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Eye-Fixation Behavior in Major Depressive Disorder and the Influence of Pharmacological Therapy: A Microperimetric Study

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Abstract

Background: To evaluate retinal function and fixation stability in major depressive disorder (MDD) and the influence of antidepressant therapy, using the MP-1 microperimeter.

Methods: 25 patients with MDD (57 ± 13.73 years) and 25 healthy subjects (HS) (56.41 ± 15.73 years) were enrolled. According to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), single (296.2) or recurrent episode (296.3) of MDD was included. Retinal sensitivity, fixation stability, and bivariate contour ellipse area (BCEA) were obtained using MP-1. Then patients were divided according to antidepressant therapy: SSRI/SNRI associated with atypical antipsychotic (group A) and SSRI/SNRI monotherapy (group B) and pharmacological washout (group C). Differences between groups were estimated using the Kruskal-Wallis test with post hoc Mann-Whitney analysis. Spearman's rank correlation was used for comparisons.

Results: Mean retinal sensitivity was significantly reduced in the MDD group than HS (P= 0.02). Six (24%) eyes had a relatively unstable fixation, and mean BCEA was larger than control group (P =0.04). The Kruskal-Wallis analysis of variance showed significant differences in log BCEA between groups (P=0.01), but no differences in mean retinal sensitivity between groups (P=0.09).

Conclusion: MDD patients showed impairment in retinal sensitivity and fixation stability respect to the HS. Despite these findings, the impairment of fixation stability seems to be related to antidepressant therapy.

Keywords

Fixation stability; Bivariate Contour Ellipse Area (BCEA); Microperimetry; Major depressive disorder (MDD)

Introduction

Visual pursuit and fixation share similar behavior and affecting similar cerebral areas in cortical and subcortical regions, including prefrontal cortex, superior parietal cortex, superior colliculi, brainstem and cerebellum [1,2]. In the last years, several studies were conducted about saccadic movements, visual pursuit and fixation in schizophrenia, depression, bipolar and obsessive compulsive disorder. Rapid and saccadic eye movements seem to provide a selective index of cognitive function [3,4]. Despite this interest, there have been no studies regarding visual fixation stability in major depressive disorder.

Fixation is defined as a period between saccades. During fixation there are some involuntary eye movements such as physiological nystagmus, drifts and microsaccades and correcting movements to compensate for motion of the head [5]. In healthy eyes fixation mostly remains within the foveola.

Fundus-related perimetry (microperimetry - MP) is used in various diseases to evaluate fixation stability and retinal sensitivity [6-8]. The most commonly device used is the MP-1 microperimeter (Nidek Technologies, MP-1, Padova, Italy).

The aims of this study were to evaluate retinal function and fixation stability in major depressive disorder (MDD) and to investigate the influence of the pharmacological therapies on quality of fixation.

Materials and Methods

This prospective case-control study was conducted at the Department of Medical–Surgical Sciences and Biotechnologies, University of Rome La Sapienza, Polo Pontino. A total of 25 patients with major depressive disorder, and 25 healthy subjects were enrolled. All subjects gave written informed consent before enrollment. Institutional board approval (IRB) was obtained from ethics committee of our institution and the research was conformed to the Declaration of Helsinki.

A diagnosis of major depressive disorder (MDD) was obtained

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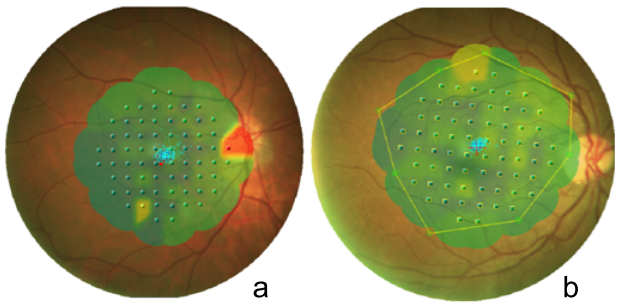

Figure 1: MP-1 images. Interpolated color map of retinal sensitivity and bivariate contour ellipse area (BCEA) analysis (A), and calculation of mean sensitivity by drawing a polygon (B) in two different patients with major depressive disorder

after one or more clinical interviews performed in the Psychiatry Unit. Inclusion criteria were: single (296.2) or recurrent episode (296.3) of MDD according to the Diagnostic and Statistical Manual of Mental Disorders 4th edn (DSM-IV); BCVA ≤ 0.04 logMAR; age greater than or equal to 30 years; We excluded patients who had a history of or current ocular disease; history of intravitreal or laser therapy; refractive errors more than ± 5 diopters (D); amblyopia; history of intraocular surgery; Patients with any other diagnosed mental illness were also excluded;

All patients received antidepressants at the time of examination, selective serotonin reuptake inhibitor (SSRI), or serotonin-norepinephrine reuptake inhibitor (SNRI), whereas 8 (32%) patients added therapy with atypical antipsychotics (olanzapine or quetiapine). All patients also were taking benzodiazepines (clonazepam, elorazepam, lorazepam, alprazolam, and flurazepam). Moreover 5 (20%) patients were in therapeutic wash-out by at least five days.

The control population consisted of hospital staff volunteers; they underwent ophthalmological and psychiatric evaluations to exclude any disease.

All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA) using the Snellen chart, biomicroscopy of the anterior segment, Goldmann applanation tonometry, and dilated fundus examination with indirect ophthalmoscopy. Only one eye from each patient was randomly selected for the study.

All subjects underwent microperimetry examination (NAVIS, software version 1.7.6; Nidek Technologies). Microperimetry tests were performed in a darkened room and pupils were dilated with 1 drop each of tropicamide 1% and phenylephrine 2.5%. A red cross of 2 degrees was used as the fixation target. Before microperimetry test, all patients were instructed to maintain fixation on the central target and to push the handheld button every time a light stimulus was seen, then a 30 second fixation test was performed. For the exam, we used monochromatic white background set to 4 apostilbs (1.27cd/m^2), the stimulus size was Goldmann III with a projection time of 200ms. A customized grid of 68 stimuli covering the central 20° of the macula. A 4-2-1-staircase strategy was employed, and the first stimulus was fixed at 16dB. Results about retinal sensitivity were reported in decibels (dB).

MP-1 quantified stability of fixation in two ways. According to Fuji et al. fixation is 'stable' when more than 75% of fixation points fall within a 2° circle, 'relatively unstable' if more than 75% are located within a 4° circle and 'unstable' if less than 75% of fixations are within the 4° diameter circle [9].

The second way use the bivariate contour ellipse area (BCEA), this is based on the values of the standard deviations of the horizontal and vertical eye movements during fixation and the correlation coefficient (Pearson product-moment correlation coefficient) of the horizontal and vertical eye positions. BCEA was calculated using the formula previously reported by Timberlake et al. [10].

$$BCEA=\pi\chi^2\sigma_x\sigma_y\sqrt{1-\rho^2}$$

where χ^2 is the chi-squared value (*2df*) corresponding to a probability of 0.682 (±1 SD), σx and σy are the standard deviations of the horizontal and vertical eye movements (x and y), and ρ is the Pearson product moment correlation coefficient (Figure 1).

The data collected included retinal sensitivity, fixation stability, fixation points within 2 and 4 degree, and BCEA value (1 SD).

On the basis of the preliminary data, the recruited patients were subsequently categorized into three groups. Group A consisted of 8 patients (8 eyes) who received one or more antidepressants and atypical antipsychotic drugs. The second group (group B) consisted of 12 patients (12 eyes) who received one or more antidepressants but not atypical antipsychotic drugs. The third group (C) consisted of 5 patients (5 eyes) who received no treatment.

All quantitative values are presented as mean ± standard deviation (SD). The normality of distribution for each variable was analyzed by the Shapiro-Wilk test. BCEA values in deg^2 were normalized with a log transform. Student two-tailed t test was used for continuous variables – nonpaired. The chi-squared test was used to compare categorical patient variables. P value less than 0.05 were considered statistically significant, and P<0.001 was considered to be highly statistically significant. Subgroups analysis was performed using the Kruskal-Wallis test followed by Mann-Whitney post hoc analysis. Spearman's rank correlation or Pearson product moment correlation was used for comparisons. All calculations were carried out using the SPSS statistical software (ver. 20; SPSS, Inc., Chicago, IL).

Table 1: Baseline characteristics of the study subjects.

	MDD (n=25 eyes)	Controls (n=25 eyes)	P-value
Age (yrs)	57 ± 13.73	56.28 ± 6.21	0.41[a]
Female, n (%)	19 (76%)	17 (68%)	0.09[b]
Therapy, n (%)			
Washout	5 (20%)		
SSRI/SNRI monotherapy	12 (48%)		
SSRI/SNRI + atypical antipsychotic	8 (32%)		

MDD: Major Depressive Disorder; yrs: Years; SSRI: Serotonin reuptake inhibitor; SNRI: Serotonin-Norepinephrine reuptake inhibitor; Data are expressed as mean ± standard deviation (SD); P-value less than 0.05 were considered statistically significant; [a]unpaired t test; [b]χ-square test;

Table 2: Statistical significance in retinal sensitivity and fixation stability between groups.

	Group A n=8	Group B n=12	Group C n=5	Controls n=25	P-value
Mean sensitivity (dB)	15.65	14.74	14.9	17.53	0.09
SD	4.83	3.32	7.12	1.99	
Mean logBCEA (deg²)	-0.63	-0.16	-0.75	-0.67	0.01
SD	0.36	0.47	0.27	0.42	

dB: Decibel; BCEA: Bivariate Contour Ellipse Area; Group A: SSRI/SNRI + atypical antipsychotic drugs; Group B: SSRI/SNRI monotherapy; Group C: pharmacological washout; Differences between groups were estimated using Kruskal-Wallis test.P value less than 0.05 were considered statistically significant, and P<0.001 was considered to be highly statistically significant.

Results

25 eyes of 25 patients and 25 eyes of 25 healthy controls were compared. Baseline characteristics of the study subjects were summarized in Table 1. Mean retinal sensitivity was 17.53 ± 1.99dB in the control group and 15.07 ± 4.5dB in the MDD group, and this difference was statistically significant (-2.45dB, CI95%: 0.38, 4.53, P=0.02). The mean logBCEA was larger in the MDD compared to the control group (-0.44 ± 0.47deg^2 vs. -0.67 ± 0.42deg^2 respectively, -0.37 deg^2, CI95%: -0.75, 0.005, P=0.04) (Figure 2). In the MDD group, fixation patterns according to Fuji classification were stable in 19 (76%) eyes and relatively unstable in 6 (24%) eyes (χ^2= 5.98, P=0.02 with respect to the control group).

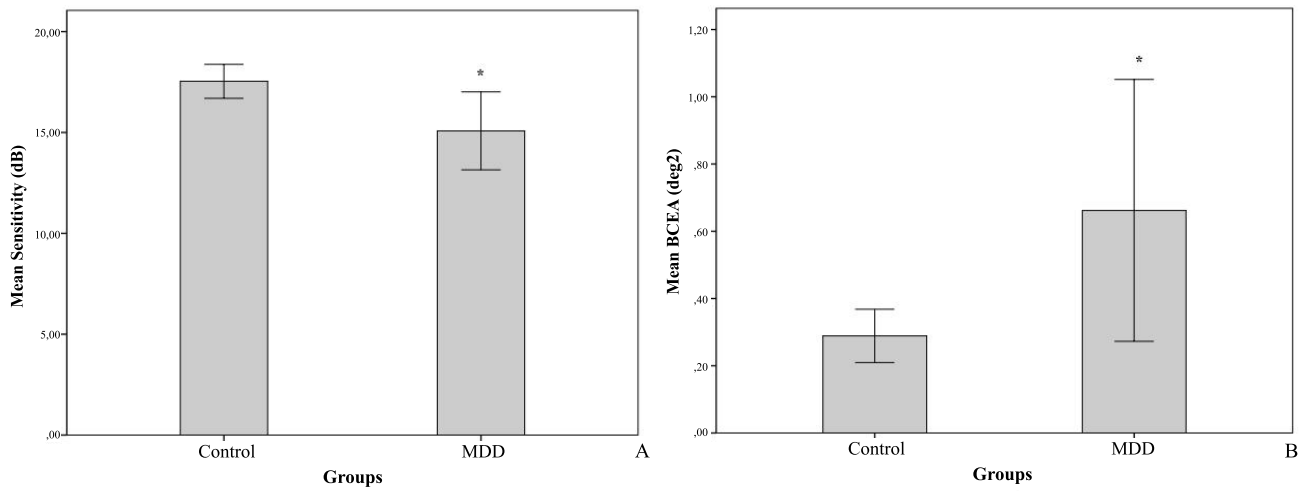

Figure 2: Bar graphs reported mean values and errors (standard deviation) of A) mean sensitivity and B) bivariate contour ellipse area (BCEA) between controls and major depressive disorder (MDD) group; the mean BCEA was reported as mean values without logarithmic conversion in order to facilitate the graphical interpretation of the results.

*P value statistically significant, less than 0.05

Moreover there was a significant negative relationship between BCEA and mean retinal sensitivity both in MDD and control group (r=-0.43, P=0.03 and r= -0.39, P=0.05 respectively).

In the group A (mean age: 53.25 ± 18.54 years, P=0.29 vs. control group) 7 (87.5%) eyes had stable fixation and only 1 (12.5%) eye had a relatively unstable fixation (χ^2=0.37, P>0.05 vs. control group). Group B (mean age: 59.77 ± 4.79, P=0.08) presented a stable fixation in 6 (58.33%) eyes and a relatively unstable fixation in 5 (41.66%) eyes (χ^2=8.74, P=0.02). In the group C (mean age: 52.4 ± 5.83 years, P=0.16) all patients had a stable fixation (χ^2= 0.05, P>0.05).

Table 2 summarizes the data about retinal sensitivity and means logBCEA and the significance between subgroups using Kruskal-Wallis analysis of variance.

Post-hoc analysis showed a statistically significant reduction of mean retinal sensitivity in the B subgroup with respect to the control group (P=0.01).

Instead mean BCEA was significantly larger in the group B than control (P<0.01), group A (P=0.02) and group C (P=0.01) and control group (P=0.01) (Table 2).

Discussion

Several studies [4,11-14] have focused on the role of the eye movements in psychiatric disorders, especially in schizophrenic patients.

In this small prospective case-control study we analyze fixation stability and retinal sensitivity in patients with MDD in order to understand the influence of mood in fixation performance, and if antidepressant or antipsychotic drugs could influence visual fixation.

We have chosen to use microperimeter as fixation stability analyzer because it has some important advantages. MP-1 allows a reliable detection of fixation behavior and reproducibility thanks to its automated real-time fundus tracking and alignment that minimize the influence of eye movements. The main uses of microperimetry include evaluation of the function of the macula and central visual fields as well as fixation behavior in patients with macular disease [15-16].

Recently, Brzezicka et al. [13] analyzed the two main theories of information processing: defocused attention and analytical rumination. They concluded that dysphoric patients have not a deterioration of task performance but are sensitive to shrinkage of the available visual field, supporting the defocused attention hypothesis. This mode of attention is unfocused and unselective but allows acquiring more information from outside.

In our study, MDD patients had a significant reduction in mean retinal sensitivity than control group, whereas BCEA was larger than controls and stability of fixation according to Fuji was relatively unstable in 24% of eyes.

Despite these findings, the impairment of fixation stability seems to be a consequence of antidepressant therapy. In order to confirm this hypothesis we divided the MDD patients into three subgroups on the basis of antidepressant pharmacological therapy.

However no differences were found in retinal sensitivity between subgroups, but only between SSRI/SNRI monotherapy group and control group. These patients had a larger BCEA than all other groups. Moreover MDD patients in pharmacological washout showed no significant differences respect to the control group in fixation stability.

Other studies hypothesized that medications may interfere with performance, especially atypical antipsychotic drugs [12,14]. Although there are a lot of studies about the effect of atypical antipsychotic drugs, this is still unclear. These studies were focused on smooth pursuit movements using different methodologies and in most cases it has been conducted in schizophrenic patients [4,11-14,17,18]. Both in visual pursuit and fixation anomalies there is an increased rate of saccadic events [12]. In our opinion MP-1 eye tracking system underestimating eye movements allows a better evaluation of fixation function, thus our results cannot be comparable with other studies investigating the role of atypical antipsychotic drugs.

The main limitation of our study is represented by small sample size of the MDD subgroups.

Our findings are interesting for two main reasons. First, the results of microperimetric examination may be influenced by depressive disorder. Second, as well note, patients with low vision due to ophthalmic pathologies has a co-occurrence of depressed mood or MDD; therefore the administration of antidepressive drugs may interfere with visual performance and with a possible visual rehabilitation.

Conversely atypical antipsychotic drugs in association with SSRI/SNRI agents could improve their effect on fixation stability performance and mean retinal sensitivity.

To our knowledge this is the first study that analyzed retinal sensitivity and fixation stability in MDD patients using microperimetry. Further studies with a large sample are required to clarify the role of pharmacological agents and the role of fixation

stability in MDD patients using microperimetric examination. Moreover could be even more interesting an integrate approach with psychiatric data in order to assess the relation with visual fixation and cognitive function.

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