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The impact of age on both BIS values and EEG bispectrum during anesthesia with sevoflurane in children.

Eric Wodey [1], MD, PhD.
Olivier Tirel [2], MD
Jean Yves Bansard [3], Eng.
Anne Terrier [2], MD
Charles Chanavaz [2], MD
Rupert Harris[2], MD
Claude Ecoffey [1], MD
Lotfi Senhadji [4], PhD.

1: Professor, Department of Anesthesiology and Surgical Intensive Care.
2: Resident, Department of Anesthesiology and Surgical Intensive Care.
3: Statistician, LTSI-INSERM U 642
4: Professor, LTSI-INSERM U 642

Received from the Departments of Anesthesiology and Surgical Intensive Care 2, Hospital Pontchaillou and from LTSI (Laboratoire Traitemenent du Signal et de l'Image), INSERM U642, Groupe de Recherche Cardio-vasculaire (EA 3194), University of Rennes 1, Rennes, France.

Corresponding author : Pr Eric Wodey, Service d'Anesthésie - Réanimation Chirurgicale 2, Centre Hospitalier Regional et Universitaire, 2 rue Henri le Guilloux, 35033 Rennes Cedex 9, France. E mail: eric.wodey@chu-rennes.fr

Short Title: Impact of age on BIS and EEG bispectrum during anesthesia with sevoflurane in children.

Implication: This study reports the relationship between the age of children and the values of the bispectrum of the EEG and of the BIS (Aspect™) during anesthesia with sevoflurane, and suggests that modification of the current BIS algorithm is necessary for it to accurately follow changes in depth of anesthesia in children.

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Abstract

The aim of this study was to evaluate the potential relationship between age, BIS (Aspect™) and the EEG bispectrum during anesthesia with sevoflurane. BIS and raw EEG sampled at 400 Hz were recorded at a steady state of 1 MAC sevoflurane in 100 children, and during a decrease from 2 MAC to 0.5 MAC in a sub-group of 29 children. The bispectrum of the EEG was estimated on successive epochs of 20 seconds using MATLAB© software, independently of the Aspect™ device. For analysis, the bispectrum was divided into 36 frequencies of coupling (P_i) - the MatBis. A multiple correspondence analysis (MCA) was used to establish an underlying structure of the pattern of each individual's MatBis at the steady state of 1 MAC. Clustering of children into homogeneous groups was conducted by a hierarchical ascending classification (HAC). The level of statistical significance was set at 0.05. At the steady state of 1 MAC sevoflurane, the BIS values for all 100 children ranged from 20 to 74 (median 40). Projection of both age and BIS value recorded at 1 MAC (T10) onto the structured model of the MCA showed them to be distributed along axis F1 of this model. In contrast, projection of children's position during the decrease in sevoflurane concentration was linked to axis F2. At 1 MAC sevoflurane, six homogeneous groups of children were obtained through the HAC. Groups 5 (30 months; range 23-49) and 6 (18 months; range 6-180) were the younger children and group 1 (97 months; range 46-162) the older. Groups 5 and 6 had the highest median values of BIS (54; range 50-59)(55; range 26-74) and the group 1 the lowest values (29; range 22-37). The EEG bispectrum, as well as the BIS (Aspect XP™) measured at 1 MAC sevoflurane appeared to be strongly related to the age of children.

Key Words: Monitoring, EEG Bispectrum, BIS, Sevoflurane, Anesthesia, Children

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Introduction:

The correlation between the Bispectral Index Scale (BIS) values obtained from the Aspect™ device and end-tidal concentrations of sevoflurane has been reported in only a few studies in children[1-3]. In the majority of these studies, a wide range of BIS values has been reported for each level of end-tidal concentration of sevoflurane. Given that, to our knowledge, only adult data was used by Aspect™ to derive the BIS index, it is possible that the wide range of BIS values found in children for each level of end-tidal concentration of anesthetic agent could be due to a physiological difference between the EEG of the adult and that of the child.

The algorithms of Aspect™ are confidential for commercial reasons, and this makes it difficult for clinicians or those involved in research to interpret and explain the scatter of BIS values reported in children. However, in contrast to the BIS, the bispectrum values of the EEG can easily be estimated with various signal processing methods. The result of this calculation is a matrix of quantitative variables corresponding to the power of various couplings of frequencies. All parameters constituting this matrix are well known and can be used to perform various static or dynamic analyses during anesthesia.

The aim of this study was to evaluate the potential relationship between the age of children and the values of the bispectrum of the EEG and of the BIS (Aspect™) during anesthesia with sevoflurane, and highlight any consequent implications regarding the use of BIS in children.

Patients and Methods:

100 children who required elective surgery were studied following approval by the Human Studies Committee and after informed parental consent was obtained. Inclusion criteria were ASA PS I, age 6-180 months, and consent for inhalation induction of anesthesia. Exclusion

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criteria included neurologic disease and any centrally acting agents. Patients were not premedicated. Anesthesia was induced with sevoflurane at 8% (inspired) in oxygen, without nitrous oxide and intravenous access gained. Spontaneous respiration continued until endotracheal intubation was possible without the use of muscle relaxants. The children were then ventilated. Anesthetic gas and carbon dioxide concentrations were measured continuously in order to maintain normocapnia.

After intubation, expired Sevoflurane concentration was stabilized at 2 MAC (age corrected) [4] and maintained during 4 minutes for all children. EEG leads (3M Red Dot Silver/Silver Chloride model 2269T) were placed as close as possible to the pediatric BIS lead placement (Aspect™). Recording was then started (T0) and sevoflurane concentration was decreased to 1 MAC corrected for age [4]. Recording was performed continuously for 10 mins until stabilization of end-tidal concentration (T10) [4]. After this first phase of stabilization at 1 MAC, for a sub-group of 29 children, sevoflurane concentration was then secondarily decreased from 1 MAC to 0.5 MAC (age-corrected) and recording continued for another 10 minutes until stabilization of end-tidal concentration at 0.5 MAC (T20).

ECG and EEG were recorded continuously and sampled at 400 Hz (PowerLab™). Independently, Bispectral Index Scale (BIS; Aspect XP™) was recorded every minute. Systolic blood pressure (SBP) was measured every minute using an automated blood pressure cuff. The heart rate (HR) was obtained from the measurement of ECG cardiac cycle lengths (R-R interval). All recordings were performed before surgery and without stimulation. EEG was high-pass filtered, and the power spectrum and the bispectrum of the EEG were estimated on successive epochs of 20 seconds using MATLAB© software (The Mathworks Inc, Natick, USA) and Matlab function from the Higher Order Signal Analysis toolbox (bispecd.m with frequency smoothing using 11 as the length of the side of the square of the optimal Rao-Garb

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window and a frequency resolution about 0.78 Hz). For analysis the resulting matrix of the bispectrum was divided into 36 blocks of frequencies of coupling (P_i), and denoted by MatBis (Figure 1). An individual value for each of the 36 4Hz-by-4Hz blocks was derived, this corresponding to the mean of the bispectrum for each block. Thus, each child is represented by 36 descriptors evolving over the time of recording.

Firstly, a multiple correspondence analysis (MCA) was used to establish an underlying structure of the pattern of each individual's EEG bispectrum (MatBis) [5,6]. For this purpose, the EEG acquired during the last epoch of the stabilization phase (T10) was used. Thus, positions of children on the structured model of the MCA are related to the values of their MatBis derived at the steady state at 1 MAC of sevoflurane (see appendix for further explanation). To explore the relationships between a child's clinical variables and those resulting from their EEG bispectrum, the distribution of the considered variables (age, weight and BIS recorded at 1 MAC) were determined in the structured model of the MCA (again for more details, see appendix) [7]. Any correlation between clinical variables and children's coordinates on the two most dominant axes (F1 and F2) of the MCA model were evaluated by means of a Spearman test.

Secondly, the clustering of children into homogeneous groups was conducted by means of an hierarchical ascending classification (HAC) (see appendix for details) [8]. Comparison of the clinical characteristics of each group of children obtained by the HAC at 1 MAC of sevoflurane was performed with a Mann-Whitney test.

In order to explore the effect of change in sevoflurane concentration on the EEG bispectrum, the change in position in the structured model of the MCA during the decrease of sevoflurane

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concentration was analyzed for a sub-group of 29 children. This change in position within the structured model of MCA was determined by changes in the MatBis (i.e. EEG bispectrum) during the decrease from 2 MAC to 0.5 MAC sevoflurane.

A Kruskal Wallis test was conducted to investigate the effect of decrease in sevoflurane on various parameters. A Wilcoxon test was used to establish significant changes in parameters at various points during the decrease in sevoflurane. A probability value less than 0.05 was considered significant. All statistical analyses were performed with the BI© LOGINSERM 1979/1987 software.

Results

In the whole population studied (n=100), median (range) of age and weight were 50 months (6-180) and 18 kg (10-55) respectively. In the sub-group 29 children for which sevoflurane was decreased from 2 MAC to 0.5 MAC, age and weight were 55 months (15-180) and 17 kg (7-55) respectively.

At the steady state at 1 MAC of sevoflurane, in the whole population of 100 children, the BIS values ranged from 20 to 74 (median 40). For the sub-group of 29 children, the changes in BIS and end-tidal sevoflurane concentration over time are represented in Figure 2. This shows that during the first decrease of sevoflurane (from 2 MAC to 1 MAC), BIS index did not change significantly (T0 versus T10) whereas during the second decrease from 1 MAC to 0.5 MAC, the BIS increased significantly.

The structured model of the MCA obtained with the MatBis of all 100 children at the steady state of 1 MAC sevoflurane is shown in Figure 3 (top). The contribution of all 36 frequencies

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of coupling (P_i) of the MatBis to the position of each child on the structured model of MCA at 1 MAC sevoflurane is displayed in Figure 3 (bottom). The arrows on Figure 3 (bottom) visually represent the influence of the most discriminating frequencies of coupling as determined by the statistical software. Thus, it can be seen that high values in P1, P2 and P9 and low values in P27 will position a child towards the right hand side of Figure 3 (top); and high values in P2, P16 and P17 with low values in P15 and P27 will position a child towards the upper half of Figure 3 (top).

For the whole population, age, weight and BIS recorded at steady state 1 MAC sevoflurane (T10) were distributed along axis F1 of the structured model (Figure 4).

The correlation coefficients at the steady state of 1 MAC sevoflurane were calculated both between the clinical parameters themselves (age, BIS and end-tidal sevoflurane concentration) and between the clinical parameters and children's coordinates on axes F1 and F2 of the MCA model (Table 1 - top). Both age and BIS were significantly correlated to axis F1, and showed no correlation with axis F2. Furthermore, we found that the value of BIS was inversely related to age.

By looking for similarities in the patterns of the individual MatBis of all 100 children at 1 MAC sevoflurane, six homogeneous groups of children were obtained through the hierarchical ascending classification. Age, weight, BIS and other clinical data recorded in these six groups of children at 1 MAC sevoflurane are summarized in table 2. Groups 5 and 6 correspond to the younger children, and group 1 to the older children. Similarly, groups 5 and 6 have the higher median values of BIS and the group 1 the lower values. The projection of

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these groups onto the structured model of the MCA (figure 3 – top) also confirmed that age and BIS were principally linked to axis F1.

Positions in the MCA model of the sub-group of 29 children for whom sevoflurane was decreased from 2 MAC to 0.5 MAC, are shown in Figure 5. Each dot represents the centre of distribution for all 29 children at each minute interval during the decrease in sevoflurane. The distribution of the position of these 29 children along axes F1 and F2 during the decrease in Sevoflurane concentration is shown in detail in Figure 6. Table 1 (bottom), shows the correlation coefficients calculated between BIS and end-tidal sevoflurane concentration at each minute during the decrease of sevoflurane concentration. It also shows the correlation coefficients calculated between these two clinical parameters and children's coordinates on axes F1 and F2 of the MCA model during the decrease of sevoflurane concentration. BIS remained mainly correlated to axis F1, in contrast end-tidal sevoflurane concentration was predominantly correlated to axis F2.

Discussion

The EEG bispectrum as well as the BIS (Aspect XP™) measured at 1 MAC sevoflurane appears to be strongly related to both the age and weight of children. This relationship could explain in part the large range of BIS values found in children at 1 MAC sevoflurane.

To our knowledge, few studies have reported the relationship between sevoflurane concentration and BIS values (Aspect™) in children. In 2000, Denman et al. reported the relationship between end-tidal sevoflurane concentration and BIS in 22 patients [1]. Even though the authors found that BIS decreased as sevoflurane concentration increased in both infants and older children, a large scatter of BIS values was seen at each level of

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concentration. For example, at 2% sevoflurane, BIS index ranged from 0 to 65 in older children and from 30 to 70 in infants. McCann et al. reported a similar scatter of BIS values in their study of 30 children of 12 to 72 months of age, values ranging from 20 to 60 at 2% sevoflurane [2]. In another prospective study, Degoute et al. compared BIS values recorded in both children and adults at various specific periods during sevoflurane anesthesia [3]. The age of children ranged from 3.5 to 13 years. At the time of both loss of movement and skin incision, the standard deviation of BIS values found in adults was approximately half of that found in children. The results of these studies are similar to our findings. Indeed, a large scatter of BIS values was found in our children at the steady state at 1 MAC of sevoflurane. For the whole population of 100 children, the BIS values ranged from 20 to 74.

Thus at this time, it appears uncertain that BIS can accurately determine the depth of anesthesia in children at 1 MAC sevoflurane. However, we can explain the large range of BIS values found in children by the effect of age on the EEG. Using a MCA model derived from the MatBis of 100 children at the steady state of 1 MAC sevoflurane, we have found that age is linked to certain frequencies of coupling of the EEG bispectrum - axis F1 of the MCA (Figures 4, 3 and table 1, see appendix). Furthermore, BIS values were also correlated (inversely) to this axis (Figure 4 and Table 1). The fact that both the BIS and age were linked to the same axis of a model derived only from the bispectrum of the EEG suggests that one of the components of the BIS, which makes it age dependent in children, is the EEG bispectrum itself.

By comparing groups of children obtained through the hierarchical ascending classification (obtained by finding similarities in the patterns of all the individual EEG bispectra) we were

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able to confirm statistically that the MatBis calculated in children at 1 MAC sevoflurane was dependent on age (Table 2).

During the decrease in sevoflurane concentration in the sub-group of 29 children, as a result of the change in each child's EEG bispectrum, children moved mainly along axis F2 of our MCA model (Figures 5 and 6). It was only at less than 1 MAC sevoflurane that we saw any change in position along axis F1. This result appeared surprising, knowing that BIS was mainly linked to axis F1 of the MCA model, and suggests that the BIS values are not always related to change in sevoflurane concentration in children, i.e. depth of anesthesia (Table 1). Therefore, a more careful analysis of the change in children's position in the MCA model during the decrease in sevoflurane concentration is necessary (see appendix).

During the decrease from 2 MAC to 1 MAC sevoflurane, children's positions in the MCA model moved mainly vertically upwards along axis F2 (Figures 5 and 6). Given that few changes (or even a reverse change) in the position of children along axis F1 were seen during this first decrease in sevoflurane concentration from 2 MAC to 1 MAC (figures 5 and 6), it is not surprising that no significant changes were noted in BIS values (Figure 2), as the BIS is mainly linked to axis F1 of the MCA model at the steady state of 1 MAC sevoflurane. In the same way, even though no statistical comparison was performed by the authors, no significant change in BIS occured between 3% and 4% sevoflurane in the relationship reported by Denman et al [1]. During the second decrease from 1 MAC to 0.5 MAC sevoflurane in our study, changes in children's positions in the MCA model continued vertically upwards along axis F2 (Figures 5 and 6), but were now associated with a significant horizontal movement to the left along axis F1. During this second decrease in sevoflurane concentration, a significant increase in BIS value was noted (figure 2) corresponding to the movement of children along

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axis F1. Thus, the link established between the BIS and axis F1 of the MCA model at 1 MAC sevoflurane was confirmed.

These results do not challenge the potential ability of BIS to distinguish the changes occurring in the EEG during arousal from light anesthesia in children. Indeed, Davidson et al. have reported significant changes in BIS value in children for small changes in sevoflurane concentration during arousal, with BIS values of 62.5 ±8.1, 70.8 ±7.4 and 74.1±7.1 for sevoflurane concentrations of 0.9%, 0.7% and 0.5% respectively [9].

In adults, the relationship between the concentration of inhalational anesthetic agent and BIS value is well described by sigmoid curves [10]. Theoretically, these curves help us understand why BIS monitoring cannot accurately determine depth of anesthesia for high concentrations of anesthetics. Our results show that the algorithms that determine the BIS index could themselves be the determinant of the shape of these sigmoid curves. In our study, using all 36 frequencies of coupling of the EEG bispectrum (MatBis) we were able to distinguish changes induced by the decrease of sevoflurane from 2 MAC to 1 MAC by the change in position of children along axis F2 of the MCA model (Figure 6). The BIS monitor failed in this respect (Figure 2). We suggest that if an additional frequency of coupling were added to the BIS algorithm, this could improve the accuracy of BIS at deeper levels of anesthesia.

Indeed, our results show that the lower frequencies of coupling (< 8 Hz), such as P_1, P_2 or P_9, and the higher frequencies of coupling (> 16Hz), such as P_{27}, are the main determinants of the position of children along axis F1 of the MCA model (Figure 3, bottom). The relationship established between the BIS values and axis F1 at 1 MAC sevoflurane (Figure 4 and Table 1), suggests that the frequencies of coupling P_1, P_2, P_9 and P_{27} are the main frequencies of the

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EEG bispectrum used in the algorithm of Aspect™ to calculate the BIS. However, the structured model of the MCA shows the same frequencies of coupling were also linked to the age of children at 1 MAC sevoflurane. It should be noted that the frequencies P_1, P_2 and P_9 of the MatBis also correspond to the frequencies of the classic Delta and Theta bands of the EEG and the frequency P_{27} is included in the Beta band. The changes that occur in the power spectrum of the Delta, Theta and Beta bands with changes in concentration of isoflurane, desflurane and sevoflurane, have been reported in adults [11]. As the concentration of these inhalational agents is decreased the power spectrum in Delta and Theta bands also decreases, whereas the power spectrum in Beta band increases. Given that the current BIS algorithm is based on adult EEG data, it does not appear surprising that axis F1 of our MCA model (mainly dependant on the frequencies of coupling P_1, P_2, P_9 and P_{27}) is linked to the BIS. A recent study reports that the bispectral analysis gives no more information than the power spectral-based analysis. It is therefore possible to suggest that significant changes in the bands of frequencies of the classical spectrum that correspond to P_1, P_2, P_9 and P_{27} would cause BIS to change significantly [12].

In addition, our data shows that in children, changes induced by the decrease in sevoflurane concentration from 2 MAC to 0.5 MAC can be followed using different frequencies of coupling that are mainly linked to changes along axis F2 of the MCA model (P_{16} or P_{17}, Figure 3 - bottom). The fact that age and weight were both linked to axis F1 allows us to establish that using the MatBis: 1) it is possible to discriminate mathematically between the effect of age and the effect of change in sevoflurane concentration on the EEG bispectrum and, 2) it might be possible to determine more accurately the depth of anesthesia in children when concentrations of sevoflurane are higher than 1 MAC. However, further studies are needed to

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see whether these results remain valid with other anesthetics agents, or in the adult population.

Conclusion

The EEG bispectrum (MatBis) as well as the BIS (Aspect XP™) measured at 1 MAC sevoflurane appear to be strongly related to both the age and weight of children. Our results clearly demonstrate that it is mathematically possible to discriminate between the effect of age and the effect of change in sevoflurane concentration on the EEG bispectrum in children. Indeed, using specific frequencies of coupling extracted from MatBis, it was possible to find changes in the EEG induced by a decrease of sevoflurane from 2 MAC to 0.5 MAC, independently of age, in contrast to the BIS of Aspect™.

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Figure 1: An example of the representation of the 36 frequencies of coupling (P_i) of the bispectrum calculated every 20 sec for one child's EEG (MatBis).

Figure 2: Top: Expired sevoflurane concentration in the sub-group of 29 children during recording. Bottom: BIS index recorded during the decrease of sevoflurane concentration in the sub-group of 29 children. TO: at 2 MAC (4 mins after intubation); T10: at the steady state at 1 MAC; T20: at the steady state at 0.5 MAC. Box plot (Range; 10-90th centile; 25-75th centile; Median). * vs T0: p< O.05; †vs T10 (1 MAC): p< 0.05.

Figure 3: Top: Structured model of the MCA obtained with the pattern of each individual EEG bispectrum, also showing the groups of children obtained through the hierarchical ascending classification. Bottom: Representation of the 36 frequencies of coupling (P_i) of the MatBis used to establish the structured model of the MCA. Arrows represent the contribution of the main P_i to the position of each child in the structured model of MCA. The units of axes F1 and F2 are arbitrary - representing distance between children as a function of the similarity or difference in their EEG bispectra at 1 MAC.

Figure 4: Projection of age, weight and BIS index values (recorded at the steady state at 1 MAC sevoflurane) onto the two dominant axes (F1 and F2) of the structured model of the MCA . The units of axes F1 and F2 are arbitrary - representing distance between children as a function of the similarity or difference in their EEG bispectra at 1 MAC.

Figure 5: Change in position in the structured model of MCA of the sub-group of 29 children during the decrease of sevoflurane. From higher concentration (2 MAC) to 1 MAC (T10; steady state) and from 1 MAC to 0.5 MAC (T20: steady state). Each point represents one minute. The units of axes F1 and F2 are arbitrary.

Figure 6: Position of the sub-group of 29 children on axis F1 (top) and axis F2 (bottom) of the structured model of the MCA during the decrease of sevoflurane concentration over time. T0: 2 MAC; T1 and T5 intermediate time ; T10: steady state at 1 MAC; T15 intermediate time; T20: steady state at 0.5 MAC. Box plot (Range; 10-90th centile; 25-75th centile; Median). * vs T0: p< O.05; †vs T10 (1 MAC): p< 0.05.

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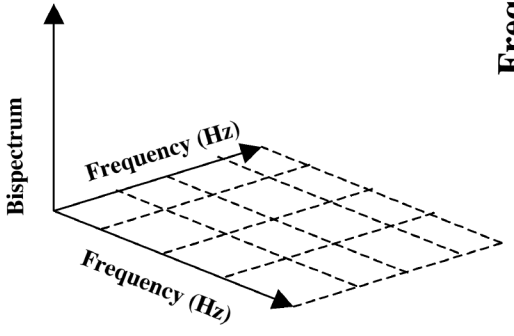
Table 1: Correlations coefficient calculated between clinical variables themselves and between clinical variables and children's coordinates on the two most dominant axes (F1 and F2) of the MCA model at the steady state 1 MAC sevoflurane in all children (Top; n=100) and during the decrease in sevoflurane concentration from 2 MAC to 0.5 MAC in the sub-group of 29 children (Bottom; n= 580: 29 readings at each minute interval from T0 to T20)

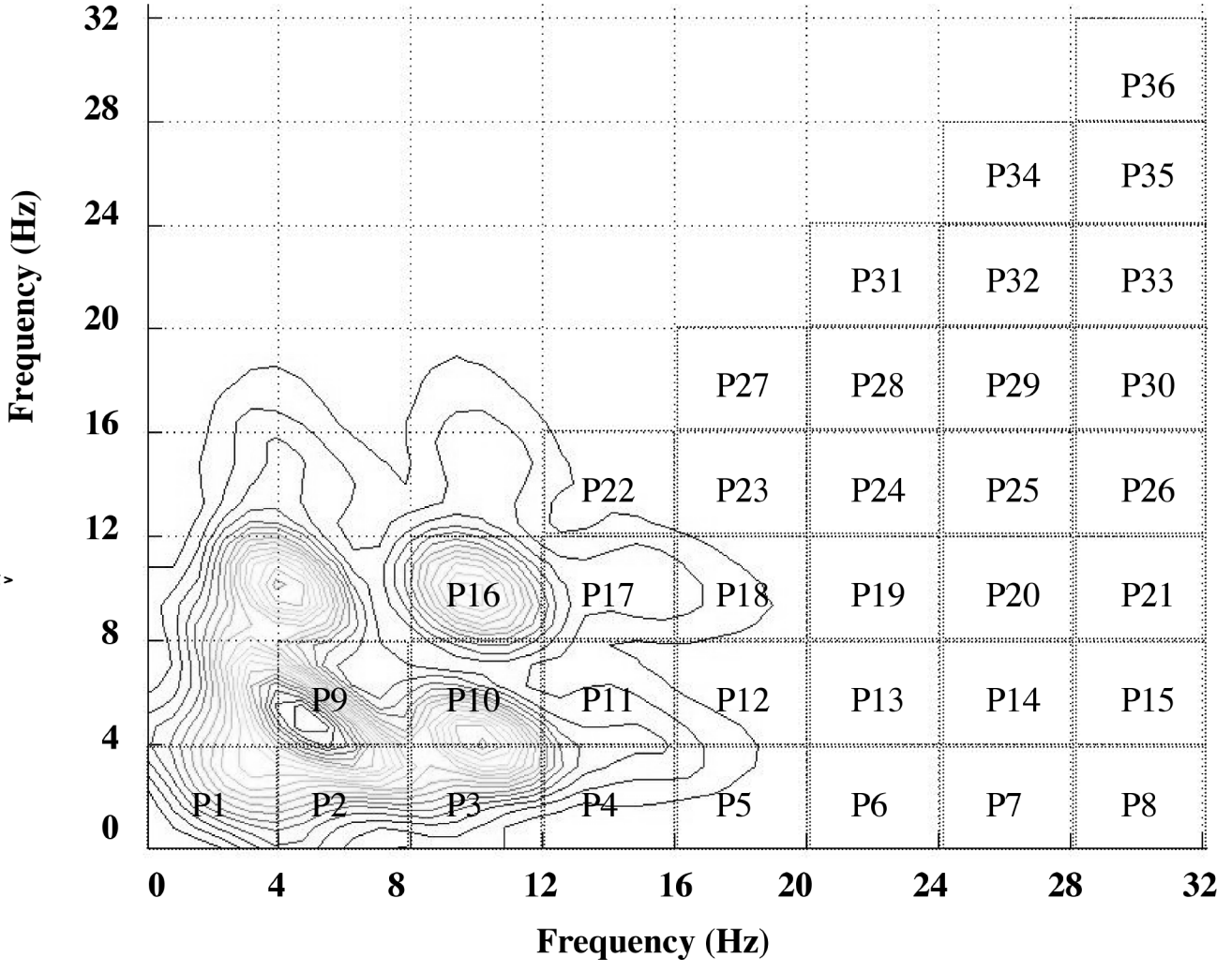
Table 2: Groups of children obtained through the hierarchical ascending classification, according to similarities in their individual EEG bispectra. HR: heart rate; MAP: mean blood pressure; SEVO: end-tidal expired sevofurane concentration. BIS: Bispectral Index Scale (Aspect™). * vs 6; £ vs 4; # vs3; † vs 2: $p<0.05$.

Steady state at 1 MAC of sevoflurane			
Variable	by Variable	Spearman Rho	Prob >|Rho|
F1	**Age**	**0.726**	**<.0001**
BIS	Sevo E	0.470	<.0001
F2	*Age*	*0.181*	*0.0717*
F2	*BIS*	*-0.020*	*0.8423*
F2	sevo E	-0.230	0.0215
F1	sevo E	-0.474	<.0001
Sevo E	**Age**	**-0.620**	**<.0001**
F1	**BIS**	**-0.709**	**<.0001**
BIS	**Age**	**-0.716**	**<.0001**

During sevoflurane concentration decrease			
Variable	by Variable	Spearman Rho	Prob >|Rho|
F2	BIS	0.475	<.0001
F1	Sevo E	0.315	<.0001
F2	F1	-0.286	<.0001
BIS	Sevo E	-0.417	<.0001
F2	**Sevo E**	**-0.649**	**<.0001**
F1	**BIS**	**-0.709**	**<.0001**

Groups	1 (n = 10)	2 (n = 16)	3 (n = 23)	4 (n = 18)	5 (n = 4)	6 (n = 29)
AGE (month)	97*£#† (56-162)	58*£ (36-134)	62*£ (15-129)	37* (21-62)	30 (23-49)	18 (6-180)
Weight (kg)	25*£ (13-49)	18*£ (11-33)	20*£ (10-44)	14* (10-23)	15 (12-18)	11 (8-55)
HR ($b.min^{-1}$)	104*£ (81-125)	105*£ (75-115)	103*£ (75-139)	119* (100-141)	113 (102-127)	131 (80-158)
MAP (mmHg)	65 (49-71)	62 (42-80)	60 (48-90)	62 (50-76)	55 (50-59)	62 (46-74)
CO2 (mmHg)	33 (28-39)	34 (28-41)	35 (26-42)	36 (31-42)	38 (36-40)	36 (28-51)
SEVO (%)	2,40* (2,30-2,60)	2,50* (2,30-2,80)	2,40*£ (2,20-2,60)	2,55* (2,3-2,7)	2,55 (2,50-2,60)	2,60 (2,30-2,70)
BIS	29*£# (22-37)	36*£ (22-47)	37*£ (20-63)	44 (31-60)	54 (50-59)	55 (26-74)


Bispectrum
Frequency (Hz)
Frequency (Hz)


Frequency (Hz)
32
28
24
20
16
12
8
4
0
0
4
8
12
16
20
24
28
32
Frequency (Hz)
P1
P2
P3
P4
P5
P6
P7
P8
P9
P10
P11
P12
P13
P14
P15
P16
P17
P18
P19
P20
P21
P22
P23
P24
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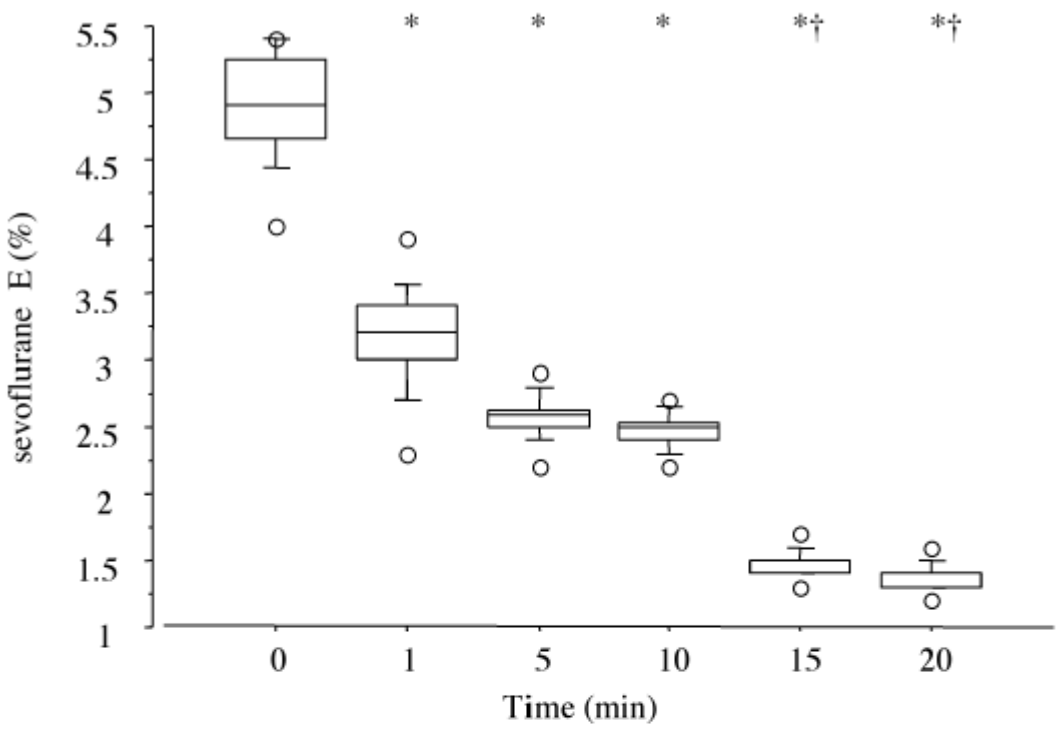
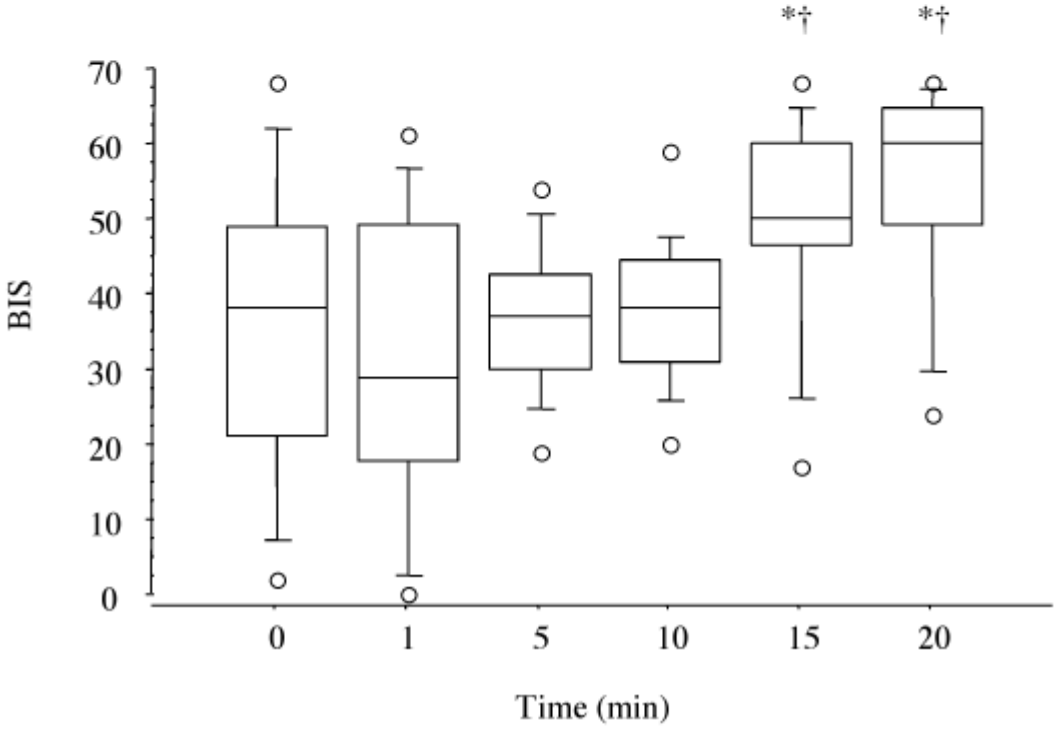
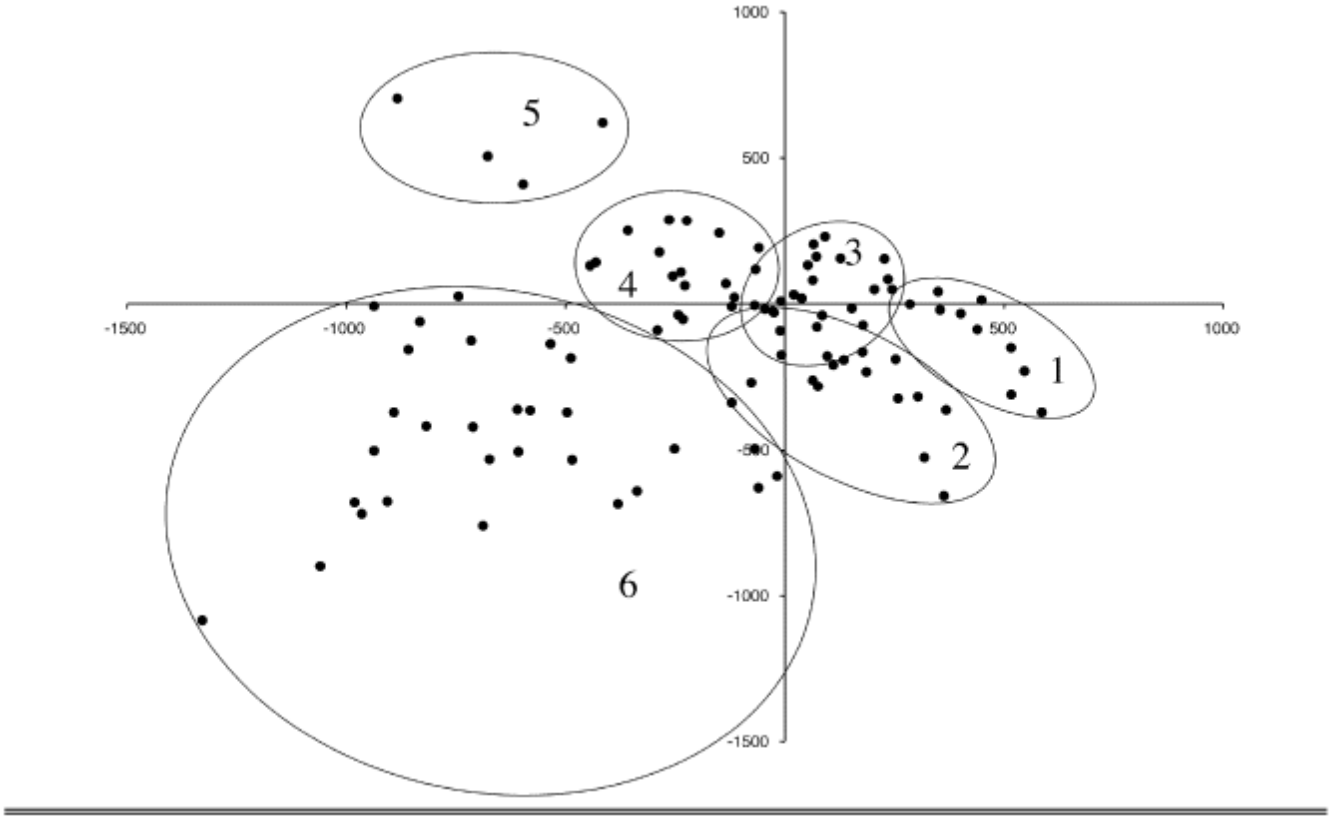
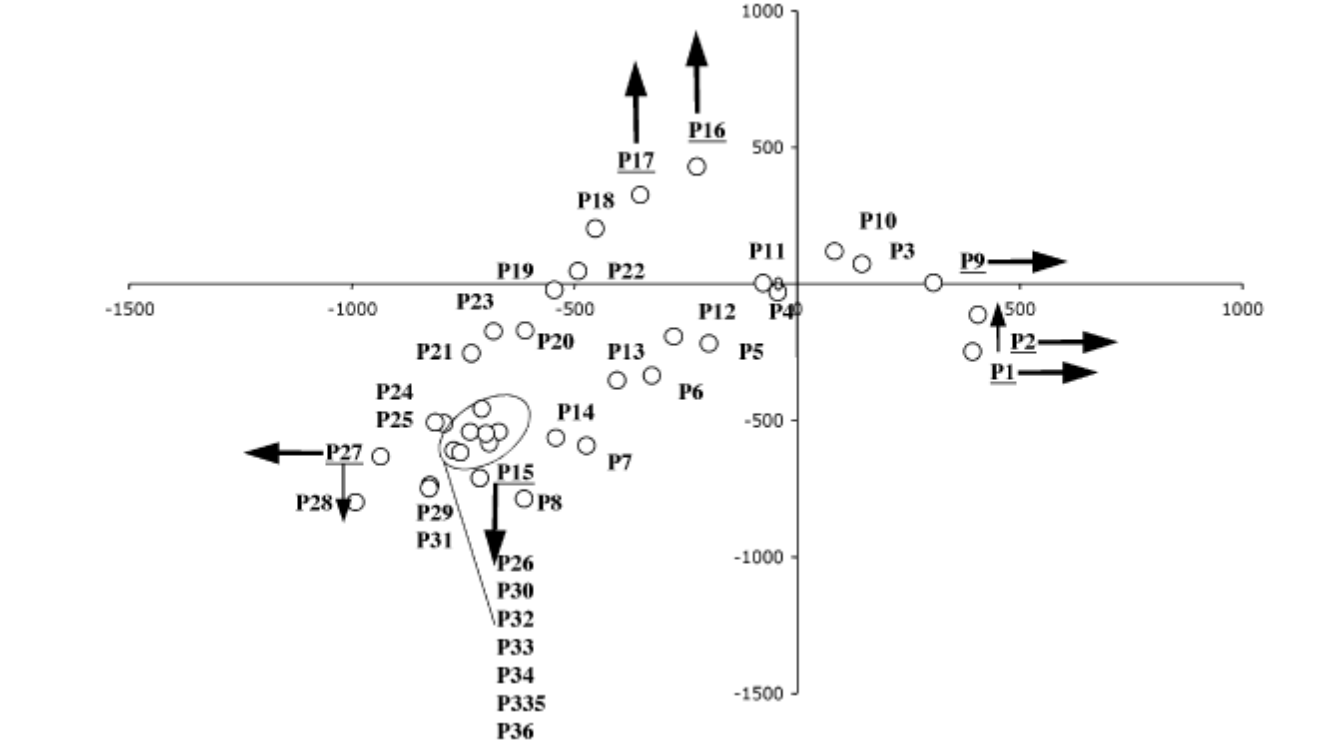
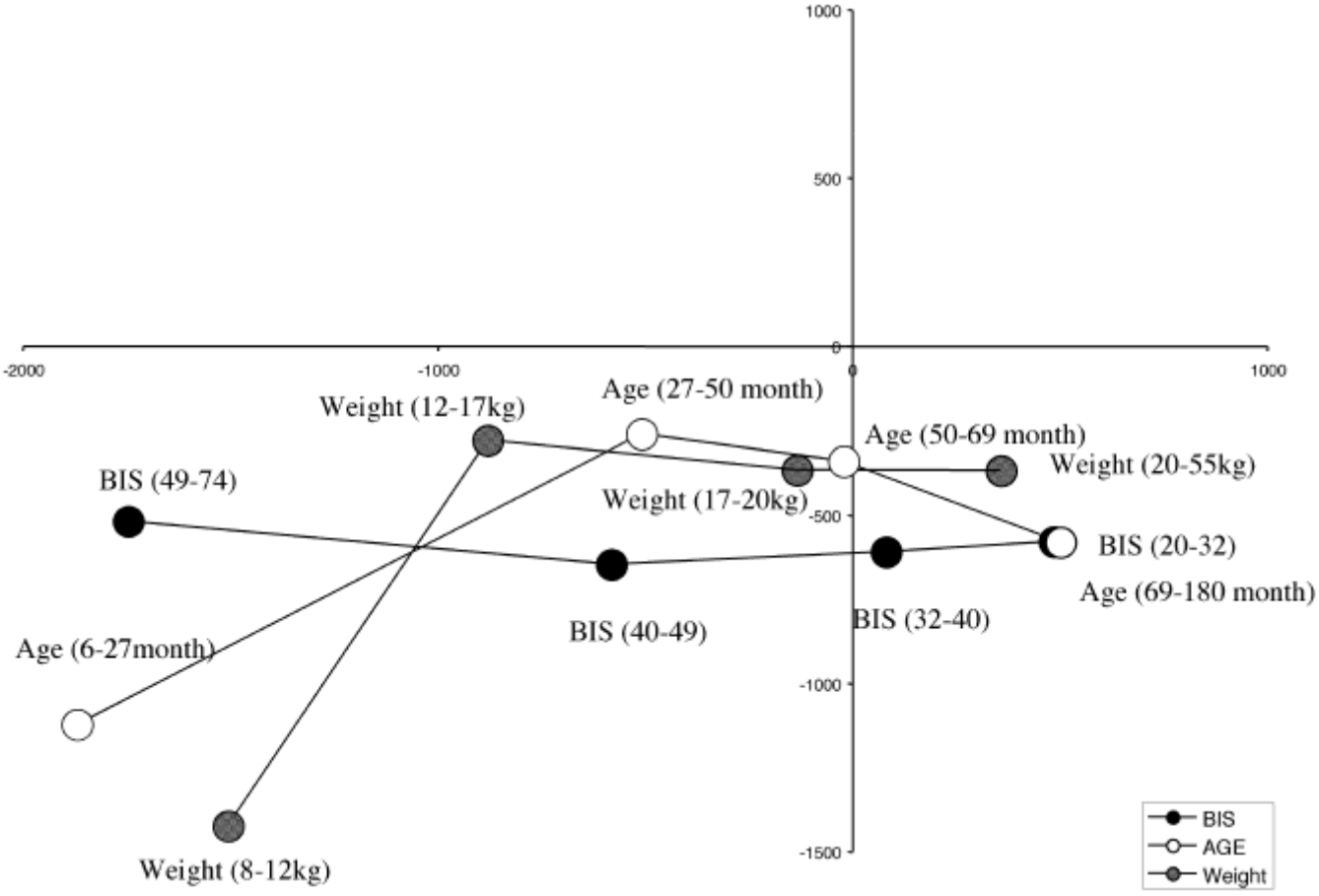
P26
P27
P28
P29
P30
P31
P32
P33
P34
P35
P36

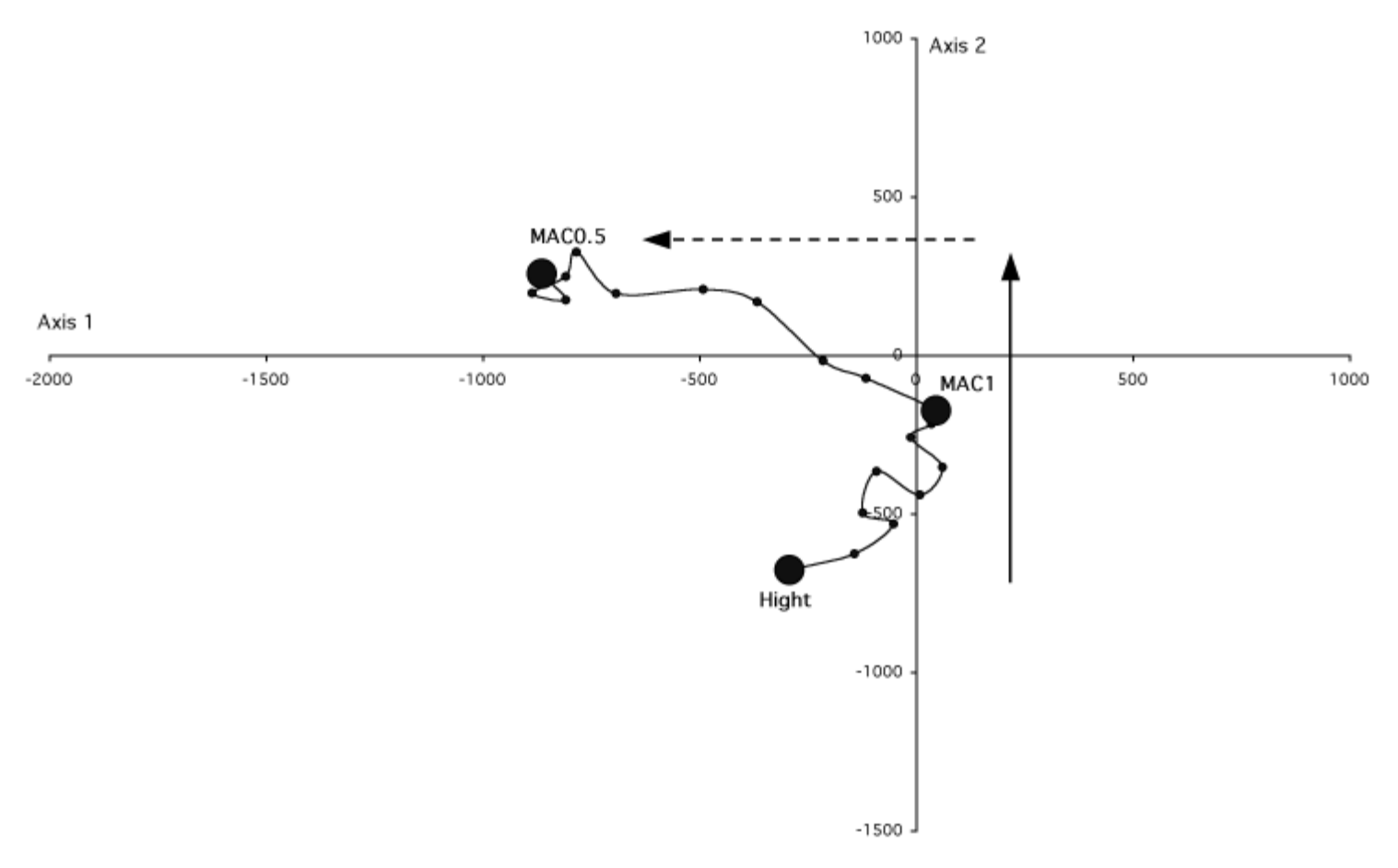

sevoflurane E (%)
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
* * * *† *†
0 1 5 10 15 20
Time (min)

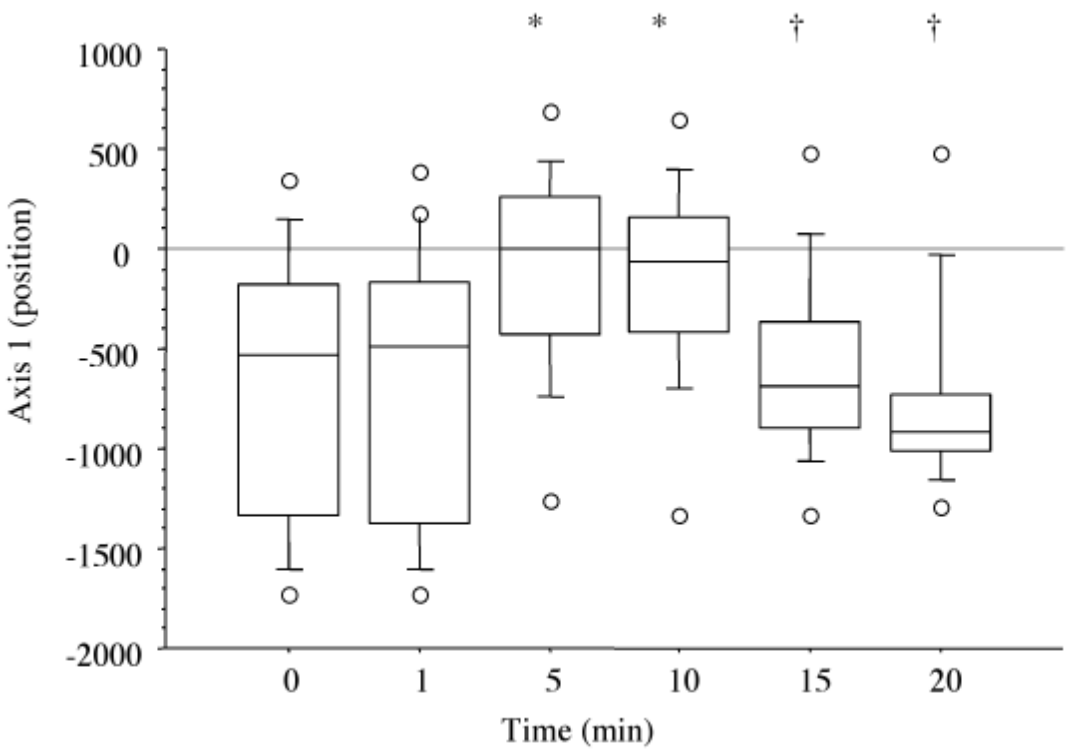

BIS
70
60
50
40
30
20
10
0
*† *†
0 1 5 10 15 20
Time (min)

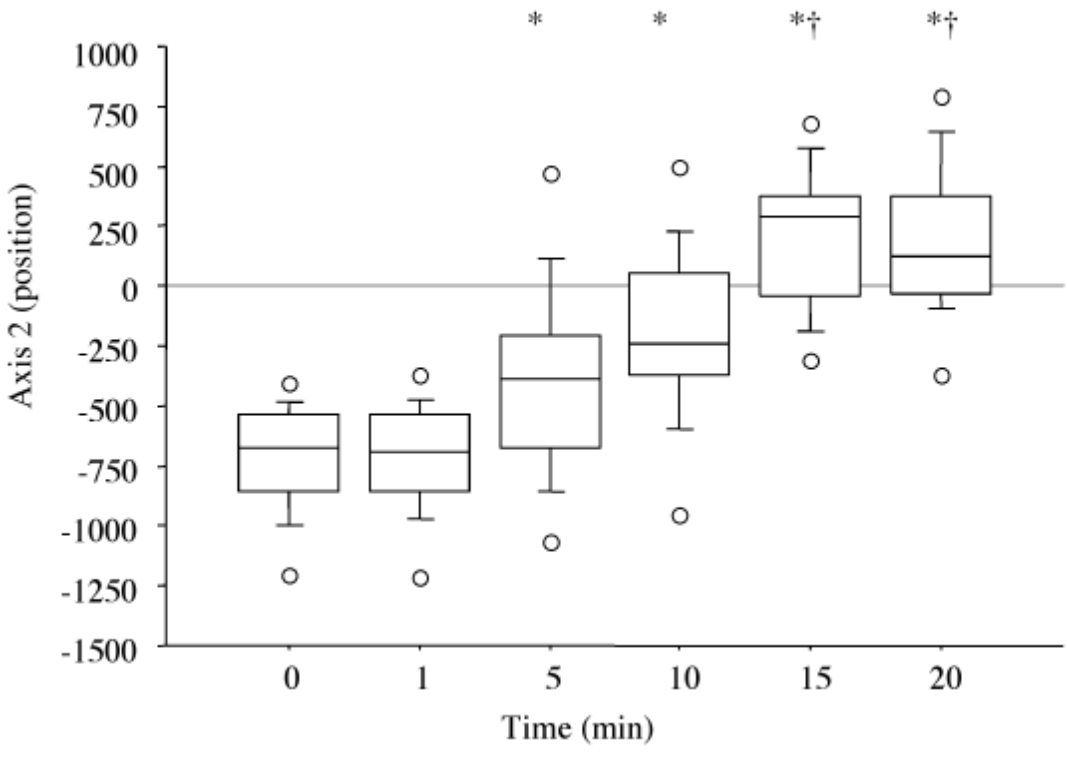

1000
500
-500
-1000
-1500
-1500
-1000
-500
500
1000
1
2
3
4
5
6


1000
500
-500
-1000
-1500
-1500
-1000
-500
500
1000
P16
P17
P18
P10
P11
P3
P9
P19
P22
P23
P12
P4
P2
P1
P21
P20
P13
P5
P24
P25
P6
P14
P27
P7
P15
P28
P29
P31
P8
P26
P30
P32
P33
P34
P335
P36


1000
500
0
-500
-1000
-1500
-2000
-1000
0
1000
Weight (12-17kg)
Age (27-50 month)
Age (50-69 month)
Weight (20-55kg)
BIS (49-74)
Weight (17-20kg)
BIS (20-32)
Age (69-180 month)
BIS (40-49)
BIS (32-40)
Age (6-27month)
Weight (8-12kg)
BIS
AGE
Weight


Axis 2
1000
500
0
-500
-1000
-1500
Axis 1
-2000
-1500
-1000
-500
0
500
1000
MAC0.5
MAC1
Hight


Axis 1 (position)
1000
500
0
-500
-1000
-1500
-2000
0
1
5
10
15
20
Time (min)
*
*
†
†


Axis 2 (position)
1000
750
500
250
0
-250
-500
-750
-1000
-1250
-1500
0
1
5
10
15
20
Time (min)
*
*
*†
*†

Appendix

A multiple correspondence analysis (MCA) is a statistical method used to explore the relationships between different entities represented by chosen variables. With such a tool, we thought it would be interesting to analyse the relationship between the EEG bispectra of children and their clinical variables. In order to establish and explain the potential links between BIS and the age of children, we decided initially to look at the main component of the BIS index, the matrix of the EEG bispectrum.

Firstly the reader must understand that whilst each child can be characterized by its clinical parameters, he or she can also be characterized by any other set of chosen variables. In our study we chose to characterize children by the 36 blocks of frequencies of coupling of the EEG bispectrum obtained at the steady state at 1 MAC (age-corrected) sevoflurane (T10) (see figure 1). We can then use a MCA to extract the common points between children when they are described by this set of principle variables.

In the first stage of the multiple correspondence analysis, the distribution of children in the multidimensional space, corresponding to the structured model of the MCA (Figure 3, top), reveals similarities among subjects (Figure A1). In the graphical representation of the MCA, if two children are close, they can be considered as being very similar in terms of the variables that place each of them in the structured model (i.e. the 36 blocks of frequencies of coupling of the EEG bispectrum).

In the second stage of the analysis, the MCA gives the contribution of each variable (i.e. each single block of frequency of coupling of the MatBis in this study) to the position of children in the structured model (Figure 3, bottom). In the present work, at the steady state at 1 MAC

sevoflurane, children who are positioned towards the upper half of the structured model of the MCA have higher values of the block labeled “P16”. Similarly, the children positioned towards the right of the structured model have higher values of the blocks labeled “P1, P2 and P9”.

In a third stage of analysis, the distribution within the structured model of any other secondary variable (i.e. a variable that was not used in deriving the MCA) can be obtained. For each of our secondary variables (age, BIS and weight), we chose to classify children into their respective inter-quartile ranges. The mean position of each of these four groups in the MCA model was then determined. For example, if we represent the MCA model in the dimensions of its two most dominant axes (F1 and F2), the mean position of children in the first inter-quartile range of “Age” (6 to 27 months) is found in the lower left part of this graph (Figure 4). When the positions of all four inter-quartile ranges are determined within the structured model of the MCA, it is possible to establish the main axis (i.e. main factor of analysis) linked to the considered variable (figure 4). It is important to understand that if two variables are distributed along the same axis, they must be linked. In our study, for example, given that both “Age” and “BIS” are mainly distributed along Axis F1, we can say that the age and the value of the BIS are interdependent at 1 MAC of sevoflurane.

These points can be confirmed using two other statistical methods:

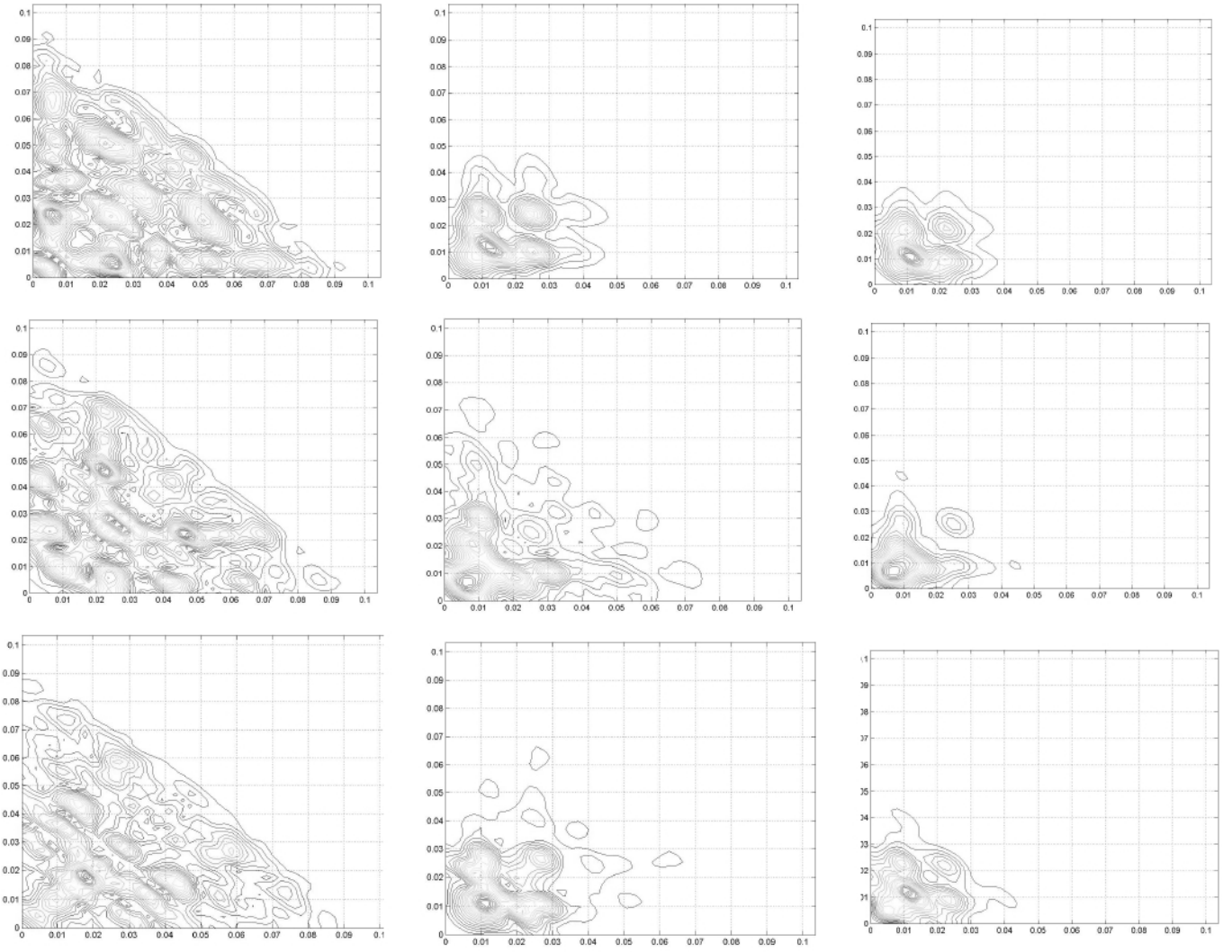
It is possible to establish the correlation coefficient between a chosen clinical variable for a child and his or her coordinates on one axis of the MCA (Table 1 and Figure A2). For example in this study, at the steady state at 1 MAC sevoflurane, both age and BIS were linked to axis F1 of the MCA. In contrast, the BIS was not significantly linked to axis F2. Thus, along any line parallel to axis F2 children will have similar values for BIS and similar ages.

Secondly, we can confirm the links between variables using a Hierarchical Ascending Classification (HAC). In this method of analysis, children are divided into homogeneous groups according to their coordinates on the two most dominant axes (F1 and F2) of the Multiple Correspondence Analysis. These groups can then be projected onto the structured model of the MCA. The number and boundaries of the groups is determined directly by the statistical method of the HAC. By comparing secondary variables between these groups, we can describe each of these groups of children by their clinical parameters (Table 2). For example in our study Group 1 of the HAC contains the oldest children with the lowest values of BIS and Group 6 of the HAC has the youngest children with highest values of BIS. Their respective positions, when projected onto the structured model of the MCA, confirms the link established between age, BIS and axis F1 (Figure 3, top).

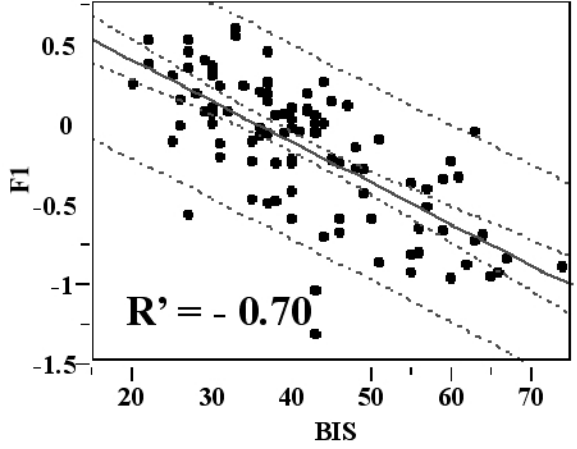
The same MCA structure may also be used to analyze changes in the EEG whilst varying the concentration of sevoflurane, as any change in the EEG bispectrum will change the position of the child within the MCA model. For example, here we plot the change in position in the MCA model of our sub-group of 29 children, represented by the change in their EEG bispectra, as sevoflurane is decreased from 2 MAC to the steady state of 1 MAC sevoflurane, and subsequently to 0.5 MAC (Figure 5, each dot representing the centre of distribution for all 29 children at each minute interval)

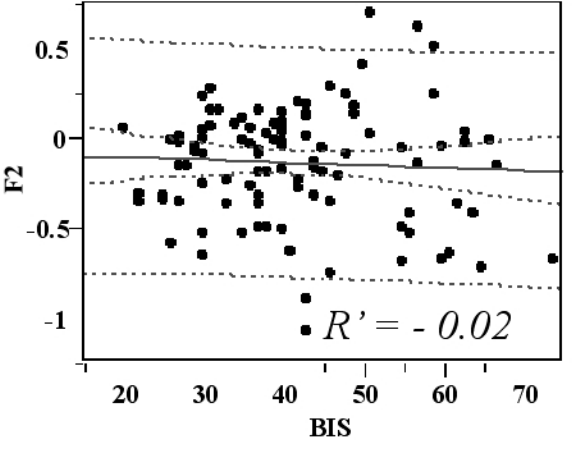
Figure A1: Examples of the EEG bispectra of nine children at the steady state of 1 MAC of sevoflurane. The children represented in the first column are all under 2 years old, in the middle column between 6 and 7 years old, and in the third column greater than 10 years old. They are unordered examples of children in these age groups.

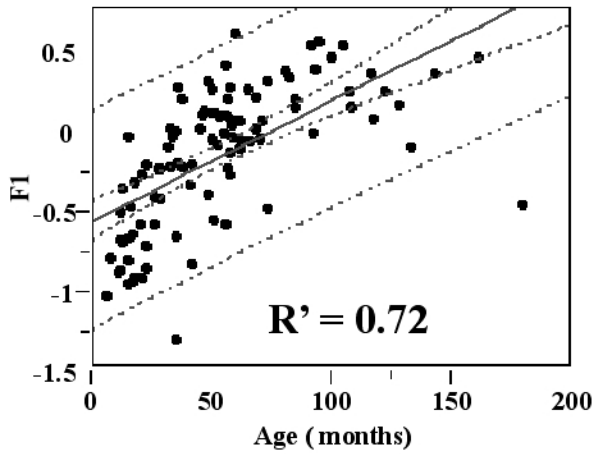
Figure A2: Top: Representation of the correlation between clinical variables (age, BIS and end-tidal sevoflurane concentration) and children's coordinates on the two most dominant axes (F1 and F2) of the MCA model at the steady state 1 MAC sevoflurane (age-corrected) in all children. Bottom: Representation of the correlation between BIS values measured in all children at the steady state of 1 MAC sevoflurane (age-corrected) with age, and end-tidal sevoflurane concentration respectively.

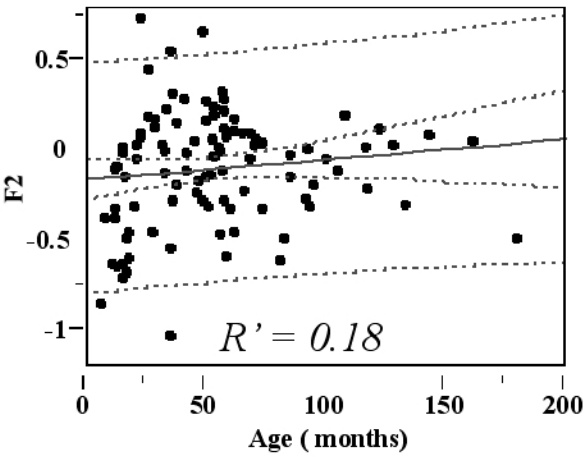


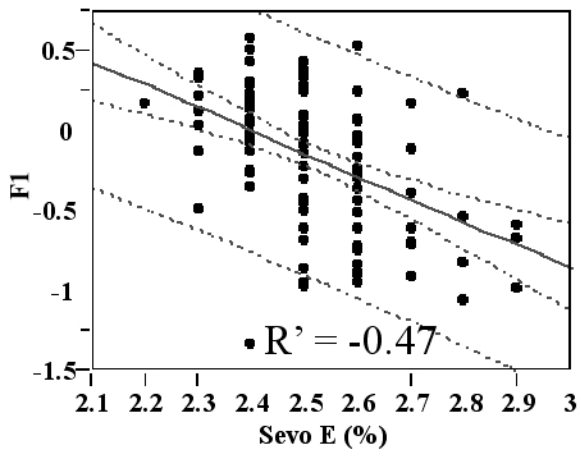
Younger ⟷ Older

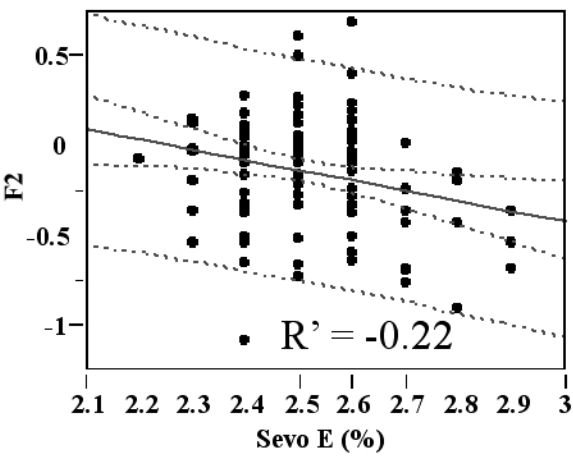

F1
BIS
R' = - 0.70

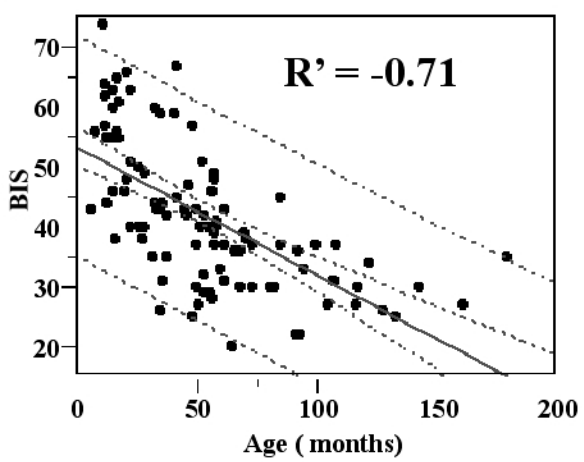

F2
BIS
R' = - 0.02

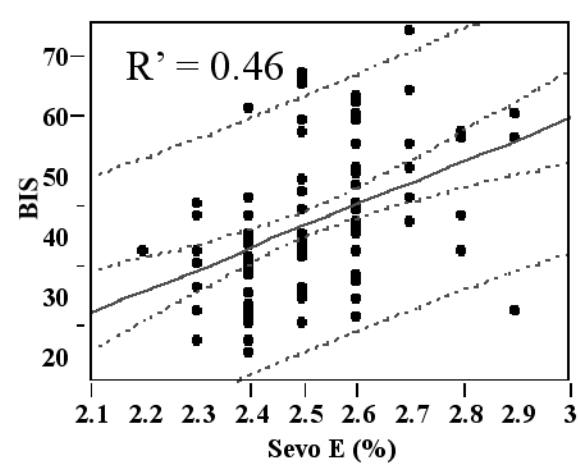

F1
Age (months)
R' = 0.72


F2
Age (months)
R' = 0.18


F1
Sevo E (%)
R' = -0.47


F2
Sevo E (%)
R' = -0.22


BIS
Age (months)
R' = -0.71


BIS
Sevo E (%)
R' = 0.46