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Electroretinographic anomalies in medicated and drug free patients with major depression: Tagging the developmental roots of major psychiatric disorders

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ABSTRACT

The retina is tagged as an approachable part of the brain due to its common embryonic origin and appears as a promising site of investigation for psychiatric disorders. Retinal function is assessed best with the electroretinogram (ERG), which was obtained in a large sample of patients with major depressive disorder and matched controls. ERG cone and rod luminance response functions were recorded in non-dilated eyes in 100 major depressive disorder patients (MDD) and 100 controls, (mean age of 42.8 and 40.9 y. o. respectively). Amongst MDD patients, 17 were drug free (mean age 41.2 y. o). In medicated patients, at the cone level, a prolonged b-wave was observed ($p \leq 0.01$). In drug free patients a prolonged b-wave was discovered only when averaging the implicit time of the 3 highest b-wave amplitudes of the photopic hill. For the medicated patients, the mixed rods/cones a-wave was reduced ($p = 0.01$) whereas a trend ($p = 0.06$) was observed for the pure rod b-wave (reduced) and the mixed rods/cones (reduced and prolonged; $p = 0.05$). In drug free patients, a similar pattern could be observed in terms of effect sizes. Overall, medicated and drug free MDD patients shared some deficits suggesting that some anomalies are present above and beyond the effect of medication. Of interest, the prolonged cone and reduced rod amplitude were reported by our group in schizophrenia patients, suggesting a common neurodevelopmental root of major psychiatric disorders.

1. Introduction

Psychiatric disorders are complex conditions involving multiple physiological and structural changes in the brain. Also, their interactions with the environment make it challenging to clarify their pathophysiology. The retina, which is considered part of the central nervous system (Dowling and Dubin, 2011) has been recognized as a promising site of investigation for psychiatric illnesses. The electroretinogram technique (ERG) has been used for that purpose since the end of the 70's and later on with breaking findings (Filip and Balik, 1978; Perossini and Fornaro, 1990; Fornaro et al., 2014; Silverstein and Rosen, 2015; Gagne et al., 2015; Lavoie et al., 2014a) The full-field ERG, as used in this study and those we referred to is a light-evoked potential recorded at the surface of eye following light stimulation. Cone (day vision) and rod (night vision) photoreceptors can be assessed separately. This technique is often preferred over focal ERG because it assesses a widespread response of the retina instead of the specific area of the macula and because it requires less compliance from the patient since keeping fixation is less critical. The last comment is also true for the electrooculogram technic. Unlike pattern ERG, the full-field ERG allows to isolate rods and cones responses. Over the years, our group have also demonstrated meaningful ERG anomalies in various conditions namely seasonal affective disorder (SAD), schizophrenia and child at high risk to develop a psychiatric illness (Hebert et al., 2015, 2010, 2004, 2002; Lavoie et al., 2009; Gagné and Hébert, 2011; Gagne et al., 2011). We have also validated a protocol to simplify the used of ERG in non-dilated eyes (Gagne et al., 2010) that makes the technique easier for psychiatric patients and children at risk. The typical ERG waveform is composed of a negative component called the a-wave followed by a positive component called the b-wave. The a-wave originates from the photoreceptors whereas the b-wave originates from the bipolar and Muller cells complex (Hébert and Lachapelle, 2003). Animal research has also revealed that the ERG can be affected by brain neuromodulation of dopamine and serotonin (Lavoie et al., 2014b), neurotransmitters that have a key role in various psychiatric disorders. Studies have reported ERG anomalies in schizophrenia patients (Warner et al., 1999; Balogh et al., 2008; Hebert et al., 2015) as well as in our group of non-medicated youth at high genetic risk to develop a psychiatric disorder (Hebert et al., 2010). Research in major depressive disorder (MDD), however, have been scarce despite its high prevalence. In the only research so far,

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MDD patients were investigated with the ERG during a treatment of duloxetine in which it was observed that responders versus non-responders carried a different ERG. In their study, 20 patients who received duloxetine 60 mg/day for 12 weeks demonstrated, at baseline, a rod b-wave amplitude significantly higher in responders compared to non-responders and healthy controls followed by a normalization after 12 weeks of treatment. The authors suggested that hypothetically responders to duloxetine may exhibit a peculiar ERG pattern, but the interpretations were limited due to the small sample size (Fornaro et al., 2011).

The aim of the current study was to compare the cone and rod ERGs in a large sample of MDD patients and healthy controls. Considering that depression occurring with a seasonal pattern has been shown to impact the ERG (Lavoie et al., 2009; Gagné and Hébert, 2011; Gagne et al., 2011) only MDD patients with non-seasonal pattern were selected. Amongst the MDD patients, seventeen patients were drug free and were thus compared separately to identify possible ERG anomalies that would be specific to the disease without the confounding effect of medications.

2. Methods and materials

2.1. Sample characteristics

According to power calculations based on our previous findings in schizophrenia cases (Hebert et al., 2015), we needed a sample of at least 82 cases and controls to have 80% of power to detect an effect size of 0.39 at an uncorrected significance level of 0.05. We recruited 100 MDD out-patients referred by their treating psychiatrists in a university hospital or in regional psychiatric departments. The inclusion criteria were a diagnosis of DSM-IV of MDD, age between 21 and 55, normal vision and no known ocular pathology. Exclusion criteria were: brain and metabolic disorders; being pregnant; working on night shifts; substance use or having traveled two time zones within one month before the experiment as well as having a score of 11 or higher on the seasonal pattern assessment questionnaire (SPAQ). Amongst these 100 MDD cases, a subgroup of 17 patients was found to be medication free for a minimum of 3 weeks at the time of the ERG recording. Our sample of patients was thereafter stratified according to the use of medication (83 medicated MDD and 17 drug free patients).

A sample of 100 healthy controls (CT) was then selected from the same population of Eastern Quebec with very similar mean age and proportion of males (see Table 1): the **exclusion criteria** were brain and metabolic disorders; being pregnant; working on night shifts; substance use or having traveled two time zones within one month before the experiment, the presence of any Axis I DSM-IV diagnosis; a positive family history of Schizophrenia, Bipolar or Major Depression Disorders, substance use and a score of 11 or higher on the SPAQ. Signed consent was obtained, as reviewed by our Institutional Ethics Committee.

Table 1
Characteristics of the sample: 100 MDD cases, 17 drug free MDD patients and 100 sex and age matched controls.

	Cases N = 100		Controls N = 100
	MDD n = 100	Drug free MDD n = 17	
Age mean in years (SD)	42.8 (9.0)	41.2 (8.7)	40.9 (10.2)
[range in years]	[22–55]	[28–55]	[21–55]
Male (%)	24 (24)	6 (35)	24 (24)
Pupil size mm (mean)	4.2 (1.1)*	3.5 (1.1)	3.6 (0.9)
[range in mm]	[2–7]	[2–6]	[1–6]
With MD recurrence (%)	69 (69)	7 (41)	n/a
With psychotic characteristic (%)	11 (11)	1 (6)	n/a
Age of onset (mean)	31.1 (9.4)	30.3 (10)	n/a
[range in years]	[11–50]	[15–48]	n/a
Duration of illness (mean)	11.4 (7.7)	10.4 (5.3)	n/a
[range in years]	[1–42]	[2–20]	n/a

* Comparison with controls: $p < 0.01$.

2.2. Diagnosis and clinical assessments

We used a lifetime best estimate diagnostic procedure in patients which included information acquired from all available medical records across lifetime according to a method we previously used and that showed high reliability (Maziade et al., 2005, 1992; Roy et al., 1997). Based on this lifetime information, we also recorded the age of onset (age at first probable or definite episode of disease), the duration of illness (time between age of onset and ERG evaluation), the history of medications taken systematically from the lifetime information.

2.3. Electroretinogram recording

A full-field cone and rod ERG was performed with Espion systems (E2 or E3) (Diagnosys LLC, MA, USA). Recordings were obtained in non-dilated eyes as previously described (Gagne et al., 2010) using DTL electrodes (Shieldex 33/9 Thread, Statex, Bremen, Germany) secured deep into the conjunctival sac. Ground and reference electrodes (Grass gold cup electrodes filled with Grass EC2 electrode cream) were pasted on the forehead and external canthi (Hebert et al., 1995). Flashes and background were provided by a ganzfeld (Color dome; Diagnosys LLC, MA, USA).

For the cone ERG, participants were first light adapted for 10 min to a white background light set at 80 cd/m^2 as per Gagne et al. (2010, 2011), Gagné and Hébert (2011) and Hebert et al. (2015) for recordings performed in non-dilated eyes. A cone luminance-response function (LRF) was achieved using 12 white flash luminance ranging from 0.75 to 800 cd·s/m^2 (i.e. −0,12 to 2,9 log unit). The flash interval was set at 2 s for the first 9 luminance and 5 s for the last four. Following 30 min of dark adaptation, participants were stimulated with 13 green (peak: 509 nm) flash luminance ranging from 0.001 to 1 cd·s/m^2 (i.e. −3 to 0 log unit) in order to generate a rod LRF. The flash interval was set at 5 s. Pupil size was measured in mm and used as a covariate for analyses since pupils were not pharmacologically dilated.

2.4. ERG variables and measurements

By convention, the a-wave amplitude is measured from baseline to trough of the waveform, and b-wave from the trough of the a-wave to the peak of the b-wave. The implicit time of both the a- and b- waves corresponds to the time (ms) to reach the trough of the a-wave and the peak of the b-wave respectively as measured from flash onset. For the cone ERG, amplitudes and implicit times of both a- and b- waves were measured at a fixed luminance of 7.5 cd·s/m^2 and at Vmax (amplitude at the peak of the photopic hill see * symbol at Fig. 1a). For the scotopic ERG, implicit time and amplitudes of both the a- and b- waves were measured from the waveforms obtained at a fixed luminance of 0.1 cd·s/m^2 (pure rods) and 1 cd·s/m^2 (mixed rods-cones, see arrows at Fig. 2).

2.5. Statistical analysis

All statistical analyses were performed using the SAS/STAT software version 9.4 for Windows. First, we created a group factor that included 3 subgroups: the group of 83 MDD patients with medication, the 17 dug free MDD patients and the 100 controls. Then, the group factor entered an ANCOVA with age, gender and pupil sizes as covariables in order to estimate the mean of each ERG measurement within subgroups with the corresponding effect size when compared to controls. We tested the differences between the mean of the 83 medicated cases and that of controls but no tests were performed between the subgroup of drug free patients and any of the other two subgroups given that the comparisons involving the drug free subgroups had low power. Rather,