Impact of age on both BIS values and EEG bispectrum during anaesthesia with sevoflurane in children

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Background. The aim of this study was to evaluate the potential relationship between age, BIS (Aspect™), and the EEG bispectrum during anaesthesia with sevoflurane.

Methods. BIS and raw EEG were recorded at a steady state of 1 MAC in 100 children, and during a decrease from 2 to 0.5 MAC in a sub-group of 29 children. The bispectrum of the EEG was estimated using MATLAB® software. For analysis, the bispectrum was divided into 36 frequencies of coupling (Pi)—the MatBis. A multiple correspondence analysis (MCA) was used to establish an underlying structure of the pattern of each individual’s MatBis at 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.

Results. At 1 MAC, the BIS values for all children ranged from 20 to 74 (median 40). Projection of both age and BIS value recorded at 1 MAC onto the structured model of the MCA showed them to be distributed along the same axis, demonstrating that the different values of BIS obtained in younger or older children are mainly dependent on their MatBis. At 1 MAC, 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 Group 1 the lowest values (29; range 22–37).

Conclusion. The EEG bispectrum, as well as the BIS appeared to be strongly related to the age of children at 1 MAC sevoflurane.


Keywords: anaesthesia, paediatric; anaesthetics volatile, sevoflurane; monitoring, bispectral index; monitoring, EEG bispectrum

Accepted for publication: March 16, 2005

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. This wide range may be explained by the fact that preferentially adult data were used by Aspect™ to derive the BIS index and that there are differences 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 anaesthesia.

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 anaesthesia with sevoflurane, and to highlight any implications regarding the use of BIS in children.

Patients and methods
One hundred children undergoing elective surgery were studied following approval by the Human Studies Board of Management and Trustees of the British Journal of Anaesthesia 2005. All rights reserved. For Permissions, please e-mail: journal.permissions@oupjournals.org
Committee and after informed parental consent was obtained. Inclusion criteria were ASA PS I, age 6–180 months, and consent for inhalation induction of anaesthesia. Exclusion criteria included neurologic disease and any centrally acting agents. Patients were not pre-medicated. EEG leads (3M Red Dot Silver/Silver Chloride model 2269T) were placed as close as possible to the paediatric BIS lead placement (Aspect™).

Anaesthesia was induced with sevoflurane at 8% (inspired) in oxygen, without nitrous oxide and i.v. access gained. Spontaneous respiration continued until tracheal intubation was possible without the use of muscle relaxants. The children were then ventilated. Anaesthetic 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 min for all children to ensure that a steady state at the effect site (EEG signal during this period remains stationary).

Recording for analysis was then started (T0) and sevoflurane concentration was decreased to 1 MAC (corrected for age).4 Recording was performed continuously for 10 min 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 to 0.5 MAC (age-corrected) and recording continued for another 10 min until stabilization of end-tidal concentration at 0.5 MAC (T20).

ECG and EEG were recorded continuously and sampled at 400 Hz (PowerLab™). Independently, BIS (Aspect Xp™) was recorded every minute. Systolic arterial pressure (SBP) was measured every minute using an automated arterial 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 s using MATLAB® software (The Mathworks Inc., Natick, USA) and Matlab function from the Higher Order Signal Analysis toolbox (bispectd.m with frequency smoothing using 11 as the length of the side of the square of the optimal Rao-Garb 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 (Fig. 1). An individual value for each of the 36 4×4 Hz blocks was derived, corresponding to the mean of the bispectrum for each block. Thus, each child is represented by 36 descriptors evolving over the time of recording.

First, 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 a hierarchical ascending classification (HAC) (see Appendix for details).8 Thus,
children were divided into homogeneous groups according to their respective bispectrum EEG pattern (MatBis) corresponding to their coordinates on the two most dominant axes (F1 and F2) of the Multiple Correspondence Analysis. 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 concentration was analysed 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 to 0.5 MAC sevoflurane.

A Kruskal–Wallis test was conducted to investigate the effect of a 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 $<0.05$ 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 (8–55), respectively. In the sub-group of 29 children for which sevoflurane was decreased from 2 to 0.5 MAC, age and weight were 55 months (15–180) and 17 kg (10–55), respectively.

At the steady state of 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 to 1 MAC), the BIS index did not change significantly ($T_0$ vs $T_{10}$) whereas during the second decrease from 1 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 3A. The contribution of all 36 frequencies 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 3B. The arrows on Figure 3B 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 $P_1$, $P_2$, and $P_9$ and low values in $P_{27}$ will position a child towards the right-hand side of Figure 3A; and high values in $P_2$, $P_{16}$, and $P_{17}$ with low values in $P_{15}$ and $P_{27}$ will position a child towards the upper half of Figure 3A.

For the whole population, age, weight, and BIS recorded at steady state 1 MAC sevoflurane ($T_{10}$) were distributed along axis F1 of the structured model (Fig. 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). 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 Group 1 the lower values. The projection of these groups onto the structured model of the MCA (Fig. 3A) 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 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 concentration. 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 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 was found to be strongly related to both the age and weight of children. This may explain in part the large range of BIS values found in children at 1 MAC sevoflurane.

To our knowledge, only a few studies have reported the relationship between sevoflurane concentration and BIS values (Aspect™) in children. In 2000, Denman and colleagues reported the relationship between end-tidal sevoflurane concentration and BIS in 22 patients. 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 concentration. For example, at sevoflurane 2%, the BIS index ranged from 0 to 65 in older children and from 30 to 70 in infants. McCann and co-workers reported a similar scatter of BIS values in their study of 30 children of 12–72 months of age, values ranging from 20 to 60 at sevoflurane 2%. Finally, Degoute and colleagues compared BIS values recorded in both children and adults at specific periods during sevoflurane anaesthesia. The age of children ranged from 3.5 to 13 yr. At the time of both loss of movement and skin incision, the SD 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 at 1 MAC of sevoflurane.

For the entire population of 100 children, the BIS values ranged from 20 to 74.

Thus, it is uncertain whether BIS can accurately determine the depth of anaesthesia 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 (Figs 3 and 4 and Table 1, see Appendix). Furthermore, BIS values were also correlated (inversely) to this axis (Fig. 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 we were 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 to 0.5 MAC 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 (Figs 5 and 6). It was only at less than 1 MAC sevoflurane that we saw any change in position along the F1 axis. This is surprising, considering that BIS was primarily linked to axis F1 of the MCA model, and suggests that the BIS values are not always related to changes in sevoflurane concentration in children, that is depth of anaesthesia (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 to 1 MAC sevoflurane, children’s positions in the MCA model moved mainly vertically upwards along axis F2 (Figs 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 to 1 MAC (Figs 5 and 6), it is not surprising that no significant changes were noted in BIS values (Fig. 2), as the BIS is primarily linked to axis F1 of the MCA model at the steady state of 1 MAC sevoflurane. Similarly, even though no statistical comparison was performed by the authors no relevant change in BIS occurred between sevoflurane 3 and 4% in this relationship, reported by Denman and colleagues.2 The small change of BIS values between 2 and 1 MAC could be attributed to the fact that the steady state was not obtained at 2 MAC. If this hypothesis was true, the concentration of anaesthetics at the effect site should be similar at T0 (2 MAC) and T10 (1 MAC).

### 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 sevoflurane concentration. BIS, Bispectral Index Scale (Aspect™). *vs 6; †vs 4; ‡vs 3; †vs 2: \( P<0.05 \)

<table>
<thead>
<tr>
<th>Groups</th>
<th>1 (n=10)</th>
<th>2 (n=16)</th>
<th>3 (n=23)</th>
<th>4 (n=18)</th>
<th>5 (n=4)</th>
<th>6 (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>97±19 (56–162)</td>
<td>58±3 (36–134)</td>
<td>62±4 (15–129)</td>
<td>37±2 (21–62)</td>
<td>30 (23–49)</td>
<td>18 (6–180)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25±4 (13–49)</td>
<td>18±3 (11–33)</td>
<td>20±4 (10–44)</td>
<td>14±5 (10–23)</td>
<td>15 (12–18)</td>
<td>11 (8–55)</td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>104±4 (81–125)</td>
<td>105±7 (75–115)</td>
<td>103±7 (75–139)</td>
<td>119±9 (100–141)</td>
<td>113 (102–127)</td>
<td>131 (80–158)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>65 (49–71)</td>
<td>62 (42–80)</td>
<td>60 (48–90)</td>
<td>62 (50–76)</td>
<td>55 (50–59)</td>
<td>62 (46–74)</td>
</tr>
<tr>
<td>CO₂ (mm Hg)</td>
<td>33 (28–39)</td>
<td>34 (28–41)</td>
<td>35 (26–42)</td>
<td>36 (31–42)</td>
<td>38 (36–40)</td>
<td>36 (28–51)</td>
</tr>
<tr>
<td>SEVO (%)</td>
<td>2.40* (2.30–2.60)</td>
<td>2.50* (2.30–2.80)</td>
<td>2.40** (2.20–2.60)</td>
<td>2.55* (2.3–2.7)</td>
<td>2.55 (2.50–2.60)</td>
<td>2.60 (2.30–2.70)</td>
</tr>
<tr>
<td>BIS</td>
<td>29±19 (22–37)</td>
<td>36±4 (22–47)</td>
<td>37±3 (20–63)</td>
<td>44 (31–60)</td>
<td>54 (50–59)</td>
<td>55 (26–74)</td>
</tr>
</tbody>
</table>
However, analysis of the projection of children onto the structured model of the MCA has shown that the EEG pattern was significantly different at, respectively, 2 and 1 MAC (Figs 5 and 6), even if the BIS obtained by the Aspect® device did not exhibit any significant change. This could be explained by the fact the BIS probably relies on frequencies of coupling mainly linked to the first axis (F1) and, from 2 to 1 MAC, changes occurring on EEG signal appeared in frequencies of coupling linked to the second axis (F2) (Figs 3, 5 and 6). Thus, the lack of significant change on BIS values from 2 to 1 MAC cannot be attributed to the absence of significant change in EEG pattern. Moreover, from a clinical point of view, it was possible to demonstrate that the concentration at the effect site could not remain at 1 MAC level at T0 because it was possible to intubate easily all children without muscle relaxant and it is well established that at 1 MAC intubation is not possible.

During the second decrease from 1 to 0.5 MAC sevoflurane in our study, changes in children’s positions in the MCA model continued vertically upwards along axis F2 (Figs 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 (Fig. 2) corresponding to the movement of children along 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 anaesthesia in children. Indeed, Davidson and colleagues 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 inhalation anaesthetic 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 anaesthesia for high concentrations of anaesthetics. 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 to 1 MAC by the change in position of children along axis F2 of the MCA model (Fig. 6). The BIS monitor failed in this respect (Fig. 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 anaesthesia. Indeed, our results show that the lower frequencies of coupling (≤8 Hz), such as P1, P2, or P9, and the higher frequencies of coupling (>16 Hz), such as P27, are the main determinants of the position of children along axis F1 of the MCA model (Fig. 3b). The relationship established between the BIS values and axis F1 at 1 MAC sevoflurane (Fig. 4 and Table 1), suggests that the frequencies of coupling P1, P2, P9, and P27 are the main frequencies of the 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 P1, P2, and P9 of the MatBis also correspond to the frequencies of the classic Delta and Theta bands of the EEG and the frequency P27 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 inhalation 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 P1, P2, P9, and P27) 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.\textsuperscript{12}

In addition, our data show that in children, changes induced by the decrease in sevoflurane concentration from 2 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 $P_{17}$, Fig. 3b). 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 anaesthesia in children when concentrations of sevoflurane are higher than 1 MAC. However, further studies are needed to see whether these results remain valid with other anaesthetics agents, or in the adult population.

The main clinical implication of our finding is that age, in children, can modify significantly the value of BIS during anaesthesia with sevoflurane at 1 MAC. As this effect is not linked to the depth of anaesthesia, the BIS should be considered with caution in paediatric anaesthesia. Further studies are needed to establish if this problem appears with other gas (Desflurane, Halothane for example) or i.v. agents. Moreover, in the paediatric population, the fact that the BIS Aspect\textsuperscript{TM} device appeared to be insensitive to concentration variations of sevoflurane between 2 and 1 MAC should be taken into account when deep anaesthesia is required. Therefore, particular attention should be paid to pharmacodynamical model construction using the BIS as regard to its possible inaccuracy for the determination of the maximal effect of anaesthetic agents.

In conclusion, the EEG bispectrum (MatBis) as well as the BIS (Aspect XPTM) 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 to 0.5 MAC, independently of age, in contrast to the BIS of Aspect\textsuperscript{TM}.

Acknowledgements
The authors wish to thank paediatric surgeons, Olivier Azzis, MD and Edouard Habonimana, MD, for their kind patience during the recordings. Part of this study was presented at the annual meeting of ASA, San Francisco, 2003. These works were financed partly by the French Ministry of Research and Technology (Grant: DT 03 B 107).

Appendix
A 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.

First, 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 Fig. 1). We can then use an 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 multi-dimensional space, corresponding to the structured model of the MCA (Fig. 3a), reveals similarities among subjects (Fig. 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 (Fig. 3b). 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 labelled ‘P16’. Similarly, the children positioned towards the right of the structured model have higher values of the blocks labelled ‘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’ (6–27 months) is found in the lower left part of this graph (Fig. 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 (Fig. 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 inter-dependent 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 Fig. 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 MCA. 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, confirm the link established between age, BIS, and axis F1 (Fig. 3A).

The same MCA structure may also be used to analyse 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 (Fig. 5, each dot representing the centre of distribution for all 29 children at each minute interval).
Fig A2 (A) 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. (B) 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.

References
1 Denman WT, Swanson EL, Rosow D, Ezbicki K, Connors PD, Rosow CE. Pediatric evaluation of the bispectral index (BIS) monitor and correlation of BIS with end-tidal sevoflurane concentration in infants and children. Anesth Analg 2000; 90: 872–7
6 Benzecri JP. *Correspondence Analysis Handbook*. New York: Marcel Dekker, 1992
10 Olofsen E, Dahan A. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. *Anesthesiology* 1999; 90: 1345–53