Positron Emission Tomography Study of Regional Cerebral Metabolism during General Anesthesia with Xenon in Humans

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Background: The precise mechanism by which the gaseous anesthetic xenon exerts its effects in the human brain remains unknown. Xenon has only negligible effects on inhibitory γ-aminobutyric acid receptors, one of the putative molecular targets for most general anesthetics. Instead, xenon has been suggested to induce anesthesia by inhibiting excitatory glutamatergic signaling. Therefore, the authors hypothesized that xenon, similar to ketamine and nitrous oxide, increases global and regional cerebral metabolism in humans.

Methods: The regional cerebral metabolic rate of glucose (rcMRGlu) was sequentially assessed in two groups of six volunteers each, using 18F-fluorodeoxyglucose as tracer. In the xenon group, rcMRGlu was determined at baseline and during general anesthesia induced with propofol and maintained with 1 minimum alveolar concentration xenon. In the control group, rcMRGlu was measured using the identical study protocol but without administration of xenon. rcMRGlu was assessed after the plasma concentration of propofol had decreased to subanesthetic levels (1.0 μg/ml). rcMRGlu was quantified in 10 cerebral volumes of interest. In addition, voxel-wise changes in rcMRGlu were analyzed using statistical parametric mapping.

Results: Xenon reduced whole-brain metabolic rate of glucose by 26 ± 7% (from 43 ± 5 μmol · 100 g −1 · min −1 to 31 ± 3 μmol · 100 g −1 · min −1; P < 0.005) and significantly decreased rcMRGlu in all volumes of interest compared with the control group receiving propofol only. Voxel-based analysis revealed metabolic depression within the orbitofrontal, frontomesial, temporomesial, occipital, dorsolateral frontal, and lateral temporal cortices and thalami. No increases in rcMRGlu were detected during xenon anesthesia.

Conclusions: Xenon induces metabolic depression in the human brain, suggesting that the inhibition of the glutamatergic system is likely to be of minor significance for the anesthetic action of xenon in vivo.

THE exact mechanism by which the gaseous anesthetic xenon exerts its effects in the brain remains to be confirmed in humans. Unlike the majority of general anesthetics, xenon does not enhance the activity of inhibitory γ-aminobutyric acid type A receptors.1–3 Instead, xenon has been shown to interfere with excitatory neuronal mechanisms by inhibiting N-methyl-D-aspartate (NMDA) glutamate channels.5,6 However, xenon was also shown to activate background potassium channels, thereby inducing neuronal hyperpolarization by increasing potassium conductance.4 Interestingly, background potassium channels represent molecular targets that are also involved in the mechanism of action of volatile anesthetics.5–7

Neuronal activity and energy metabolism are tightly coupled within the brain.8 Changes in both global and regional cerebral glucose metabolism as a surrogate marker of neuronal activity can be elegantly measured in vivo using 18F-labeled fluorodeoxyglucose ([18F]FDG) as a tracer for positron emission tomography (PET). Hence, this technique can be used to identify neural structures related to anesthetic actions in the human brain.9 Several volatile anesthetics10–12 and propofol13 have been shown to depress both global and regional cerebral metabolism. In contrast, the NMDA antagonists ketamine14–16 and nitrous oxide12,17 were shown to increase cerebral metabolism. To further explore the neural mechanism of xenon anesthesia in humans, we analyzed the effects of general anesthesia with 1 minimum alveolar concentration (MAC) xenon on the regional cerebral metabolic rate of glucose (rcMRGlu) using PET. Based on the fact that xenon shows an anesthetic profile comparable to that of ketamine and nitrous oxide (but dissimilar to that of volatile anesthetics or propofol),18,19 we hypothesized that NMDA antagonism is the primary mechanism of action for xenon in vivo. We therefore expected xenon anesthesia to increase global and regional cerebral metabolism.

Materials and Methods

This study was approved by the institutional review board (Ethik-Kommission, Medical Faculty, Rheinisch-Westfälische Technische Hochschule, Aachen, Germany) and the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz, Salzgitter, Germany). After the experimental procedure and possible side effects...
had been explained in detail, all subjects gave written informed consent.

Subjects
Twelve adult, right-handed, male volunteers were recruited through flyers and the Internet and underwent a careful medical examination before being admitted to the study. All subjects were nonsmokers and in excellent medical condition (American Society of Anesthesiologists physical status I). None of them had a history of neuropsychiatric or other severe diseases or drug abuse, which was confirmed with a toxicologic urine test. All volunteers received financial compensation for their inconvenience.

Study Protocol
The effects of xenon anesthesia on rCMRGlucose were studied in six participants (xenon group). Each subject underwent two separate PET scans in randomized order: One to assess rCMRGlucose in the awake state, the other to analyze rCMRGlucose during general anesthesia with 1 MAC xenon. rCMRGlucose was analyzed using \([^{18}\text{F}]\text{FDG}\) as PET tracer. Because of the long half-life of \([^{18}\text{F}]\text{FDG}\), the two PET scans were separated by at least 2 days.

Subjects fasted for at least 8 h and were free of caffeine for 24 h before undergoing a PET scan. Anesthetic procedures, administration of \([^{18}\text{F}]\text{FDG}\), and the PET scans were performed in a soundproof room with dim lighting. The volunteers were instructed to close their eyes and not to move during the uptake period of \([^{18}\text{F}]\text{FDG}\) and the scanning procedure. All subjects breathed room air during the PET scans.

During each scan, physiologic monitoring consisted of three-lead electrocardiography; intermittent oscillometric noninvasive blood pressure measurement; pulse oximetry (all Datex Ohmeda GmbH, Duisburg, Germany); continuous measurements of inspired and expired oxygen, nitrogen, carbon dioxide, and xenon (Physioflex; Dräger Medical Deutschland GmbH, Lübeck, Germany); and the scanning procedure. All subjects breathed room air during the PET scans.

Anesthesia
After denitrogenation with 100% oxygen, anesthesia was induced with a target-controlled infusion (TCI) of propofol (Pilot Anesthesia syringe pump with a Master TCI unit; Becton Dickinson, Heidelberg, Germany). The pump was controlled by the Diprifusor TCI software algorithm (AstraZeneca, Macclesfield, United Kingdom). Anesthesia was induced with a target plasma concentration of approximately 11 \(\mu\text{g/ml}\) to allow the insertion of a laryngeal mask (LMA). The propofol infusion was stopped when the airway had been instrumented. Anesthesia was then maintained with xenon (61 ± 1% in oxygen) using a closed-circuit anesthesia machine (Physioflex). Subjects were ventilated with pressure control maintaining normocapnia.

\(^{18}\text{F}\)-labeled fluorodeoxyglucose was administered when (1) the calculated propofol plasma concentrations were below 1.0 \(\mu\text{g/ml}\), i.e., in a subanesthetic range; and (2) a deep level (Bispectral Index < 35) and steady state of general anesthesia with 1 MAC xenon was achieved. Both criteria were achieved within 41 ± 7 min of xenon anesthesia. After this time, the equilibration of xenon with the gray and the white matter of the brain is accomplished. Furthermore, the duration of the inhalation period reflects the typical clinical use of xenon in high concentrations for longer lasting anesthetic procedures.

After the uptake period, administration of xenon was stopped, and the LMA was removed after spontaneous breathing had resumed. After emergence from anesthesia, subjects underwent PET scanning.

To minimize confounding effects by the remaining subanesthetic levels of propofol on xenon-induced changes in rCMRGlucose, six additional control subjects (propofol group) were examined with the identical study protocol but without using xenon or an LMA. Where necessary, ventilation was assisted with a face-mask. Again, \([^{18}\text{F}]\text{FDG}\) was administered when the calculated propofol plasma concentrations had decreased from the induction level of approximately 11 \(\mu\text{g/ml}\) to less than 1.0 \(\mu\text{g/ml}\).

Positron Emission Tomography/Imaging Protocol
Positron emission tomography examinations were run on an ECAT 922/47 Scanner (Siemens/CTI, Knoxville, TN). Subjects were positioned according to the canthomeatal line using a head holder and laser guidance.
Approximately 250 MBq [18F]FDG was administered as a bolus injection. Forty minutes after tracer injection, PET acquisition was started in two-dimensional mode with an acquisition time of 20 min. Reconstruction of 47 transversal slices in a 128 × 128 matrix was performed using filtered back projection with a Hanning filter (cutoff frequency 0.45). Using a zoom of 3 resulted in pixel sizes of 1.72 × 1.72 × 3.38 mm³. Calculated attenuation correction of the data was performed to avoid interference from misalignment between emission and transmission scans. Arterialized venous blood samples were taken 10, 20, and 40 s and 1, 2, 4, 6, 8, 10, 20, 30, 40, and 60 min after [18F]FDG injection.

Quantification of the global and regional metabolic rate of glucose was performed as described in detail elsewhere. Briefly, plasma 18F activity was determined using an automated cross-calibrated well counter (HPGe-Spectrummy master 92X, EG&G Ortec, Oak Ridge, TN) to obtain the [18F]FDG input function. The absolute glucose consumption rate was calculated for each pixel (autoradiography method according to Sokoloff and Phelps) using the measured input function as well as tissue radioactivity and blood glucose concentration. For quantification, a set of rate constants, k1–k4 (k1: 0.095, k2: 0.125, k3: 0.069, k4: 0.0055), and a lumped constant of 0.52 were used. It was assumed that xenon has no effect on this constant.

Analysis of Image Data
Reconstructed and quantified images (pixel-wise units: μmol · 100 g⁻¹ · min⁻¹) were imported into a commercially available pixel-wise modeling software (PMOD; PMOD Technologies, Adliswil, Switzerland). All image data sets were reoriented and projected onto an isotropic [18F]FDG brain template, which was aligned with the anterior commissure–posterior commissure line (pixel size 2 × 2 × 2 mm³) by an iterative elastic projection method. In the individual elastic projections, volumes of interest (VOIs) were identified using a standard VOI set defined on the isotropic [18F]FDG brain template. The VOI set sampled cortical and subcortical brain regions: frontal cortex (117 ml per side on 49 image planes), temporal cortex (56 ml per side on 30 image planes), temporomesial cortex (16 ml per side on 15 image planes), insula (3 ml per side on 5 image planes), striatum (10 ml per side on 14 image planes), thalamus (5 ml per side on 10 image planes), cerebellum (91 ml on 13 image planes), pons (6 ml on 7 image planes), occipital cortex (14 ml per side on 17 image planes), and parietal cortex (66 ml per side on 26 image planes). Except for the pons and the cerebellum, all VOIs were defined bilaterally. The mean regional metabolic rate of glucose was calculated for all VOIs by averaging all pixels within the respective VOI. The global metabolic rate of glucose was calculated as the volume-weighted average of rCMRGlus of all evaluated regions.

Statistical Analysis of VOI and Physiologic Variables
Power analysis reveals a minimal sample size of five volunteers to detect a 25% effect on whole-brain metabolic rate of glucose (given an SD of 20%), when a level of significance of 0.05 and a power of 80% are to be achieved.

Results were statistically analyzed using a commercially available software package (Statistica for Windows version 6.0; Statsoft, Tulsa, OK).

The effects of the drugs on rCMRGlus in both hemispheres were compared using repeated-measures analysis of variance with the two factors treatment (awake vs. drug) and side (left vs. right hemisphere). To test the global hypothesis that cerebral metabolism and physiologic variables are affected by 1 MAC xenon compared with subanesthetic levels of propofol alone, we performed a repeated-measures analysis of variance with the factors treatment (awake vs. drug) and group (xenon vs. propofol). Whenever the repeated-measures analysis of variance indicated a significant interaction effect, horizontal (treatment vs. awake) and vertical (xenon vs. propofol) pairwise contrasts were analyzed using paired or unpaired Student t test. Statistical comparisons of percentage data between groups were performed using the nonparametric Mann–Whitney U test.

Data from each VOI were treated as independent variables. Following the literature, P values obtained for each brain region were not corrected for the numbers of all analyzed VOIs. A two-sided P value of less than 0.05 was considered statistically significant. Data are presented as mean ± SD.

Voxel-based Analyses: Statistical Parametric Mapping
To assess voxel-wise changes in rCMRGlus, PET data were analyzed using the statistical parametric mapping (SPM2) software package (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, United Kingdom) implemented on Matlab (The Mathworks, Inc., Natick, MA). All scans were spatially normalized to the standard anatomical SPM space with the voxel size being interpolated to 2 × 2 × 2 mm³. Subsequently, all scans were smoothed by an isotropic gaussian filter (10 mm full-width at half-maximum). All analyses were performed on parametric rCMRGlus images (i.e., without proportional scaling). SPM(t) were calculated with a threshold for a cluster size of 30 voxels (0.24 cm³) and a t value corresponding to P < 0.001 (i.e., t = 5.89 in case of a paired t test and t = 4.14 in case of an unpaired t test). Paired t tests were used for comparing the awake and anesthesia conditions within groups. Unpaired t tests were used for between-group comparisons (awake vs. awake and propofol only vs. xenon, respectively). Given the limited statistical power of our study and its explorative nature, we did not correct for multiple comparisons.
not apply a correction for multiple comparisons to avoid too-conservative testing.34 As guidance for anatomical localization, the Talairach Daemon software (University of Texas Health Science Center at San Antonio, San Antonio, TX)** was used. Beforehand, the Montreal Neurologic Institute (McGill University, Montreal, Quebec, Canada) coordinates received from the SPM analyses were converted to Talairach coordinates.35

Results

Groups were comparable with respect to biometric data (table 1). General anesthesia with 1 MAC xenon (61 ± 2 vol%) was associated with a deep state of anesthesia, as judged by clinical signs. Moreover, the Bispectral Index showed a profound decrease. On the other hand, subanesthetic plasma levels of propofol alone (0.55 ± 0.06 μg/ml) led only to light sedation according to the Bispectral Index (table 1). Xenon anesthesia was well tolerated by all participants. Cardiopulmonary parameters did not differ from those in the low-dose propofol group. When compared with the awake state, xenon caused a slightly lower heart rate.

VOI-based Analyses

 Differences between hemispheres could be excluded in all analyzed brain regions, in both the waking and the anesthetized states.

The effects of xenon on rcMRGlu were highly significant compared with subjects receiving propofol alone (figs. 1–3). Whole-brain metabolic rate of glucose was reduced by 26 ± 7% in general anesthesia with 1 MAC xenon (from 43 ± 5 μmol · 100 g−1 · min−1 to 31 ± 3 μmol · 100 g−1 · min−1).

Xenon significantly decreased cerebral metabolism in all brain areas. The greatest decrease was detected in the parietal (−28 ± 9%) and cerebellar (−28 ± 6%) cortex, whereas rcMRGlu was least affected in the striatum (−20 ± 6%) and the pons (−16 ± 5%) (fig. 2). An absolute increase of rcMRGlu could not be found in any of the studied VOIs.

Propofol alone did not affect cerebral metabolism, neither globally nor in any analyzed cerebral region (figs. 1–3). SDs for absolute rcMRGlu in the propofol group were significantly higher than in the xenon group. One participant consistently showed a metabolism approximately twice as high in all brain areas, both in the waking state and during propofol sedation.

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Table 1. Biometric, Apparative, and Physiologic Variables in the Two Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Xenon Group Awake</th>
<th>Anesthesia</th>
<th>Propofol Group Awake</th>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>33 ± 3</td>
<td>33 ± 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size, cm</td>
<td>184 ± 10</td>
<td>180 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86 ± 11</td>
<td>85 ± 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xe\textsubscript{Inspir}, %</td>
<td>61 ± 2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TC\textsubscript{Inspir}, μg/ml</td>
<td>11.56 ± 2.17</td>
<td>11.35 ± 0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC\textsubscript{FIDG}, μg/ml</td>
<td>0.69 ± 0.17</td>
<td>0.55 ± 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS</td>
<td>96 ± 1</td>
<td>97 ± 1</td>
<td>89 ± 4*‡</td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>63 ± 6</td>
<td>59 ± 10</td>
<td>56 ± 9</td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92 ± 6</td>
<td>85 ± 5</td>
<td>79 ± 6</td>
<td></td>
</tr>
<tr>
<td>SpO\textsubscript{2}, %</td>
<td>96 ± 1</td>
<td>98 ± 2</td>
<td>97 ± 2</td>
<td></td>
</tr>
<tr>
<td>ETCO\textsubscript{2}, mmHg</td>
<td>40 ± 3</td>
<td>40 ± 2</td>
<td>41 ± 2</td>
<td></td>
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<tr>
<td>Temperature, °C</td>
<td>36.0 ± 0.4</td>
<td>35.7 ± 0.3</td>
<td>36.0 ± 0.5</td>
<td>35.5 ± 0.1</td>
</tr>
</tbody>
</table>

Data are mean ± SD. All parameters except calculated propofol plasma concentration for induction of anesthesia (TC\textsubscript{Ind}) are averaged for the uptake period of 18F-labeled fluorodeoxyglucose.

* P < 0.05, † P < 0.0001 vs. awake, ‡ P < 0.0001, propofol vs. xenon.

BIS = Bispectral Index; ETCO\textsubscript{2} = end-tidal carbon dioxide concentration; HR = heart rate; MAP = mean arterial pressure; SpO\textsubscript{2} = partial oxygen saturation; TC\textsubscript{FIDG} = calculated propofol plasma concentration during 18F-labeled fluorodeoxyglucose-uptake period; Xe\textsubscript{Inspir} = inspiratory xenon concentration.

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Fig. 1. (A) Absolute values of regional cerebral metabolic rate of glucose (rcMRGlu) in the awake condition and during general anesthesia with 1 minimum alveolar concentration xenon. (B) rcMRGlu in the awake condition and during sedation with subanesthetic concentrations of propofol (target concentration level < 1.0 μg/ml). For comparison, values of global MRGlu are in addition shown. Data are presented as mean ± SD. *** P < 0.01, **** P < 0.005, †††† P < 0.0001, drug versus awake. † P < 0.05, ‡ P < 0.005, xenon versus propofol.
Voxel-based Analyses: Statistical Parametric Mapping

Statistical parametric mapping analyses revealed no significant differences between the groups in the awake condition (even after decreasing the threshold to $P < 0.01$). Subanesthetic plasma levels of propofol alone were not associated with any increases or decreases in rcMRGlu (even at $P < 0.01$) when compared with the waking state. General anesthesia with 1 MAC xenon resulted in a widespread metabolic depression within the brain when compared with the waking state (data not shown). In comparison with the control group receiving subanesthetic concentrations of propofol alone, subjects undergoing general anesthesia with 1 MAC xenon showed a significant decrease in rcMRGlu in several brain areas, including the bilateral orbitofrontal, frontomesial, temporomesial, occipital, dorsolateral frontal (pronounced on right side), and lateral temporal (pronounced on right side) cortices and thalami ($P < 0.001$; table 2 and figure 4). No increases in rcMRGlu could be detected during xenon anesthesia (even at $P < 0.01$).

Discussion

We could demonstrate that general anesthesia with 1 MAC xenon induces a global decrease in cerebral metabolism. Although rcMRGlu was decreased in all analyzed VOIs, the effects of xenon on cerebral metabolism were not uniformly distributed throughout the brain. Voxel-based analyses revealed the greatest decreases in several cortical areas and in the thalamus. No increases in rcMRGlu could be detected during xenon anesthesia.

In the current study, 1 MAC xenon significantly depressed cerebral metabolism, both globally and regionally. These findings are opposite to observations with anesthetics known to interact with the excitatory NMDA receptor system. Both nitrous oxide$^{12,17}$ and ketamine$^{14}$ have been reported to increase cerebral metabolism. This difference may, at least in part, be attributed to the fact that less potent anesthetic concentrations were used in the above-mentioned studies. Ketamine was infused to target subanesthetic plasma levels, whereas nitrous oxide was administered either as an adjunct to other anesthetics$^{12}$ or in subanesthetic concentrations.$^{17}$ Lack of equipotency might also explain why in one study 70% xenon was found not to affect mean cerebral metabolism in rats.$^{36}$ However, because the MAC of xenon in rats is higher than 1.6 atm,$^{37}$ only less than 0.5 MAC xenon was analyzed. In contrast, we studied the effects of more than 60% xenon, i.e., 1 MAC in humans.$^{38}$ In fact, the xenon concentration chosen in our study was associated with a deep state of anesthesia, as suggested by clinical signs. Although not validated for xenon, the Bispectral Index accordingly showed a profound decrease, probably indicative of a pattern of high-voltage/low-frequency electroencephalographic activity characteristic of anesthesia.$^{39,40}$

However, our findings of metabolic depression during xenon anesthesia cannot entirely be attributed to differences in anesthetic potency. Even when administered in high anesthetic concentrations allowing general anesthesia, ketamine was found not to depress global cerebral metabolism but to increase regional metabolism in the
thalamus. Hence, cerebral metabolic activation seems to be a common pattern of anesthesia with NMDA antagonists, irrespective of the administered doses. Consequently, the cerebral metabolic pattern of xenon anesthesia observed in our study is not confirmative for NMDA antagonism as the primary mode of anesthetic action for xenon *in vivo*. In contrast, the metabolic pattern of xenon anesthesia resembles more that reported for volatile anesthetics. Because background potassium channels have been shown as molecular targets being involved in the mechanism of action of both volatile anesthetics and xenon, it is tempting to speculate that xenon anesthesia may be predominantly mediated *via* this mechanism.

Although we could demonstrate a xenon-induced reduction in cerebral metabolism, this decrease was less pronounced than reported from volatile anesthetics or propofol administered in less potent doses. The reasons why xenon affected cerebral metabolism less prominently than reported from volatile anesthetics or xenon, it is tempting to speculate that xenon anesthesia may be predominantly mediated *via* this mechanism. 

Another important finding in our study was that xenon—according to VOI- and voxel-based analysis with SPM—profoundly decreased cerebral activity in the thalamus. Hyperpolarization of thalamocortical neurons has been recently postulated as the essential common neurophysiologic mechanism underlying anesthetic-induced unconsciousness. Thalamocortical hyperpolarization is described to result from different mechanisms, one of which is the inhibition of excitatory cholinergic pathways evolving from the pontine reticular formation and projecting to the basal forebrain and the thalamus.

In fact, SPM analysis also revealed a profound metabolic depression in both orbitofrontal cortices. Hence, our data apparently confirm recent theories on the neurobiology of anesthesia. Other cerebral regions remarkably affected by xenon were the temporal cortex and the temporomesial region, including the amygdala and hippocampal fields. These brain regions are critically involved in the control of pain, memory, and autonomic cardiovascular regulation.

### Table 2. Brain Areas with Xenon-induced Significant Decreases in rcMRGlut, Assessed by Voxel-based Analysis with Statistical Parametric Mapping

<table>
<thead>
<tr>
<th>Area</th>
<th>BA</th>
<th>Voxel Number</th>
<th>t Value</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe Rectal gyrus</td>
<td>R 11</td>
<td>9,741</td>
<td>8.64</td>
<td>10</td>
</tr>
<tr>
<td>Frontal lobe Rectal gyrus</td>
<td>R 11</td>
<td>7.84</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Temporal lobe Temporal pole</td>
<td>L 38</td>
<td>7.78</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Sublobar Thalamus</td>
<td>L 27</td>
<td>975</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Sublobar Thalamus</td>
<td>R</td>
<td>6.66</td>
<td>16</td>
<td>32</td>
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<tr>
<td>Sublobar Thalamus</td>
<td>L</td>
<td>4.84</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Occipital lobe Lingual gyrus</td>
<td>L 18</td>
<td>1,305</td>
<td>6.62</td>
<td>6</td>
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<tr>
<td>Occipital lobe Lingual gyrus</td>
<td>R</td>
<td>5.57</td>
<td>22</td>
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<td>R 18</td>
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<td>86</td>
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<tr>
<td>Frontal lobe Middle frontal gyrus</td>
<td>R 9</td>
<td>875</td>
<td>5.73</td>
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<tr>
<td>Frontal lobe Middle frontal gyrus</td>
<td>R 6</td>
<td>5.52</td>
<td>34</td>
<td>20</td>
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<tr>
<td>Frontal lobe Superior frontal gyrus</td>
<td>R 8</td>
<td>5.38</td>
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<tr>
<td>Temporal lobe Parahippocampal gyrus</td>
<td>R 28</td>
<td>106</td>
<td>4.77</td>
<td>24</td>
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<tr>
<td>Parietal lobe Inferior parietal lobule</td>
<td>R 39</td>
<td>63</td>
<td>4.69</td>
<td>54</td>
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<td>Temporal lobe Middle temporal gyrus</td>
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<td>4.67</td>
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<tr>
<td>Frontal lobe Superior frontal gyrus</td>
<td>L 11</td>
<td>32</td>
<td>4.54</td>
<td>18</td>
</tr>
</tbody>
</table>

General anesthesia with 1 minimum alveolar concentration xenon was compared with sedation using subanesthetic concentrations of propofol (target concentration level < 1.0 μg/ml). Only clusters exceeding the height threshold *t* > 4.14 (*P* < 0.001) and the extent threshold of 30 voxels are listed. A maximum of three submaxima are reported being at least 8 mm apart from each other.

BA = Brodmann area; L = left hemisphere; MNI = Montreal Neurological Institute; R = right hemisphere; rcMRGlut = regional cerebral metabolic rate of glucose.
the unique characteristics of xenon—including its analgesic properties and the minor impairment of hemodynamic parameters—may be partly associated with depression of distinct cerebral areas.

In this study, high doses of propofol were required to induce anesthesia and to allow the insertion of an LMA in unpremedicated healthy subjects. To reduce the confounding impact of propofol on xenon-mediated effects on rcMRGlu, propofol was immediately stopped after insertion of the LMA, and [18F]FDG was only administered after the calculated propofol plasma levels had decreased below 1.0 μg/ml. To avoid arterial cannulation and its inherent risks for the participating subjects, propofol plasma concentrations were not determined directly. Instead, a TCI system was used to predict propofol values as a surrogate for actual plasma concentrations. Precision of the TCI system used in our study was shown to be relatively low, resulting in plasma levels of 0.44–1.38 μg/ml when 1.0 μg/ml is targeted.51 Nevertheless, we suggest that neither the use of propofol nor the TCI system significantly affected the effects observed during xenon anesthesia. In a range of plasma concentrations of 0.5–1.5 μg/ml, propofol induces only a light sedation and does not affect or only slightly affects regional cerebral blood flow.21,52,53 This indicates that propofol doses as used in our study are most probably devoid of effects on cerebral metabolism because coupling between cerebral metabolism and flow is not disturbed by propofol.12 Moreover, a control group was included to analyze the effects of propofol alone on rcMRGlu. In this group, subanesthetic levels of propofol were devoid of any metabolic effects in the brain. Therefore, it seems unlikely that the observed effects during xenon anesthesia were significantly confounded by residual propofol concentrations, although small effects of propofol on our findings during xenon anesthesia cannot entirely be ruled out.

Fig. 4. Brain areas with xenon-induced significant decreases in regional cerebral metabolic rate of glucose, assessed by voxel-based analysis with statistical parametric mapping (SPM). General anesthesia with 1 minimum alveolar concentration xenon was compared with sedation using subanesthetic concentrations of propofol (target concentration level < 1.0 μg/ml). (A) SPM t map glass brain illustration (right lateral view, back to front view, top to bottom view). Voxel darkness increases with increasing t value. (B) Overlay of the t maps on the SPM single-subject template. Areas of metabolic depression are color coded in dependency of statistical significance. (C) Overlay of the t map onto transversal sections of the SPM T1 magnetic resonance imaging template illustrating the crescent-shaped area of metabolic depression within the thalamus. For illustration of the results, the t map was thresholded at \( P < 0.005 \) (i.e., \( t = 3.17 \)).
In summary, the anesthetic state evident during general anesthesia with 1 MAC xenon is associated with a global metabolic depression in the human brain. This suggests that NMDA antagonism is not the primary mechanism of action for xenon in the human brain.

References