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Dynamical analysis of balance in vestibular schwannoma patients

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Highlights:

- The complexity in CoP time series is lower in vestibular schwannoma patients
- The ablation of the vestibular tumor lead to an immediate decrease of complexity
- This decrease is followed by a progressive restoration of complexity over time
- The SampEn method is able to highlight the postural effects of vestibular pathology

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Abstract

The analysis of the complexity of postural fluctuations is a recent method for assessing postural control. Complexity relates to the irregularity of the center of pressure time series and characterizes the ability of postural control to meet a changing environment. In our study, we used the sample entropy (SampEn) parameter to evaluate the complexity of postural sway velocity time series in patients with vestibular schwannoma ($n=19$) compared to healthy controls ($n=20$), using the sensory organization test. Patients performed postural assessments

three days before surgical ablation of the tumor, then three times after surgery, at eight, thirty, and ninety days. The control group underwent posturographic tests only once. Our results demonstrated that SampEn values distinguished both groups before surgery only in postural tasks where vestibular afferences significantly contribute to maintaining balance. We also found an immediate decrease of complexity after the surgical resection of the tumor. Our results are in line with the theory of complexity loss of physiological systems stating that reducing the number of their structural components or altering their coupling leads to a decrease in complexity. Finally, our findings showed that progressive restoration of complexity over time was such that no difference was found between the two groups ninety days after surgery, due to the implementation of central adaptive mechanisms and the substitution by other sensory afferences. Thus, the SampEn parameter can highlight the postural effects of vestibular pathology, and complexity analysis appears to be a valuable tool for investigating the temporal structure of CoP time series.

Keywords: Center of pressure; Sample Entropy; Vestibular pathology; Sensory organization test; Changing complexity profile

INTRODUCTION

Postural control relies on feedback from the somatosensory, vestibular, and visual systems [1]. The alteration of one of these systems can lead to increased postural instability. This degradation arises notably in patients with vestibular schwannoma (VS) – a benign tumor affecting Schwann cells surrounding the vestibular nerve – whose slow growth leads to a gradual vestibular dysfunction. This process is progressively compensated by central adaptive mechanisms [2], but the surgical resection of the tumor using a translabyrinthine approach induces unilateral vestibular deafferentation (uVD), leading to a decompensation of the previously compensated situation. Therefore, the uVD results in serious deterioration of balance control, which is progressively restored due to the implementation of central adaptive mechanisms. These could be of vestibular origin and could be the result of learning mechanisms involving neural structures and pathways beyond the vestibular nuclei [3].

In clinical practice, the quantification of center of pressure (CoP) displacement – using classic stabilometric measures such as sway area, sway path or length, mean velocity and variability of CoP fluctuations – is an important outcome to assess balance control [4]. Typically, low values for these parameters are interpreted as indicators of stability [5,6]. The sensory organization test (SOT), a common protocol used to study balance disorders, gives a good knowledge of the time-course of balance compensation in VS [3]. Yet, previous studies highlighted the limitations of the main calculated variable, called equilibrium score (ES), to produce an accurate assessment of balance control. Among these limitations, it was emphasized that the ES computation is based only on the two extreme sway angle values recorded during trial, thus ignoring all other postural fluctuations, and on a 12.5° theoretical range of sway limit of stability without taking into account individual differences (see [7] for a review). These limitations questioned the validity of this method for analyzing postural

fluctuations to distinguish between individuals presenting different health status, and capture accurately the balance compensation in VS patients following the ablation of the tumor. Moreover, conflicting results were reported in the literature concerning the effectiveness of stabilometric measures to highlight the effects of disease [8], as well as to distinguish between populations of various ages [9], and between various experimental conditions [10]. Thus, the assumption of an association between stability of posture and variability of classical parameters is currently debated [11,12]. Newell et al. [12] were the first to advocate not to associate these two concepts systematically. Likewise, Woollacott [13] showed that quantity of displacements of CoP is not correlated to the quality of postural control. These discrepancies prevented us from drawing conclusions regarding factors (e.g. aging and disease) that could modulate these measures and suggest that new methods may be necessary to investigate the changes in postural control.

For several decades new methods based on dynamics systems were increasingly used for characterizing the dynamical features of postural sway [14-17]. Among them, some techniques consist in assessing CoP dynamics through the quantification of the complexity of CoP signals. In this context, complexity is related to regularity, predictability and temporal correlations. Authors developed the theory of complexity loss suggesting that advancing in age and disease – hence the deterioration of physiological systems – seems to be associated with a decrease of complexity of CoP trajectories [15-16]. The two basic principles behind this theory are that (i) the output of a healthy system reveals a type of complex variability associated with long-range correlations and nonlinear interactions; (ii) and this complexity breaks down with aging and disease, reducing the adaptive capabilities of the individual. Over the years, various algorithms were developed to better estimate the entropy (i.e. complexity) of a system [14,18-19]. Recently, Richman and Moorman [17] introduced the sample entropy (SampEn) method to quantify the regularity of time series. The more irregular the signal is,

the higher the SampEn is. The SampEn acts as a good measurement of complexity in many applications such as heart rate variability [17], EMG recordings [20], and postural sway [21]. Therefore, the purpose of this study was to use SampEn (i) to evaluate the effect of vestibular dysfunction on the complexity of CoP trajectories and (ii) to assess the time-course of this complexity (pre- and post-uVD). According to the theory of loss complexity, we assumed that SampEn values decrease with VS compared to controls; and we predict a decrease of complexity in VS patients early after uVD, which will be progressively restored over time.

METHODS

Participants

Nineteen patients (Table 1) with unilateral VS who were scheduled for surgical ablation using translabyrinthine approach took part in the protocol. Patients were compared to a healthy control group ($n=20$). The patients performed postural assessment three days before surgery (BS) and three times after surgery, at eight (AS₈), thirty (AS₃₀), and ninety days (AS₉₀). Participants enrolled in the control group underwent posturographic tests only once. Each participant provided written informed consent prior to participation in the study. All procedures were approved by the local ethics committee and complied with the Declaration of Helsinki.

Table 1 about here

Sensory organization test (SOT)

The SOT was performed on a computerized dynamic balance platform (Equitest[®], NeuroCom System[®], Natus Medical Inc., Pleasanton, CA, USA). The testing consisted of three 20 s trials in six conditions that combined three visual conditions with two platform support conditions: (Condition 1 – C1) patient's eyes were open, or (C2) closed with fixed surrounding and support; (C3) the support was fixed and patient's eyes were open within a sway-referenced

surrounding (i.e. the visual surround follows the anteroposterior sways of the patient's center of gravity); for conditions 4-6, somatosensory information is disrupted by a sway-referenced support (i.e. the support surface follows the anteroposterior sways of the patient's center of gravity) while patient's eyes were open (C4), or closed (C5), or open within a sway-referenced surrounding (C6). Participants were instructed to maintain an upright stance, as stable as possible, and to keep their arms held alongside their body.

The CoP time series was extracted from the Equitest® software at a sampling rate of 100 Hz. The recording lasted 20 s so that the obtained time series had 2,000 samples length. Data were low-passed filtered using a 4th-order Butterworth with a 20 Hz cutoff frequency. As previously suggested in the literature, we used the CoP velocity signals to explore the dynamical features of postural sway [9,21]. CoP velocity was calculated in the anteroposterior (AP) and mediolateral (ML) directions using the first difference of the original data (x_i): $v_i = x_{i+1} - x_i$. Differenced (v_i) time series allow reducing temporal correlations and non-stationarity that usually characterize COP time series and constitute obstacles for the application of nonlinear analysis [22-23].

Sample Entropy (SampEn)

Formally, the calculation of *SampEn* was based on the following equation used by previous authors [24]:

$$SampEn(m, r, N) = -\log \left(\frac{A(r)}{B(r)} \right),$$

where each coarse-grained time series was calculated using the negative natural logarithm of the conditional probability that a time series of length N , having repeated itself for m samples within a tolerance r , will also repeat itself for $m+1$ samples, excluding the selected on itself (i.e. self-matches). $A(r)$ and $B(r)$ were the total number of template matches of length $m+1$

and m , respectively, within a tolerance r . Parameters for the analysis were set at $m=3$ and $r=0.30$ for both AP and ML directions [21,24]. The PhysioToolkit-PhysioNet SampEn software was used for the estimation of the SampEn values [25].

Statistical analysis

All trials were used for subsequent analysis. All data were examined for normality and homogeneity of variance using Skewness, Kurtosis and Brown-Forsythe tests. To determine the healthy profile of complexity of CoP trajectories, a one-way repeated measure ANOVA was used to test for any significant effect of conditions (C1, C2, C3, C4, C5, C6) on the changes in SampEn values in the control group. Two repeated measures ANOVA with group (VS, control) as a between factor and conditions (C1, C2, C3, C4, C5, C6) as within-group factors were performed to compare VS's to controls' complexity of CoP time series at BS and AS₉₀. In addition, repeated measures ANOVA with conditions (C1, C2, C3, C4, C5, C6) and time (BS, AS₈, AS₃₀, AS₉₀) as within-group factors were performed to evaluate the significance of pre- and post-uVD change in complexity of CoP trajectories over time. All p values were computed after Greenhouse and Geisser corrections, yet with uncorrected degrees of freedom. The Tukey's post-hoc test was performed when a more detailed analysis of the main and interaction effects was required. A significance level of $p<0.05$ was used for all comparisons. For further statistical analysis, we used an effect size (η_p^2) which is considered as small if $\eta_p^2 \geq 0.01$, medium ≥ 0.06 , large ≥ 0.14 [26]. This procedure was conducted for each AP and ML direction.

RESULTS

Healthy profile of complexity

The one-way ANOVA showed significant changes in SampEn of both AP- and ML-direction CoP time series between SOT conditions (AP: $F_{(5,295)}=124.70$, $p<0.001$, $\eta_p^2=0.68$; ML:

$F_{(5,295)}=51.13, p<0.001, \eta_p^2=0.46$). Tukey's post hoc test indicated that the complexity of AP time series declined as the degree of task's sensory difficulty increased (i.e. $C1>C2>C3>C4>C5$ and $C6$, all $p<0.05$), except for the $C5$ - $C6$ comparison where the complexity tended to increase in $C6$ compared to $C5$ ($p=0.06$). In ML direction, the SampEn was lower in $C5$ and $C6$ compared to the first four conditions (all $p<0.05$), and was lower in $C5$ than in $C6$ ($p<0.001$). Together, these results indicated that the combination of sway-referenced support, along with absent (i.e. $C5$) or disrupted vision (i.e. $C6$) causes the biggest loss of complexity, notably when participants were instructed to close their eyes.

Before surgical resection of the tumor

The SampEn of both AP- and ML-direction CoP time series in the VS group were significantly lower than those of the control group ($F_{(1,115)}=12.41, p<0.001, \eta_p^2=0.10$; $F_{(1,115)}=14.82, p<0.001, \eta_p^2=0.11$; respectively; Figure 1). The complexity of CoP time series changed significantly according to the conditions (AP: $F_{(5,575)}=311.04, p<0.001, \eta_p^2=0.73$; ML: $F_{(5,575)}=125.19, p<0.001, \eta_p^2=0.52$). ANOVA also revealed a significant group \times conditions interaction ($F_{(1,575)}=29.35, p<0.001, \eta_p^2=0.20$). Detailed analysis showed that the SampEn of AP time series in the VS group was only lower than those of the control group in $C6$ ($p<0.001$), and failed to reveal significant differences in $C5$ ($p=0.07$). In ML direction, the VS group exhibited lower complexity for the fifth and sixth conditions compared to healthy controls (all $p<0.001$). These results suggested that $C5$ and $C6$ are the conditions that are the most likely to disturb the dynamics of the postural system and, consequently, to reflect the specific changes in complexity of patients with vestibular pathology.

Figure 1 about here

Longitudinal changes in complexity profile of VS patients

A main effect of time was found for both AP- and ML-direction CoP time series (AP: $F_{(3,168)}=4.43$, $p<0.01$, $\eta_p^2=0.07$; ML: $F_{(3,168)}=23.33$, $p<0.001$, $\eta_p^2=0.29$; Figure 2), so that the SampEn of AP time series decreased early after uVD (BS vs. AS₈, $p<0.01$), then returned to its pre-uVD level (BS vs. AS₃₀, $p=0.94$; AS₈ vs. AS₃₀, $p<0.05$) and maintained at AS₉₀ (all $p>0.05$; except for AS₈-AS₉₀ comparison, $p<0.05$). The complexity of ML time series followed the same profile than in AP direction, except that the SampEn values also increased significantly at AS₉₀ (all $p<0.05$). A main effect of SOT conditions was also found (AP: $F_{(5,280)}=276.55$, $p<0.001$, $\eta_p^2=0.83$; ML: $F_{(5,280)}=235.55$, $p<0.001$, $\eta_p^2=0.81$). ANOVA revealed a significant time \times conditions interaction (AP: $F_{(15,840)}=6.49$, $p<0.001$, $\eta_p^2=0.10$; ML: $F_{(15,840)}=6.32$, $p<0.001$, $\eta_p^2=0.10$). Pairwise comparisons revealed no significant differences among the four evaluation stages for conditions 2-4 for both AP- and ML-direction CoP time series. However, post hoc tests indicated that SampEn values decreased significantly for the first condition at AS₃₀ and AS₉₀ compared to BS (all $p<0.05$). In addition, detailed analysis showed a significantly higher complexity in C5 and C6 at AS₃₀ and AS₉₀ compared to AS₈ (all $p<0.05$). The SampEn for ML time series also increased in C6 between BS and AS₉₀ ($p<0.001$). These findings highlighted the deterioration of complexity induced by uVD and the gradual balance compensation over time.

Figure 2 about here

Ninety days after surgical resection of the tumor

The SampEn of AP-direction CoP time series in the VS group was significantly lower compared to the control group ($F_{(1,115)}=12.31$, $p<0.001$, $\eta_p^2=0.10$; Figure 3), whereas the results did not show significant differences between groups in ML direction ($F_{(1,115)}=1.10$, $p=0.30$). As pre-uVD, the SampEn values changed significantly according to the conditions (AP: $F_{(5,575)}=227.69$, $p<0.001$, $\eta_p^2=0.66$; ML: $F_{(5,575)}=127.18$, $p<0.001$, $\eta_p^2=0.53$). The analysis revealed a significant group \times conditions interaction (AP: $F_{(5,575)}=3.21$, $p<0.01$,

$\eta_p^2=0.03$; ML: $F_{(5,575)}=12.78$, $p<0.001$, $\eta_p^2=0.10$). However, detailed analysis indicated that the complexity in the AP and ML directions were identical in both groups (all $p>0.05$).

Figure 3 about here

DISCUSSION

The aim of this study was to use the sample entropy method to explore the temporal structure of postural fluctuations in patients with VS compared to healthy controls. The main results are that (i) SampEn values distinguished both groups before uVD only in postural tasks which require a substantial contribution of vestibular afferences in maintaining balance (i.e. C5 and C6); (ii) the surgical resection of the tumor led to an immediate decrease of complexity in CoP time series which was followed by a progressive restoration of complexity over time; (iii) the restoration is such that no difference was found between the two groups ninety days after the surgical removal of the tumor.

The observed decrease in complexity in VS patients is in line with the theory of complexity loss of physiological systems stating that reducing the number of their structural components or altering their coupling leads to a decrease in complexity [18]. In this context, a reduced complexity indicates an inability of the postural system to adapt to a constantly changing environment [27]. This result is consistent with previous studies concerning the impact of other pathologies on postural complexity [18], but contradicts other studies [28]. These discrepancies may be due to (i) the use of velocities and not the displacement time series to explore the dynamics of CoP fluctuations; (ii) the use of different input parameters m and r^1 ; (iii) the use of different tasks (i.e. quiet stance vs. SOT).

¹ In our study, we computed SampEn using classical parameters $m=3$ and $r=0.30$ [21,24]. We performed the same statistical analyses on complexity estimated for r -values ranging from 0.20 to 0.30 with a step of 0.05 and $m=2-3$, revealing similar results.

Before surgery, our results suggested that in the first four conditions the complementarity and the redundancy of the different sensory cues, or the compensation of the dysfunction of the affected inner-ear by the contralateral – healthy – one, allowed VS patients to maintain postural control stability. As the task difficulty changes, the system emphasizes the use of different sensory information according to the constraints set by the situation, and the gain of the different inputs is modified [29]. In the last two conditions, the postural regulation relied almost exclusively on vestibular inputs, and tasks appeared too challenging to allow the normal side of inner ear to perform its compensatory effect, resulting in postural instability and in an increased risk of fall. Immediately after surgery, similar findings were observed (i.e. AS₈), where the complexity of postural fluctuations was deteriorated in the two last conditions. These results could be related to changes in the time elapsed before the activation of regulatory mechanisms of postural control due to the alteration of the vestibular system by the pathology and surgery. Naturally, the central nervous system needs more than eight days to implement adaptive mechanisms effectively. A complementary explanation could be that the two last conditions required higher attentional demands from patients with VS, leading to lower values of complexity. Indeed, Roerdink et al. [24] highlighted the relation between the regularity of CoP time series and the amount of attention invested in posture. More precisely, they demonstrated that the higher the required attentional demand is, the lower the complexity value is. Thus patients with VS may exhibit lower complexity in the last two conditions because they need more attention to be achieved due to the alteration of their vestibular system.

In the medium to long term, it is interesting to note that the complexity for both AP- and ML-direction CoP time series was progressively restored thirty days after surgical resection of the tumor and, for ML-direction in sensory conflict situations, even increased ninety days after surgery. The time-course of complexity recovery was similar to the changes in vestibular

function reported in the literature [3]. The implementation of central adaptive mechanisms, which compensate the high vestibular asymmetry caused by uVD, leads to postural control improvement when facing conditions challenging the vestibular inputs [2]. The lower complexity of ML time series before surgery compared to that observed ninety days later may be due to the tumor growth which led the central nervous system to implement compensation mechanisms that were however still unable to provide a postural control similar to that of healthy subjects [30]. Moreover, these compensation mechanisms can reduce the amount of attention paid to posture, thus leading to an increase of complexity over time [24].

As mentioned in the introduction, SOT is currently one of the main tools used to study balance disorders. However, the method based on the calculation of ES is affected by limitations. Notably, ES is a linear parameter related to the amplitude of only the two extreme sway angle values. In contrast, complexity is a nonlinear parameter that is not sensitive to the amplitude of postural fluctuations. Indeed, a decrease of postural stability could be associated with a decrease of postural fluctuations amplitude and with reduced complexity. Moreover, by taking into account the full history of CoP fluctuations, the SampEn method could provide insights into the ability of the central nervous system to adjust the postural control to a constantly changing environment in real time, thus providing a finer-grained analysis of the patients' ability to use sensory information to regulate their posture.

CONCLUSION

As a conclusion, our results revealed changes in complexity in patients with VS as well as healthy controls according to the constraints – information available for postural regulation – set by conditions. Moreover, a decrease in complexity of CoP fluctuations was found in VS patients compared to healthy controls, especially in situations involving vestibular inputs to maintain balance. In addition to this, the surgical resection of the tumor leads to a decrease in complexity of CoP displacement, which is followed by the restoration of complexity over

time due to the implementation of central adaptive mechanisms and the substitution by other sensory afferences. Thus, the SampEn method can highlight the postural effects of vestibular pathology, and complexity analysis appears to be a valuable tool for investigating the temporal structure of CoP time series.

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Figure Legends

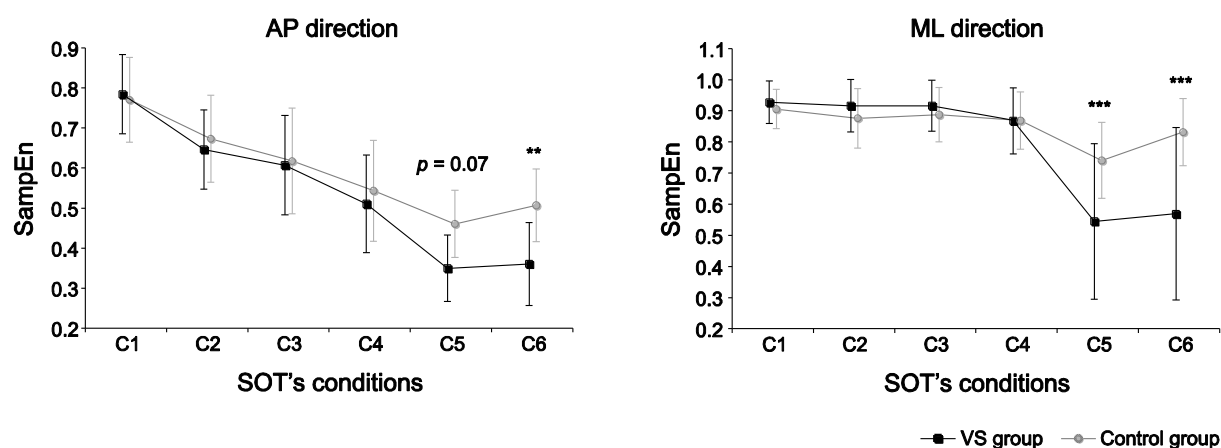


Fig.1 Complexity profile under the six SOT conditions comparing VS group to control group before surgery. *Error bars* represent standard errors. *Indicates significant differences (** $p < 0.01$; *** $p < 0.001$) between the two groups.

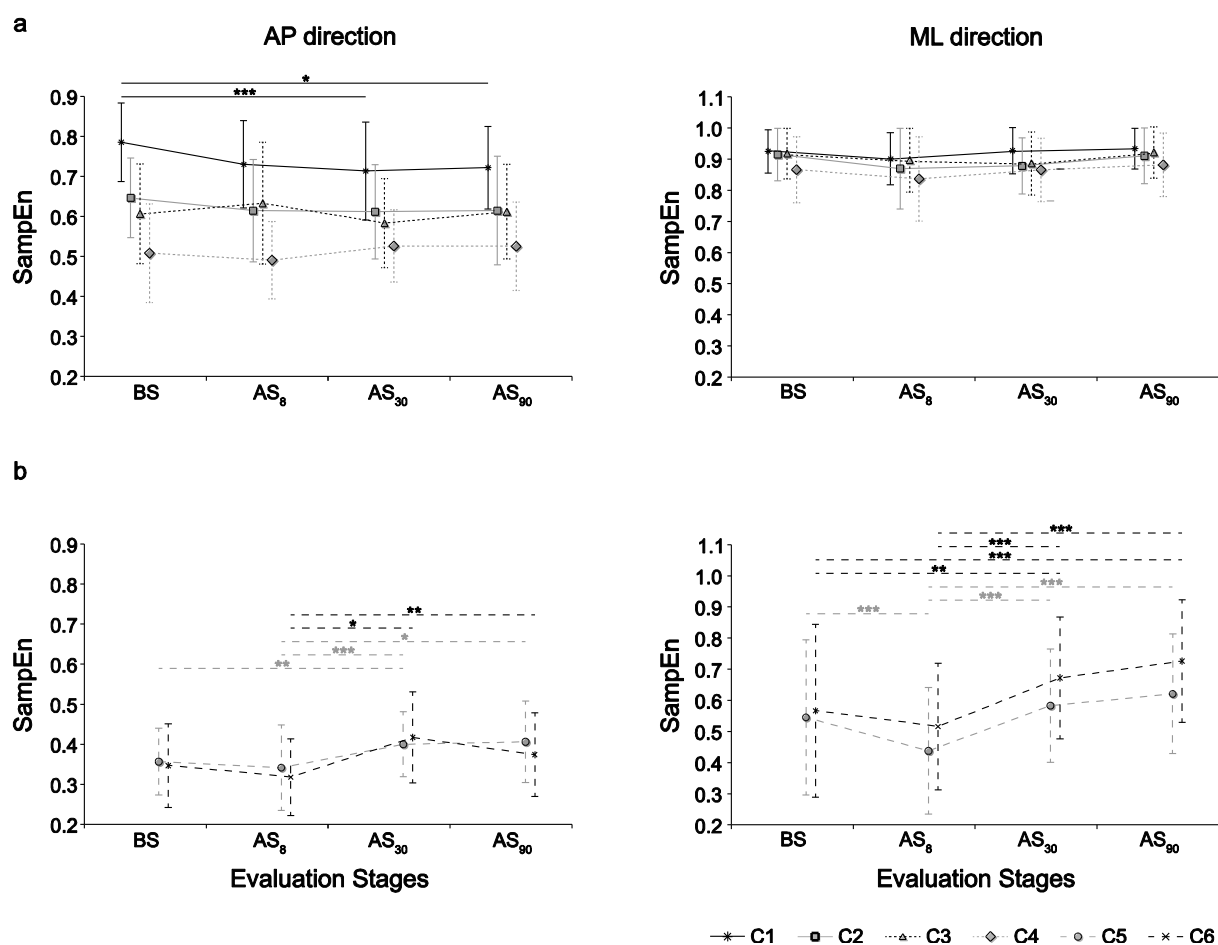


Fig.2 Complexity profile of VS group under **a** the first four SOT conditions and **b** the last two ones among the four evaluation stages. *Error bars* represent standard errors. *Indicates significant differences (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

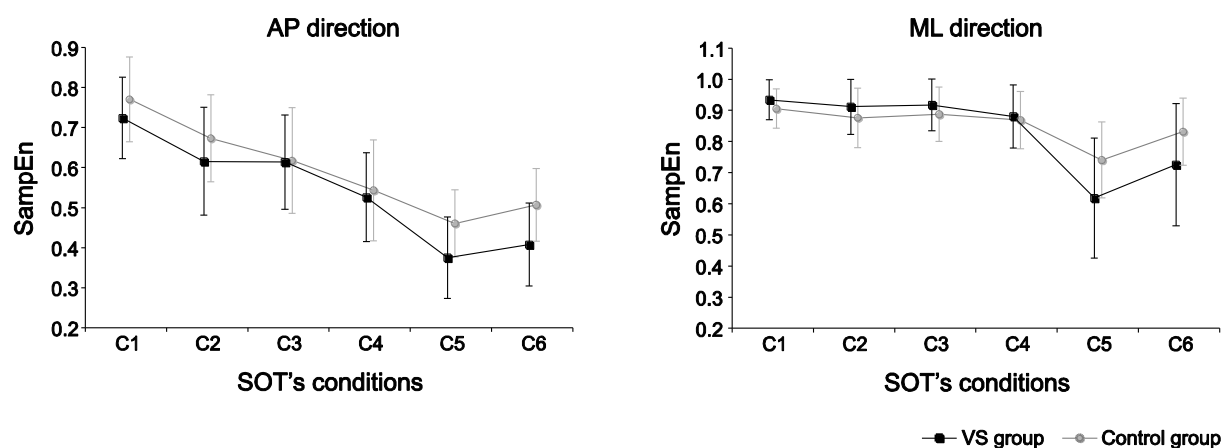


Fig.3 Complexity profile under the six SOT conditions comparing VS group to control group ninety days after surgery. *Error bars* represent standard errors. No significant differences were found between the two groups.

Table 1. Participants' characteristics (Mean \pm Standard Deviation)

Variables/groups	VS patients; $n = 19$	Healthy controls; $n = 20$	p
Age (yrs)	53.4 \pm 11.5	50.9 \pm 12.0	0.21
Height (cm)	169.3 \pm 11.2	173.4 \pm 8.8	0.78
Weight (kg)	74.6 \pm 15.8	73.2 \pm 13.5	0.51

The p value is based on Student's t-test for groups.