prescribed as hormonal contraceptives and/or those treating ADHD symptoms. In order to minimize their possible impact on the ERG, medicated subjects with ADHD were instructed not to take their ADHD medication at least 24 h before the assessment. This time interval was considered on the basis of the known pharmacokinetics of psychostimulants in their various forms, as well as their known duration of clinical effect (Groom and Cortese, 2022), without restricting the use of necessary therapy. None of the participants used a non-stimulant product.

2.2. Procedures

Full-field cone and rod ERGs were performed with the Espion E3 system (Diagnosys LLC, Lowell, MA), using a procedure well known to the research team and already proven in psychiatry (see Hébert et al. (2020)). Recordings were obtained in nondilated eyes using self-adhesive skin electrodes (LKC Technologies, Gaithersburg, MD) positioned 2 mm below the eye as instructed by the company. Flashes and background light were provided by a Ganzfeld ColorDome to achieve full-field stimulation (Diagnosys LLC, Lowell, MA).

Before the photopic ERG (cone response), subjects were adapted for 3 min to a white background light set at 80 cd/m^2, according to Gagné et al. (2010) for recordings in nondilated eyes. A cone luminance-response function (LRF) (McCulloch et al., 2019) was obtained using 7 levels of white flashes ranging from 1.33 to 50 cd·s/m^2 (i.e., 0.12 to 1.7 log units). The interval between flashes was set at 2 s.

The PhNR was collected immediately after the photopic recording using red flashes (640 nm) set at 4.49 cd·s/m^2 (0.65 logs) on a blue background (465 nm) light set at 80 cd/m^2. This setting was the closest our devices could get to the one established by Rangaswamy et al. (2007) who sought to maximize the wave amplitude through different flash and background wavelengths, and the one recommended by the ISCEV extended protocol for the photopic negative response of the full-field electroretinogram (Frishman et al., 2018).

The scotopic condition (rod and mixed rod-cone responses) took place after 20 min of dark adaptation. To generate a scotopic LRF (Johnson et al., 2019), subjects were stimulated using 12 levels of green flashes (peak: 509 nm) ranging from 0.0018 to 1 cd·s/m^2 (i.e., −2.75 to 0 log units). The flash interval was set at 2 s for the first 8 intensities and at 5 s for the last 4.

Pupil size was obtained with a hand-held ERG device called RETeval® (LKC Technologies, Gaithersburg, MD) immediately after each condition and using the same background luminance, i.e., 80 cd/m^2 white (photopic), 80 cd/m^2 blue (PhNR), or darkness (scotopic).

To limit the impact of background noise on the measurement, data for each intensity were obtained using an average of 40 flashes. Both eyes were recorded simultaneously, but since they are highly correlated, we averaged their data as well. This allowed us to obtain a single data entry per ERG parameter for each subject, while avoiding falsely increasing the sample size, which would have artificially inflated the power of the study.

2.3. Measures

By convention, two measures are used to define the three ERG waveform, namely the amplitude and latency of the a-wave, the b-wave and the PhNR (see typical ERG tracing at Fig. 1 and supplementary material S.2 for more typical examples) (Hébert and Lachapelle, 2003). The amplitude of the a-wave is measured from the baseline to its trough, the b-wave from the trough of the a-wave to its peak and the PhNR from the baseline to its trough. Although it is also common to measure the PhNR amplitude from the b-wave peak, we chose to measure it as per Demmin et al. (2018), i.e., from the baseline to its trough, to limit a potential bias generated by a hypothetical b-wave amplitude variation between groups (Frishman et al., 2018). The latency, also called implicit time, of the three waveforms is the time (in milliseconds) needed to reach their maximum amplitude, as measured from the flash onset.

Depending on the flash intensity used, the scotopic condition allows the identification of different parameters. Indeed, although the amplitude of the b-wave increases positively with flash intensity, a stagnation of its growth due to rods saturation leads to a first plateau in the LRF, occurring at around 0.1 cd·s/m^2. By further increasing the flash intensity, a second plateau can be derived owing to the contribution of the cones. For this reason, as per Hébert et al. (2020), we classify 0.1 cd·s/m^2 intensity as a "pure" rod activity measurement, and 1 cd·s/m^2 intensity as a mixed rod-cone activity measurement. The lack of cone contribution at 0.1 cd·s/m^2 results in a very small a-wave that is not large enough in all subjects to provide a valid measurement, yielding only two parameters, the amplitude and latency of the b-wave. By contrast, due to the presence of cone contribution at 1 cd·s/m^2, the four usual parameters can be measured (amplitudes and latencies of the a- and b-waves). Overall, 4 measurements were obtained for the cones, 2 for the "pure" rods, 4 for the mixed rod-cone response and 2 for the PhNR, for a total of 12 parameters.

To limit the impact of some methodological biases, a single experimenter with several years of experience was responsible for conducting the entire procedure, including electrode placement, ERG recordings, and data processing. In addition, a single device was used to collect recordings from all subjects over a 6-month period. Prior to each recording, electrode placement was validated using the camera present in the Ganzfeld (Diagnosys LLC, Lowell, MA) and corrected if necessary. We also measured (see Table 1) and analyzed the eye-to-electrode distance between groups using images taken by the RETevel (LKC Technologies, Gaithersburg, MD). No significant differences were observed in terms of electrode placement.

2.4. Statistical analyses

All statistical analyses were performed using SAS/STAT software (Version 9.4; SAS Institute Inc., Cary, NC). The statistical tests considered for this study were influenced by the possible impact of age and sex

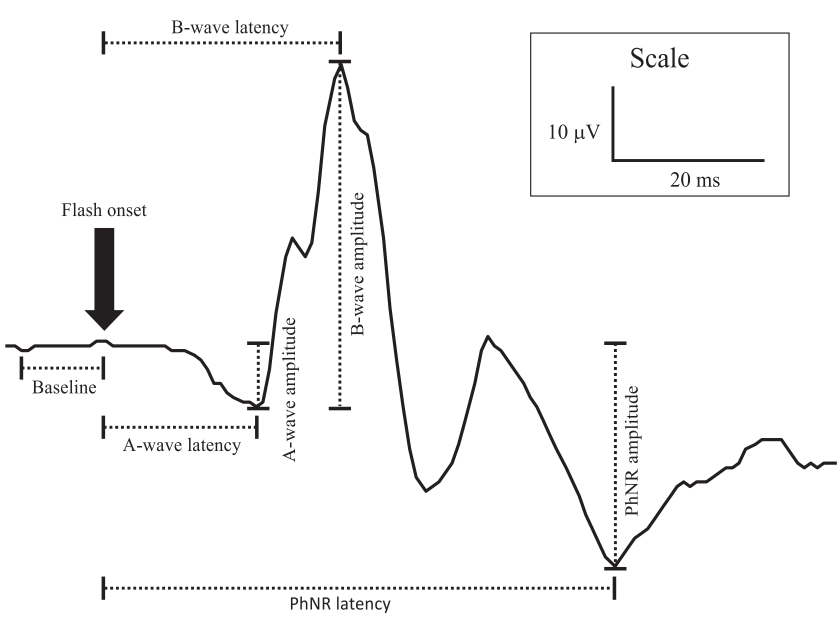

Fig. 1. The parameters of the electroretinogram.
Note. This figure constitutes an example of a cone ERG response, represented by the continuous plot, and its parameters. Note that PhNR amplitude is determined from the baseline.

Table 1
Age, pupil size, eye-electrode distance and medication use by group and sex.

Characteristics	ADHD			CTRL		
	Men (n=9)	Women (n=17)	Mixed (n=26)	Men (n=9)	Women (n=16)	Mixed (n=25)
Age (years)	27.6 ± 5.2	27.1 ± 4.7	27.3 ± 4.7	27.7 ± 5.1	27.3 ± 4.5	27.4 ± 4.6
Photopic pupil size (mm)	3.66 ± 0.55	3.88 ± 0.68	3.80 ± 0.63	3.90 ± 0.38	3.73 ± 0.52	3.80 ± 0.47
PhNR pupil size (mm)	2.75 ± 0.32	2.83 ± 0.36	2.80 ± 0.34	2.87 ± 0.21	2.73 ± 0.33	2.78 ± 0.3
Scotopic pupil size (mm)	6.33 ± 0.72	6.19 ± 0.66	6.24 ± 0.67	6.74 ± 1.06	6.14 ± 0.61	6.29 ± 0.86
Eye-electrode distance (mm)	2.4 ± 0.5	2.2 ± 0.9	2.2 ± 0.8	2.3 ± 0.4	2.3 ± 0.4	2.3 ± 0.4
ADHD medication						
Concerta	5 (55%)	9 (53%)	14 (54%)	___	___	___
Biphentin	___	1 (6%)	1 (4%)	___	___	___
Vyvanse	2 (22%)	3 (18%)	5 (19%)	___	___	___
Ritalin	1 (11%)	___	1 (4%)	___	___	___
Contraceptive medication	___	9 (53%)	___	___	8 (50%)	___

Note. Values represent means ± standard deviations or *n* (%).

on ERG parameters (Brûlé et al., 2007; Weleber, 1981), but also by the results of preliminary analyses that showed no difference or correlation between the pupil size of the different groups, justifying the exclusion of this variable in the analyses. Between-group comparisons for the 12 ERG parameters were therefore performed using Student *t*-tests matched for age (±5 years) and sex. Considering the current objective of this exploratory study, which is simply to put forward various ERG parameters that could potentially be used to elaborate a specific biomarker of ADHD, we choose not to correct the alpha threshold. For transparency, we performed unpaired analyses as well as paired analyses adjusted for multiple testing. Adjusted *p*-values were obtained with the SAS MULTTEST procedure using the adaptive Bonferroni stepwise method of Hochberg and Benjamini (1990). These analyses can be consulted in supplementary material S.3. As a high-powered model, paired t-tests represent a considerable advantage in the context of an exploratory study composed of a relatively small sample size that limits the likelihood of obtaining significant interaction effects with analyses of variances. Matching yielded 9 men and 16 women pairs, corresponding to a single excluded subject. Because differences in the dopaminergic system between men and women were previously reported, gender was targeted as having an impact on ADHD symptomatology (Andersen and Teicher, 2000). For this reason, we also opted to analyze men and women separately. All effect sizes subsequently reported were determined using Cohen's d.

3. Results

Analyses shows no differences between the groups (ADHD vs. Controls; men vs. women) in terms of pupil size, age and eye-electrode distance. Medications used was similarly distributed between sexes except for one woman who took Biphentin and one man who took Ritalin (see Table 1). No significant differences were found between groups or sexes regarding the time of recording or the use of alcohol, drug, tobacco/nicotine and contraceptive.

3.1. Photopic condition

We found no significant difference between the mixed (n = 25 pairs) ADHD and control groups in the photopic condition. For men (n = 9 pairs), the ADHD group shows a significantly prolonged a-wave latency than the control group at the maximum flash intensity of 50 cd·s/m^2 (p = 0.004), which is equivalent to a mean difference of 0.74 ms between groups and a strong effect size (ES) of 1.19. For women (n = 16 pairs), analysis revealed significantly lower a-wave ($p = 0.01$; ES = 0.58) and b-wave ($p = 0.004$; ES = 0.76) amplitudes for the ADHD group compared to the control group, and these differences tended to increase positively with intensities (see Figs. 2 and 3). At the highest intensity of 50 cd·s/m^2, the amplitude decrease for the ADHD group reaches 6.66 μV (17.3%) for the b-wave and 1.90 μV (13.4%) for the a-wave. A trend suggestive of a prolonged b-wave latency was observed in women of the ADHD group, with the strongest difference observed again at 50 cd·s/m^2 ($p = 0.08$; ES = 0.37). No significant differences were observed for PhNR. In summary, whereas in men (ADHD) only a prolonged latency of the a-wave was observed at the highest intensity, in women (ADHD) a reduction of both a- and b-waves was observed at different intensities as well as a tendency for a prolonged latency of the b-wave at the highest intensity, when each sex was compared to its respective controls.

3.2. Scotopic condition

As per Hébert et al. (2020), and in order to limit the type 1 error, we chose to only analyze intensities 0.1 cd·s/m^2 (termed "pure" rod response) and 1 cd·s/m^2 (mixed rod-cone response). We found no significant difference between the mixed ($n = 25$ pairs) ADHD and control groups in the scotopic condition as well. Trends ($p < 0.1$) suggesting an increased a-wave amplitude was observed for the mixed rod-cone response at 1 cd·s/m^2 ($p = 0.079$; ES = 0.37) but only for the women ADHD group.

4. Discussion

This exploratory study aimed to determine whether the use of ERG represents a promising avenue for the search for a biomarker of ADHD. Analyses revealed significant decreases in a-wave and b-wave amplitudes at the cone level in subjects with ADHD, but only in females. In addition, several trends were observed that may prove positive with a larger sample size.

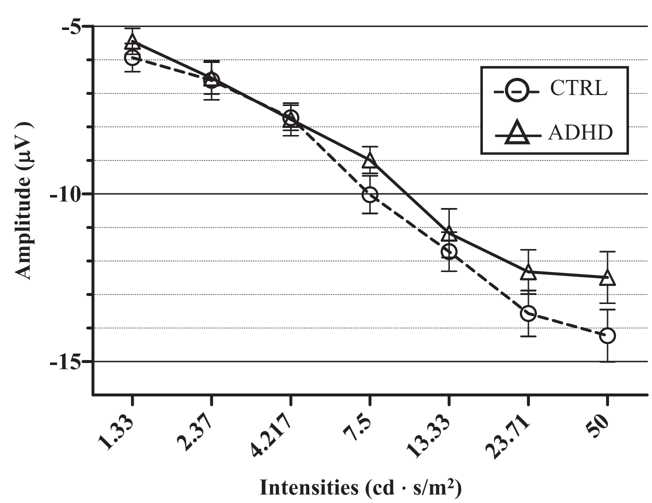

Fig. 2. Women photopic A-wave amplitudes by intensities.
Note. Photopic A-wave amplitude comparisons between control women (dotted line) and women diagnosed with ADHD (solid line). Error bars represent the standard error of the mean.

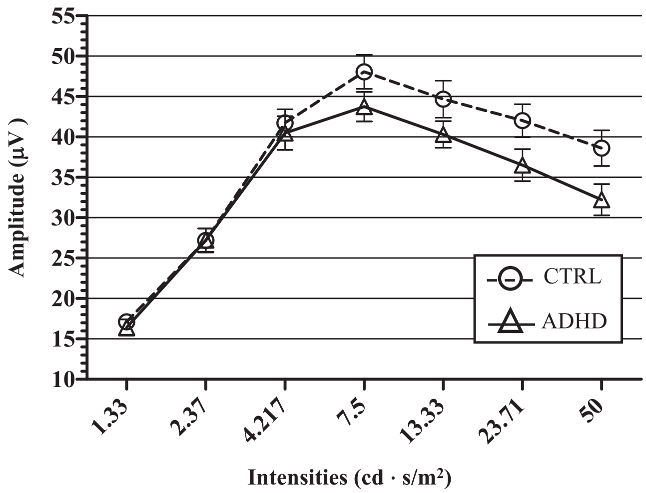

Fig. 3. Women photopic B-wave amplitudes by intensities.
Note. Photopic B-wave amplitude comparisons between control women (dotted line) and women diagnosed with ADHD (solid line). Error bars represent the standard error of the mean.

Even if our results remain preliminary, the sex difference observed is not unusual. A large number of studies have already shown differences in the central nervous system between men and women, and more specifically in the visual system (see Shansky (2016); Vanston and Strother (2017) for reviews). These differences are strongly associated with sexual hormones and dopamine in addition to being linked to several psychiatric issues (Andersen and Teicher, 2000; Lindamer et al., 2004; Marrocco and McEwen, 2016; Tannock et al., 2006; Zagni et al., 2016). ERG sex differences have been reported by Brûlé et al. (2007), and also observed in psychiatric ERG studies (Hébert et al., 2004, 2020) and in a depression mouse model (Arsenault et al., 2021).

It is possible, however, that phenotypic and symptomatologic differences between men and women help explain why most ERG findings were observed in women (Biederman et al., 2004; Martin et al., 2018), but it is also possible that a systemic gender bias (London and Landes, 2021), which would further complicate the already difficult diagnostic process, is at least partially responsible for the observed ERG gender differences. Indeed, it is reported that professionals involved in the diagnostic process are likely to consider ADHD as a typically men disorder. This phenomenon puts professionals at risk of being more likely to consider, and therefore diagnose, men as having ADHD than women, thus making the men's group more heterogeneous than the women's from a neurophysiological point of view (London and Landes, 2021). These potential misidentifications directly bias the recruitment process for ADHD studies, which is often based on a formal diagnosis. Within samples, this would lead to an increased rate of false positives in the men's ADHD group but also false negatives in the women's control group.

Our data are also consistent with those obtained for other dopamine-related neurodevelopmental disorders studied, such as autism spectrum disorder (ASD), schizophrenia (SZ) and bipolar disorder (BP) (Hayden and Nurnberger, 2005; Horga et al., 2016; Pavăl, 2017). In fact, the ERG findings observed in women with ADHD tend to be quite similar to those reported by Constable et al. (2020) for ASD and those reported by Hébert et al. (2020) for SZ (see Supplementary Table S.1 for a summary of the ERG results reported by these studies, with their respective effect sizes, including the present ADHD study). In fact, both studies found smaller cone a- and b-wave amplitudes and prolonged b-wave latency. Similarly, we found a cone a- and b-waves reduction albeit only a trend for a prolonged b-wave latency. Regarding the magnitude of changes observed in ERG parameters, effect sizes show that subjects with ADHD have more acute changes than subjects with ASD, but less than SZ. However, it is difficult to speculate on the degree of causality associated with this observation since our sample size was relatively small. Some authors propose that other neurotransmitters are involved in the etiology of ADHD, such as GABA, glutamate (Naaijen et al., 2017; Puts et al., 2020) and norepinephrine (Mehta et al., 2019). Therefore, it is possible that the involvement of other neurotransmitters comes into play concerning the ERG profile of individuals with ADHD. Although animal studies suffer from several limitations, they are the best option currently available to provide models for understanding ADHD in humans (see Lee and Yoon (2023) for a review).

On the other hand, our results are quite opposite to those reported in a recent preliminary ERG study conducted by Lee et al. (2022) involving 15 subjects with ADHD, 57 with ASD and 59 controls. The authors reported at Vmax (highest amplitude of the luminance response curve) a cone b-wave amplitude of 38,18 μV and 30,24 μV in the ADHD and control groups, respectively, representing an increase of 26% in amplitude in the ADHD group. These results seem counterintuitive in both the magnitude and direction of the observed difference. To date, including the current study where the largest observed b-wave decrease was 17.3% in the ADHD group, all psychiatric disorders tested with the ERG have shown modest decreases in ERG parameter amplitudes, even in the largest study to date in schizophrenia ($N = 150$) where a reduction of only 10.3% was found to be highly significant ($p = 0.001$) (Hébert et al., 2020). These opposing results further emphasize the fact that large scale studies are warranted. However, it is worth noting that Lee et al. (2022) reported an averaged eye-to-electrode distance, being about 0.9 mm lower in the CTRL compared to the ADHD group. As shown by Hobby et al. (2018) larger eye-to-electrode distances result in lower a- and b-wave amplitudes, which in Lee et al. (2022) study could have resulted in lower ERG amplitudes in their CTRL group when compared to their ADHD group.

5. Limitations

The major limitation of our project is that we did not conduct an independent assessment of ADHD diagnosis, nor did we measure ADHD severity or symptom patterns. Considering that ADHD is a very heterogeneous disorder (Nigg et al., 2005), it is therefore possible that different symptomatologic profiles (e.g. the presence or absence of hyperactivity) influence how ERG parameters are affected by the disorder, thus reducing our ability to accurately detect what might be described as a more "generic" expression of the disorder. It is also possible that our university-educated sample has different characteristics than the general population (e.g., in terms of coping skills). It may be more relevant to adapt the method to multiple profiles and characteristics. Another possibility is that ERG parameters are sensitive to symptom severity, which could manifest as more subtle differences in subjects with less severe symptoms. This implies that a larger sample size is needed to achieve a more refined technique capable of detecting the presence of these milder symptoms with a high level of confidence. A more exhaustive assessment of the subjects' profile could have led to differential diagnoses or allowed the detection of comorbidity. Such factors may have had an influence on the results. Another limitation is that the women's menstrual cycles were not taken into account, albeit about 50% of the women were using hormonal contraceptives, which could have affected the ERG parameters, as shown by Brûlé et al. (2007).

Few studies have investigated the very long-term or even permanent physiological effects of medications used to treat ADHD symptoms (Craig et al., 2015). We therefore raise the possibility that long-term medications have prolonged effects in the patient's brain and that stopping the medication long enough, as we tried to do, may not be sufficient to compensate for this. This "prolonged" alteration would therefore not be detectable in a pre-post-medication comparison, leading us to falsely believe that medication has no effect on ERG parameters. Therefore, even if our subsequent analyses show no drug-related effects, as also reported by Lee et al. (2022), these prolonged effects remain a possibility.

6. Conclusion

Despite the reported limitations and small sample size, our study demonstrates the high value of the ERG in psychiatry and provides ample justification for a larger study. Our data show that several ERG parameters could potentially be used as specific ADHD biomarkers. Since the earlier in life disorders are detected, the less impact they have (Sonuga-Barke et al., 2011), the ERG, which is non-invasive and relative easy to administer (especially when using skin recording electrodes), may have even greater potential in children. The other perspective would be to conduct a large-scale study including a comprehensive diagnostic evaluation that would allow us to design a robust algorithm capable of detecting ADHD and distinguishing it from other similar disorders, as per Hébert et al. (2020) who demonstrated that the ERG could distinguish schizophrenia and bipolar disorder with great accuracy (0.86). Only after this step will it be possible to test the predictive potential of the algorithm using its accuracy, sensitivity and specificity.

Ethical statement

The authors confirm that the work presented was conducted in accordance with the World Medical Association Code of Ethics (Declaration of Helsinki) for Experiments Involving Human Subjects, complies with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarship in Medical Journals, and aims to include representative human populations (gender, age, and ethnicity) in accordance with these recommendations.

The authors confirm that the manuscript met ethical standards in the treatment of their participants and that all subjects gave their voluntary and informed consent when signing the informative and agreement form previously approved by the CIUSSS-CN Neurosciences and Mental Health Institutional Ethics Committee.

CRediT authorship contribution statement

Marc-André Dubois: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Charles-Antoine Pelletier:** Methodology, Software, Validation, Investigation, Data curation, Writing – review & editing. **Chantal Mérette:** Formal analysis, Writing – review & editing, Funding acquisition. **Valérie Jomphe:** Formal analysis, Writing – review & editing. **Rose Turgeon:** Formal analysis, Investigation, Writing – review & editing. **Richard E. Bélanger:** Conceptualization, Writing – review & editing, Funding acquisition. **Simon Grondin:** Conceptualization, Writing – review & editing, Supervision. **Marc Hébert:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors attest that the material presented in this article is entirely original and has in no way appeared or been published in other submitted articles. The study is not a reanalysis of previously analyzed data and the data presented in this study were analyzed for the first time. No other previously published or submitted articles from this data set address a related topic. The manuscript has not been and is not posted on a website. All authors previously agreed with the content of the manuscript and with the order of authorship and the corresponding author will take responsibility for informing coauthors in a timely manner of editorial decisions, reviews received, changes made in response to editorial review, and content of revisions. None of the authors report any conflicts of interest in connection with this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110807.

References

Andersen, S.L., Teicher, M.H., 2000. Sex differences in dopamine receptors and their relevance to ADHD. Neurosci. Biobehav. Rev. 24 (1), 137–141. https://doi.org/10.1016/S0149-7634(99)00044-5.

Arnsten, A.F.T., Paspalas, C.D., Gamo, N.J., Yang, Y., Wang, M., 2010. Dynamic network connectivity: a new form of neuroplasticity. Trends Cogn. Sci. 14 (8), 365–375 (https://doi.org/10/b4k4gp).

Arsenault, E., Lavigne, A.-A., Mansouri, S., Gagné, A.-M., Francis, K., Bittar, T.P., Quessy, F., Abdallah, K., Barbeau, A., Hébert, M., Labonté, B., 2021. Sex-specific retinal anomalies induced by chronic social defeat stress in mice. Front. Behav. Neurosci. 15, 714810 https://doi.org/10.3389/fnbeh.2021.714810.

Ayano, G., 2016. Dopamine: receptors, functions, synthesis, pathways, locations and mental disorders: review of literatures. J. Mental Disorders Treat. 2 (2) (https://doi.org/10/gh3zsm).

Baggio, S., Bayard, S., Cabelguen, C., Desseilles, M., Gachet, M., Kraemer, C., Richard-Lepouriel, H., Nicastro, R., Bioulac, S., Sauvaget, A., Weibel, S., Perroud, N., Lopez, R., 2020. Diagnostic accuracy of the French version of the adult attention deficit/hyperactivity disorder self-report screening scale for DSM-5 (ASRS-5). J. Psychopathol. Behav. Assess. 43, 367–375 (https://doi.org/10/gh23k4).

Balogh, Z., Benedek, G., Kéri, S., 2008. Retinal dysfunctions in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 32 (1), 297–300 (https://doi.org/10/fpbhbv).

Bernardin, F., Schwitzer, T., Angioi-Duprez, K., Giersch, A., Jansen, C., Schwan, R., Laprevote, V., 2020. Retinal ganglion cells dysfunctions in schizophrenia patients with or without visual hallucinations. Schizophr. Res. 219, 47–55. https://doi.org/10.1016/j.schres.2019.07.007.

Biederman, J., Faraone, S.V., Monuteaux, M.C., Bober, M., Cadogen, E., 2004. Gender effects on attention-deficit/hyperactivity disorder in adults, revisited. Biol. Psychiatry 55 (7), 692–700. https://doi.org/10.1016/j.biopsych.2003.12.003.

Brûlé, J., Lavoie, M.-P., Casanova, C., Lachapelle, P., Hébert, M., 2007. Evidence of a possible impact of the menstrual cycle on the reproducibility of scotopic ERGs in women. Doc. Ophthalmol. 114 (3), 125–134 (https://doi.org/10/cggxzf).

Bush, G., Valera, E.M., Seidman, L.J., 2005. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol. Psychiatry 57 (11), 1273–1284 https://doi.org/10/ftb79k.

Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S., Blumenthal, J.D., James, R.S., Ebens, C.L., Walter, J.M., Zijdenbos, A., Evans, A.C., Giedd, J.N., Rapoport, J.L., 2002. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. Jama 288 (14), 1740–1748 https://doi.org/10/bjh8bn.

Cheon, K.-A., Ryu, Y.H., Kim, Y.-K., Namkoong, K., Kim, C.-H., Lee, J.D., 2003. Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. Eur. J. Nucl. Med. Mol. Imaging 30 (2), 306–311 https://doi.org/10/cb46pf.

Constable, P.A., Ritvo, E.R., Ritvo, A.R., Lee, I.O., McNair, M.L., Stahl, D., Sowden, J., Quinn, S., Skuse, D.H., Thompson, D.A., McPartland, J.C., 2020. Light-adapted electroretinogram differences in autism spectrum disorder. J. Autism Dev. Disord. 50 (8), 2874–2885 https://doi.org/10/gh23k2.

Craig, S.G., Davies, G., Schibuk, L., Weiss, M.D., Hechtman, L., 2015. Long-term effects of stimulant treatment for ADHD: what can we tell our patients? Curr. Dev. Disord. Rep. 2 (1), 1–9 https://doi.org/10/ggtrgp.

Cumyn, L., French, L., Hechtman, L., 2009. Comorbidity in adults with attention-deficit hyperactivity disorder. Can. J. Psychiatry 54 (10), 673–683 https://doi.org/10/gf992w.

Danielson, M.L., Bitsko, R.H., Ghandour, R.M., Holbrook, J.R., Kogan, M.D., Blumberg, S. J., 2018. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. J. Clin. Child Adolesc. Psychol. 47 (2), 199–212 https://doi.org/10/gctsgb.

Demmin, D.L., Davis, Q., Roché, M., Silverstein, S.M., 2018. Electroretinographic anomalies in schizophrenia. J. Abnorm. Psychol. 127 (4), 417–428 https://doi.org/10/gdkh2t.

Dougherty, D.D., Bonab, A.A., Spencer, T.J., Rauch, S.L., Madras, B.K., Fischman, A.J., 1999. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 354 (9196), 2132–2133 https://doi.org/10/bg8rhn.

Dowling, J.E., 2012. The Retina: An Approachable Part of the Brain, Revised Edition (2e éd.). Belknap Press.

Dresel, S., Krause, J., Krause, K.-H., LaFougere, C., Brinkbäumer, K., Kung, H.F., Hahn, K., Tatsch, K., 2000. Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. Eur. J. Nucl. Med. 27 (10), 1518–1524 https://doi.org/10/cpm9n6.

French, B., Perez Vallejos, E., Sayal, K., Daley, D., 2020. Awareness of ADHD in primary care: stakeholder perspectives. BMC Fam. Pract. 21 (45) https://doi.org/10/gh23kx.

Frishman, L., Sustar, M., Kremers, J., McAnany, J.J., Sarossy, M., Tzekov, R., Viswanathan, S., 2018. ISCEV extended protocol for the photopic negative response (PhNR) of the full-field electroretinogram. Doc. Ophthalmol. 136 (3), 207–211. https://doi.org/10.1007/s10633-018-9638-x.

Fusar-Poli, P., Rubia, K., Rossi, G., Sartori, G., Balottin, U., 2012. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to

psychostimulants? A meta-analysis. American Journal of Psychiatry 169 (3), 264–272. https://doi.org/10.1176/appi.ajp.2011.11060940.
Gagné, A.-M., Lavoie, J., Lavoie, M.-P., Sasseville, A., Charron, M.-C., Hébert, M., 2010. Assessing the impact of non-dilating the eye on full-field electroretinogram and standard flash response. Doc. Ophthalmol. 121 (3), 167–175. https://doi.org/10.1007/s10633-010-9242-1.
Ginsberg, Y., Quintero, J., Anand, E., Casillas, M., Upadhyaya, H.P., 2014. Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: a review of the literature. Primary Care Compan. CNS Disord. 16 (3) https://doi.org/10/f3nj62.
Groom, M.J., Cortese, S., 2022. Current pharmacological treatments for ADHD. In: Stanford, S.C., Sciberras, E. (Eds.), New Discoveries in the Behavioral Neuroscience of Attention-Deficit Hyperactivity Disorder, vol. 57. Springer International Publishing, pp. 19–50.
Gualtieri, C.T., Johnson, L.G., 2005. ADHD: is objective diagnosis possible? Psychiatry 2 (11), 44–53.
Hayden, E.P., Nurnberger, J.I., 2005. Molecular genetics of bipolar disorder: bipolar disorder. Genes Brain Behav. 5 (1), 85–95 https://doi.org/10/dn73t3.
Hébert, M., Lachapelle, P., 2003. Evaluation of retinal function: electroretinography. In: Levin, L.A., Di Polo, A. (Eds.), Ocular Neuroprotection. CRC Press, p. 344.
Hébert, M., Beattie, C.W., Tam, E.M., Yatham, L.N., Lam, R.W., 2004. Electroretinography in patients with winter seasonal affective disorder. Psychiatry Res. 127 (1–2), 27–34. https://doi.org/10.1016/j.psychres.2004.03.006.
Hébert, M., Mérette, C., Paccalet, T., Émond, C., Gagné, A.-M., Sasseville, A., Maziade, M., 2015. Light evoked potentials measured by electroretinogram may tap into the neurodevelopmental roots of schizophrenia. Schizophr. Res. 162 (1–3), 294–295. https://doi.org/10.1016/j.schres.2014.12.030.
Hébert, M., Mérette, C., Gagné, A.-M., Paccalet, T., Moreau, I., Lavoie, J., Maziade, M., 2020. The electroretinogram may differentiate schizophrenia from bipolar disorder. Biol. Psychiatry 87 (3), 263–270 https://doi.org/10/gh23jc.
Hobby, A.E., Kozareva, D., Yonova-Doing, E., Hossain, I.T., Katta, M., Huntjens, B., Hammond, C.J., Binns, A.M., Mahroo, O.A., 2018. Effect of varying skin surface electrode position on electroretinogram responses recorded using a handheld stimulating and recording system. Doc. Ophthalmol. 137 (2), 79–86. https://doi.org/10.1007/s10633-018-9652-z.
Hochberg, Y., Benjamini, Y., 1990. More powerful procedures for multiple significance testing. Stat. Med. 9 (7), 811–818. https://doi.org/10.1002/sim.4780090710.
Horga, G., Cassidy, C.M., Xu, X., Moore, H., Slifstein, M., Van Snellenberg, J.X., Abi-Dargham, A., 2016. Dopamine-related disruption of functional topography of striatal connections in Unmedicated patients with schizophrenia. JAMA Psychiatry 73 (8), 862–870 https://doi.org/10/gh23kj.
Johnson, M.A., Jeffrey, B.G., Messias, A.M.V., Robson, A.G., 2019. ISCEV extended protocol for the stimulus–response series for the dark-adapted full-field ERG b-wave. Doc. Ophthalmol. 138 (3), 217–227. https://doi.org/10.1007/s10633-019-09687-6.
Jucaite, A., Fernell, E., Halldin, C., Forssberg, H., Farde, L., 2005. Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: association between striatal dopamine markers and motor hyperactivity. Biol. Psychiatry 57 (3), 229–238 https://doi.org/10/bj7t8t.
Kessler, R.C., Adler, L., Barkley, R., Biederman, J., Conners, C.K., Demler, O., Faraone, S. V., Greenhill, L.L., Howes, M.J., Secnik, K., Spencer, T., Ustun, T.B., Walters, E.E., Zaslavsky, A.M., 2006. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am. J. Psychiatr. 163 (4), 716–723 https://doi.org/10/ggw99s.
Kooij, J.J.S., Bijlenga, D., Salerno, L., Jaeschke, R., Bitter, I., Balázs, J., Thome, J., Dom, G., Kasper, S., Nunes Filipe, C., Stes, S., Mohr, P., Leppämäki, S., Casas, M., Bobes, J., Mccarthy, J.M., Richarte, V., Kjems Philipsen, A., Pehlivanidis, A., Asherson, P., 2019. Updated European consensus statement on diagnosis and treatment of adult ADHD. Eur. Psychiatry 56 (1), 14–34 https://doi.org/10/gftgpx.
Lavoie, J., Illiano, P., Sotnikova, T.D., Gainetdinov, R.R., Beaulieu, J.-M., Hébert, M., 2014. The electroretinogram as a biomarker of central dopamine and serotonin: potential relevance to psychiatric disorders. Biol. Psychiatry 75 (6), 479–486 https://doi.org/10/f5tmj3.
Lee, W.-S., Yoon, B.-E., 2023. Necessity of an Integrative Animal Model for a Comprehensive Study of Attention-Deficit/Hyperactivity Disorder. https://doi.org/10.3390/biomedicines11051260.
Lee, I.O., Skuse, D.H., Constable, P.A., Marmolejo-Ramos, F., Olsen, L.R., Thompson, D. A., 2022. The electroretinogram b-wave amplitude: a differential physiological measure for attention deficit hyperactivity disorder and autism Spectrum disorder. J. Neurodev. Disord. 14 (1), 30. https://doi.org/10.1186/s11689-022-09440-2.
Lindamer, L.A., Lohr, J.B., Harris, M.J., Jeste, D.V., 2004. Gender, Estrogen, and Schizophrenia. FOCUS 2 (1), 138–145. https://doi.org/10.1176/foc.2.1.138.
London, A.S., Landes, S.D., 2021. Cohort change in the prevalence of ADHD among U.S. adults: evidence of a gender-specific historical period effect. J. Atten. Disord. 25 (6), 771–782. https://doi.org/10.1177/1087054719855689.
MacCormick, I.J., Czanner, G., Faragher, B., 2015. Developing retinal biomarkers of neurological disease: an analytical perspective. Biomark. Med 9 (7), 691–701 https://doi.org/10/gh23km.
Marrocco, J., McEwen, B.S., 2016. Sex in the brain: hormones and sex differences. Dialogues Clin. Neurosci. 18 (4), 373–383. https://doi.org/10.31887/DCNS.2016.18.4/jmarrocco.
Martin, J., Walters, R.K., Demontis, D., Mattheisen, M., Lee, S.H., Robinson, E., Brikell, I., Ghirardi, L., Larsson, H., Lichtenstein, P., Eriksson, N., Werge, T., Mortensen, P.B., Pedersen, M.G., Mors, O., Nordentoft, M., Hougaard, D.M., Bybjerg-Grauholm, J., Wray, N.R., Werge, T., 2018. A genetic investigation of sex bias in the prevalence of attention-deficit/hyperactivity disorder. Biol. Psychiatry 83 (12), 1044–1053. https://doi.org/10.1016/j.biopsych.2017.11.026.
McCulloch, D.L., Kondo, M., Hamilton, R., Lachapelle, P., Messias, A.M.V., Robson, A.G., Ueno, S., 2019. ISCEV extended protocol for the stimulus–response series for light-adapted full-field ERG. Doc. Ophthalmol. 138 (3), 205–215. https://doi.org/10.1007/s10633-019-09685-8.
Mehta, T.R., Monegro, A., Nene, Y., Fayyaz, M., Bollu, P.C., 2019. Neurobiology of ADHD: a review. Curr. Dev. Disord. Rep. 6 (4), 235–240. https://doi.org/10.1007/s40474-019-00182-w.
Money, K.M., Stanwood, G.D., 2013. Developmental origins of brain disorders: roles for dopamine. Front. Cell. Neurosci. 7 https://doi.org/10/gh3zs3.
Naaijen, J., Bralten, J., Poelmans, G., Glennon, J.C., Franke, B., Buitelaar, J.K., 2017. Glutamatergic and GABAergic gene sets in attention-deficit/hyperactivity disorder: association to overlapping traits in ADHD and autism. Transl. Psychiatry 7 (1), e999 https://doi.org/10/f9mktj.
Nakamura, Y., Okada, N., Koshiyama, D., Kamiya, K., Abe, O., Kunimatsu, A., Okanoya, K., Kasai, K., Koike, S., 2020. Differences in functional connectivity networks related to the midbrain dopaminergic system-related area in various psychiatric disorders. Schizophr. Bull. 46 (5), 1239–1248. https://doi.org/10.1093/schbul/sbz121.
Nigg, J.T., Willcutt, E.G., Doyle, A.E., Sonuga-Barke, E.J.S., 2005. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? Biol. Psychiatry 57 (11), 1224–1230 https://doi.org/10/dfzvg6.
Pavăl, D., 2017. A dopamine hypothesis of autism Spectrum disorder. Dev. Neurosci. 39 (5), 355–360 https://doi.org/10/gbp969.
Poelmans, G., Pauls, D.L., Buitelaar, J.K., Franke, B., 2011. Integrated genome-wide association study findings: identification of a neurodevelopmental network for attention deficit hyperactivity disorder. Am. J. Psychiatr. 168 (4), 365–377 https://doi.org/10/dx955m.
Prasad, V., West, J., Kendrick, D., Sayal, K., 2019. Attention-deficit/hyperactivity disorder: variation by socioeconomic deprivation. Arch. Dis. Child. 104 (8), 802–805. https://doi.org/10.1136/archdischild-2017-314470.
Puts, N.A., Ryan, M., Oeltzschner, G., Horska, A., Edden, R.A.E., Mahone, E.M., 2020. Reduced striatal GABA in unmedicated children with ADHD at 7T. Psychiatry Res. Neuroimaging 301, 111082. https://doi.org/10.1016/j.pscychresns.2020.111082.
Rangaswamy, N.V., Shirato, S., Kaneko, M., Digby, B.I., Robson, J.G., Frishman, L.J., 2007. Effects of spectral characteristics of ganzfeld stimuli on the photopic negative response (PhNR) of the ERG. Investig. Ophthalmol. Vis. Sci. 48 (10), 4818–4828 https://doi.org/10/bb473q.
Reis, R.A.M., Ventura, A.L.M., Kubrusly, R.C.C., de Mello, M.C.F., de Mello, F.G., 2007. Dopaminergic signaling in the developing retina. Brain Res. Rev. 54 (1), 181–188 https://doi.org/10/frhrd4.
Rowland, A.S., Skipper, B.J., Umbach, D.M., Rabiner, D.L., Campbell, R.A., Naftel, A.J., Sandler, D.P., 2015. The prevalence of ADHD in a population-based sample. J. Atten. Disord. 19 (9), 741–754 https://doi.org/10/f7m77b.
Rubia, K., Alegria, A.A., Cubillo, A.I., Smith, A.B., Brammer, M.J., Radua, J., 2014. Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Biol. Psychiatry 76 (8), 616–628 https://doi.org/10/f6k4dv.
Sayal, K., Prasad, V., Daley, D., Ford, T., Coghill, D., 2018. ADHD in children and young people: prevalence, care pathways, and service provision. Lancet Psychiatry 5 (2), 175–186 https://doi.org/10/gczdg4.
Sciutto, M.J., Eisenberg, M., 2007. Evaluating the evidence for and against the overdiagnosis of ADHD. J. Atten. Disord. 11 (2), 106–113 https://doi.org/10/c8pgmz.
Shansky, R.M. (Ed.), 2016. Sex Differences in the Central Nervous System. Elsevier Academic Press.
Sonuga-Barke, E.J., Koerting, J., Smith, E., McCann, D.C., Thompson, M., 2011. Early detection and intervention for attention-deficit/hyperactivity disorder. Expert. Rev. Neurother. 11 (4), 557–563. https://doi.org/10.1586/ern.11.39.
Spencer, T.J., Biederman, J., Madras, B.K., Faraone, S.V., Dougherty, D.D., Bonab, A.A., Fischman, A.J., 2005. In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: a focus on the dopamine transporter. Biol. Psychiatry 57 (11), 1293–1300 https://doi.org/10/fn25gm.
Tannock, R., Banaschewski, T., Gold, D., 2006. Color naming deficits and attention-deficit/hyperactivity disorder: a retinal dopaminergic hypothesis. Behav. Brain Funct. 2 (1), 4 https://doi.org/10/ftbrjr.
Thomas, R., Sanders, S., Doust, J., Beller, E., Glasziou, P., 2015. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics 135 (4), e994–e1001 https://doi.org/10/b6pq.
Vaidya, C.J., 2011. Neurodevelopmental abnormalities in ADHD. In: Stanford, C., Tannock, R. (Eds.), Behavioral Neuroscience of Attention Deficit Hyperactivity Disorder and Its Treatment, vol. 9. Springer, Berlin Heidelberg, pp. 49–66. https://doi.org/10.1007/7854_2011_138.
van Dyck, C.H., Quinlan, D.M., Cretella, L.M., Staley, J.K., Malison, R.T., Baldwin, R.M., Seibyl, J.P., Innis, R.B., 2002. Unaltered dopamine transporter availability in adult attention deficit hyperactivity disorder. Am. J. Psychiatr. 159 (2), 309–312 https://doi.org/10/c9975t.
Vanston, J.E., Strother, L., 2017. Sex differences in the human visual system: visual system sex differences. J. Neurosci. Res. 95 (1–2), 617–625. https://doi.org/10.1002/jnr.23895.
Warner, R., Laugharne, J., Peet, M., Brown, L., Rogers, N., 1999. Retinal function as a marker for cell membrane omega–3 fatty acid depletion in schizophrenia: a pilot study. Biol. Psychiatry 45 (9), 1138–1142 https://doi.org/10/c679tk.
Weleber, R.G., 1981. The effect of age on human cone and rod ganzfeld electroretinograms. Invest. Ophthalmol. Vis. Sci. 20 (3), 392–399.
Wolraich, M.L., McKeown, R.E., Visser, S.N., Bard, D., Cuffe, S., Neas, B., Geryk, L.L., Doffing, M., Bottai, M., Abramowitz, A.J., Beck, L., Holbrook, J.R., Danielson, M.,

2014. The prevalence of ADHD: its diagnosis and treatment in four school districts across two states. J. Atten. Disord. 18 (7), 563–575 https://doi.org/10/f245gm.

Wooltorton, E., 2005. Suicidal ideation among children taking atomoxetine (Strattera). Can. Med. Assoc. J. 173 (12), 1447 https://doi.org/10/fw8tmp.

Youssef, P., Nath, S., Chaimowitz, G.A., Prat, S.S., 2019. Electroretinography in psychiatry: a systematic literature review. Eur. Psychiatry 62, 97–106 https://doi.org/10/gh23jf.

Zagni, E., Simoni, L., Colombo, D., 2016. Sex and gender differences in central nervous system-related disorders. Neurosci. J. 2016, 1–13. https://doi.org/10.1155/2016/2827090.