Propofol attenuates responses of the auditory cortex to acoustic stimulation in a dose-dependent manner: a FMRI study

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Propofol attenuates responses of the auditory cortex to acoustic stimulation in a dose-dependent manner: A FMRI study

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Background: Functional magnetic resonance imaging (fMRI) using blood-oxygen-level-dependent (BOLD) contrasts is a common method for studying sensory or cognitive brain functions. The aim of the present study was to assess the effect of the intravenous anaesthetic propofol on auditory-induced brain activation using BOLD contrast fMRI.
Methods: In eight neurosurgical patients, musical stimuli were presented binaurally in a block design. Imaging was performed under five conditions: no propofol (or wakefulness) and propofol plasma target concentrations of 0.5, 1.0, 1.5, and 2.0 μg ml^{-1}.
Results: During wakefulness we found activations in the superior temporal gyrus (STG) corresponding to the primary and secondary auditory cortex as well as in regions of higher functions of auditory information processing. The BOLD response decreased with increasing concentrations of propofol but remained partially preserved in areas of basic auditory processing in the STG during propofol 2.0 μg ml^{-1}.
Conclusions: Our results suggest a dose-dependent impairment of central processing of auditory information after propofol administration. These results are consistent with electrophysiological findings measuring neuronal activity directly, thus suggesting a dose-dependent impairment of central processing of auditory information after propofol administration. However, propofol did not totally blunt primary cortical responses to acoustic stimulation, indicating that patients may process auditory information under general anaesthesia.

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There is increasing knowledge about the actions of anaesthetic agents at the molecular level, whereas their effect on selected pathways of the central nervous system (CNS) remains an open issue. In general, auditory input is considered the last sensory modality to be blunted during anaesthesia (1). Functional magnetic resonance imaging (fMRI) is a non-invasive tool for studying the functioning of the human brain with the advantage of a much improved spatial resolution compared to the EEG-related method. It offers a promising approach for evaluating functional networks within the CNS, which has been demonstrated in previous studies of human central auditory processing (2).

The aim of the present study was to assess the activation of the auditory cortex at increasing targeted plasma concentrations of the intravenous anaesthetic propofol after acoustic stimulation using blood-oxygen-level-dependent (BOLD) contrast fMRI. Based on previous studies (3, 4), we hypothesized that propofol attenuates the auditory-induced fMRI signal in a dose-dependent manner.

Methods

Subjects

The institutional review board of the University of Cologne approved the study. After obtaining written informed consent, we studied eight patients with ASA physical status I–III scheduled for stereotactically guided surgery of a brain tumour under

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general anaesthesia. All patients had to be non-musicians and were examined neurologically prior to surgery. Exclusion criteria were a history of psychiatric disease (e.g. claustrophobia and depression), persisting neurological symptoms at the time of data acquisition (disturbances of auditory perception in particular), and left-handedness. A neuroradiologist reviewed preoperative MRI and/or CT-scans of all patients. Patients with shifts in midline or other tumour mass effects and localization of the tumour in brain areas associated with the auditory system were excluded.

Experimental design and procedure

Patients were kept fasting for at least 6 h prior to the investigation. During the experiment patients were placed supine on the gantry of the scanner and their heads were fixated to minimize involuntary head movements. Patients routinely received supplemental oxygen through a nasal canula at a rate of 3 l min^{-1}. Heart rate (HR), non-invasive mean arterial blood pressure (MAP), oxygen saturation (SaO_2), and endexpiratory CO_2 ($etCO_2$) were recorded in the middle of each functional run (Fig. 1) using a MR-compatible monitoring system.

Assessing the effect of propofol on the auditory-evoked BOLD signal requires an acoustic stimulus reliably inducing a stable and significant BOLD response in the auditory cortex. It has been shown that increasing stimulus complexity is associated with increased activation throughout the auditory cortical core and surrounding auditory regions (5). Therefore, a complex musical stimulus was presented binaurally. A digitally recorded sequence of the first 25 s of the Fourth Movement of L. vs. Beethoven's Ninth Symphony was delivered to the patients via air conduction through a semirigid silicone tube with an average intensity of 95 dB. A Y-connector split the tube for binaural stimulation through a tightly fitting noise-shielding headphone which reduced the scanner noise to a maximum of 65 dB during the functional imaging sequences.

The experimental protocol comprised five experimental conditions (Fig. 1): wakefulness (or no propofol) and four levels of sedation defined by four propofol plasma target concentrations (0.5 μg ml^{-1}, 1.0 μg ml^{-1}, 1.5 μg ml^{-1}, and 2.0 μg ml^{-1}) administered by a target-controlled-infusion (TCI) system (Diprifusor™, ALARIS, Medical Systems, Hampshire, UK). Each experiment started at wakefulness. Then, larger propofol target concentrations were delivered in ascending order. Plasma target levels were rapidly titrated by administration of bolus doses and maintained by a declining infusion rate. For each experimental condition, equilibration of the targeted plasma concentration and effect-site concentration as indicated by the TCI device had to be achieved before fMRI data acquisition was started.

During each experimental condition one functional data set (= 'functional run') was acquired (Fig. 1). During these functional runs the auditory

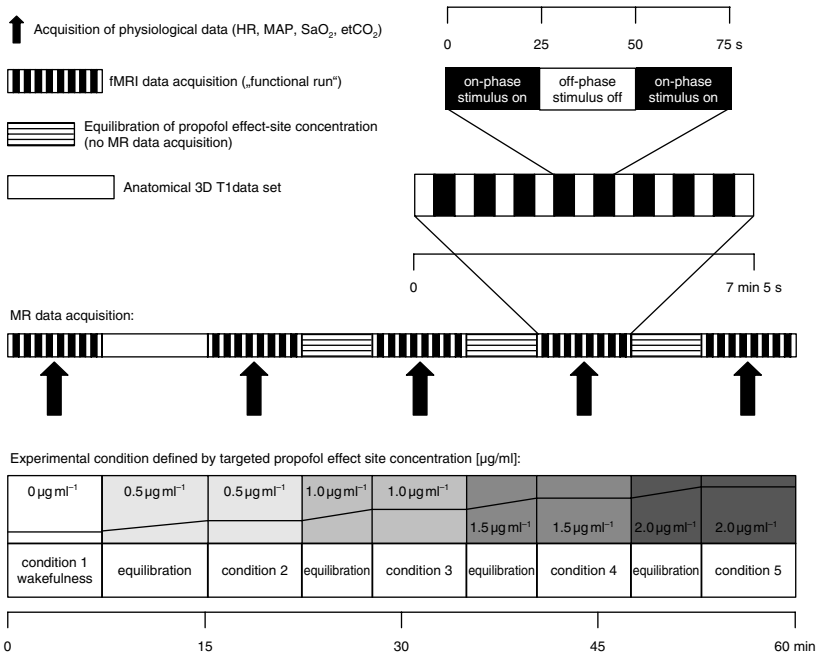

Fig. 1. Scheme of the experimental protocol. The auditory stimulus was presented during five experimental conditions: wakefulness (or no propofol), and four levels of sedation defined by four propofol plasma target concentrations of 0.5 μg ml^{-1}, 1.0 μg ml^{-1}, 1.5 μg ml^{-1}, and 2.0 μg ml^{-1} using a target-controlled infusion system. Equilibration of targeted propofol plasma concentration and effect-site concentration was achieved prior to fMRI data acquisition. One functional run was acquired during each experimental condition. During these functional runs the auditory stimulus was presented in a block design composed of stimulation periods (stimulus on) alternating with resting periods defined by the absence of the experimental stimulus (stimulus off), with each period lasting 25 s. Physiological data (HR, MAP, SaO_2, $etCO_2$) were recorded in the middle of each functional run.

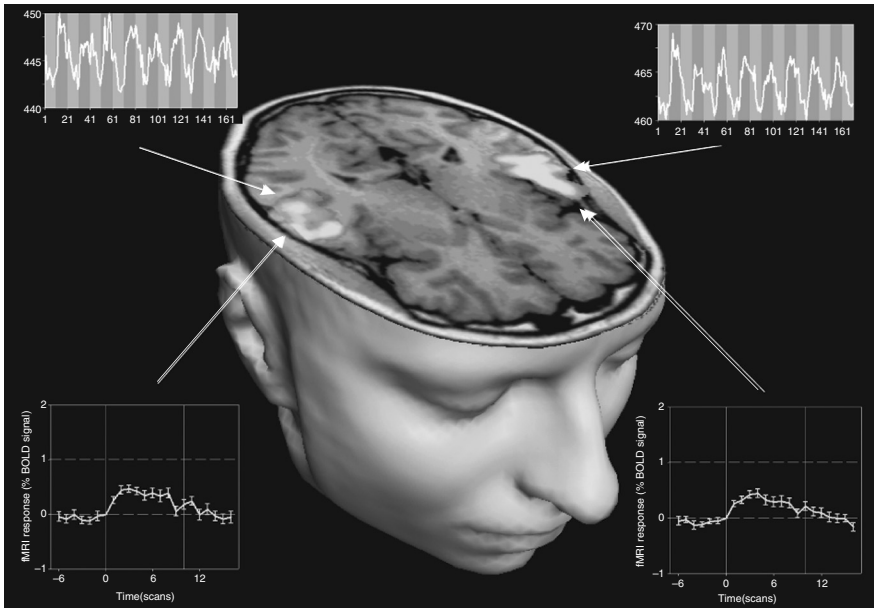

Fig. 2. Activation of the auditory cortex during acoustic stimulation. The transversal tomography shows the result of a group statistical parametric map of all subjects during wakefulness. The signal time courses (upper rectangles) depict the course of the BOLD signal of an individual subject while the lower rectangles demonstrate the mean BOLD signal plus standard deviation of the group analysis (n = 6).

stimulus was presented in a block design composed of nine resting periods defined by the absence of the experimental stimulus (off-phase) interleaved with eight stimulation periods (on-phase). The total scan time for each functional run was 7 min 5 s.

Throughout the study, an anaesthesiologist closely monitored the patients. MR-compatibleresuscitation material was readily available in the scanner room.

Functional magnetic resonance imaging

The MRI unit used was a commercial clinical whole body scanner with a magnetic field strength of 1.5 tesla (Gyroscan Intera, Powertrak 6000 Gradient Amplifier, Philips, Best, the Netherlands) provided with a standard quadrature head coil. Functional images were obtained using a single shot gradient-echo planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2500 ms, echo time (TE) = 50 ms, flip angle (FA) = 90°, matrix size = 64×64, field of view (FOV) = 230×230, slice order = descending, interleaved. Twenty-five contiguous horizontal slices with a slice thickness of 6 mm were orientated in parallel to the intercommissural line to cover the whole brain, including both the cortex and the cerebellum. For anatomical reference, a high-quality whole brain 3D T1-weighted data set (scan parameters: TR = 30 ms, TE = 4.6 ms, FA = 30°, number of slices = 200, slice thickness = 1.0 mm, no gap, total scan time = 7 min 54 s) was acquired for every patient after the first functional run and before administration of propofol (Fig. 1).

Statistical analysis

Physiological data

Physiological variables (HR, MAP, SaO_2, and $etCO_2$) were analyzed using ANOVA for repeated measures. A P-value <0.05 was considered significant. Results are presented as mean ±SD unless otherwise stated. The Statistical Package for the Social Sciences (SPSS, release 11.0, SPSS Inc., IL) was used for analysis of the physiological data.

Functional magnetic resonance imaging data

Data preprocessing

Prior to further statistical analysis, each of the five functional runs per subject (corresponding to the five experimental conditions) was subjected to a series of preprocessing steps: temporal high-pass filtering, interscan motion detection and correction, smoothing of each functional volume by spatial convolution with a Gaussian kernel with a full width at a half maximum of 4 mm, and Talairach-transformation of all anatomical and functional volumes to compare activated brain regions across subjects (6). Data sets with head movements >3 mm or 3° were excluded from further analysis. Only patients with a complete set of all five functional runs were included in the group analysis.

Statistical analysis

The statistical analysis was performed using a General Linear Model (GLM)-based statistical model of the expected changes of the fMRI signal.

In our study the model included five predictors (or explanatory variables) corresponding to the five experimental conditions: wakefulness (predictor 1), propofol 0.5 μg ml^{-1}, 1.0 μg ml^{-1}, 1.5 μg ml^{-1}, and 2.0 μg ml^{-1} (predictors 2–5). The fit of the model compared to the data is expressed as a statistical map, providing a statistical value for each individual voxel.

First, to analyze auditory processing in the unanaesthetized brain, a group-statistical parametric map of all subjects during wakefulness using *t* statistics was calculated. A voxel was considered activated if the *t*-test comparing mean on-phase to off-phase BOLD signals resulted in *t*-values corresponding to a threshold of $P < 0.05$ after a Bonferroni correction for multiple comparisons.

In a second step, one activated cluster in each auditory cortex (left and right) during wakefulness (no propofol) in the group map was defined as a region-of-interest (ROI) for a subsequent ROI analysis of experimental conditions 2–5. This assured that the ROI was defined in an independent experiment. Accordingly, data during wakefulness were not included in the ROI analysis itself. ROI analysis was then performed referring to the mean of the fMRI signal of all voxels defining the ROI. Thus, the ROI analysis does not consider multiple voxels but analyzes only one single volume, resulting in a less conservative statistics, since correction for multiple comparisons is not necessary. Beta weights for both ROIs were then calculated for each of the propofol conditions to estimate the fit of the model to the data (in the least squares sense). High beta values indicate a 'strong' activation or good fit and low beta values indicate a 'weak or absent' activation or poor fit. Furthermore, the significance of the beta weights is estimated with a *t*- and corresponding *P*-value.

As a third analysis step, individual statistical parametric maps of each patient during increasing propofol concentrations were examined and the last brain areas that demonstrated activation during increasing concentrations of propofol were determined for each individual.

The Brain Voyager 2000 software package (Version 4.7; Brain Innovation, Maastricht, the Netherlands) was used for all steps of the analysis of fMRI data. For anatomical reference the computed individual and group statistical maps were overlaid to anatomical scans. Activated clusters are reported using Talairach coordinates of the cluster's centre of spatial gravidity. Anatomical reference was checked using the Talairach Deamon Client (Version 1.1, Research Imaging Center, University of Texas, San Antonio, TX). Furthermore, the minimal distances between brain tumour and ROI clusters of the auditory system for each patient was calculated using the respective Talairach coordinates.

Results

Demographic and physiological data

Two patients were excluded from data analysis due to massive head movement. Therefore, data sets of one female and five male patients with an average height of 177 ± 13 cm, weight of 79 ± 24 kg, and age of 44 ± 15 years were used for the final analysis. All patients were sedated during propofol target plasma concentrations of 2 μg ml^{-1}, and promptly opened their eyes to verbal command. At this anaesthetic state all subjects spontaneously moved their heads and their upper and lower extremities to various degrees.

HR ($P = 0.29$) and MAP ($P = 0.49$) showed a slight but not significant decrease with increasing propofol plasma concentrations. Oxygen saturation was stable during the entire experiment. Three patients did not tolerate the nose canula necessary for measuring $etCO_2$. $EtCO_2$ values of the remaining three patients demonstrated a mean increase of 0.4 kPa during propofol 2 μg ml^{-1} compared with wakefulness.

The mean minimal distance between brain tumour and the two ROIs within the auditory system was 49.6 ± 21.1 mm (smallest distance = 29 mm).

Functional magnetic resonance imaging data

In the group analysis the complex binaural musical stimulus evoked two large coherent clusters of activation in the bilateral auditory cortex during wakefulness, with the left cluster being greater than the right (Table 1). Both clusters included areas of superior temporal gyrus and adjoining regions, which are all involved in auditory processing (7), in particular music processing (8, 9). According to Brodmann's classification, these areas were further divided into area (BA) 41 or primary auditory cortex, BA 42 and 22 (secondary or associative auditory cortex), BA 13 (insula), BA 6 (premotor cortex), and BA 40 (somatosensory association cortex) (Table 1, Fig. 2). In the awake state, activation was additionally detected in the right prefrontal cortex (BA 45), an area related to higher functions of auditory music processing (10).

Region-of-interest analysis revealed a decline of the beta weights for each increase in propofol

Table 1

Auditory-induced brain activation during wakefulness.

Location	Cluster size Number of voxels	Functional and anatomical subregion (Brodmann's area)	Talairach-coordinates			
			x	*y*	*z*	t_{max}
Left auditory cortex	18,377		−48	−20	9	12.90
		Left superior temporal gyrus (BA 22)	−52	−4	3	12.90
		Left transverse temporal gyrus (BA 41)	−53	−20	9	11.58
		Left superior temporal gyrus (BA 42)	−60	−26	14	9.31
		Left precentral gyrus (BA 6)	−51	−5	6	11.79
		Left postcentral gyrus (BA 40)	−57	−22	15	11.85
		Insula (BA 13)	−44	−18	4	12.48
Right auditory cortex	12,654		54	−19	9	
		Right superior temporal gyrus (BA 22)	53	−5	4	10.82
		Right transverse temporal gyrus (BA 41)	51	−21	9	12.49
		Right superior temporal gyrus (BA 42)	61	−26	14	11.08
		Right postcentral gyrus (BA 40)	58	−23	15	11.91
		Right precentral gyrus (BA 6)	54	−3	6	10.09
		Insula (BA 13)	49	−12	10	9.78
Right prefrontal cortex	142	Right inferior frontal gyrus (BA 45)	42	21	13	5.49

Acoustic stimulation during wakefulness resulted in two bilateral activation clusters of the auditory cortex plus an activated area in the right prefrontal cortex; a cluster represents an area of the statistical map that shows a significant difference of the on-phase BOLD (blood oxygen level-dependent) signal compared to the off-phase BOLD signal with a probability of $P < 0.05$ (one-tailed, Bonferroni-corrected for multiple comparisons), which corresponds to a *t*-value >4.90; *x,y,z*-coordinates represent the centre of spatial gravity of a region in standardized Talairach space (6); functional and anatomical subregions are specified using the Talairach Deamon Client (Version 1.1, Research Imaging Center, University of Texas, San Antonio, TX); t_{max} represents the local maximum of activation within an activated cluster; depicted data are results of a group analysis (n = 6).

plasma target concentration in the left as well as in the right auditory cortex (Table 2). Thus, administration of propofol seems to attenuate the acoustically induced BOLD signal dose-dependently. Furthermore, ROI analysis demonstrated the persistence of an auditory-evoked cortical activation even during propofol plasma target concentrations of 1.5 μg ml^{-1} (right auditory cortex) and 2.0 μg ml^{-1} (left auditory cortex) (Table 2). In the individual analysis, the primary (BA 41) and non-primary (BA 42, 22) auditory corteces were found to be the last activated brain regions during administration of increasing doses of propofol, whereas activation was abolished in all other areas that had been active during wakefulness (BA 6, 13, 40, and 45). Likewise, activation of the right prefrontal cortex during wakefulness was completely abolished during propofol plasma target concentrations of 0.5–2.0 μg ml^{-1}.

Table 2

Auditory-induced brain activation during different propofol plasma target concentrations.

Region-of-interest	Propofol plasma	Beta weight	*t*-value	*P*-value concentration
Left auditory cortex	0.5 μg ml^{-1}	0.509	7.015	<0.00001
	1.0 μg ml^{-1}	0.333	4.595	<0.00001
	1.5 μg ml^{-1}	0.310	3.314	0.00093
	2.0 μg ml^{-1}	0.203	2.506	0.01227
Right auditory cortex	0.5 μg ml^{-1}	0.481	6.626	<0.00001
	1.0 μg ml^{-1}	0.366	5.047	<0.00001
	1.5 μg ml^{-1}	0.356	3.805	0.00014
	2.0 μg ml^{-1}	0.152	1.876	0.06069

Regions-of-interest (ROI) analysis of left and right auditory cortex; defined as those two clusters of activation in the auditory cortex that demonstrated auditory-induced activation during wakefulness. Note the decreasing beta weights, while corresponding propofol plasma concentrations increase. High beta values indicate a 'strong' activation, and low beta values indicate 'weak' activation. Corresponding *t* and *P*-values describe the significance of the beta weights. Depicted data are results of a group analysis (n = 6).

Discussion

The main findings of this study are: (1) Auditory-induced activation during wakefulness was demonstrated in areas that are known to be involved in music processing; (2) propofol dose-dependently attenuated these acoustically induced BOLD responses in the auditory cortex, suggesting a dose-dependent impact of propofol on the central processing of auditory information; and (3) areas of higher functions of processing musical input were immediately lost when propofol was administered, whereas basic auditory information processing was preserved.

1. Listening to a complex musical stimulus during wakefulness induced activation in the superior temporal gyrus (STG) in regions adjacent to the STG and in the right inferior frontal gyrus, confirming results of previous studies (7–11). Zattore et al. found increases in cerebral blood flow in the superior temporal cortex during listening to melodies (7) and Griffiths et al. described the planum temporale [auditory association cortex (BA 42)] as engaged in the analysis of complex sounds (9). Furthermore, presenting complex auditory information as realized in our study activates a complex neural network, including sensory-motor functions (BA 6) and activation of frontal areas (BA 45 10).
2. During the awake state we found a larger area of auditory-induced activation in the left brain compared with the right brain. In contrast to traditional theories proposing a strong hemispheric specialization for music perception, it has been shown that musical information processing is based on highly individual cross-hemisphere networks (12). Therefore, the (pseudo-) lateralization of music processing observed in our study could be the result of individual aspects of musicality of the six patients examined and should not be generalized.
3. Our study supports previous findings that propofol affects central (cortical) auditory processing in a dose-dependent manner, since an increasing impairment of auditory-induced BOLD responses in the primary and non-primary auditory cortex during increasing propofol plasma target concentrations is demonstrated. The impact of anaesthesia on the auditory cortex, first reported by Erulkar et al. (13), has mostly been investigated by means of auditory evoked potentials (AEPs), which represent a direct measure of neuronal activation. Whereas brain stem auditory-evoked potentials, representing those early portions of the AEP generated in the auditory nerve and brainstem (14), remain largely unchanged during clinical anaesthesia (15), midlatency auditory evoked potentials (MLAEPs) are significantly affected by general anaesthetics (1, 16, 17) and are now used for monitoring depth of anaesthesia (15). Midlatency auditory evoked potentials are widely accepted as generated from the medial geniculate and primary auditory cortex (1, 14). Previous studies reported that propofol dose-dependently attenuated MLAEP (4), thus suggesting a dose-related influence of propofol on cortical processing of auditory stimuli.
4. Another finding of this study is that auditory information is still processed in the STG at propofol plasma concentrations of 2 $\mu g\ ml^{-1}$. 'Surviving' areas during administration of propofol were Heschl's gyrus and adjoining regions (BA 41, 42, 22). These parts of the auditory cortex are involved in primary, fundamental steps of central auditory information processing. In contrast, areas of higher functions of auditory information processing lost music-induced activation when increasing doses of propofol were administered. This finding of our study suggests a differential effect of propofol on central auditory information processing: complex analysis of acoustic input is impaired already at low propofol plasma concentrations, whereas basic auditory information is still being processed at high levels of sedation.

This is consistent with a clinical observation in the present study. All patients were sedated at the final plasma target concentration but promptly opened their eyes to verbal command. Since equilibration of targeted plasma concentration and effect-site concentration was achieved prior to each functional run, the effect-site concentration of propofol during the final functional run was approximately 2 $\mu g\ ml^{-1}$, which is slightly less than the 'effect-site awakening propofol concentration' (18).

Our observation of a differential impairment of acoustic information processing is also consistent with previous studies (19–22). Ongoing auditory input processing potentially inducing implicit or explicit awareness during anaesthesia is a well-known phenomenon (19–21). Recently, Heinke et al. reported that primary language processing in the temporal lobe was more resistant to propofol compared to areas of high-level processing in frontal brain regions (22).

The basic principle of the BOLD signal depends on the association of neuronal activation with an increase of regional cerebral blood flow and a proportional reduction in oxygen extraction resulting in a regional decrease of deoxyhemoglobin. This

change of regional deoxyhemoglobin concentration can be detected by fMRI, thus representing an indirect measure of neuronal activation. Therefore, one might hypothesize that the depressing effect of propofol on acoustically evoked BOLD signals reported in our study may actually be due to different mechanisms: (1) a propofol-induced impairment of stimulus processing in the auditory cortex resulting in a reduction of neuronal activity or (2) a propofol-related uncoupling of the oxidative metabolism and the cerebral haemodynamics reducing the BOLD signal independently of a change in brain activity.

Alkire et al. reported that propofol produced a global metabolic depression of the central nervous system (CNS), decreasing cortical metabolism to a greater extent than subcortical metabolism (23). Fiset et al. found propofol to preferentially decrease rCBF in the thalamus and the cingulated cortex (24), and Ogawa et al. described pronounced suppression in rCBF in the brain stem, thalamus, and parietal association cortex (25). However, it has been shown in animals (26) and in humans (27) that cerebral autoregulation is preserved after administration of propofol. The decrease in blood pressure observed in our subjects during propofol anaesthesia remained within the limits of cerebral autoregulation. An impact of propofol on CBF directly affecting the BOLD signal cannot be totally excluded. However, the authors suppose that the potential mechanism of an altered CBF can only induce slight effects, not explaining the observed change in the haemodynamic response. This suggests that the changes in acoustically evoked BOLD signal intensities during application of propofol found in our study are indeed caused by a change of neuronal activation.

The experiments of the current study were performed in patients scheduled for stereotactically guided surgery of a brain tumour. To minimize potentially confounding effects, patients with disturbances of auditory perception or tumour in the vicinity of the auditory system were excluded prior to the study. In fact, the actual distances between tumour and the auditory system were found to be at least 29 mm in each patient. Therefore, an impact of tumour-induced CBF changes on the BOLD response detected in our study seems unlikely.

BOLD contrast fMRI is a relatively new method to assess the effect of anaesthetic agents on brain functions. Our data confirm results of previous electrophysiological and neuroimaging studies demonstrating preserved auditory information processing during administration of propofol in the primary cortical processing areas. However, due to its high spatial resolution the fMRI method presents additional and more detailed information, showing that propofol has a differential impact on the cortical components of the auditory system. The fMRI method therefore goes beyond the scope of more traditional methods (i.e. electroencephalography, evoked potentials, magnetencephalography). It offers an approach to evaluate the effects of anaesthetic agents on functional and neuronal networks within the CNS. Clinically, our study offers a potential mechanism for awareness or recall phenomena reported by patients. Furthermore, fMRI is increasingly used as a diagnostic tool (28–30). Sometimes this requires appropriate sedation, particularly in children (31, 32). Our study shows that fMRI data analysis has to consider an impairment of auditory-induced brain activation if propofol is used for sedation during fMRI of the auditory system.

In summary, our study confirms the hypothesis that propofol bilaterally attenuates the auditory-induced BOLD signal of the auditory cortex in a dose-dependent manner. These results are consistent with electrophysiological findings directly measuring neuronal activity, indicating that our data reflect a propofol-induced dose-dependent impairment of central processing of auditory information. Despite its impact, propofol did not totally blunt primary cortical responses to acoustic stimulation, indicating that patients may process auditory information under general anaesthesia.

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