European Psychiatry 62 (2019) 97–106

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Review / Meta-analyses

Electroretinography in psychiatry: A systematic literature review

Peter Youssef[a], Siddharth Nath[b], Gary A Chaimowitz[c,d], Sebastien S. Prat[c,d,*]

[a] Bachelor of Health Sciences Program, McMaster University, Hamilton, Ontario, Canada
[b] MD/PhD Program, McMaster University, Hamilton, Ontario, Canada
[c] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada
[d] Forensic Psychiatry Program, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada

ARTICLE INFO

Article history:
Received 7 September 2019
Accepted 7 September 2019
Available online 22 September 2019

Keywords:
Electroretinography
Electroretinogram
Psychiatry
Diagnostic tools

ABSTRACT

This review aims to consolidate the available information on use of electroretinography as a diagnostic tool in psychiatry. The electroretinogram (ERG) has been found to have diagnostic utility in cocaine withdrawal (reduced light-adapted b-wave response), major depressive disorder (reduced contrast gain in pattern ERG), and schizophrenia (reduced a- and b-wave amplitudes). This review examines these findings as well as the applicability of ERG to substance use disorder, Alzheimer's disease, autism spectrum disorder, panic disorder, eating disorders, attention deficit hyperactivity disorder, and medication use. While there have been promising results, current research suffers from a lack of specificity. Further research that quantifies anomalies in ERG present in psychiatric illness is needed.

1. Introduction

Diagnosis of mental illness is often a lengthy and involved process. As definitions and categorizations of diseases become increasingly complex, a search for objective biomarkers of mental illness is underway to facilitate swift and accurate clinical assessment [1]. Because the retina uses neurotransmitters for phototransduction, it is hypothesized that the deregulation of neurotransmitter physiology present in many mental illnesses may be detectable through assessment of retinal function.

The electroretinogram (ERG), is a non-invasive diagnostic test that measures electrical activity generated by neuronal and non-neuronal cells within the retina and has shown utility in the assessment of psychiatric illnesses [1–3]. It measures electrical impulses through a contact lens which can detect summation of retinal electrical activity at the corneal surface. In mouse models, it has been shown that alterations in retinal dopaminergic and serotonergic neurotransmission parallel abnormalities observed in ERG recordings [2].

The ERG outputs multiple waveforms, which represent different components of retinal electrophysiology [4]. Of these, two waveforms have been shown to be especially important in the setting of psychiatry: the a-wave and the b-wave. The a-wave is representative of photoreceptor function and is measured as the height of the baseline electrical activity before flash onset to the trough of the first wave. The b-wave reflects bipolar cell function and is measured from the trough of the a-wave to the peak of the second wave [4]. Examples of ERG waveforms are shown in Fig. 1.

There exist different types of ERGs, which can assess varied components of the retina. The full-field flash ERG (fERG) assesses the electrophysiological response to a flash of light and is well-established and routinely used in ophthalmology [4]. It is also under investigation for applications in psychiatry. The fERG assesses retinal function under dark-adapted (scotopic) or light-adapted (photopic) settings. The scotopic fERG is usually indicative of rod function, while the photopic fERG commonly correlates with cone function [4]. Mixed cone/rod responses may also be elicited on scotopic ERG. In addition to fERG, pattern ERG (PERG) is also under evaluation in psychiatric populations. PERG provides information regarding macular, bipolar, and retinal ganglion cell function by stimulation with a rapidly reversing high-contrast black and white checkerboard or alternating horizontal and vertical lines, and therefore also allows for inferences of retinal contrast sensitivity [7,8]. Moreover, some investigators have also begun to study the newer multifocal ERG (mfERG) in the setting of mental illness. This ERG measures the response from hundreds of points on the retina simultaneously and creates a 'topographic map' of retinal functioning [9].

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval; ERG, electroretinogram/electroretinography; fERG, flash electroretinogram/electroretinography; ISCEV, international society for clinical electrophysiology of vision; MDD, major depressive disorder; mfERG, multifocal electroretinography/electroretinogram; ms, millisecond; pERG, pattern electroretinogram/electroretinography; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

* Corresponding author at: Forensic Psychiatry Program, St. Joseph's Healthcare Hamilton, Hamilton, ON L8N 3K7, Canada.
E-mail address: prats@mcmaster.ca (S.S. Prat).

http://dx.doi.org/10.1016/j.eurpsy.2019.09.006
0924-9338/

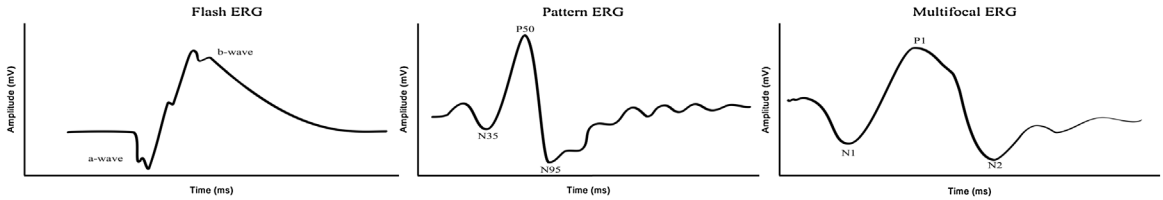

Fig. 1. fERG, PERG, and mfERG waveforms and parameters. Waveforms based on information provided in included studies.

Although there remains contention with regards to the neurochemical basis of ERG waves, retinal physiology is known to be primarily dependent on glutamate [7]. Thus, it is hypothesized that changes to the glutamate neurotransmitter system, as are observed in many psychiatric illnesses, may manifest in different ERG profiles in varied disease states. Some groups hypothesize that the retinal endocannabinoid system, dopamine system, or the GABAergic system may also be at play, allowing for insight into psychiatric conditions resulting from aberrant functioning of these signaling pathways [2,5,6].

This review explores variations in ERG waveforms across several different psychiatric populations and highlights potential applications for ERG in the detection and assessment of mental illness.

2. Material and methods

2.1. General methods

The present review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

2.2. Literature search

We performed a systematic search of the Web of Science electronic database using the following keywords: 'electroretinogram', 'electroretinography', and ['electroretinography' + psychiatry (topic)]. To ensure we captured all available evidence in the

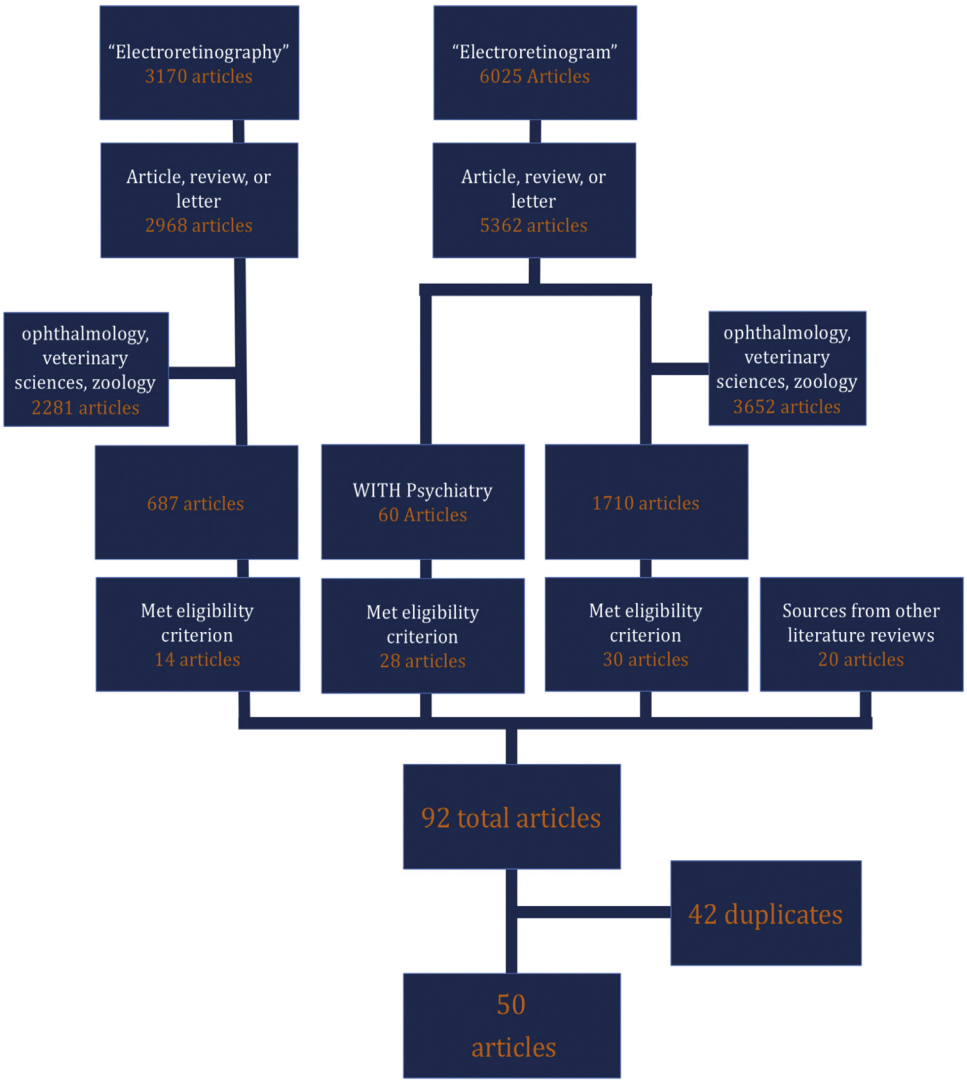

Fig. 2. PRISMA flow diagram. The selection process for identifying eligible studies is shown.

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

field, our sole eligibility criteria was that ERG was used on human subjects for diagnosis or assessment of mental illness. We excluded articles not investigating psychiatric conditions, articles with the keyword 'ophthalmology', as well as wet lab research and animal studies. Our electronic search was supplemented by reviewing the references of included articles. For the purposes of our review, Alzheimer's disease was considered a psychiatric condition and was thus included, while epilepsy was considered a neurological condition and was excluded. We included both full reports and conference proceedings, provided that a subsequent article had not been published.

2.3. Data collection

We downloaded the complete articles of all included studies. We created data extraction forms with fields for: population studied, type of ERG (fERG, PERG, mfERG), study design, and ERG results.

3. Results

3.1. General results

Our literature search yielded 9,195 results, from which 55 articles met our inclusion criteria (Fig. 2). Articles covered a spectrum of psychiatric illnesses including substance use, depressive disorders, schizophrenia, panic disorder, and eating disorders. Most articles focused on the applicability of ERG to substance use, depressive disorders, and schizophrenia, with a minority investigating panic disorder and eating disorders. Distribution of psychiatric illnesses amongst the articles is shown in Fig. 3.

Included articles covered over 30 years of research and a timeline of how the landscape of the field has evolved is shown in Fig. 4. Notably, there has been increased interest in the applicability of ERG to psychiatric illness. Use of ERG as a diagnostic tool has had an early start in the scientific literature, however, there has been little success in establishing it for clinical use. As shown, there are also periods with little research progress, concordant with periods of plateauing in technological innovation.

3.2. Substance use

We found 15 articles evaluating the effects of various substances on ERG [6,11–24]. Of these, nine studied the effects of cocaine, three studied cannabis, two studied alcohol, and one studied mixed drug use. A complete summary of the included studies and their findings is shown in Table 1.

In the setting of cocaine use, it was noted that there was decreased light-adapted b-wave amplitude on fERG. Moreover, cocaine craving was observed to correlate with a depression in the b-wave amplitude [12,14,17,18]. Variable levels of correlation were noted across studies, with calculated r-values ranging from 0.35 to 0.9.

Studies reporting on cannabis use presented varied parameters. Two articles [5,23] reported an increase in implicit time, with Schwitzer et al. [5] reporting a sensitivity of 78.6% (95% CI 60.5–89.8) and a specificity of 75.0% (95% CI 55.1–88.1) for an N95 implicit time longer than 93.15 ms for PERG.

For alcohol consumption, one study [6] found a reduced dark-adapted b-wave amplitude on fERG.

3.3. Alzheimer's disease

Four studies evaluating differences in ERG waveforms in Alzheimer's disease met our inclusion criteria [25–28], all of which used PERG. No studies were able to determine a statistically significant difference in PERG in patients with Alzheimer's disease, however, a trend was noted towards a reduced b-wave amplitude. Details of studies investigating Alzheimer's disease are shown in Table 2.

3.4. Autism spectrum disorder

Similar to Alzheimer's disease, four articles studying ERG in the context of autism spectrum disorder were included in our review [29–32]. Three articles [29,30,32] used a fERG while one used a PERG [31]. Articles using a fERG found a decreased b-wave amplitude (rod function) in patients with autism spectrum disorder, however, quantitative analyses were not provided. Realmuto et al. [30] showed a similar reduction in a families of patients with four siblings and two fathers affected, congruent with the neurodevelopmental origin of autism. Results from studies in this group are shown in Table 3.

3.5. Depressive disorders

12 articles evaluating ERG in depressive disorders were eligible [33–44]. Seven of these studied seasonal affective disorder (SAD) and the remaining five major depressive disorder (MDD). There was little consistency in protocol across studies, making cross-comparisons difficult. For MDD, a trend was noted towards decreased contrast gain on PERG, especially for moderate-to-severe depression, although Fam et al. [42], were unable to replicate these findings. Notably, studies also evaluated the impact of interventions on MDD and found that ERG abnormalities resolved with treatment. Similarly, studies evaluating SAD showed variable results on ERG, although there was normalization of irregularities with light therapy or during the summer months [36]. Details of the studies investigating depressive disorders are shown in Table 4.

3.6. Schizophrenia

In total, 11 articles investigating ERG in the context of schizophrenia were eligible [45–55]. All but one of the articles used the fERG [45–53,55], with the remaining article implementing PERG [54]. Hébert et al. [50] noted an increase in implicit time in patients with schizophrenia. Across articles, there was also a trend of reduced a- and b-wave amplitudes in schizophrenia. Interestingly, Gerbaldo et al. [46] failed to find this reduction, although their study population differed from that of other articles as it included individuals with a history of sungazing. The most powered study in this group, by Hébert et al. [48], showed reductions in both a- and b-wave amplitudes. Notably, Demmin et al. [55] also provided data on photopic negative response, noting that the schizophrenia group demonstrated attenuated negativity in comparison to healthy controls. Full details of articles investigating ERG in schizophrenia are available in Table 5.

3.7. Panic disorder

Two articles evaluating the diagnostic ability of fERG in participants with panic disorder were included in our review [56,57]. Both articles found decreased b-wave amplitudes in patients, and reduced differences between right and left eyes in the b-wave amplitudes. The details of these two studies are discussed in Table 6.

3.8. Eating disorders

Only two studies evaluating ERG in the context of eating disorders met our inclusion criteria [58,59]. Nasser et al. [58]

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

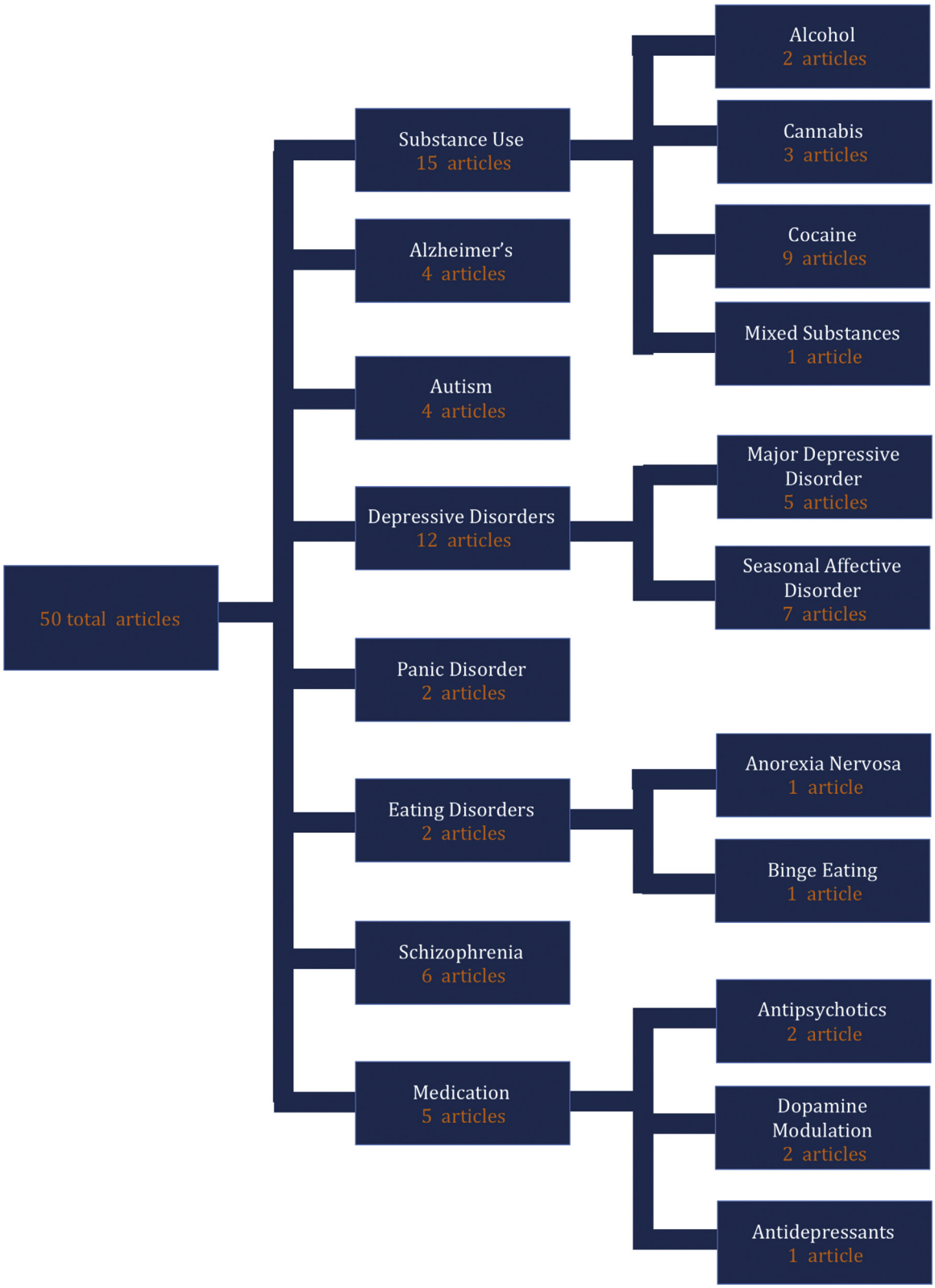

Fig. 3. Number of articles by specific psychiatric illness and topic.

discussed oral food stimulation in the setting of binge eating, while the study by Moschos et al. [59] discussed anorexia nervosa. An increase in b-wave amplitude in response to brownie consumption and a correlation between the Gormally Binge Eating Scale and increased b-wave amplitude ($r = 0.68$) was noted on fERG for binge eating. Moreover, the authors noted that there was a similar increase in b-wave amplitude following administration of methylphenidate [58]. In anorexia nervosa, a decreased P1 retinal response density amplitude was found for ring 1 using mfERG [59]. Complete details of studies in this group are available in Table 7.

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

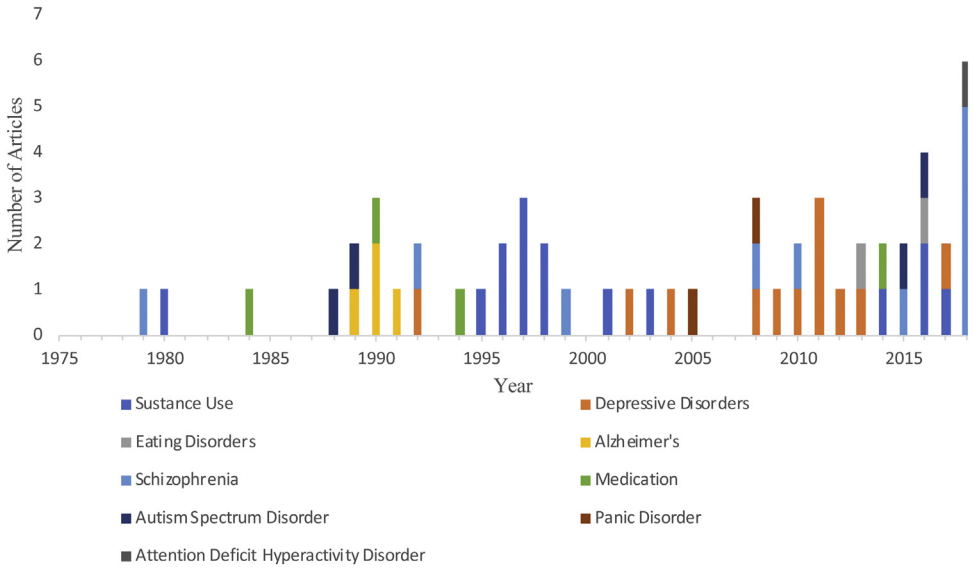

Fig. 4. Timeline of the literature on applications of ERG in psychiatry stratified by specific illness and topic.

Table 1
Articles on substance use.

Study	Substance Studied	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Ladien 1980	Alcohol	–	Letter	fERG	Reduced dark-adapted b-wave amplitude	Not stated
Pérez 1995	Heroin, Cannabis, Cocaine	15	Cross-sectional	fERG	Decreased amplitudes and decreased implicit times in more than 50% of participants compared to controls	Not stated
Roy 1996	Cocaine, recently withdrawn	14	Cross-sectional	fERG, blue filter	Reduced light-adapted b-wave amplitude in response to blue light; negative correlation between b-wave amplitude and cocaine craving (r=−0.54)	Cones
Smelson 1996	Cocaine, recently withdrawn	6	Cross-sectional	fERG, blue filter	Reduced light-adapted b-wave amplitude in response to blue light; correlation between reduction and cocaine craving (r = 0.90)	Cones
Roy 1997	Cocaine, recently withdrawn	20	Cross-sectional	fERG, multiple color filters	Reduced light-adapted b-wave amplitudes, many cocaine withdrawn participants had amplitudes below 0.5 mV	Cones
Roy 1997	Cocaine, recently withdrawn	30	Cross-sectional	fERG, blue filter	Negative correlation between blue cone b-wave amplitude and scores on cocaine craving questionnaire (r=−0.35)	Cones
Roy 1997	Cocaine, withdrawn	8	Longitudinal	fERG, blue filter	No difference in light-adapted b-wave amplitude over duration of study	Cones
Roy 1998	Cocaine, recently withdrawn	8	Longitudinal	fERG, blue filter	No increase in light-adapted b-wave amplitude with risperidone	Cones
Smelson 1998	Cocaine, recently withdrawn	14	Cross-sectional	fERG, blue filter	Reduced light-adapted b-wave amplitude correlated with higher cocaine craving	Cones
Smelson 2001	Cocaine, recently withdrawn	21	Cross-sectional	fERG, multiple color filters	Participants with lower light-adapted b-wave amplitudes had higher craving scores	Cones
Roy 2003	Cocaine, recently withdrawn	17	Cross-sectional	fERG, blue and red filters	Lower light-adapted b-wave amplitude correlated with lower CSF homovanillic acid (dopamine metabolite) (r = 0.57)	Cones
Schwitzer 2014	Cannabis	—	Cross-sectional	fERG	Increased implicit time for a- and b-waves in light- and dark-adapted conditions	Not stated
Kim 2016	Alcohol	15	Prospective	mfERG	Shortening of P1 implicit time of ring 1	Cones
Schwitzer 2016	Cannabis	1	Case study	fERG	Decreased dark-adapted a-wave amplitude 30 minutes after smoking	Not stated
Schwitzer 2017	Cannabis	28	Cross-sectional	PERG	Increase in N95 implicit time; suggest that an N95 implicit time longer than 91.13 ms demonstrates regular cannabis use: sensitivity 78.6% (95% CI 60.5–89.8), specificity 75.0% (95% CI 55.1–88.0)	Not stated

Notes: **CI** = confidence interval; **CSF** = cerebrospinal fluid; **ERG** = electroretinogram; **fERG** = flash electroretinogram; **mfERG** = multifocal electroretinogram; **PERG** = pattern electroretinogram.

3.9. Attention deficit hyperactivity disorder

One article discussing attention deficit hyperactivity disorder (ADHD) was eligible, and it utilized the PERG [60]. Treatment with methylphenidate was also discussed. The authors found that there was increased background noise on PERG in patients and that this normalized with treatment. Table 8 includes details of the article investigating ERG in ADHD.

3.10. Medication

Five articles assessed the effects of medication on healthy participants by ERG [61–65]. Two articles found that perphenazine decreased b-wave amplitudes, while bromocriptine increased them [62,63]. Several dopamine antagonists such as haloperidol, chlorpromazine, fluphenazine, and metoclopramide, reduced b-wave amplitudes, although these decreases were not

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

Table 2
Articles on Alzheimer's disease.

Study	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Katz 1989	6	Cross-sectional	PERG	B-wave amplitude was reduced by half in participants with Alzheimer's disease, no difference in latencies	Not stated
Pollock 1990	—	Letter, response to Katz et al., 1989	PERG	Katz 1989 had a small sample size and cannot conclude statistical significance	Not stated
Katz 1990	—	Letter, response to Pollock & Schneider 1990	PERG	PERG was reduced in participants with Alzheimer's but not statistically significant	Not stated
Strenn 1991	8	Cross-sectional	PERG	No anomalies noted	Not stated

Notes: **PERG** = pattern electroretinogram.

Table 3
Articles on autism spectrum disorder.

Study	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Ritvo 1988	27	Cross-sectional	fERG, blue and red filters	13/27 participants (48%) had below normal b-wave amplitudes	Not stated
Realmuto 1989	10	Cross-sectional	fERG	6/10 participants (60%) had decreased dark-adapted b-wave amplitudes	Cones and rods
van Elst 2015	33	Cross-sectional	PERG	No differences between disease and healthy groups	No photoreceptor - ganglion cell involved
Constable 2016	11	Cross-sectional	fERG	Decreased light- and dark-adapted b-wave amplitudes, however, dark-adapted b-wave amplitudes not as low Ritvo 1988	Cones and rods

Notes: **fERG** = flash electroretinogram; **PERG** = pattern electroretinogram.

Table 4
Articles on depressive disorders.

Study	Disorder Studied	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Lam 1992	SAD	24	Cross-sectional	fERG	Males had higher b-waves than control, while females had lower b-waves than controls; implicit time longer in left eyes of males	Cones and rods
Hébert 2002	SAD, sub-syndromal	12	Longitudinal	fERG	Changes in Global Seasonality Score were reflected in retinal sensitivity in SAD participants, SSAD participants showed differences between winter and summer response curves	Not stated
Hébert 2004	SAD	27	Cross-sectional	fERG	40% of SAD participants had dark-adapted light sensitivity (logK) below 1 SD that of the control group	Not stated
Danilenko 2008	SAD	22	Cross-sectional	fERG	Diet had no effect, dark-adapted amplitude diminished after eating for all groups	Cones and rods
Lavoie 2009	SAD	22	Longitudinal	fERG	Light-adapted ERG had lower amplitude and light sensitivity before light therapy in SAD participants which normalized after treatment; b-wave implicit time 7% longer in winter months than summer months in SAD participants; dark-adapted sensitivity increased with treatment	Cones and rods
Bubl 2010	MDD	40	Cross-sectional	PERG	Below-normal PERG contrast gain in MDD participants compared to control; below-normal contrast gain predicts low score on HAM-D with specificity of 92.5% and sensitivity of 77.5%	Not stated
Fornaro 2011	MDD	20	Longitudinal	fERG	Participants who responded to treatment had higher baseline ERG which normalized within the 12 weeks	Cones and rods
Gagne 2011	SAD	12	Longitudinal	fERG	SAD participants had lower light-adapted a-wave amplitudes, amplitudes for this group was higher in summer than in winter, SAD patients had lower b-wave dark-adapted VMax amplitudes for 5 and 10000 lux exposures	Cones and rods
Vandewalle 2011	SAD	14	Cross-sectional	fERG	No difference in light sensitivity (logK)	Cones and rods
Bubl 2012	MDD	14	Longitudinal	PERG	At baseline, MDD participants had lower contrast gain than controls, this normalized with treatment; if HAM-D is greater than or equal to 7, and BDI score is between 10-11 (moderate-severe depression), then sensitivity and specificity is 100%	Not stated
Fam 2013	MDD	20	Cross-sectional	fERG and PERG	No significant differences between groups	Not stated
Hébert 2017	MDD	100	Cross-sectional	fERG	Light-adapted b-wave implicit time was prolonged in participants with MDD, b-wave VMax was reached at a lower luminance in non-medicated participants than in medicated participants	Cones and rods

Notes: **BDI** = Beck Depression Inventory; **ERG** = electroretinogram; **fERG** = flash electroretinogram; **HAM-D** = Hamilton Depression Rating Scale; **MDD** = major depressive disorder; **PERG** = pattern electroretinogram; **SAD** = seasonal affective disorder; **SSAD** = sub-syndromal seasonal affective disorder.

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

Table 5
Articles on schizophrenia.

Study	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Gagrat 1979	3	Case series	fERG	No differences before and after treatment	Not stated
Gerbaldo 1992	9	Cross-sectional	fERG	No difference between participants with schizophrenia and controls; participants with history of sun gazing had decreased light-adapted retinal sensitivity	Not stated
Warner 1999	9	Cross-sectional	fERG	Reduced dark- and light-adapted a- and b-waves (both cone and rod)	Cones and rods
Balogh 2008	26	Longitudinal	fERG	Reduced a-wave amplitude; as positive PANSS scores increased, a-wave amplitude decreased for participants with schizophrenia (r=−0.51) for cones only during the acute phase of the disease	Cones
Hébert 2010	29	Cross-sectional	fERG	Reduced dark-adapted b-wave VMax amplitude	Cones and rods
Hébert 2015	105	Cross-sectional	fERG	Reduced a-and b-wave amplitudes at the cone	Cones and rods
Gagné 2018	33	Longitudinal	fERG	Reduced dark-adapted b-wave amplitude; large variation in ERG over time	Cones and rods
Maziade 2018	84	Cross-sectional	fERG	Lengthened light-adapted b-wave latency, reduced dark-adapted b-wave amplitude and latency	Cones and rods
Silverstein 2018	25	Cross-sectional	fERG	Weaker photoreceptor response	Photoreceptor type not stated - bipolar and ganglion cells involved
Laprevote 2018	15	Cross-sectional	PERG	Increased N95 implicit time for patients with visual hallucinations	Not stated
Demmin 2018	25	Cross-sectional	fERG	Reduced dark- and light-adapted a- and b-wave amplitude, reduced amplitudes for a flicker test; attenuated negativity of photopic negative response	Cones and rods

Notes: **ERG** = electroretinogram; **fERG** = flash electroretinogram; **PANSS** = Positive and Negative Syndrome Scale; **PERG** = pattern electroretinogram.

Table 6
Articles on panic disorder.

Study	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Pieraccini 2005	29	Cross-sectional	fERG	Decreased b-wave amplitude; differences in b-wave amplitudes between eyes reduced	Not stated
Bossini 2008	22	Cross-sectional	fERG	Decreased b-wave amplitude; difference between b-wave amplitudes in right and left eyes decreased	Not stated

Notes. **fERG**= flash electroretinogram.

Table 7
Articles on eating disorders.

Study	Disorder Studied	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Nasser 2013	Binge eating, oral food stimulation	9	Cross-sectional	fERG	Increase in b-wave amplitude for brownie consumption and correlation between Gormally Binge Eating Scale and increase in b-wave amplitude (r = 0.68); correlation between Stunkard and Messick Three Factor Eating Questionnaire and increase in b-wave amplitude (r = 0.67)	Cones
Moschos 2016	Anorexia nervosa	13	Cross-sectional	mfERG	Lower P1 retinal response density amplitude for ring 1	Not stated

Notes. **fERG**= flash electroretinogram; **mfERG**= multifocal electroretinogram.

Table 8
Articles on ADHD.

Study	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Bubl 2018	20	Longitudinal	PERG	Elevated background noise (127%) before treatment, which normalized after methylphenidate administration; background noise correlated with severity of ADHD symptoms	Cones and rods

Notes. **ADHD**= attention deficit hyperactivity disorder; **PERG**= pattern electroretinogram.

quantified [63,64]. Details of studies in this group are discussed in Table 9.

4. Discussion

The present review aimed to evaluate the utility of ERG as a diagnostic tool within a psychiatric setting in a systematic manner. Because of the lack of consistency amongst protocols, small sample sizes, and lack of replicable findings, there remains much work that needs to be done before ERG may be used reliably in psychiatry. The major findings of our review are summarized in Table 10.

In performing our review, we found it exceedingly difficult to make comparisons across studies and draw conclusions for specific disease groups. There was little consistency between protocols in included articles, and studies within disease groups often examined distinct forms of therapy and were conducted over drastically different timelines, leading to variable results. Moreover, many studies did not quantify their results, making it

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

Table 9
Articles on medication use.

Study	Medication (Class)	Sample Size	Study Design	ERG Modality	Findings	Photoreceptor
Filip 1978	Thioridazine (typical antipsychotic)	10	Cross-sectional	fERG	Drug intake prolonged a-wave latency and b-wave evolution time, while decreasing b-wave amplitude	Not stated
Fornaro 1984	Perphenazine (typical antipsychotic), Bromocriptine (dopamine agonist)	18	Cross-sectional	fERG	Perphenazine decreased b-wave amplitude; bromocriptine increased b-wave amplitude	Not stated
Perossini 1990	Perphenazine (typical antipsychotic), Haloperidol (typical antipsychotic), Levodopa/ Carbidopa (dopaminergic), Nomifensine (NDRI), Bromocriptidine (dopamine agonist), Imipramine (TCA), Diazepam (benzodiazepine)	60	Cross-sectional	fERG	Perphenazine decreased b-wave amplitude; bromocriptine increased b-wave amplitude; Nomifensine increased b-wave amplitude, Levodopa/Carbidopa increased b-wave amplitude; Haloperidol decreased b-wave amplitude; Imipramine and Diazepam had no effect	Not stated
Holopigian 1994	Chlorpromazine (typical antipsychotic), Fluphenazine (typical antipsychotic), Metoclopramide (dopamine antagonist)	22	Cross-sectional	fERG	Reduced b-wave amplitudes and amplitudes for first oscillatory potential	Cones and rods
Fornaro 2014	Agomelatine (atypical antidepressant)	23	Cross-sectional	fERG	Slight increase in b-wave amplitude and latency in both eyes	Cones

Notes: **fERG** = flash electroretinogram; **NDRI** = norepinephrine-dopamine reuptake inhibitor; **TCA** = tricyclic antidepressant.

Table 10
Summary of ERG findings across psychiatric illnesses and groups.

Group	Finding(s)
Cocaine withdrawal	Reduced light-adapted b-wave in response to blue light, reduction correlated with cocaine craving
Cannabis use	Increased implicit time
Alcohol use	—
Alzheimer's disease	—
Autism spectrum disorder	Reduced b-wave amplitude
MDD	Reduced contrast gain in PERG, PERG normalization with treatment
SAD	Various abnormalities that normalize with remission
Schizophrenia	Reduced a- and b-wave amplitudes
Panic disorder	Reduced b-wave amplitudes, Reduced differences between right and left eyes in b-wave amplitudes
Eating disorders	—
ADHD	—
Perphenazine use	Reduced b-wave amplitudes
Bromocriptine use	Increased b-wave amplitudes
Dopamine antagonists	Reduced b-wave amplitudes

Notes: **ADHD** = attention deficit hyperactivity disorder; **ERG** = electroretinogram; **MDD** = major depressive disorder; **PERG** = pattern electroretinogram; **SAD** = seasonal affective disorder.

challenging to draw comparisons and eliminating any possibility of aggregating results meaningfully through a meta-analysis. While qualitative observations of waveform reductions and increases are insightful at an exploratory level, they do not provide an objective assessment of diagnostic utility.

In order for ERG to become a diagnostic modality in psychiatry, there is a need for quantifiable data that allows for determination of important measures such as sensitivity, specificity, and positive and negative predictive values in comparison to gold standard diagnostic methods. To facilitate this, we suggest that future studies implement the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines for the measurement of ERG waveforms and should quantify anomalies and calculate the magnitude of correlations with disease states. Prior studies were largely underpowered due to a small sample size. This may have been a result of requiring trained technicians and nurses to carry out pharmacological pupil dilation prior to ERG. Newer ERG technology permits gathering of data without the need for pupil dilation. Thus, authors should ensure that their studies have sufficient sample sizes and are adequately powered to assess outcomes of interest. To enrich results and minimize bias, future studies should be multi-center. At present, most of the research on a particular condition is conducted by the same authors. For instance, of 12 articles on depressive disorders, seven were from the same research group, and out of 15 articles on substance use, nine were from the same group of authors. Having multiple centers participate in studies would serve to both internally and externally validate study protocol and improve the reliability of findings.

Future studies should also consider expanding the use of ERG to yet unexplored psychiatric conditions. For example, our search did not identify any eligible studies examining bipolar disorder, indicating a gap in the present evidence.

An inherent difficulty of using ERG as a diagnostic tool in psychiatry is the limited number of detectable anomalies, restricting diagnostic specificity. For example, a reduction in b-wave amplitude on fERG may be indicative of cocaine withdrawal, autism spectrum disorder, panic disorder, perphenazine use, or intake of dopamine blockers. From a neurobiological perspective, this is perhaps due to the high degree of interconnectedness between many neurotransmitter systems [66]. Emerging research in animal suggests that ERG responses can also be affected by dopamine, accounting for observed anomalies in relevant psychiatric illnesses and medication use [2]. To be used reliably as a diagnostic tool, ERG will have to demonstrate more particular anomalies for each condition. If this proves to be unfeasible, however, then the diagnostic utility of ERG may be limited and its use in psychiatry may be better suited to measuring the effect of treatments or predicting relapse in patients.

5. Limitations

Our review is not without its limitations. We do not present quantitative analyses or a meta-analysis summarizing the results of ERG anomalies in specific psychiatric conditions as included studies did not provide such data.

Moreover, our review is at risk for publication bias as many of the studies included were conducted by a limited number of research groups and were largely single-center in design. Our review is also limited by its broad research question. There is a paucity of literature when examining the applicability of ERG to specific psychiatric illnesses, and thus we chose to look at a myriad of pathologies in order to provide the most comprehensive summary of the current evidence.

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

As the pace of research in this field accelerates, we anticipate future reviews will have well-refined and focused research questions and will allow for quantitative analyses.

6. Conclusions

This review systematically examined the literature on the use of ERG as a diagnostic tool in psychiatry. Although it was difficult to draw quantitative conclusions, consistent trends in ERG waveform anomalies in specific psychiatric conditions were observed across included studies. ERG is a non-invasive, quickly administered, and well-characterized test that has the potential to become an objective tool for the diagnosis of psychiatric illness. Further investigation through adequately powered multi-center studies, in concordance with the rapid pace of technological advancement, will allow for thorough evaluation of ERG in comparison to existing gold standard modalities and permit its successful integration into the diagnostic repertoire of modern psychiatry.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Lavoie J, Maziade M, Hébert M. The brain through the retina: the flash electroretinogram as a tool to investigate psychiatric disorders. Prog Neuropsychopharmacol Biol Psych 2014;48:129–34.
[2] Lavoie J, Illiano P, Sotnikova TD, Gainetdinov RR, Beaulieu JM, Hébert M. The electroretinogram as a biomarker of central dopamine and serotonin: potential relevance to psychiatric disorders. Biol Psychiatry 2014;75(6):479–86.
[3] Brown KT. The electroretinogram: its components and their origins. Vision Res 1968;8(6):633–77.
[4] McCulloch DL, Marmor MF, Brigell MG. ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol 2015;130(1):1–12.
[5] Schwitzer T, Schwan R, Angioi-Duprez K, Giersch A, Laprevote V. The endocannabinoid system in the retina: from physiology to practical and therapeutic applications. Neural Plast 2016 2016;1–10.
[6] Ladien K, Levett J, Clarke M. Effects of alcohol on electroretinogram light/dark adaptation. Drug Alcohol Depend 1980;6(1):93–5.
[7] Hildebrand GD, Fielder AR. Anatomy and physiology of the retina. In: Reynolds J, Olitsky SE, editors. Pediatric retina. New York: Springer-Verlag Berlin Heidelberg; 2011. p. 39–65.
[8] Bach M, Brigell MG, Hawlina M, et al. ISCEV standard for clinical pattern electroretinography (PERG) 2012 update. Doc Ophthalmol 2013;126(1):1–7.
[9] Hood DC, Bach M, Brigell M, et al. International society for clinical electrophysiology of vision. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 ed.). Doc Ophthalmol 2012;124(1):1–3.
[10] McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA 2018;319(4):388–96.
[11] Pérez JG, Mato MP, García AS, Rey AD. Intraocular motility, electrophysiological tests and visual fields in drug addicts. Ophthalmic Physiol Opt 1995;15(5):493–8.
[12] Roy M, Smelson DA, Roy A. Abnormal electroretinogram in cocaine-dependent patients. Relationship to craving. Br J Psychiatry 1996;168(4):507–11.
[13] Roy M, Roy A, Williams J, Weinberger L, Smelson D. Reduced blue cone electroretinogram in cocaine-withdrawn patients. Arch Gen Psychiatry 1997;54(2):153–6.
[14] Roy M, Roy A, Smelson D, Brown S, Weinberger L. Reduced blue cone electroretinogram in withdrawn cocaine dependent patients: a replication. Biol Psychiatry 1997;42(7):631–3.
[15] Roy M, Smelson D, Roy A. Longitudinal study of blue cone retinal function in cocaine-withdrawn patients. Biol Psychiatry 1997;41(2):252–3.
[16] Roy A, Roy M, Smelson DA. Risperidone, ERG, and cocaine craving. Am J Addict 1998;7(1):90.
[17] Roy A, Roy M, Berman J, Gonzalez B. Blue cone electroretinogram amplitudes are related to dopamine function in cocaine-dependent patients. Psychiatry Res 2003;117(2):191–5.
[18] Smelson DA, Roy A, Roy M. The electroretinogram and neuropsychological functioning in cocaine addicts. Can J Psychiatry 1996;41(6):415.
[19] Smelson DA, Roy M, Roy A, Santana S. Electroretinogram in withdrawn cocaine-dependent subjects: relationship to cue-elicited craving. Br J Psychiatry 1998;172(6):537–9.
[20] Smelson DA, Roy A, Roy M, Tershakovec D, Engelhart C, Losonczy MF. Electroretinogram and cue-elicited craving in withdrawn cocaine dependent patients: a replication. Am J Drug Alcohol Abuse 2001;27(2):391–7.
[21] Schwitzer T, Ingster-Moati I, Angioi K, Giersch A, Schwan R, Laprevote V. Impaired retinal processing in regular cannabis users: potential benefit of electroretinogram as a biomark. Eur Psychiatry 2014;29(8):529–30.
[22] Schwitzer T, Robert MP, Giersch A, et al. Transient retinal dysfunctions after acute cannabis use. Eur Addict Res 2016;22(6):287–91.
[23] Schwitzer T, Schwan R, Albuisson E, et al. Association between regular cannabis use and ganglion cell dysfunction. JAMA Ophthalmol 2017;135(1):54–60.
[24] Kim JT, Yun CM, Kim SW, Oh J, Huh K. The effects of alcohol on visual evoked potential and multifocal electroretinography. J Korean Med Sci 2016;31(5):783–9.
[25] Katz B, Rimmer S, Iragui V, Katzman R. Abnormal pattern electroretinogram in Alzheimer's disease: evidence for retinal ganglion cell degeneration? Ann Neurol 1989;26(2):221–5.
[26] Katz B, Rimmer S, Klauber MR, Katzman R. The electroretinogram in Alzheimer's disease (Reply). Ann Neurol 1990;28(5):725.
[27] Pollock VE, Schneider LS. The electroretinogram in Alzheimer's disease. Ann Neurol 1990;28(5):724–5.
[28] Strenn K, Dal-Bianco P, Weghaupt H, Koch G, Vass C, Gottlob I. Pattern electroretinogram and luminance electroretinogram in Alzheimer's disease. J Neural Transm 1991;33(suppl):73–80.
[29] Ritvo ER, Creel D, Realmuto G, Crandall AS, Freeman BJ. Electroretinograms in autism: a pilot study of b-wave amplitudes. Am J Psychiatry 1988;145(2):229–32.
[30] Realmuto G, Purple R, Knobloch W, Ritvo E. Electroretinograms (ERGs) in four autistic probands and six first-degree relatives. Can J Psychiatry 1989;34(5):435–9.
[31] van Elst LT, Bach M, Blessing J, Riedel A, Bubl E. Normal visual acuity and electrophysiological contrast gain in adults with high-functioning autism spectrum disorder. Front Hum Neurosci 2015;9:460.
[32] Constable PA, Gaigg SB, Bowler DM, Jägle H, Thompson DA. Full-field electroretinogram in autism spectrum disorder. Doc Ophthalmol 2016;132(2):83–99.
[33] Lam RW, Beattie CW, Buchanan A, Mador JA. Electroretinography in seasonal affective disorder. Psychiatr Res 1992;43(1):55–63.
[34] Hébert M, Dumont M, Lachapelle P. Electrophysiological evidence suggesting a seasonal modulation of retinal sensitivity in subsyndromal winter depression. J Affect Disord 2002;68(2):191–202.
[35] Danilenko KV, Plisov IL, Hebert M, Kräuchi K, Wirz-Justice A. Influence of timed nutrient diet on depression and light sensitivity in seasonal affective disorder. Chronobiol Int 2008;25(1):51–64.
[36] Lavoie MP, Lam RW, Bouchard G, et al. Evidence of a biological effect of light therapy on the retina of patients with seasonal affective disorder. Biol Psychiatry 2009;66(3):253–8.
[37] Bubl E, Kern E, Ebert D, Bach M, van Elst LT. Seeing gray when feeling blue? Depression can be measured in the eye of the diseased. Biol Psychiatry 2010;68(2):205–8.
[38] Bubl E, Ebert D, Kern E, van Elst LT, Bach M. Effect of antidepressive therapy on retinal contrast processing in depressive disorder. Br J Psychiatry 2012;201(2):151–8.
[39] Fornaro M, Bandini F, Ogliastro C, et al. Electroretinographic assessment in major depressed patients receiving duloxetine: Might differences between responders and non-responders indicate a differential biological background? J Affect Disord 2011;135(1):154–9.
[40] Gagné AM, Hébert M. Atypical pattern of rod electroretinogram modulation by recent light history: a possible biomarker of seasonal affective disorder. Psychiatr Res 2011;187(3):370–4.
[41] Vandewalle G, Hébert M, Beaulieu C, et al. Abnormal hypothalamic response to light in seasonal affective disorder. Biol Psychiatry 2011;70(10):954–61.
[42] Fam J, Rush AJ, Haaland B, Barbier S, Luu C. Visual contrast sensitivity in major depressive disorder. J Psychosom Res 2013;75(1):83–6.
[43] Hébert M, Mérette C, Paccalet T, Gagné AM, Maziade M. Electroretinographic anomalies in medicated and drug free patients with major depression: tagging the developmental roots of major psychiatric disorders. Prog Neuropsychopharmacol Biol Psych 2017;75:10–5.
[44] Hébert M, Beattie CW, Tam EM, Yatham LN, Lam RW. Electroretinography in patients with winter seasonal affective disorder. Psychiatr Res 2004;127(1):27–34.
[45] Gagrat D, Maggiano J, Belmaker RH. Effect of neuroleptic treatment in schizophrenia on the electroretinogram, electrooculogram, and color vision. Psychiatr Res 1979;1(1):109.
[46] Gerbaldo H, Thaker G, Tittel PG, Layne-Gedge J, Moran M, Demisch L. Abnormal electroretinography in schizophrenic patients with a history of sun gazing. Neuropsychobiol 1992;25(2):99–101.
[47] Warner R, Laugharne J, Peet M, Brown L, Rogers N. Retinal function as a marker for cell membrane omega–3 fatty acid depletion in schizophrenia: a pilot study. Biol Psychiatry 1999;45(9):1138–42.
[48] Balogh Z, Benedek G, Kéri S. Retinal dysfunctions in schizophrenia. Prog Neuropsychopharmacol Biol Psych 2008;32(1):297–300.
[49] 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):270–4.

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press

[50] Hébert M, Mérette C, Paccalet T, et al. Light evoked potentials measured by electroretinogram may tap into the neurodevelopmental roots of schizophrenia. Schizophrenia Res 2015;162(1):294–5.
[51] Gagné AM, Paccalet T, Jomphe V, Lussier D, Maziade M. Electroertinographic response in youths at genetic risk of Schizophrenia and Bipolar Disorder and in normal controls: transversal and longitudinal differences and implication for the risk trajectory. Schizophr Bull 2018;44(suppl. 1):124.
[52] Maziade M, Paccalet T, Gagné AM, et al. Electroretinographic anomalies seen in patients affected by Schizophrenia or Bipolar Disorder are detectable early in children born to an affected parent: implications for the staging of risk status in childhood-adolescence. Schizophr Bull 2018;44(suppl. 1):11.
[53] Silverstein S, Demmin D, Erickson M, Thompson J, Paterno D. Netser R.v7.1 Electroretinographic anomalies in Schizophrenia and their relationships with retinal structure, visual functions, clinical symptoms, and medical comorbidities. Schizophr Bull 2018;44(suppl. 1):10–1.
[54] Laprevote V, Bernardin F, Schwitzer T, Schwan R. Electroretinogram anomalies in Schizophrenia patients with visual hallucinations. Schizophr Bull 2018;44 (suppl. 1):169.
[55] Demmin DL, Davis Q, Roché M, Silverstein SM. Electroretinographic anomalies in schizophrenia. J Abnorm Psychol 2018;127(4):417.
[56] Pieraccini E, Bossini L, Martinucci M, et al. Assessment of photosensitivity through electroretinogram in patients with panic disorder (PD) and relationship with dopaminergic function. Eur Neuropsychopharmacol 2005;15(suppl. 3):5434.
[57] Bossini L, Padula L, Valdagno M, Castrogiovanni P. Electroretinogram B wave amplitude, dopaminergic system and panic disorder. Eur Neuropsychopharmacol 2008;18(suppl. 4):501.
[58] Nasser JA, Parigi AD, Merhige K, Wolper C, Geliebter A, Hashim SA. Electroretinographic detection of human brain dopamine response to oral food stimulation. Obesity 2013;21(5):976–80.
[59] Moschos MM, Moustafa GA, Gonidakis F, Papageorgiou C. Retinal and choroidal alterations in patients with anorexia nervosa without vision loss. Int J Eat Disord 2016;49(4):386–90.
[60] Bubl E, Werner L, Liang Y, et al. Evaluating the neurobiological correlates and impact of treatment on cognitive dysfunction in ADHD and Schizophrenia by means of the pattern electroretinogram. Schizophr Bull 2018;44(suppl. 1):11.
[61] Filip V, Balik J. Possible indication of dopaminergic blockade in man by electroretinography. Int Pharmacopsychiatry 1978;13:151–6.
[62] Fornaro M, Bandini F, Cestari L, et al. Electroretinographic modifications induced by agomelatine: a novel avenue to the understanding of the claimed antidepressant effect of the drug? Neuropsychiatr Dis Treat 2014;10:907.
[63] Perossini M, Fornaro P. Electroretinographic effects induced in humans by psychopharmacologic agents. Doc Ophthalmol 1990;75(1):1–6.
[64] Holopigian K, Clewner L, Seiple W, Kupersmith MJ. The effects of dopamine blockade on the human flash electroretinogram. Doc Ophthalmol 1994;86 (1):1–10.
[65] Fornaro P, Perossini M, Placidi GF, Dell'Osso L, Tassi G, Castrogiovanni P. Electroretinography (ERG) as a tool of investigation on dopaminergic activity in man. Res Comm Psychol Psychiatr Behav 1984;9(3):307–23.
[66] Morgane PJ, Galler JR, Mokler DJ. A review of systems and networks of the limbic forebrain/limbic midbrain. Prog Neurobiol 2005;75(2):143–60.

https://doi.org/10.1016/j.eurpsy.2019.09.006 Published online by Cambridge University Press