Postural control after traumatic brain injury in patientswith neuro-ophthalmic deficits

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*5. Manuscript

Abstract

Postural instability is a common and devastating consequence of Traumatic Brain Injury (TBI). The majority of TBI patients also suffer from neuro-ophthalmic deficits that may be an important contributing element to their sensation of vertigo and dizziness. Static posturography aims at the objective evaluation of patient balance impairment, but it is usually affected by large inter- and intra- subject variability. Here we propose a protocol based on ten randomized trials stimulating in different ways the visual and vestibular systems. Due to its completeness, our protocol highlights the specific residual difficulties of each patient in the various conditions. In this way, it was possible to evidence significant balance abnormalities in TBI patients with respect to controls. Moreover, by means of a multivariate analysis we were able to discriminate different levels of residual neuro-ophthalmic impairment.

1. Introduction

Traumatic Brain Injury (TBI) is an important cause of disability at all ages [1]. In the USA the annual incidence of emergency department visits and hospital admission are respectively 403 per 100,000 and 85 per 100,000 [2]. The mean annual incidence rate of hospitalized and fatal TBI for Europe is 235 per 100,000 [3]. Approximately 80% of injuries are classified as mild, 10% as moderate, and 10% as severe [3]. Severity is usually described by the Glasgow Coma Scale (GCS) [4], evaluated when the patient enters the emergency department. However, GCS may change during hospitalization and it does not describe the nature and the entity of the residual impairments. One of the most common complaints among TBI patients is postural instability and balance impairment [5-6].

Neuro-ophthalmic deficits commonly follow TBI, since the afferent and efferent pathways are vulnerable to traumatic injury. Commonly described categories of oculomotor dysfunctions are anomalies of accommodation, version, vergence (nonstrabismic, as well as strabismic), photosensitivity, visual field integrity, and ocular health [7]. Authors indicate different percentages of neuro-ophthalmic impairments following TBI, ranging from 39% to 90%, as described in [8-11]. Neuro-ophthalmic deficits may have important consequences on balance, since postural control integrates information from the visual, vestibular, and somatosensory systems.

Subjective complaints of dizziness that occur in the absence of objective clinical signs are difficult to assess [12-13]. Static stabilometry may provide an objective evaluation of postural instability [14-18] by characterizing the performance of the postural control system during quiet standing.

This technique is based on the study of the trajectories of the Center of Pressure (CoP) on the support surface. CoP trajectories are recorded by a force platform and analyzed using different techniques and extracting different kinds of parameters [16,18]. A possible limit of static stabilometry was highlighted by [15,19] due to the high inter-subject and intra-subject variability that many studies report.

Previous studies [12-13, 20-25] addressed the problem of quantifying the consequences of TBI on balance assessment using static stabilometry. None of the studies published in the past specifically considered a group of TBI patients with a significant residual visual impairment.

Studies on static posturography are usually based on an acquisition protocol consisting of two trials, with eyes open and closed respectively, to take into account the role of the visual system.

Our study differs from the previous ones for two aspects. First, we consider a group of TBI patients with residual neuro-ophthalmic deficits. Secondly, this study is based on a more complete acquisition protocol that adds to frontal open- and closed-eye trials, trials in which quiet standing of the subject is evaluated after a fast or a slow head rotation, both with eyes open and closed. In this way, it is possible to highlight the specific difficulties of each patient in various conditions that stimulate the visual and vestibular systems.

The aim of this study is to present a more complete acquisition protocol that allows to evaluate balance impairments in TBI patients and to demonstrate that such a protocol can discriminate between controls and patients. Furthermore, we demonstrate that the presented protocol can also distinguish patients with different levels of visual impairment.

2. Materials and Methods

2.1 Subjects

TBI patients were recruited from the outpatients of the Clinica Oculistica “C. Sperino”, Ospedale Oftalmico (Torino), Italy, where they were referred to for a neuro-ophthalmologic examination. On the average, 73% of approximately 70 TBI patients that refer to Clinica Sperino in a year have neuro-ophthalmic impairments. The assessment of the severity of trauma was based on patient’s history and medical records obtained from the Post-traumatic Rehabilitation Centre of Caraglio (Cuneo, Italy) where they were treated after the injury. Our greater sample was formed by 50 subjects. The inclusion criteria were the typology of brain injury, its localization, and the presence of visual impairment only at the time of the test. We considered patients whose injuries were localized in the frontal, fronto-temporal, and fronto-temporo-parietal lobe, to select subjects with a high probability of suffering from neuro-ophthalmic deficits caused by the trauma. We excluded patients who showed residual sensorimotor or vestibular impairments. Thus, 13 TBI patients out of 50 were included in this study. These were 4 females (age 28 - 41 years, mean 34.5±6.0 years; height 160 - 170 cm, mean 163.0±4.8 cm; weight 53 - 85 kg, mean 62.5±15.1 kg) and 9 males (age 22 - 63 years, mean 33.7±13.9 years; height 170 - 186 cm, mean 181.0±3.4 cm; weight 70 - 90 kg, mean 79.0±6.4 kg). Table 1 shows patient characteristics.

The control group consisted of 43 healthy subjects, 26 females and 17 males, matched for age, height and body mass index, with no orthopedic, neurological or visual problems.

Both TBI patients and controls underwent a neuro-ophthalmologic examination prior to the test to evaluate the visual system. They were examined for pupillary reflex, smooth pursuit, saccades and optokinetic nystagmus. The last column of Table 1 reports the clinical evaluation of the residual visual impairment at the time of the balance test. In all patients abnormal saccades were observed. In five patients global deficits of the eyes version were found. These patients were classified as "severe" in the last column of Table1. Three patients showed both saccades and smooth pursuit anomalies and were classified as "moderate". Patients in which only abnormal saccades were observed were classified as "mild". All the subjects belonging to the control group did not show any neuro-ophthalmologic abnormality.

The experimental protocol was approved by the local ethical committee and all participants gave their written informed consent to the study.

2.2 Acquisition protocol

Subjects were asked to stand quietly, in upright position, over a Kistler 9286A force platform. The inter-malleolar distance was fixed at 4 cm and the feet opening angle was 30°. The acquisition protocol consisted of 10 different trial conditions, five with eyes open (looking at a visual target) and five with eyes closed. The head positions were: 1) frontal: Open Eyes Frontal (OEF), Closed Eyes Frontal (CEF), 2) head rotated after a slow left rotation: Open Eyes Left slow (OELs), Closed Eyes Left slow (CELs) 3) head rotated after a slow right rotation: Open Eyes Right slow (OERs), Closed Eyes Right slow (CERs) 4) head rotated after a fast left rotation: Open Eyes Left fast (OELf), Closed Eyes Left fast (CELf), 5) head rotated after a fast right rotation: Open Eyes Right fast (OERf), Closed Eyes Right fast (CERf). At the operator order, the subject reached the requested head position and then the signal acquisition started. A biaxial accelerometer fixed on the forehead of the subject was employed for monitoring the head rotation. Each recording started at the end of the head rotation and lasted 60 s.

The sequence of trials was randomized to avoid learning and/or fatigue effects [26]. Every two trials the subject rested for one minute moving away from the platform.

The platform signal was recorded with a sampling frequency of 2 kHz and then down-sampled to 50 Hz. The acquisition system was Step32 (DemItalia, Italy).

2.3 Data analysis

We calculated the major geometrical and time-domain parameters based on the CoP trajectory [16-17]. Table 2 describes the set of parameters we considered.

First, we compared TBI and controls - for each trial condition and CoP parameter - by means of a two-sample t-test, after having verified the gaussianity of the distributions.

Moreover, we were interested in taking into account the inter-relations among CoP parameters in the different trials, using the global information arising from the complete protocol: for each subject we have a total of 70 dependent variables (10 trials × 7 parameter values). To this purpose, we applied a multivariate analysis of variance (MANOVA) approach [27-29]. We reduced the number of CoP parameters considered, preserving those containing non-redundant information and discarding parameters highly correlated among them or with high within-group variability. To select the reduced set of parameters we used Wilks' Lambda statistic (Λ) [27]. Λ is an index of the parameters' discrimination capability. It is defined as the ratio between the within-groups generalized variability and the total generalized variability, the latter being the sum of the within-groups and between-groups generalized variability. This index takes values between zero and one, lower Λ-values indicating a better discrimination among groups.

The procedure we adopted is the following. As a first step, we calculated Λ for each parameter separately and sorted the parameters in Λ ascending order. We kept the parameter with lower Λ-value. Then we considered all the possible combinations of two parameters, recalculated the corresponding Λ-values and sorted them in ascending order, keeping the combination with lower Λ-value. The process was carried out iteratively adding one parameter at a time, each time recalculating the Λ-value and choosing the combination of parameters showing the lowest Λ-value. The parameter selection stopped when, adding more parameters, Λ did not significantly decrease [27].

After the selection of the reduced set of CoP parameters we summarized the information arising from the ten-trial protocol applying a canonical variate analysis (CVA) [27]. The canonical variables C are linear combinations of the original variables, chosen to maximize the separation among groups. Specifically, the first canonical variable C1 is the linear combination of the original variables that has the maximum separation among groups. This means that among all possible linear combinations, it is the one with the most significant F statistic in a one-way analysis of variance. The second canonical variable C2 has the maximum separation while being orthogonal to C1, and so on. We represented the two populations of TBI and controls in the plane of the first two canonical variables.

3. Results

Fig. 1 shows, for each parameter, mean and standard deviation of TBI patients and controls in the ten typologies of acquisition. Differences between groups which are statistically significant (two-sample t-test, $p \leq 0.05$) are indicated with an asterisk. Major and Minor Axis and the RMS values show significant differences in all of the trials. Mean Velocity highlights significant differences between TBI and controls mainly in trials after head rotation (slow or fast). On the contrary, Mean Velocity is not significantly different in trials with a frontal head position, both with eyes open and closed. Sway Area and Eccentricity do not differentiate the two groups.

We tested also open eyes vs. closed eyes performances: significant differences are indicated with triangles in controls and with circles in TBI patients. In controls, differences were observed in all the test conditions for the Mean Velocity. For the other parameters, statistically significant differences were observed only in a few test conditions. In TBI patients there were significant differences between open eyes and closed eyes trials only in a single test condition (Mean Velocity, OERf vs. CERf).

Fig. 2 shows the values of Λ on which we based the parameter selection. The single parameter that better differentiates the two populations is Minor Axis ($\Lambda = 0.42$), the best combination of two parameters is Minor and Major Axes ($\Lambda = 0.31$), that of three parameter is Minor Axis, Major Axis, and RMS AP ($\Lambda = 0.15$), that of four parameters is Minor Axis, Major Axis, RMS AP, and Eccentricity ($\Lambda = 0.076$), and, finally, that of five parameters is Minor Axis, Major Axis, RMS AP, Eccentricity, and Sway Area ($\Lambda = 0.0035$). Therefore, the Λ-value decreases remarkably each time a parameter is added to the set of the best CoP parameters and it falls below 0.05 when considering the best combination of five parameters. Hence, in the rest of the analysis, we consider only these five parameters. Note that Eccentricity and Sway Area do not play a role in differentiating the two populations if they are considered as standalone parameters, but they become useful if they are considered in combination with the other parameters.

The parameter selection procedure was performed considering all the 10 trials. The effect of considering a smaller number of trials is evidenced by Fig. 3, which shows multivariate data from TBI patients and controls plotted against the first two canonical variables C1 and C2. Fig. 3a) and 3b) show the results of multivariate analysis to compare controls and TBI patients, while fig. 3c) and 3d) show the differences among the three sub-groups of TBI patients and controls. The procedure of parameter selection was not redone, while we recomputed the canonical variables for this specific case. Fig. 3a shows the results on two acquisition trials only (Open Eyes Frontal and Closed Eyes Frontal), while Fig. 3b refers to the complete set of ten trials. In Fig. 3a TBI patients and controls are partially overlapped, even if some of the TBI patients fall outside the control group cloud ($\Lambda = 0.63$, $p = 0.014$). In Fig. 3b the two populations are completely separated ($\Lambda = 0.0035$, $p = 3.3\times10^{-13}$). Therefore, considering all the ten trials, TBI patients are completely differentiated from controls.

Fig. 3c and Fig. 3d show controls and patients suffering from mild, moderate, and severe residual visual impairment, as reported by Table1. When only two trials are considered, the various groups are scarcely separated (Fig. 3c). On the contrary, when all the ten trials are taken into account, not only the patients are well differentiated from controls, but also the three groups are completely separated among them (Fig. 3d). Moreover, the distance between controls and the three TBI groups increases with increasing level of visual impairment.

4. Discussion

The most widely used parameters in posturography are the total length of the CoP path (Sway Path Length) and the Mean Velocity. They are essentially the same parameter, except that Mean Velocity is normalized with respect to the test duration and hence does not depend on it. They are usually evaluated with the subject in quiet stance on the platform with the head in frontal position, both with eyes open and closed. It is important to notice that velocity integrates both amplitude and frequency changes, thus a concomitant reduction in sway frequency can reduce the discriminant power of velocity. Dehail et al. [20] studied a group of sixty-eight TBI patients (60 of which with a GCS score < 8, and 33 with a residual neurological impairment) and found that Sway Path Length was significantly increased, compared to controls, both with eyes open and closed. In our sample population, we found that Mean Velocity did not separate TBI patients from controls in the trials with the head in frontal position (both with eyes open and closed), while it separated the two populations in the newly proposed test conditions (after slow or fast head rotation). The difference between our results and those reported in [20] may be explained by the fact that in our study patients reported, in general, less severe TBI and suffered from no vestibular or sensorimotor impairment.

We hypothesized that subjects with visual impairment rely less than controls on the information arising from the visual system. Geurts et al. [13], working with a group of TBI patients who complained of reduced gross motor skills without sensory-motor impairments, report that visual deprivation was most detrimental for TBI patients, particularly for the Medio-Lateral control. In our patients, differences between the open- and closed-eyes balance performances are almost never statistically significant, while they are significant in controls for the parameter Mean Velocity. These results are coherent with our hypothesis, since we found that visual deprivation is less detrimental for patients.

Among others, Visser et al. [12] pointed out that the poor discriminative ability (between health and disease) of posturography may relate to the substantial inter-subject and intra-subject variability. Given these uncertainties, many researchers record a broad range of different parameters and/or perform repeated tests in the same or in different test conditions. As a consequence, for each subject, many parameters and many test conditions are considered which are partially correlated among them.

To take into account all the information arising from the complete protocol, we used a multivariate approach. Multivariate analysis requires a prior variable selection, as described in [27]. The results of variables selection are often counterintuitive. In our study, we excluded from the 'best combination of five parameters' parameters that were discriminative in univariate analysis. This is not surprising, since univariate analysis does not take into consideration the correlation among parameters.

Thanks to the representation of subjects in the plane of the first two canonical variables, we demonstrated (see Fig. 3) that it is possible to obtain a complete separation of patients from controls when all the 10 test conditions are considered and that it is also possible to discriminate among groups of patients with different residual visual impairment. Specifically, C1 discriminates patients from controls, while C2 summarizes the information needed to separate patients according to the degree of their residual visual impairment.

5. Conclusions

Using the proposed 10-trial protocol it was possible to clearly distinguish balance abnormalities of TBI patients with respect to controls. Moreover, we found that the severity of the residual neuro-ophthalmic deficit is correlated to the severity of the balance impairment. This is of paramount importance from a clinical perspective since it demonstrates that static posturography, associated to the presented protocol, can be applied to objectively evaluate the balance performances of a patient enrolled in a rehabilitation program and assess his/her progresses.

Conflict of interest statement

None of the Authors on this manuscript had or has any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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Table 1

Characteristics of Traumatic Brain Injury patients.

Patient	Age (years)	Gender (M/F)	GCS score[1]	CT/MRI	Time (months)[2]	Cause	Residual damage[3]
1	26	M	15	Negative	37	Violence	Mild
2	62	M	14	Positive	130	Traffic accident	Moderate
3	25	M	4	Positive	35	Fall from scaffolding	Severe
4	41	F	8	Positive	42	Traffic accident	Severe
5	28	M	8	Positive	95	Traffic accident	Severe
6	31	M	6	Positive	71	Traffic accident	Severe
7	22	M	Not available	Positive	55	Traffic accident	Mild
8	28	F	9	Positive	64	Fall from horse	Severe
9	31	F	8	Positive	38	Traffic accident	Mild
10	38	F	6	Positive	66	Traffic accident	Moderate
11	38	M	6	Positive	143	Traffic accident	Mild
12	21	M	14	Positive	15	Traffic accident	Mild
13	50	M	14	Positive	17	Fall from scaffolding	Moderate

[1] Lowest Glasgow Coma Scale score after hospitalization.

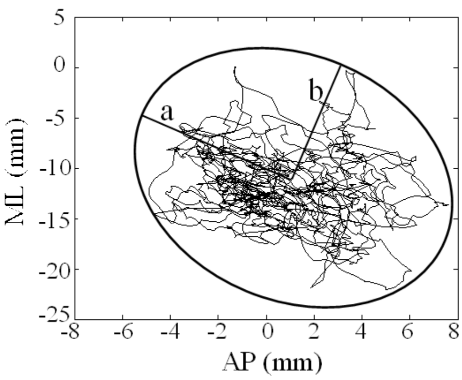
[2] Time elapsed from head trauma.

[3] Assessed from the clinical neuro-ophthalmic evaluation of the patients prior to the balance test.

Table 2

Posturographic parameters.

Parameter	Dimension	Description	Definition[1]
Mean velocity	mm/s	Length of CoP trajectory on the base of support in the unit of time	$^{1}/_{\mathrm{T}}\sum_{n=1}^{N-1}\sqrt{(\mathrm{AP(n+1)\text{-}\,AP(n)})^2+(\mathrm{ML(n+1)\text{-}\,ML(n)})^2}$
Sway area	mm^2/s	Area of the surface enclosed by the CoP path per unit of time	$^{1}/_{2\mathrm{T}}\sum_{n=1}^{N-1}[\mathrm{AP(n+1)*ML(n)}\ -\mathrm{AP(n)*\,ML(n+1)}]$
RMS AP	mm	Root mean square of the antero-posterior time series	$\sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(\mathrm{AP(n)}-\overline{\mathrm{AP}})^2}$
RMS ML	mm	Root mean square of the medio-lateral time series	$\sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(\mathrm{ML(n)}-\overline{\mathrm{ML}})^2}$
Major Axis	mm	Length of the major axis of the smallest ellipse containing the CoP trajectory on the base of support	2a
Minor Axis	mm	Length of the minor axis of the smallest ellipse containing the CoP trajectory on the base of support	2b
Eccentricity	adimentional	Eccentricity of the smallest ellipse containing the CoP trajectory on the base of support	$e=\sqrt{1-\frac{b^2}{a^2}}$



[1]AP and ML are respectively the antero-posterior and the medio-lateral coordinates of the displacement of the CoP on the platform surface.

Captions to illustrations

Fig. 1 – Comparison of posturographic parameters between TBI patients and controls: mean values and standard deviation are shown for each parameter and each trial condition listed in the legenda.

* Significant difference between TBI and controls ($p < 0.05$)

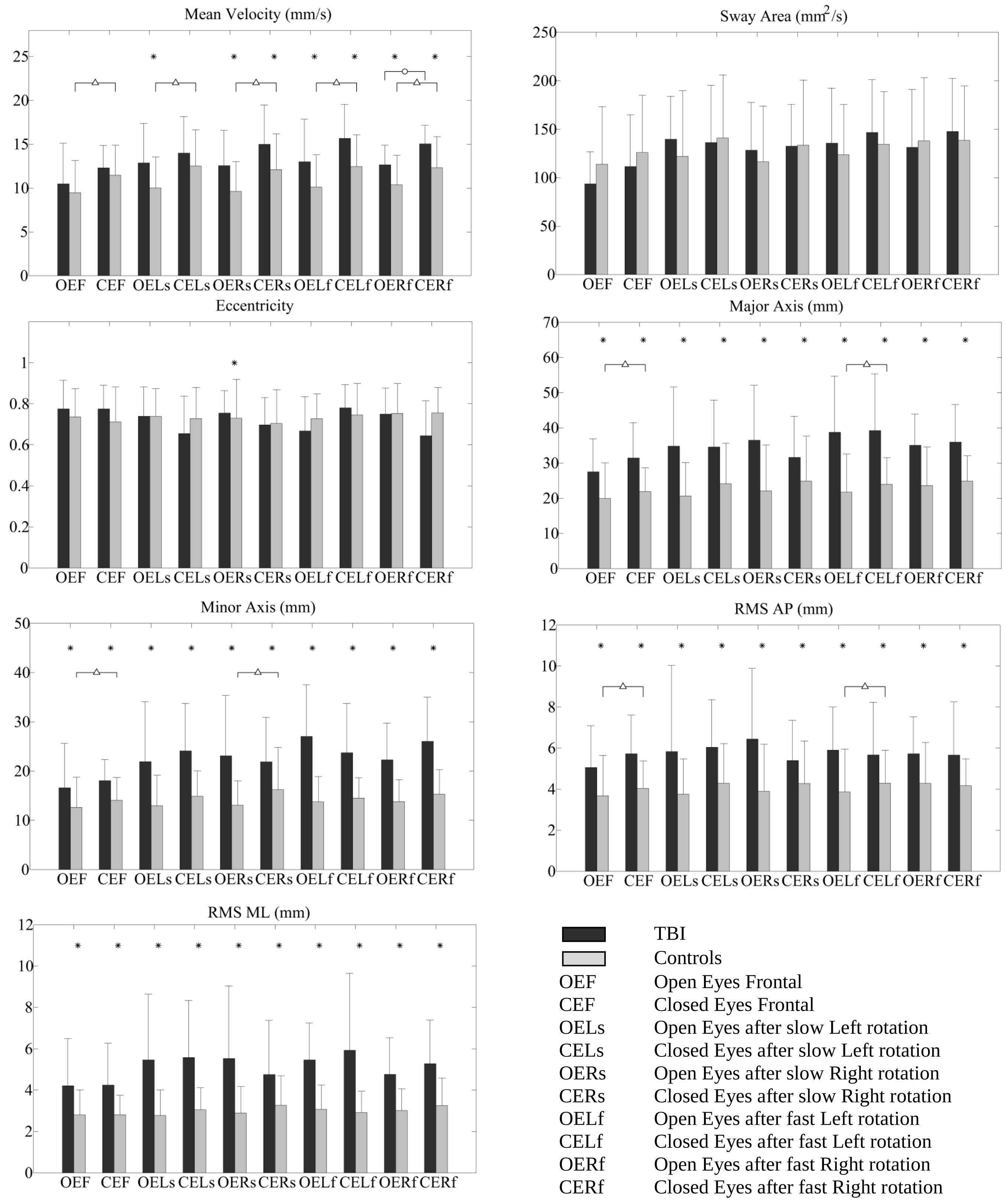
△ Significant difference, in controls, between eyes open and closed ($p < 0.05$)

○ Significant difference, in TBI patients, between eyes open and closed ($p < 0.05$)

Fig. 2 – Wilks' Lambda (Λ) as a function of the number of CoP parameters. 1. The best single parameter (Minor Axis). 2. The best combination of two parameters (Minor Axis and Major Axis). 3. The best combination of three parameters (Minor Axis, Major Axis and RMS AP). 4. The best combination of four parameters (Minor Axis, Major Axis, RMS AP and Eccentricity). 5. The best combination of five parameters (Minor Axis, Major Axis, RMS AP, Eccentricity and Sway Area).

Fig.3 – Scatter plots of the first (C1) vs. the second (C2) canonical variable for controls and TBI patients. (a) Two trials: Open Eyes Frontal (OEF) and Closed Eyes Frontal (CEF). (b) Ten trials: OEF, CEF, OELs, CELs, OERs, CERs, OELf, CELf, OERf, CERf. (c) Two trials: OEF and CEF. TBI patients with different levels of neuro-ophthalmic residual impairment (mild, moderate or severe) and controls. (d) Ten trials. TBI patients with different levels of neuro-ophthalmic residual impairment (mild, moderate or severe) and controls.

Figure 1



■	TBI
□	Controls
OEF	Open Eyes Frontal
CEF	Closed Eyes Frontal
OELs	Open Eyes after slow Left rotation
CELs	Closed Eyes after slow Left rotation
OERs	Open Eyes after slow Right rotation
CERs	Closed Eyes after slow Right rotation
OELf	Open Eyes after fast Left rotation
CELf	Closed Eyes after fast Left rotation
OERf	Open Eyes after fast Right rotation
CERf	Closed Eyes after fast Right rotation

Figure 2

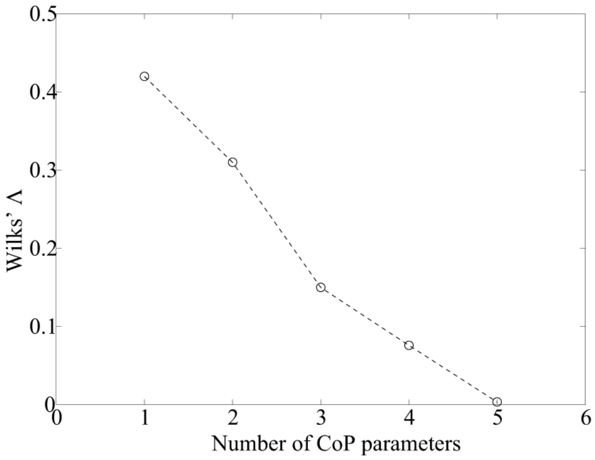
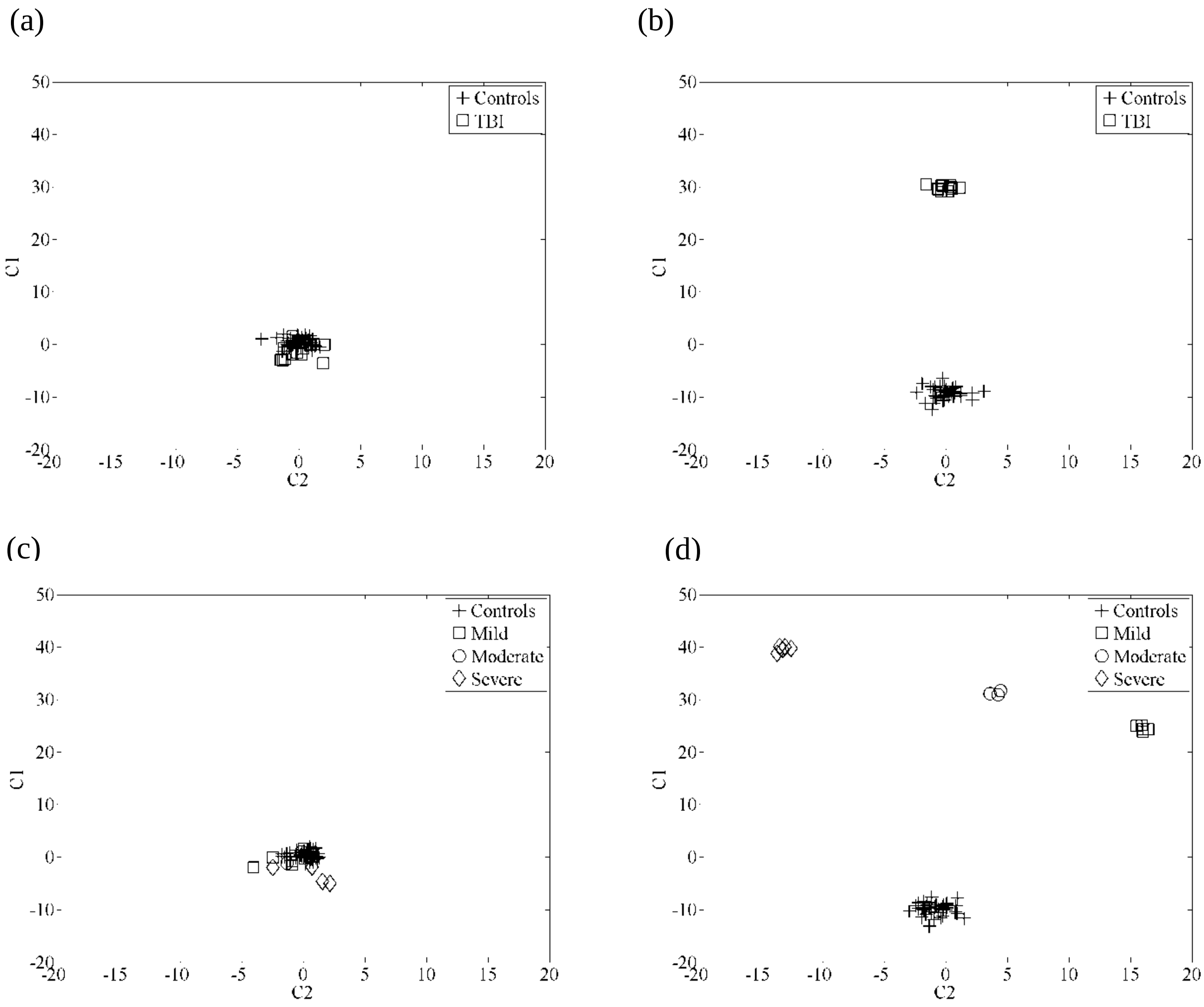


Figure 3


(a)
(b)
(c)
(d)
+ Controls
□ TBI
+ Controls
□ TBI
+ Controls
□ Mild
○ Moderate
◇ Severe
+ Controls
□ Mild
○ Moderate
◇ Severe
C1
C2
50
40
30
20
10
0
-10
-20
-20
-15
-10
-5
0
5
10
15
20

6. Table1

Table 1

Characteristics of Traumatic Brain Injury patients.

Patient	Age (years)	Gender (M/F)	GCS score[1]	CT/MRI	Time (months)[2]	Cause	Residual damage[3]
1	26	M	15	Negative	37	Violence	Mild
2	62	M	14	Positive	130	Traffic accident	Moderate
3	25	M	4	Positive	35	Fall from scaffolding	Severe
4	41	F	8	Positive	42	Traffic accident	Severe
5	28	M	8	Positive	95	Traffic accident	Severe
6	31	M	6	Positive	71	Traffic accident	Severe
7	22	M	Not available	Positive	55	Traffic accident	Mild
8	28	F	9	Positive	64	Fall from horse	Severe
9	31	F	8	Positive	38	Traffic accident	Mild
10	38	F	6	Positive	66	Traffic accident	Moderate
11	38	M	6	Positive	143	Traffic accident	Mild
12	21	M	14	Positive	15	Traffic accident	Mild
13	50	M	14	Positive	17	Fall from scaffolding	Moderate

[1] Lowest Glasgow Coma Scale score after hospitalization.

[2] Time elapsed from head trauma.

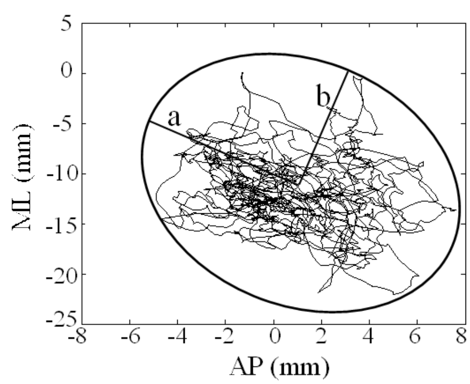
[3] Assessed from the clinical neuro-ophthalmic evaluation of the patients prior to the balance test.

6. Table2

Table 2

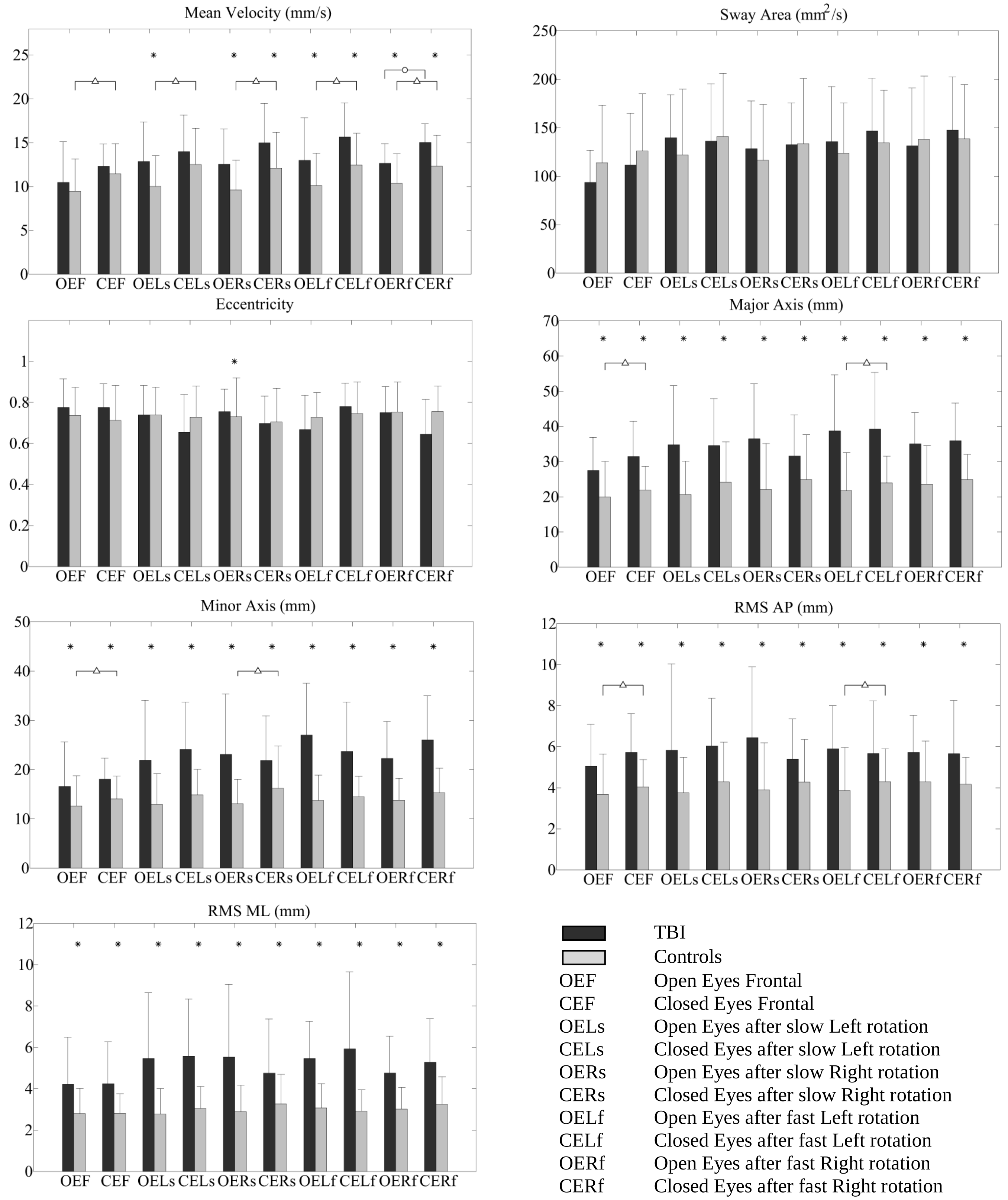
Posturographic parameters.

Parameter	Dimension	Description	Definition[1]
Mean velocity	mm/s	Length of CoP trajectory on the base of support in the unit of time	$^{1}/_{T}\sum_{n=1}^{N-1}\sqrt{(AP(n+1)-AP(n))^2+(ML(n+1)-ML(n))^2}$
Sway area	mm^2/s	Area of the surface enclosed by the CoP path per unit of time	$^{1}/_{2T}\sum_{n=1}^{N-1}[AP(n+1)*ML(n)-AP(n)*ML(n+1)]$
RMS AP	mm	Root mean square of the antero-posterior time series	$\sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(AP(n)-\overline{AP})^2}$
RMS ML	mm	Root mean square of the medio-lateral time series	$\sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(ML(n)-\overline{ML})^2}$
Major Axis	mm	Length of the major axis of the smallest ellipse containing the CoP trajectory on the base of support	2a
Minor Axis	mm	Length of the minor axis of the smallest ellipse containing the CoP trajectory on the base of support	2b
Eccentricity	adimentional	Eccentricity of the smallest ellipse containing the CoP trajectory on the base of support	$e=\sqrt{1-\frac{b^2}{a^2}}$

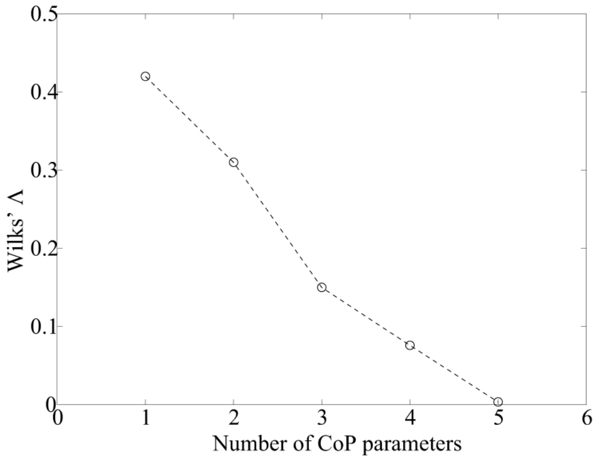


[1] AP and ML are respectively the antero-posterior and the medio-lateral coordinates of the displacement of the CoP on the platform surface.

7. Figure1


Mean Velocity (mm/s)
Sway Area (mm²/s)
Eccentricity
Major Axis (mm)
Minor Axis (mm)
RMS AP (mm)
RMS ML (mm)
OEF CEF OELs CELs OERs CERs OELf CELf OERf CERf
TBI
Controls
OEF Open Eyes Frontal
CEF Closed Eyes Frontal
OELs Open Eyes after slow Left rotation
CELs Closed Eyes after slow Left rotation
OERs Open Eyes after slow Right rotation
CERs Closed Eyes after slow Right rotation
OELf Open Eyes after fast Left rotation
CELf Closed Eyes after fast Left rotation
OERf Open Eyes after fast Right rotation
CERf Closed Eyes after fast Right rotation

7. Figure2



7. Figure3