Comparison of the Effects of Sevoflurane and Propofol Anaesthesia on Regional Cerebral Glucose Metabolism in Humans using Positron Emission Tomography

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This study compared brain glucose metabolism during sevoflurane anaesthesia and propofol anaesthesia using positron emission tomography (PET) in the same eight human volunteers. All the volunteers were anaesthetized twice, with a 1-week interval. Half of the volunteers received sevoflurane on the first occasion and propofol on the second; the other half received the two anaesthetics in the reverse order. PET scans using ¹⁸F-fluorodeoxyglucose were performed after sevoflurane or propofol anaesthesia. The relative glucose metabolic rate (rGMR) in the brain was assessed with statistical parametric mapping. Propofol suppressed the rGMR of the neocortex area more than sevoflurane, and sevoflurane suppressed the rGMR of the paleocortex and telencephalon more than propofol. These findings suggest that these two anaesthetics act via different mechanisms and may provide an important clue to the relationship between anaesthesia and the brain.

KEY WORDS: Propofol; Sevoflurane; Inhalation anaesthesia; Intravenous anaesthesia; Positron emission tomography

Introduction

Sevoflurane is increasingly being used, in many cases as a substitute for common inhalant anaesthetics such as enflurane, halothane and isoflurane. There have been a number of studies defining the effects of sevoflurane on regional brain blood flow: some have reported that sevoflurane increases blood flow,¹ – ³ whereas others have reported that sevoflurane decreases blood flow.⁴,⁵ This discrepancy may be due to the uncoupling of blood flow and metabolism. Despite a drop in brain metabolism, brain blood flow may increase due to the vasodilatation of brain vessels by inhalant anaesthetics. In order to evaluate brain metabolism accurately under anaesthetized conditions, cerebral glucose metabolism, rather than brain blood flow, should be measured.
Sevoflurane and propofol anaesthesia and cerebral glucose metabolism

In contrast to propofol, isoflurane and halothane, there have been few studies of the effect of sevoflurane on cerebral glucose metabolism in humans. In rats, mean cerebral glucose utilization was decreased by about 34% by sevoflurane at 1 minimum alveolar concentration (MAC) and by about 59% at 2 MAC, but this study did not analyse the degree of increase or decrease in each region of the brain. In patients undergoing coronary artery bypass graft surgery under sevoflurane anaesthesia, the mean glucose utilization was reported to decrease by about 39%, but again this study did not analyse regional brain metabolism. In contrast, when compared with inhalant anaesthetics, the intravenous anaesthetic propofol showed a tendency towards greater suppression of glucose metabolism in the cortex and reduced suppression in the basal ganglia and midbrain. This comparison, however, was made between non-identical groups of individuals. The study reported here compared the effects of sevoflurane and propofol on cerebral glucose metabolism in individual regions of the brain in healthy individuals using positron emission tomography (PET) and statistical parametric mapping (SPM). The results were also compared to control data collected from awake-state PET scans of other healthy people.

Subjects and methods

VOLUNTEERS

Male volunteers who were right-handed, non-smokers with class 1 physical status as classified by the American Society of Anesthesiologists and no previous psychological or neurological medical history were recruited to the study. The following examinations and tests were performed on each volunteer: electrocardiogram (ECG), chest X-ray, urine analysis, haemoglobin and haematocrit levels, electrolytes and glucose levels, blood urea nitrogen and creatinine, liver function tests, prothrombin time and activated partial thrombin time. The volunteers were asked to cease ingestion of coffee, alcohol and drugs for 48 h prior to anaesthesia, and to fast for the last 8 h.

Informed consent was obtained from all the study participants. The study protocol was approved by the institutional review board. Control data for the awake-state PET scan had been collected previously.

SEVOFLURANE AND PROPOFOL ANAESTHESIA

All the volunteers were anaesthetized twice, with a 1-week interval. Half of the volunteers received sevoflurane on the first occasion and propofol on the second; the other half received the two anaesthetics in the reverse order.

During anaesthesia, ECG, non-invasive blood pressure, peripheral oxygen saturation, end-tidal CO₂ and end-tidal sevoflurane concentration were monitored using an S/5 Anaesthesia Monitor (Datex-Ohmeda, Helsinki, Finland). The lights were dimmed and circumambient noise was reduced.

Sevoflurane was inhaled with oxygen via a tight-fitting face mask (5 l/min). The concentration was increased by 0.2 vol% every 5 – 10 min until the volunteer slipped into unconsciousness. The point of unconsciousness was confirmed by the absence of eyelash reflexes and the lack of response to verbal commands and gentle shaking of the shoulders. Following loss of consciousness, the end-tidal concentration of sevoflurane was maintained for the rest of the experiment.

Propofol was infused by target-controlled infusion using a Diprifusor® (Vial Medical, Brezins, France) while administering oxygen (5 l/min) via a face mask. Starting with an effect-site concentration of 1 mg/ml, the concentration was increased by 0.2 mg/ml
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every 5 – 10 min until the volunteer slipped into unconsciousness. Once loss of consciousness was achieved, the effect-site concentration of propofol was maintained for the rest of the experiment.

Airway instrumentation was not used; the volunteers maintained spontaneous respiration during anaesthesia, although on rare occasions simple assistance (head tilt and jaw thrust) was needed to maintain the patient’s airway.

ADMINISTRATION OF $^{18}$F-FLUORODEOXYGLUCOSE
When unconsciousness had been established and vital signs had been stable for about 10 min, 10 mCi (370 MBq) of the positron-labelled $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) was slowly administered by intravenous injection. This tracer is taken up by active brain neurons as if it were glucose. It is then metabolized to FDG-6-phosphate in the cells and emits radioactivity that can be viewed using PET. Uptake and metabolic trapping of $^{18}$F-FDG in the brain as FDG-6-phosphate is 80 – 90% complete 32 min after the intravenous injection. Anaesthesia was maintained consistently for about 35 min after $^{18}$F-FDG administration. The anaesthetic was then halted and the volunteers were allowed to wake up spontaneously. When able to open their eyes and follow verbal commands, the volunteers were moved to the PET scan room. The scanning of all volunteers began within 30 min from the end of the uptake period of $^{18}$F-FDG in the brain.

POSITRON EMISSION TOMOGRAPHY
The PET images were acquired by 5 min projection imaging and three-dimensional imaging using an ECAT HR+ scanner (Siemens Medical System, Hoffman Estate, Illinois, USA) over a period of 15 min. The images were reconstructed using ordered subset expectation maximization. Spatial resolution of the PET scanner ranges was obtained as 4.3 mm in the longitudinal mode of full width half maximum (FWHM) through 63 transverse sections of a $128 \times 128$ matrix with a pixel size of $1.72 \times 1.72$ mm.

STATISTICAL PARAMETRIC MAPPING
The PET images were converted into the Analyze file format and analysed using SPM software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). In preparation for this, the PET images were converted into linear and non-linear systems. Spatial normalization of these images was performed using a standard Montreal Neurological Institute (MNI) template provided by the SPM software. After smoothing using a Gaussian kernel with 12 mm FWHM, the whole brain scale was set to 50 by proportional scaling after global count normalization.

STATISTICAL ANALYSIS
Regional brain metabolism in the normal awake state (control data from other healthy people) and after the administration of anaesthetic was compared for sevoflurane and propofol using a generalized linear mode $t$-test. An uncorrected $P$-value $< 0.05$ and a voxel extent $< 50$ were considered to be statistically significant.

Differences in regional brain metabolism for the two anaesthetics were also compared using a generalized linear mode paired $t$-test. An uncorrected $P$-value $< 0.01$ and a voxel extent $< 50$ were considered to be statistically significant.

The results were localized by converting the MNI coordinates into Talairach coordinates, and the significance of the $z$-value was determined by converting the SPM map into a normal distribution.
Physiological parameters were compared using paired t-tests. A P-value < 0.05 was considered to be statistically significant.

Results
Eight male volunteers, aged between 22 and 34 years, were recruited to the study. The results of the preliminary examinations and tests were all normal.

The volunteers had a mean ± SD age of 27 ± 5 years, a mean height of 176 ± 6 cm and a mean weight of 76 ± 13 kg. The end-tidal sevoflurane concentration required to achieve unconsciousness ranged from 0.8 to 1.5% (mean ± SD, 1.03 ± 0.28%). The effect-site concentration of propofol required to achieve unconsciousness ranged from 1.5 to 2.8 mg/ml (mean ± SD, 1.96 ± 0.39 mg/ml).

Under sevoflurane anaesthesia the heart rate and blood pressure decreased significantly (P < 0.05), whereas the respiratory rate increased significantly (Table 1). Sevoflurane anaesthesia had no effect on peripheral oxygen saturation or end-tidal CO₂ concentration. Under propofol anaesthesia, only blood pressure was significantly (P < 0.05) altered; the other physiological parameters were not changed (Table 1). Control data for the awake-state PET scan had been collected previously from 18 healthy people and this was used to compare with the results following the administration of the two anaesthetics in this study.

EFFECTS OF ANAESTHESIA ON RELATIVE CEREBRAL GLUCOSE METABOLISM

Sevoflurane anaesthesia
When compared with the awake state, sevoflurane anaesthesia significantly decreased the relative glucose metabolic rate (rGMR) in the primary, secondary and tertiary visual cortices (Brodmann area [BA] 17, 18 and 19) of the occipital lobe, the primary somatosensory cortex (BA 2), multispatial area (BA 7) and multimodal association area (visual, somatosensory, auditory and language) (BA 40) of the parietal lobe, the premotor and supplementary motor areas of the frontal lobe (BA 6), part of the insula cortex (BA 13) and part of the cerebellum (Table 2, Fig. 1).

When compared with the awake state, sevoflurane significantly increased the rGMR in part of the olfactory-limbic cortex (BA 38) and the visual area (BA 20) of the temporal lobe, parts of the prefrontal association area (BA 10, 11, 46 and 47), parts of the limbic

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### TABLE 1:
Physiological data 5 min before sevoflurane and propofol anaesthesia and 35 min later in eight male volunteers

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane</th>
<th></th>
<th>Propofol</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre-anaesthesia</td>
<td>During anaesthesia</td>
<td>Pre-anaesthesia</td>
<td>During anaesthesia</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 9</td>
<td>61 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70 ± 5</td>
<td>65 ± 6</td>
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<tr>
<td>Arterial pressure (mmHg)</td>
<td>95 ± 14</td>
<td>77 ± 11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89 ± 11</td>
<td>71 ± 10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>13 ± 2</td>
<td>17 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 ± 3</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>Peripheral oxygen saturation (%)</td>
<td>100 ± 1</td>
<td>99 ± 0</td>
<td>99 ± 1</td>
<td>99 ± 1</td>
</tr>
<tr>
<td>End-tidal CO₂ (mmHg)</td>
<td>42 ± 3</td>
<td>40 ± 2</td>
<td>41 ± 3</td>
<td>43 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SD.

<sup>a</sup>P < 0.05 versus pre-anaesthesia value.
TABLE 2: Brain areas in which relative glucose metabolism (rGMR) measured using positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) was significantly ($P < 0.05$) decreased after sevoflurane anaesthesia in eight volunteers compared with control data for the awake state in 18 healthy people

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann’s area</th>
<th>Coordinates (mm)</th>
<th>Voxel z-score</th>
<th>Voxel P-value</th>
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<tbody>
<tr>
<td>Occipital lobe</td>
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</tr>
<tr>
<td>Lingual gyrus</td>
<td>17, 18</td>
<td>–6 –68 –8</td>
<td>3.97</td>
<td>&lt; 0.001</td>
</tr>
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<td>Cuneus (L)</td>
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<td>–16 –92 16</td>
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<tr>
<td>Cuneus (R)</td>
<td>18, 19</td>
<td>20 –92 20</td>
<td>3.42</td>
<td>&lt; 0.001</td>
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<tr>
<td>Parietal lobe</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Precuneus (L)</td>
<td>7</td>
<td>–12 –60 46</td>
<td>3.13</td>
<td>0.001</td>
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<tr>
<td>Inferior parietal lobule (R)</td>
<td>40</td>
<td>38 –32 38</td>
<td>2.07</td>
<td>0.019</td>
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<tr>
<td>Postcentral gyrus (R)</td>
<td>2</td>
<td>38 –32 38</td>
<td>2.07</td>
<td>0.019</td>
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<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Precentral gyrus (L)</td>
<td>6</td>
<td>–38 0 36</td>
<td>1.93</td>
<td>0.027</td>
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<tr>
<td>Precentral gyrus (R)</td>
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<td>32 0 40</td>
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<td>Insula (L)</td>
<td>13</td>
<td>–42 –30 20</td>
<td>1.82</td>
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<td>Cerebellum</td>
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<tr>
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<td>6</td>
<td>–80 –8</td>
<td>3.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anterior lobe (L)</td>
<td>–6 –84 –18</td>
<td>3.41</td>
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The coordinates are given for the maximally significant pixel in each cluster and other neuroanatomically significant regions within each cluster according to a standard stereotactic map. $^{11}$

R, right; L, left.

association area (BA 24, 25 and 32), part of the basal ganglia and the midbrain and pons (Table 3).

Propofol anaesthesia

When compared with the awake state, propofol induced decreased rGMR in the same regions showing decreases during sevoflurane anaesthesia, as well as in part of the visual area (BA 21) and part of the unimodal association area (visual, somatosensory, auditory and language) (BA 37) of the temporal lobe (Table 4).

Again similar to sevoflurane, propofol induced increases in the rGMR in part of the olfactory-limbic cortex (BA 38), parts of the prefrontal association areas (BA 10 and 11) and parts of the limbic association area (BA 24, 25 and 32), as well as in the primary motor area of the frontal lobe (BA 4) and parts of the insula cortex, thalamus, and medulla (Table 5).

Comparison of sevoflurane and propofol anaesthesia

The rGMR was decreased more by sevoflurane than by propofol in parts of the secondary and tertiary visual cortices of the occipital lobe (BA 18 and 19), the primary motor cortex of the frontal lobe (BA 4), the premotor and supplementary motor areas (BA 6), parts of the insula cortex (BA 13 and 43), parts of the olfactory-limbic cortex (BA 28 and 35), parts of the limbic association area (BA 24 and 31), and the thalamus, pons and cerebellum.
Sevoflurane and propofol anaesthesia and cerebral glucose metabolism

The rGMR was decreased more by propofol than by sevoflurane in parts of the visual area of the temporal lobe (BA 20 and 21), part of the olfactory-limbic cortex (BA 38), the occipital association cortex (BA 37), the multimodal association area (visual, somatosensory, auditory and language) of the parietal lobe (BA 39 and 40), the multispatial area (BA 7), the visual area of the frontal lobe (BA 8), and the prefrontal association area (cognition, recognition, planning, moral judgements and language).

Discussion

During anaesthesia with both sevoflurane and propofol, the regions of the brain in which the rGMR was decreased included the visual cortex of the occipital lobe, the multispatial area and part of the multimodal association area (visual, somatosensory, auditory and language) of the parietal lobe, part of the primary somatosensory cortex of the parietal lobe, part of the insula cortex, part of the premotor and supplementary motor areas of the frontal lobe, and part of the cerebellum. All of these regions are related to either the sensory or lower motor functions of the brain. In contrast, both anaesthetics increased the rGMR in part of the prefrontal association area (cognition, recognition, moral judgement), part of the basal ganglia and cingulate gyrus, part of the olfactory-limbic cortex of the temporal lobe, the midbrain and the pons. All of these regions are related to upper, complicated brain functions or to the embryologically old central nervous system. These findings suggest that both anaesthetics suppress the regions of lower brain function, including sensory and motor functions, but have greater difficulty suppressing regions of higher brain function, including those controlling cognition, recognition, memory.

FIGURE 1: Areas of decreased glucose metabolism after sevoflurane anaesthesia. Statistical parametric mapping (SPM) analysis shows the regions in the brain where relative regional brain glucose metabolism decreased significantly \( (P < 0.05) \) after sevoflurane anaesthesia compared with the awake baseline. The SPM projections (the three images on the left of the figure) are ‘see-through’ images showing sagittal (A), transverse (B) and coronal (C) views of the three-dimensional positron emission tomography (PET) data volume of voxels significant at this level. These projections are difficult to visualize in three dimensions, so the SPM results are also shown rendered onto a standardized magnetic resonance image (MRI) (six images on the right of the figure) marked in red for better anatomical localization. The SPM analysis shows that sevoflurane anaesthesia in humans significantly decreased relative brain glucose metabolism in part of the occipital lobe, upper cerebellar area and parietal lobe.
and concentration, as well as emotion and voluntary movement control. In addition, the brainstem was not easily suppressed by these anaesthetics, suggesting its importance to the life-support system. Conversely, the cerebellum was easily suppressed, indicating it may be less essential for life support.

The common effects of these two anaesthetics suggest an important clue to the relationship between anaesthesia and the brain. The reticular activating system was formerly considered to be the major region acted on by anaesthetics. However, the mechanism of action during anaesthesia does not seem to involve just one or two anatomical regions. The relationship between anaesthesia and the brain is thought to involve a common mechanism of activation at the electrophysiological, microscopic or molecular level. Determining the difference between the suppressed and non-suppressed regions of the brain may enable a greater understanding of the mechanism of anaesthesia.

In addition to the brain regions that were affected in a similar way by both anaesthetics, propofol showed less suppression of relative glucose metabolism in part of the primary

### TABLE 3:

Brain areas in which relative glucose metabolism (rGMR) measured using positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) was significantly (P < 0.05) increased after sevoflurane anaesthesia in eight volunteers compared with control data for the awake state in 18 healthy people

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann’s area</th>
<th>Coordinates (mm)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Voxel z-score</th>
<th>Voxel P-value</th>
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<tbody>
<tr>
<td><strong>Temporal lobe</strong></td>
<td></td>
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<tr>
<td>Superior temporal gyrus (L)</td>
<td>38</td>
<td>–28</td>
<td>20</td>
<td>–46</td>
<td>2.39</td>
<td>0.009</td>
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<tr>
<td>Superior temporal gyrus (R)</td>
<td>38</td>
<td>30</td>
<td>22</td>
<td>–40</td>
<td>2.39</td>
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<td>–42</td>
<td>–16</td>
<td>–36</td>
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<tr>
<td><strong>Frontal lobe</strong></td>
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<td></td>
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<tr>
<td>Middle frontal gyrus (R)</td>
<td>10</td>
<td>26</td>
<td>62</td>
<td>26</td>
<td>2.59</td>
<td>0.005</td>
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<td></td>
<td>46</td>
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<td>52</td>
<td>12</td>
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<td>10</td>
<td>–20</td>
<td>66</td>
<td>30</td>
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<tr>
<td>Inferior frontal gyrus (R)</td>
<td>11, 47</td>
<td>26</td>
<td>42</td>
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<td>2.89</td>
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<td>Inferior frontal gyrus (L)</td>
<td>47</td>
<td>–58</td>
<td>16</td>
<td>–2</td>
<td>1.88</td>
<td>0.030</td>
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<tr>
<td><strong>Limbic system</strong></td>
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<tr>
<td>Cingulate (L)</td>
<td>24, 25, 32</td>
<td>–8</td>
<td>42</td>
<td>2</td>
<td>3.16</td>
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<tr>
<td>Cingulate (R)</td>
<td>24, 32</td>
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<td>0</td>
<td>46</td>
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<td>Corpus callosum</td>
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<td>14</td>
<td>26</td>
<td>–4</td>
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<td><strong>Basal ganglia</strong></td>
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<tr>
<td>Putamen (L)/Lateral globus pallidus (L)</td>
<td>–34</td>
<td>–16</td>
<td>–4</td>
<td>3.00</td>
<td>0.001</td>
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<tr>
<td>Caudate body (L)</td>
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<td>26</td>
<td>–4</td>
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<td><strong>Brainstem</strong></td>
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<td>Midbrain, pons</td>
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<td>70</td>
<td>–22</td>
<td>3.03</td>
<td>0.001</td>
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</table>

<sup>a</sup>The coordinates are given for the maximally significant pixel in each cluster and other neuroanatomically significant regions within each cluster according to a standard stereotactic map. R, right; L, left.
motor area, the gustatory region of the insula, part of the thalamus and the medulla, whereas sevoflurane showed less suppression in part of the visual cortex of the temporal lobe and the prefrontal association area (cognition, recognition, language and planning). These results suggest that sevoflurane may only weakly inhibit the metabolism in areas of higher brain function and the neocortex, whereas propofol weakly inhibits metabolism in areas of motor function and thalamus function.

By comparing changes in the relative cerebral glucose metabolism induced by these two anaesthetics, we observed specific differences. The regions more suppressed by sevoflurane than by propofol were mostly distributed in parts of the insula and limbic system, as well as in the thalamus, pons and cerebellum. In contrast, the regions more suppressed by propofol than by sevoflurane were mostly distributed in the neocortex of the frontal, parietal and temporal lobes. These are mainly related to higher sensory association areas rather than primary

### TABLE 4: Brain areas in which relative glucose metabolism (rGMR) measured using positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) was significantly ($P < 0.05$) decreased after propofol anaesthesia in eight volunteers compared with control data for the awake state in 18 healthy people

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann’s area</th>
<th>Coordinates (mm)$^a$</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Voxel $z$-score</th>
<th>Voxel $P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital lobe</td>
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</tr>
<tr>
<td>Inferior occipital gyrus (L)</td>
<td>18</td>
<td>–30</td>
<td>–88</td>
<td>–24</td>
<td>2.64</td>
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<td>Lingual gyrus</td>
<td>18, 19</td>
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<td>Cuneus (R)</td>
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<td>–92</td>
<td>20</td>
<td>3.36</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Lateral occipital gyrus (L)</td>
<td>19</td>
<td>–24</td>
<td>–78</td>
<td>26</td>
<td>2.70</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus (L)</td>
<td>7</td>
<td>–12</td>
<td>–60</td>
<td>46</td>
<td>3.90</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Precuneus (R)</td>
<td>7</td>
<td>12</td>
<td>–62</td>
<td>50</td>
<td>2.59</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Inferior parietal lobule (R)</td>
<td>40</td>
<td>40</td>
<td>–56</td>
<td>42</td>
<td>2.21</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Inferior parietal lobule (L)</td>
<td>40</td>
<td>–40</td>
<td>–48</td>
<td>40</td>
<td>2.43</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Postcentral gyrus (L)</td>
<td>1, 2</td>
<td>–34</td>
<td>–40</td>
<td>72</td>
<td>2.36</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus (R)</td>
<td>37</td>
<td>–30</td>
<td>–88</td>
<td>–24</td>
<td>2.64</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus (L)</td>
<td>37</td>
<td>–24</td>
<td>–90</td>
<td>14</td>
<td>2.54</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precentral gyrus (L)</td>
<td>6</td>
<td>–40</td>
<td>0</td>
<td>38</td>
<td>2.10</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Precentral gyrus (R)</td>
<td>6</td>
<td>34</td>
<td>0</td>
<td>42</td>
<td>2.18</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Insula (L)</td>
<td>13</td>
<td>–48</td>
<td>–38</td>
<td>16</td>
<td>2.04</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Cerebellum (L)</td>
<td>13</td>
<td>–4</td>
<td>–88</td>
<td>–18</td>
<td>2.57</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

$^a$The coordinates are given for the maximally significant pixel in each cluster and other neuroanatomically significant regions within each cluster according to a standard stereotactic map.\textsuperscript{11} R, right; L, left.
sensory and motor regions, and to higher functions of the brain such as cognition, recognition and language. The results shown here may provide clues regarding the differences between the actions of these two anaesthetics. For example, our results may explain, at least in part, why propofol has a lower analgesic effect than sevoflurane. A signal generated by a stimulus perceived by a peripheral receptor reaches the thalamus via the spinothalamic and spinoreticular tracts, and is projected onto the corresponding cerebral cortex. Among these regions, the thalamus, insula, cingulate gyrus (BA 24, 25 and 32), and the primary and secondary somatosensory areas (BA 1, 2, 3 and 5) are closely associated with pain perception. 13 – 16 All these areas, except for the commonly suppressed somatosensory area, are not easily suppressed by propofol but are more suppressed by sevoflurane.

Propofol anaesthesia has been reported to decrease significantly glucose metabolism in the superior parietal gyrus and angular gyrus of the cortical area and, in general, to decrease glucose metabolism in the cortical area more than in subcortical structures. 6 We observed similar results, as shown by the greater suppression by propofol in cortical areas. We also found that sevoflurane suppressed the rGMR more than propofol in regions of the occipital lobe, thalamus, cerebellum and hippocampus, regions in which absolute cerebral glucose metabolism was greatly decreased during isoflurane 7 or halothane 8 anaesthesia. These results suggest that inhalant anaesthetics have a common interactive mechanism that differs from that of intravenous anaesthetics.

**TABLE 5:**

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann’s area</th>
<th>Coordinates (mm)a</th>
<th>Voxel z-score</th>
<th>Voxel P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal gyrus (L)</td>
<td>38</td>
<td>–26  20  –50</td>
<td>2.24</td>
<td>0.013</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>11</td>
<td>–10  70  –22</td>
<td>2.86</td>
<td>0.002</td>
</tr>
<tr>
<td>Middle frontal gyrus (R)</td>
<td>10</td>
<td>18  68  30</td>
<td>1.97</td>
<td>0.024</td>
</tr>
<tr>
<td>Precentral gyrus (L)</td>
<td>4</td>
<td>–62  –6  18</td>
<td>2.04</td>
<td>0.021</td>
</tr>
<tr>
<td>Insula</td>
<td>43</td>
<td>–62  –6  18</td>
<td>2.04</td>
<td>0.021</td>
</tr>
<tr>
<td>Limbic system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>24, 25, 32</td>
<td>–20  –10  40</td>
<td>2.97</td>
<td>0.002</td>
</tr>
<tr>
<td>Thalamus/Basal ganglia</td>
<td>–16</td>
<td>–4  26</td>
<td>2.95</td>
<td>0.002</td>
</tr>
<tr>
<td>Brainstem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medulla, midbrain, pons</td>
<td>–4</td>
<td>–12  –22</td>
<td>2.92</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*aThe coordinates are given for the maximally significant pixel in each cluster and other neuroanatomically significant regions within each cluster according to a standard stereotactic map. 11 R, right; L, left.*
In rats, sevoflurane anaesthesia was shown to increase absolute regional brain metabolism in the region of the inner habenula nucleus, part of the hippocampus and part of the substantia nigra. Regions in which absolute metabolism was increased by sevoflurane should also show an increase in relative metabolism, but we were unable to identify such an increase in these regions. Isoflurane has also been reported to increase regional brain metabolism in the same regions in rats but not in humans. These differences may be due to differences in brain structure or function between rats and humans. Indeed, specific regions of rat brains were especially resistant to the effects of anaesthetic-induced decreases in metabolism.

In the present study we found that sevoflurane significantly decreased heart rate and blood pressure, whereas propofol decreased blood pressure only. With both anaesthetics, however, heart rate and blood pressure were in the range at which cerebral autoregulation is maintained. In addition, we observed no differences in end-tidal $\text{CO}_2$ density, suggesting that these cardiovascular differences did not affect the results.

The main limitation of this study was the absence of measurements of absolute cerebral glucose metabolic rates. These may not be necessary, however, since absolute glucose metabolic rates have been shown to be uniformly decreased in other studies. In studies of halothane, isoflurane and propofol, the whole-brain glucose metabolic rate decreased by 40 – 55%, and no brain region showed an increase. Moreover, studies have shown that sevoflurane decreases cerebral $O_2$ consumption by about 30 – 52%, as well as decreasing cerebral glucose metabolic rate in humans and rats by about 39% and 34 – 59%, respectively. Thus, although we did not measure absolute metabolic rate, it was reasonable to compare the relative changes induced by both anaesthetics while assuming that the absolute metabolic rate will decrease. Further research should include measuring the absolute volume of cerebral glucose metabolic changes, quantifying the decreased metabolism induced by sevoflurane, and directly comparing sevoflurane with other anaesthetics.

In conclusion, we have shown here that, during anaesthetic-induced unconsciousness, the neocortex region was suppressed more by propofol than by sevoflurane, whereas the paleocortex, metencephalon and thalamus were suppressed more by sevoflurane than by propofol. These findings suggest that these two anaesthetics act via different mechanisms. This should prove helpful in determining the common and differing characteristics of these two anaesthetics, and may lead to a greater understanding of the mechanism of anaesthesia.

**Conflicts of interest**
No conflicts of interest were declared in relation to this article.

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