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ORIGINAL RESEARCH

Steady-State Pattern Electroretinogram and Frequency Doubling Technology in Adult Dyslexic Readers

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Purpose: Dyslexia is a reading disorder with neurological deficit of the magnocellular pathway. The aim of our study was to evaluate the functionality of the magnocellular–Y (M–Y) retinal ganglion cells in adult dyslexic subjects using steady-state pattern electroretinogram and frequency doubling perimetry.

Methods: Ten patients with dyslexia (7 females and 3 males), mean age 28.7 ± 5.9 years, and 10 subjects without dyslexia (6 females and 4 males), mean age 27.8 ± 4.1 years, were enrolled in the study and underwent both steady-state pattern-electroretinogram examination and frequency doubling perimetry.

Results: There was a significant difference in the amplitude of the steady-state pattern electroretinogram of the dyslexic group and the healthy controls (0.610 ± 0.110 µV vs 1.250 ± 0.296 µV; $p = 0.0001$). Furthermore, in the dyslexic group we found a significant difference between the right eye and the left eye (0.671 ± 0.11 µV vs 0.559 ± 0.15 µV; $p = 0.001$). With frequency doubling perimetry, the pattern standard deviation index increased in dyslexic eyes compared to healthy controls (4.40 ± 0.81 dB vs 2.99 ± 0.35 dB; $p = 0.0001$) and in the left eye versus the right eye of the dyslexic group (4.43 ± 1.10 dB vs 3.66 ± 0.96 dB; $p = 0.031$). There was a correlation between the reduction in the wave amplitude of the pattern electroretinogram and the simultaneous increase in the pattern standard deviation values ($r = 0.80$; $p = 0.001$). This correlation was also found to be present in the left eye ($r = 0.93$; $p < 0.001$) and the right eye ($r = 0.81$; $p = 0.005$) of dyslexic subjects.

Conclusion: Our study shows that there was an alteration of the activity of M–Y retinal ganglion cells, especially in the left eye. It confirms that in dyslexia there is a deficit of visual attention with damage not only of the magnocellular-dorsal pathway but also of the M-Y retinal ganglion cells.

Keywords: steady-state pattern-electroretinogram, frequency doubling technology perimetry, retino-geniculate pathways, dyslexia

Introduction

Dyslexia is a condition characterized by impairment of reading skills in subjects without alterations of visual acuity and with normal intelligence. It affects boys and girls equally and it is usually first observed during childhood. The etiology of dyslexia is still under discussion, although an alteration of the magnocellular pathway, in particular the magnocellular-dorsal (M–D) pathway, is hypothesized.[1–8] Previous autopsy studies have shown that in dyslexics the cells of the magnocellular pathway in the ventral layers of the lateral geniculate nucleus (LGN) were smaller than those of healthy controls.[4]

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The human LGN contains three distinct retinal pathways:[9] the parvocellular (P) pathway originating from the midget retinal ganglion cells,[10–12] the koniocellular pathway receiving afferents from the retinal ganglion cells driven by short-wavelength photoreceptors,[13–15] and the magnocellular (M) pathway, derived from the parasol retinal ganglion cells (RGCs),[10,12,16,17] which contains two functional cell classes that are similar to cat X and cat Y geniculate cells. About 5% of the magnocellular cells of LGN display a nonlinear Y-type response,[18] hence the term M–Y cells.

Selective electrofunctional investigation of the M pathway requires the use of electrophysiological methods based on the recording of pattern visual evoked potentials (PVEP) and appropriately modified stimuli with regard to contrast, spatial frequency, temporal frequency, and movement.[19–24]

PVEP studies appear to confirm the results of functional magnetic resonance imaging (fMRI).[25–28] The M pathway and especially the M–Y ganglion cell involved in the analysis of visual motion can also be studied using frequency doubling illusion (FDI). FDI is based on a doubling illusion created by counterphase flickering of a low spatial frequency sinusoidal grating at a high temporal frequency.[29]

This type of psychophysical examination has been proposed as a sensitive test for detecting early functional changes in M–Y ganglion cells, mainly in glaucoma and ocular hypertension,[18,30,31] but it has rarely been used in amblyopia[32] and dyslexia.[33,34] From an electrophysiological point of view, the study of M–Y cells in the M pathway can be performed using the steady-state pattern electroretinogram (SS-PERG).[35] This examination was initially proposed in patients suffering from simple chronic open-angle glaucoma and ocular hypertension since it was able to detect early alterations in the bioelectric response of retinal M–Y retinal ganglion cells. The purpose of our study was to use a SS-PERG with a stimulus that creates a doubling illusion similar to that achieved using frequency doubling technology (FDT), in order to selectively investigate the activity of the M–Y retinal ganglion cells in adult dyslexic subjects.

Materials and Methods

Ten patients with dyslexia (7 women and 3 men), mean age 28.7 ± 5.9 years, and 10 patients without dyslexia (6 women and 4 men), mean age 27.8 ± 4.1 years, were enrolled in the study. All patients underwent a complete ophthalmological evaluation, including measurement of visual acuity, slit-lamp examination of the anterior and posterior segment, and random-dot stereopsis test. Ophthalmologic evaluation excluded a refractive defect higher than ± 2 diopters of spherical equivalent (SE). All subjects had normal binocular vision with random-dot stereopsis, absence of retinal and optic nerve diseases, and transparent dioptric media.

Patients enrolled in the study were diagnosed with dyslexia by the Neuropsychiatric Center of the National Health Service in Bologna according to the diagnostic criteria for learning disabilities and with a test for reading abilities.[36,37]

All patients also underwent SS-PERG and FDT perimetry examination.

The study was approved by the Local Ethics Committee of the University of Bologna and adhered to tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

The Steady-State Pattern-Electroretinogram was recorded using the RetimaxPlus system (CSO Instruments, Florence, Italy). The patient sat on a chair at a distance of 57 cm from the television screen (resolution 1024x768; size 34 inches) and fixed binocularly on a red cross at the center of the screen, which subtended a visual angle of 48.89 degrees. The generated potential was measured with HK-LOOP ocular electrodes; the reference electrode was located near the outer canthus and the ground electrode was placed on the ear lobe. The inter-electrode resistance was less than 5 kOhm. All subjects had undilated pupils, measuring between 3 and 4 mm, with an appropriate correction for the working distance, and they were allowed to blink freely.

PERG stimulus was first presented as a full-screen black-and-white vertical bar pattern (contrast: 20%; spatial frequency: 0.3 cycles per degree/cpd; temporal frequency: 15 Hz). The number of samples acquired, mediated and processed with Discrete Fourier Transform (DFT) was 300 and the acquisition time was 133 ms.

The pattern presentation (approximately 4 mins) was preceded by an unmodulated uniform field (approximately 1 min) of the same mean luminance (blank), which was used to evaluate the background noise level. The noise level was 0.08 ± 0.03 μV in both normal and dyslexic patients.

Because SS-PERG was recorded in response to relatively fast alternating gratings, the response waveforms were sinusoidal-like with a frequency corresponding to the reversal rate. Packets were automatically evaluated in the frequency domain by DFT to isolate the component at

the reversal rate (30 Hz), and the amplitude in microvolts was displayed as a function of time.

The FDT perimetry was performed using the full-threshold program N-30 of the Humphrey FDT perimeter (Carl Zeiss Meditec, Dublin, CA) which tested 19 different points within the central 30 degrees of the visual field. Each target was displayed as a square of 10 x 10 degrees where a grid of black and white bars was projected. Furthermore, the 0.25 cycles/degree sinusoidal grid undergone counter-phase flicker at 18 Hz to create the illusion of doubling (FDI).[18] The dyslexic and the normal reader subjects underwent three different sessions of visual field tests at intervals of 4 ± 1 days to become familiar with the procedure because none of the study subjects had previous experience with FDT.

Mean defect (MD) and pattern standard deviation (PSD) were evaluated and were considered for the statistical analysis.

Statistical Analysis

For the statistical analysis of the data, we used the MedCalc 10.9.1 statistical program (MedCalc Software, Ostend, Belgium). MD and PSD of FDT and the amplitude of SS-PERG were analyzed using the Mann–Whitney U-test to assess group differences, Wilcoxon's test to evaluate within-subject comparisons, and the Spearman's correlation test, considering $p < 0.05$ as significant.

Results

The mean visual acuity (BCVA) and the spherical equivalent (SE) in the control and dyslexic groups are reported in Table 1. There was no significant difference in BCVA ($p = 0.980$) and SE ($p = 0.312$) of two groups.

In regard to the amplitude of the SS-PERG waveform, there was a significant difference between the control and dyslexic group ($p = 0.0001$) (Table 2). Furthermore, in the dyslexic group we found a significant difference between the right eye (RE) and the left eye (LE) ($p = 0.001$) but no

Table 1 Best Corrected Visual Acuity (BCVA) Values (Mean Values and Standard Deviation) and Diopter Spherical Equivalent (SE) Values (Mean Values and Standard Deviation)

	Control Group	Dyslexic Group	p-value
Men: Women	4:6	3:7	0.765
Age (yrs)	27.8 ± 3.3	28.5 ± 3.9	0.431
CI 95%	25.4/30.2	25.6/31.3	
BVCA (decimal)	1.0 ± 0.03	1.0 ± 0.04	0.980
SE (diopter)	− 0.3 ± 1.3	− 0.5 ± 1.4	0.312

Abbreviation: CI, confidence interval.

Table 2 Steady-State Pattern Electroretinogram (SS-PERG) Amplitude Values (Mean Values and Standard Deviation)

	Control Group	Dyslexic Group	p-value
SS-PERG (µV) CI 95%	1.250 ± 0.296 1.111/1.389	0.610 ± 0.110 0.559/0.661	0.0001

Abbreviation: CI, confidence interval.

difference was found in the control group ($p < 0.596$) (Table 3; Figure 1).

With regard to FDT parameters, the MD was similar in the healthy group and the dyslexic group ($p = 0.056$). The PSD was significantly higher in dyslexic subjects compared to normal subjects ($p = 0.0001$) (Table 4). Furthermore, in the dyslexic group, we found that the PSD of LE was significantly higher compared to RE ($p = 0.031$) (Table 5). For PSD, in the control group, there was no statistically significant difference between RE and LE ($p < 0.791$) (Table 5).

Statistical analysis of the SS-PERG among all groups shows a statistically significant reduction of the wave amplitude in dyslexics compared to the control group, both for the RE ($p = 0.0003$) and for the LE ($p = 0.0001$). Also, when analyzing the FDT data we found an increase in PSD values in dyslexic subjects compared to normal subjects both in the RE ($p < 0.0002$) and in the LE ($p < 0.0002$) (Table 6).

In dyslexic subjects, Spearman correlation test showed a significant correlation between the reduction in the SS-PERG wave amplitude and the simultaneous increase in PSD index values ($r = 0.80$; $p = 0.001$) (Table 7, Figure 2). Furthermore, this correlation was also found to be present in the LE ($r = 0.93$; $p < 0.001$) and the RE ($r = 0.81$; $p = 0.005$) of these subjects (Table 7, Figures 3–4). The same significant correlation between SS-PERG wave amplitude and PSD index values was found not only in the case of dyslexic subjects but also in the control group (Table 7)

Discussion

Dyslexia is a reading disorder afflicting 5–17% of the school-age population[38–40] and characterized by difficulty in accessing and manipulating the phonemic units of written language.[41,42] In recent decades, the most established hypothesis to explain developmental dyslexia was based on the presence of an auditory-phonological processing deficit;[43–49] however, recent studies would seem to show how the absence of development of fluent reading could be attributed both to a deficit in visual attention[50–55] and an oculomotor deficit.[56–58]

Table 3 Steady-State Pattern Electroretinogram (SS-PERG) Amplitude Values of the Right Eye (RE) and Left eye (LE) in Dyslexics and Control Subjects

	Dyslexic RE	Dyslexic LE	p-value	Control RE	Control LE	p-value
SS-PERG (µV)	0.671 ± 0.11	0.559 ± 0.15	0.001	1.29 ± 0.31	1.34 ± 0.32	0.596
CI 95%	0.595/0.747	0.490/0.628		1.01/1.51	1.12/1.57	

Abbreviation: CI, confidence interval.

Studies of the postmortem brains of known dyslexic subjects have shown several alterations: the normal asymmetry of the planum temporale, favoring the left side, tends to be absent. Furthermore, in the posterior parietal cortex, we have an anomalous symmetry with small aberrant "brain warts" clustered around the temporo-parietal junction.[59,60]

Neuroradiological studies using fMRI have shown that visual attention and the ability to control eye movements and identify the position of objects in space are associated with the dorsal cortical visual pathway or occipito-parietal pathway, which appears to be altered in dyslexics.[27,28,61] Furthermore, there is evidence of alterations in the functionality of the ventral cortical or occipito-temporal visual pathways, which receive information from both the M and P pathways, therefore, specializing in identifying the details relating to the shape and color of objects.[61–64] Moreover, in dyslexic subjects, a disconnection between
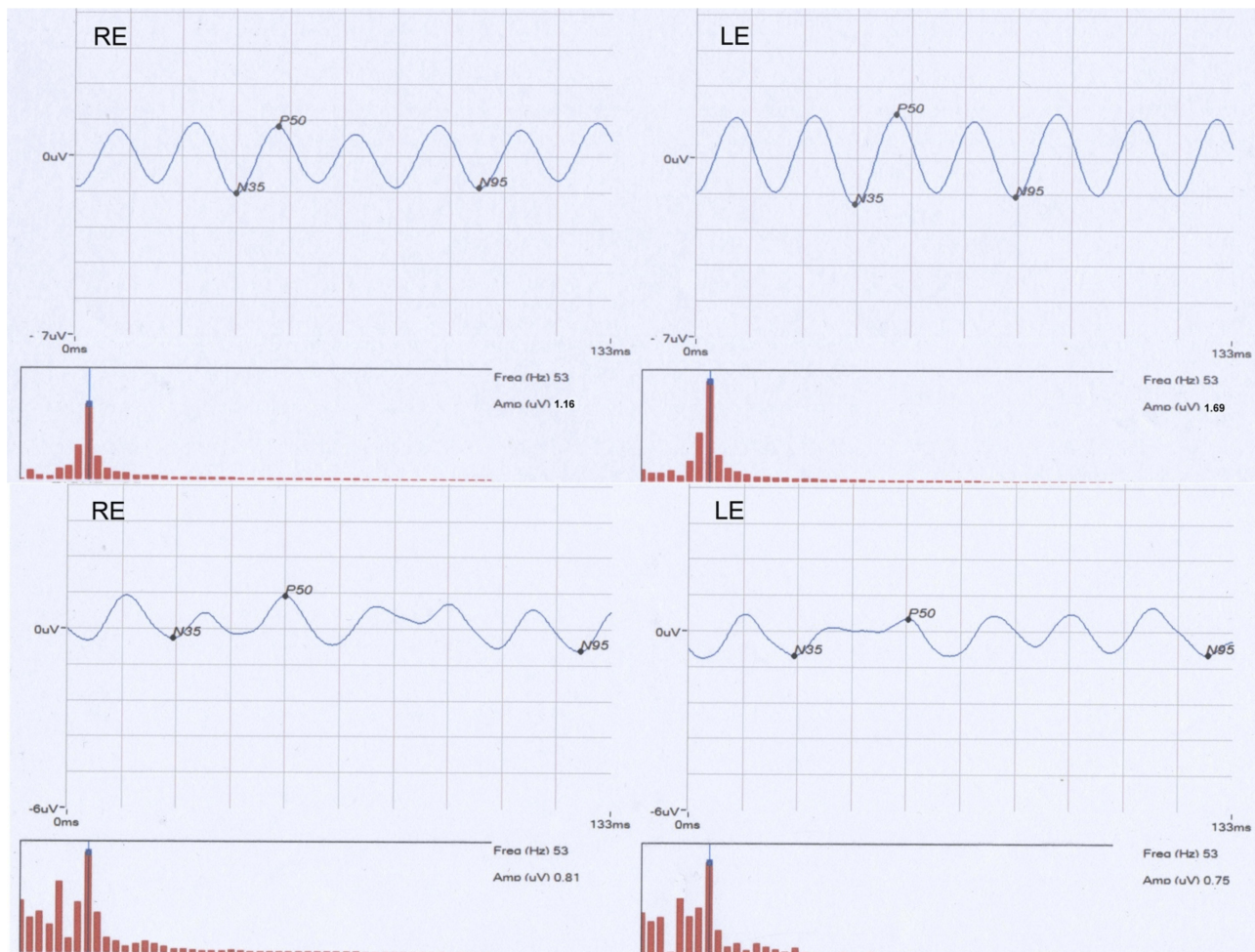

Figure 1 Steady-state pattern electroretinogram waveforms recorded in the right and left eye of control normal subject (top) and dyslexic subject (bottom). It can be observed a reduction of waveform amplitude in both eyes of the dyslexic subject (bottom) against the normal subject (top). Moreover, the dyslexics have a waveform amplitude decrease in the LE compared to the RE while in the normal subjects we have a slight increase in waveform amplitude in the LE than in the RE.
Abbreviations: RE, right eye; LE, left eye.

Table 4 Frequency Doubling Technology (FDT) Perimetry Values (Mean Values and Standard Deviation)

	Control Group	**Dyslexic Group**	**p-value**
FDT-MD (dB)	− 0.81 ± 0.61	− 2.28 ± 1.19	0.056
CI 95%	− 1.09/ - 0.52	−2.84/-1.72	
FDT-PSD (dB)	2.99 ± 0.35	4.40 ± 0.81	0.0001
CI 95%	2.79/3.17	4.10/4.78	

Abbreviation: MD, mean deviation; PSD, pattern standard deviation; CI, confidence interval.

the dorsal visual pathway and the ventral visual pathway in the middle frontal left gyrus has been found.[65]

One of the main hypotheses to explain visual deficits in dyslexia is based on the presence of a deficit in the transmission of visual stimuli along the M pathway.[4,5]

To validate the deficit theory of the M pathway and to confirm what was found with the fRMN, several authors used both psychophysical[66–68] and electrophysiological methods.[23,69,70]

The use of psychophysical methods,[66–68] above all FDT,[18,29–31,33] which allows selective stimulation of M-Y ganglion cells,[18,30,71,72] has provided definite information on the M pathway.

By using FDT perimetry in the dyslexic group, we found a significant increase in the PSD index values compared with healthy controls, confirming what was found in previous studies.[33,34] In the same group of patients, we found an insignificant increase in the MD index value. These data do not agree with other studies in which the difference between dyslexic and healthy subjects was statistically significant.[33,34] We believe that this discrepancy could be due to the fact that the subjects enrolled in our

Table 7 Spearman's Correlation Test Between Steady-State Pattern Electroretinogram (SS-PERG) and Frequency Doubling Technology (FDT) Index Values in the Right Eye (RE) and in the Left Eye (LE) of Dyslexic Subjects and of Control Subjects

	SS-PERG (μV)	**FDT-PSD (dB)**	**r**	**p-value**
Dyslexic (both eyes)	0.610 ± 0.11	4.40 ± 0.81	0.80	0.001
Dyslexic LE	0.559 ± 0.15	4.43 ± 1.10	0.93	0.001
Dyslexic RE	0.671 ± 0.11	3.66 ± 0.96	0.81	0.005
Control (both eyes)	1.250 ± 0.296	2.99 ± 0.35	0.56	0.011
Control RE	1.29 ± 0.31	2.99 ± 0.42	0.78	0.008
Control LE	1.34 ± 0.32	2.95 ± 0.40	0.68	0.032

Abbreviation: PSD, pattern standard deviation.

study were young adults and not children. We cannot forget that dyslexia over time can improve when new reading strategies are learned.[73]

In our investigation, we analyzed not only the MD index but also the PSD index because this index reflects the roughness (focal-cluster alteration) of the visual field.[74,75] Moreover, we found that in LE of dyslexic patients the PSD values were significantly more altered than in the RE, confirming the observations of a previous study.[33,34] These data confirm that dyslexics present an alteration in retinal sensitivity in the LE. This event causes an alteration in the flow of the M pathway and, consequently, a slight neuronal disorder in the right temporal-parietal area, which is essential for the development of visual attention.[76,77]

Regarding electrophysiological investigations, mainly visual evoked potentials (VEPs) were used to study

Table 5 Frequency Doubling Technology (FDT) Index Values of the Right Eye (RE) and Left eye (LE) in Dyslexics and Control Subjects

	Dyslexic RE	**Dyslexic LE**	**p-value**	**Control RE**	**Control LE**	**p-value**
FDT-PSD (dB)	3.66 ± 0.96	4.43 ± 1.10	0.031	2.99 ± 0.42	2.95 ± 0.40	0.791
CI 95%	2.97/4.35	3.65/5.22		2.69/3.3	2.66/3.23	

Abbreviations: PSD, pattern standard deviation; CI, confidence interval.

Table 6 Intragroup Steady-State Pattern Electroretinogram (SS-PERG) and Frequency Doubling Technology (FDT) Perimetry Index Values of the Right Eye (RE) and Left eye (LE) in Dyslexic Subjects and Control Subjects

	Dyslexic RE	**Control RE**	**p-value**	**Dyslexic LE**	**Control LE**	**p-value**
SS-PERG (μV)	0.671 ± 0.11	1.29 ± 0.31	0.0003	0.559 ± 0.15	1.34 ± 0.32	0.0001
CI 95%	0.595/0.747	1.01/1.51		0.490/0.628	1.12/1.57	
FDT-PSD (dB)	3.66 ± 0.96	2.99 ± 0.42	0.0002	4.43 ± 1.10	2.95 ± 0.40	0.0002
CI 95%	2.97/4.35	2.69/3.3		3.65/5.22	2.66/3.23	

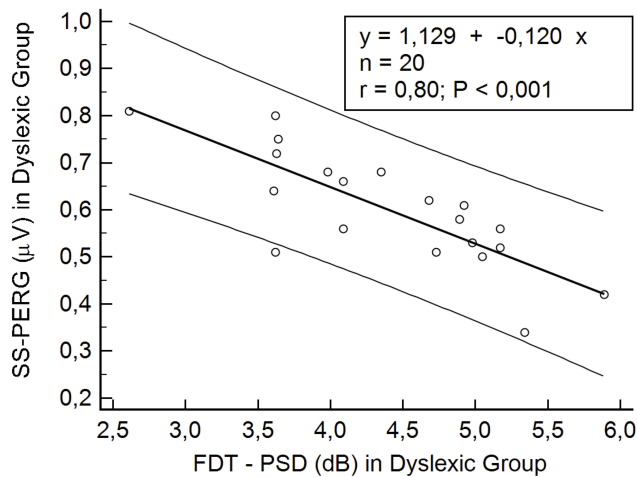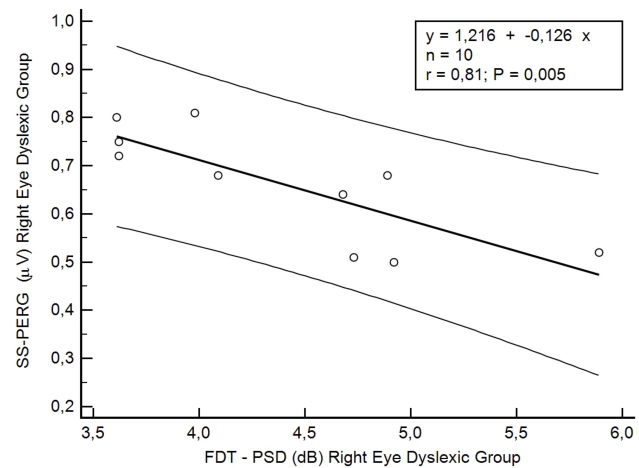**Abbreviations:** PSD, pattern standard deviation; CI, confidence interval.

Figure 2 Scatterplot of Spearman's correlation test between steady-state pattern electroretinogram (SS-PERG) and frequency doubling technology (FDT) in the dyslexic group.
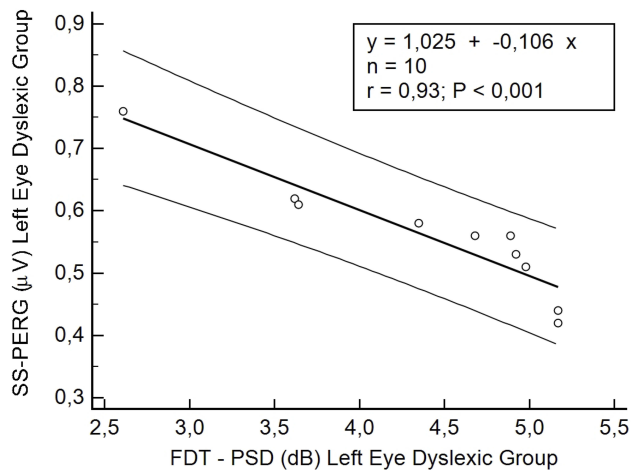**Abbreviation:** PSD, pattern standard deviation.

Figure 4 Scatterplot of Spearman's correlation test between steady-state pattern electroretinogram (SS-PERG) and frequency doubling technology (FDT) in the right eye of dyslexic group.
Abbreviation: PSD, pattern standard deviation.

Figure 3 Scatterplot of Spearman's correlation test between steady-state pattern electroretinogram (SS-PERG) and frequency doubling technology (FDT) in the left eye of the dyslexic group.
Abbreviation: PSD, pattern standard deviation.

the M pathway by applying standard methods, which gave contradictory results.[23] Recently, using the pattern visual evoked potentials (PVEP) and modifying the stimulation parameters appropriately in order to isolate the response of the MD pathway, it has been observed that for 60-arc-minute stimuli in dyslexic subjects the reduction of contrast from 100% to 25% resulted in a significant reduction in amplitude with an increase in P100 wave latency while for 15-arc-minute stimuli only latency was significantly increased.[23,78] These data confirmed the observations of Romani and coworkers, who used stimuli with a high temporal frequency of 8 Hz with fixed contrast at 50%

and spatial frequencies of the stimulus of 0.50 cpd (large stimulus) and 2 cpd (small stimulus). In this case, only low spatial frequency stimuli (large stimuli) and high temporal frequency determined a decrease in amplitude and an increase in latency of the N95 wave in dyslexic subjects.[19]

Other studies have used different electrophysiological techniques, such as fixed spatial frequencies with high temporal frequencies and luminance variation,[21,23] low spatial frequency and high temporal frequency stimuli (7.5 Hz),[20,23] and, finally, recording of VEPs with the use of moving stimuli at low contrast,[79] as well as at low contrast and radial motion full field and radial motion periphery.[69] In all cases, they showed a significant increase in latencies and a reduction in the amplitudes of the waveform in dyslexic patients.[24]

To study the activity of only M–Y retinal ganglion cells we used the SS-PERG with a stimulus similar to that used in the FDT perimetry.[32] Both transient-PERG and SS-PERG are commonly used to investigate RGCs activity, but these two examinations differ mainly in the temporal frequency of the pattern stimulus. In detail, by using a temporal frequency of 4 Hz, a transient response will be obtained; by increasing the frequency to 8 Hz, a steady-state response will be recorded[80,81] and we can study the ON pathway of the spiking retinal ganglion cells (RGCs).[82]

Now, the question is whether the Y-cells, first identified in cats, even exist in the primate's retina. Indeed, this is a controversial topic in the literature, but recent studies have identified Y-like RGCs in primates.[71,83–85] Experimental studies, with the use of microelectrodes,

have shown that when the retina is stimulated with gratings at high contrast and high spatial frequency from each parasol (M) RGCs a doubled frequency is recorded and this response is characteristic of Y-cells.[83]

In our study, we found a significant reduction in the amplitude of SS-PERG in the dyslexic group compared to the healthy controls. In dyslexic subjects, we found a significant difference between the LE and RE, with a greater amplitude reduction in the LE. A significant correlation between the amplitude of the SS-PERG and the pattern standard deviation index of FDT perimetry. The correlation between the amplitude of the SS-PERG waveform and the FDT perimetric index confirms what was found by Maddess and coworkers in glaucoma and suspect glaucoma.[35]

Our electrophysiological data could therefore confirm not only the results of a previous study using the FDT technique[33,34] but also the hypothesis that in dyslexic subjects the damage would be located not only in M–D pathway but even in the RGCs.

The small number of adult dyslexic subjects included in the study is a limitation of our research. In this first study, we only enrolled adult patients without any intellectual deficiency since the technique used for the SS-PERG required high patient compliance and visual attention. Additional studies with larger groups are needed to validate our preliminary results.

Conclusion

Previous electrophysiological studies have demonstrated with the use of PVEP in dyslexic patients there is an alteration of the M–D pathway. In our study, we found that in dyslexia there is an alteration of the activity of M–Y retinal ganglion cells, especially in the left eye. These data confirm that in dyslexia there is a "minineglect" on the left eye that justifies the onset of a deficit of visual attention.

Acknowledgments

This work was done in memory of Maria Mottes.

We thank Paola Fiorini, Cristina Tura and Giulia Cecchin, the orthoptists of the Electrophysiology Service.

Disclosure

The authors report no conflicts of interest in this work.

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