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Cortical Processing of Complex Auditory Stimuli during Alterations of Consciousness with the General Anesthetic Propofol

Gilles Plourde, M.D., M.Sc., Pascal Belin, Ph.D.,† Daniel Chartrand, M.D., Ph.D.,‡ Pierre Fiset, M.D.,‡ Steven B. Backman, M.D., Ph.D.,‡ Guoming Xie, M.D.,§ Robert J. Zatorre, Ph.D.‖*

Background: **The extent to which complex auditory stimuli are processed and differentiated during general anesthesia is unknown. The authors used blood oxygenation level–dependent functional magnetic resonance imaging to examine the processing words (10 per period; compared with scrambled words) and nonspeech human vocal sounds (10 per period; compared with environmental sounds) during propofol anesthesia.**

Methods: **Seven healthy subjects were tested. Propofol was given by a computer-controlled pump to obtain stable plasma concentrations. Data were acquired during awake baseline, sedation (propofol concentration in arterial plasma: 0.64 ± 0.13 μg/ml; mean ± SD), general anesthesia (4.62 ± 0.57 μg/ml), and recovery. Subjects were asked to memorize the words.**

Results: **During all periods including anesthesia, the sounds conditions combined elicited significantly greater activations than silence bilaterally in primary auditory cortices (Heschl gyrus) and adjacent regions within the planum temporale. During sedation and anesthesia, however, the magnitude of the activations was reduced by 40–50% ($P < 0.05$). Furthermore, anesthesia abolished voice-specific activations seen bilaterally in the superior temporal sulcus during the other periods as well as word-specific activations bilaterally in the Heschl gyrus, planum temporale, and superior temporal gyrus. However, scrambled words paradoxically elicited significantly more activation than normal words bilaterally in planum temporale during anesthesia. Recognition the next day occurred only for words presented during baseline plus recovery and was correlated ($P < 0.01$) with activity in right and left planum temporale.**

Conclusions: **The authors conclude that during anesthesia, the primary and association auditory cortices remain responsive to complex auditory stimuli, but in a nonspecific way such that the ability for higher-level analysis is lost.**

AUDITORY perception is obviously disrupted by general anesthetics, but it is unclear at what stage the disturbances occur. This report investigates the extent of auditory cortical activations during general anesthesia with propofol and whether specialized cortical areas remain capable of distinguishing different classes of complex stimuli.

The persistence of component Pa of the auditory middle latency evoked response during general anesthesia[1] suggests that processing of clicks or tone bursts persists in the primary auditory cortex (Heschl gyrus [HG]), in agreement with animal studies.[2] Animal studies indicate, however, that responses in secondary cortical areas occur much less reliably and only during light anesthesia.[3,4] The human N1 auditory evoked potential originates from the secondary auditory cortex[5] and is abolished during general anesthesia with isoflurane or thiopental.[6,7] The sensitivity of higher-order auditory cortical areas to anesthetics is consistent with the influential hypothesis[8] that anesthesia results from impairment of conduction through polysynaptic pathways.[9]

However, there is controversy about the N1 during propofol anesthesia: Two studies reported its persistence,[10,11] and one study reported its absence.[12] These studies also revealed conflicting results about the mismatch negativity[13] as evidence of a differential response to pitch.

Using blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI), Van *et al.*[14] found with one subject that activation of the primary auditory cortex by tone bursts (1,000 Hz) persisted during sevoflurane anesthesia. Kerssens *et al.*[15] examined the effect of sevoflurane on BOLD activation induced by auditory words. They reported decreased activation during 1.0% end-tidal sevoflurane and no residual activation at 2% end-tidal. Heinke *et al.*[16] reported that speech-related BOLD fMRI activations were attenuated during propofol sedation and completely abolished during anesthesia (unconsciousness). Dueck *et al.*[17] recently found that BOLD fMRI activations induced by music were attenuated during propofol sedation. They did not study anesthesia.

However, these studies have important limitations. First, the degree of specificity for complex processing remains unknown because only one type of stimulus was used, allowing only comparison with silence. Therefore, although a response may be observed during sedation or anesthesia, it is unclear whether this response is an attenuated but otherwise typical response or whether it represents residual activity no longer specific for the

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* Professor, ‡ Associate Professor, Department of Anesthesia, ‖ Professor, Department of Neurology and Neurosurgery, § Ph.D. Student, Departments of Anesthesia and Neurology and Neurosurgery, McGill University. † Postdoctoral Student, Department of Neurology and Neurosurgery, McGill University. Current position: Department of Psychology, University of Glasgow, Glasgow, United Kingdom.

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Address correspondence to Dr. Plourde: Department of Anesthesia, Montreal Neurological Hospital, 3801 University, Montreal, Quebec, Canada, H3A 2B4. gilles.plourde@staff.mcgill.ca.

complex stimulus. Furthermore, no study used noise-mitigation strategies for fMRI, raising the possibility that auditory cortex response was partly saturated by the loud noise from the scanner.[18] In particular, this is a problem in concluding that anesthesia leads to an abolition of auditory cortex responsiveness, because a weak BOLD signal would likely be undetectable if auditory cortex responses were already near maximum because of the noise.

The goal of the current study was to reassess the response of the anesthetized human brain to complex auditory stimuli using BOLD fMRI with noise-mitigation strategies (sparse sampling and clustered volume acquisition).[19,20] We addressed two questions: (1) How do activation patterns in auditory cortex change as a function of different levels of anesthesia? (2) Do cortical responses continue to distinguish between different classes of stimuli? To address the second question, we used words (compared with scrambled words) and human nonspeech vocal sounds (compared with environmental sounds) because these stimuli produce selective BOLD cortical activations[21,22] that are believed to directly reflect the neural activity elicited by these stimuli.[23]

Materials and Methods

Subjects and Design

The study was approved by the Montreal Neurologic Institute Research Ethics Committee (Montreal, Quebec, Canada), and subjects gave written informed consent. Seven healthy, right-handed native English speakers aged 20–35 yr (mean, 26 yr) (four men) were tested after a comprehensive medical evaluation. To assess memory performance without anesthesia, a second group of seven nonanesthetized subjects aged 21–36 yr (mean, 31 yr) (three men) were exposed the same stimuli (recorded on a CD and including scanner noise) with the same timing.

Imaging data were recorded during a single session (lasting approximately 4 h) comprising four successive conditions: awake baseline, sedation (blood propofol concentration of 0.6 μg/ml), anesthesia (subjects unconscious; propofol concentration of 4.6 μg/ml), and recovery (45 min after end of propofol infusion). Data acquisition during each period lasted approximately 25 min. Unconsciousness was defined as failure to respond to verbal commands.

Anesthesia

Subjects were under the care of two anesthesiologists. Testing was started in the morning after an overnight fast. A cannula was placed in a forearm vein for drug administration. A cannula was placed in the left radial artery for blood pressure monitoring and for blood sampling. Monitoring included pulse oximetry, intraarterial blood pressure, and on-line concentration of oxygen and carbon dioxide in inspired and expired gas. Subjects breathed spontaneously and received supplemental oxygen (5 l/min) by facemask during baseline, sedation, and recovery. During anesthesia, a laryngeal mask airway and Bain anesthesia circuit (oxygen; 8 l/min) were used to ensure patency of the airway and to assist breathing.

Propofol was infused with a Harvard Apparatus 22 pump (Harvard Apparatus, Holliston, MA) controlled by a laptop computer running Stanpump software (May 11, 1996 version).# The pump and computer were placed away from the scanner behind a shielded wall with a small opening for the propofol tubing. The software combines boluses and an infusion with an exponentially declining rate to achieve the desired effect site drug concentration. The dosage and rate of infusion were based on the pharmacokinetic parameters obtained in a group of subjects similar to ours.[24] Arterial blood samples were taken immediately before and after scanning in each condition for subsequent determination of the concentration of propofol and for blood gas analysis. The assay was conducted by Fance Varin, Ph.D. (Faculté de Pharmacie, Université de Montréal, Montreal, Quebec, Canada), using high-performance liquid chromatography.[25] The mean of the two values was used.

After placement of anesthesia-related devices and earphones, the subject was comfortably placed on the fMRI stretcher, with eyes closed. After acquisition of the baseline data, the propofol infusion was started, aiming for an effect site concentration of 1.0 μg/ml to produce sedation. When the predicted effect site concentration reached the target, we waited 5 min before acquiring imaging data to allow more complete equilibration. After acquisition of sedation data, the stretcher was slid out of the scanner to allow access to the subject's head. The target concentration of propofol was increased to 6–8 μg/ml for insertion of the laryngeal mask airway. The concentration of propofol was reduced by 0.5-μg increments to the lowest concentration allowing tolerance of the laryngeal mask airway. At this concentration, subjects were unconscious (*i.e.*, resting immobile with eyes closed and unresponsive to verbal commands). The fMRI stretcher was then slid back into the scanner for acquisition of anesthesia data. After acquisition of anesthesia data, the propofol infusion was stopped, and the fMRI stretcher was again removed from the scanner. After the return of consciousness and removal of the laryngeal mask airway, the stretcher was once again slid in the scanner for acquisition of recovery data (45 min after termination of propofol infusion).

Stimuli and Task

Subjects were instructed to close their eyes, to listen to the sounds, and to memorize the words. The auditory

STANPUMP program. Available at: http://anesthesia.stanford.edu/pkpd. Accessed October 27, 2005.

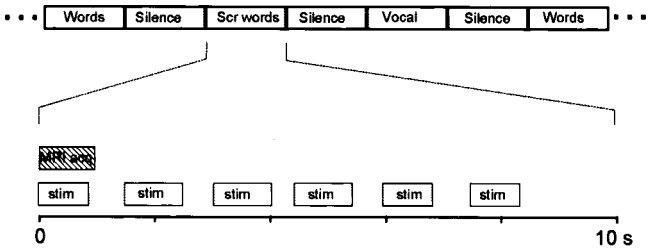

Fig. 1. Functional magnetic resonance imaging (MRI) protocol. Each period comprised 128 trials of different stimulus types including interposed silence (*top row*). Each trial lasted 10 s for presentation of six stimuli (stim) of the same category with a fixed 1.5-s interval between onsets or of silence. The *hatched rectangle* stands for functional MRI image acquisition. Scr = scrambled.

stimuli were digitized (16-bit, 22,050-Hz sampling rate) with CoolEditPro (Syntrillium software; Haslingden, Lancs, United Kingdom). They were arranged in 10-s blocks (fig. 1) containing only one type of stimuli and were delivered binaurally at mean intensity of 88- to 90-dB sound pressure level with imaging-compatible electrostatic headphones (Koss Corporation, Milwaukee, WI). **Word stimuli** consisted of common English words pronounced by a single speaker. Four lists of 10 words were used, one for each condition, with the order counterbalanced across subjects. Each 10-s block corresponded to one word repeated 6 times. There were 20 word blocks per condition, each block played twice. Each word was thus heard 12 times. **Scrambled word stimuli** were obtained by scrambling the word stimuli in the frequency domain to eliminate intelligibility while preserving the overall stimulus energy.[21] The scrambled words were ordered and presented as above. **Vocal sounds** consisted of human nonspeech vocalizations such as laughs, cries, moans, and sighs.[21] Four lists of 10 vocal sounds were used, one for each condition and counterbalanced across subjects. Each 10-s block corresponded to different exemplars. **Nonvocal sounds** consisted of environmental noises (wind, rain, cars, and so forth) and musical sounds. Mode of presentation was the same as for vocal sounds. The 10-s auditory blocks were presented in a randomized order with a 10-s silence interblock interval. Memory for words was tested with forced-choice recognition (paper-and-pencil four-choice test) after 22–26 h.**

Image Acquisition

Scanning was performed on a 1.5-T Siemens Vision Imager (Siemens Canada, Montreal, Quebec, Canada). High-resolution T1 images were obtained after each entry into the scanner for coregistration with functional series. One series of 128 functional images was acquired for each condition (gradient-echo, TE [time echo] = 50 ms, TR [time repetition] = 10 s, head coil, matrix size: 64×64, voxel size: $4 \times 4 \times 5$ mm^3, 10 slices parallel to the sylvian fissure) for a scanning time of 21 min 40 s each. The long interacquisition interval (TR) ensures low signal contamination by scanner noise.[19,20]

Image Analysis

Blood oxygenation level dependent signal images were spatially smoothed (6-mm gaussian kernel), corrected for motion artifacts and nonlinearity, and transformed into standard stereotaxic space[26] with in-house software.[27]†† Statistical maps were obtained using Fmristat.[28]‡‡ For global searches (all sounds–silence), the t values for significance at the $P < 0.05$, $P < 0.01$, $P < 0.001$, and $P < 0.0001$ levels were 4.5, 4.8, 5.2, and 5.7 after correction for multiple comparisons. For searches restricted to auditory cortical areas, we report all foci with t values of 3.2 or greater ($P < 0.01$, uncorrected). To track signal changes between periods, the magnitude of BOLD signal was sampled from the effect size maps in 5-mm radius spherical volumes of interest (VOIs) centered on local maxima of t value. In the case of the vocal–nonvocal and word–scrambled words contrasts, we used peak activations derived from the recovery phase, because these were the most robust and had similar locations to the peak activations during baseline. To determine the brain activation sites linked to later recognition performance, we ran a whole-brain voxelwise covariation analysis using recognition scores as input variable.

Statistics

Differences between periods for clinical parameters and VOI measures were evaluated with analyses of variances for repeated measures (Geisser-Greenhouse corrected) and Tukey honest significance test. For the memory results, a second factor (group) was included in the analysis of variance. One-sample *t* tests were used to determine whether the VOI measures differed form zero.

Table 1. Clinical Parameters

	Baseline	Sedation	Anesthesia	Recovery
HR, beats/min	70 ± 15	66 ± 13	67 ± 6	62 ± 9
SBP, mmHg	140 ± 17	135 ± 10	106 ± 12*	119 ± 16*
DBP, mmHg	75 ± 15	76 ± 8	66 ± 16	66 ± 9
Sa_{O_2}, %	99 ± 1	99 ± 1	99 ± 1	100 ± 1.0
Pc_{O_2}, mmHg	43 ± 3	44 ± 5	47 ± 8	45 ± 5
Propofol, μg/ml	0 ± 0	0.64 ± 0.13	4.62 ± 0.57†	0.76 ± 0.18

Data are presented as mean ± SD.

* Lower than Baseline and Sedation ($P < 0.005$). † Higher than Sedation and Recovery ($P < 0.0001$).

DBP = diastolic blood pressure; HR = heart rate; Pc_{O_2} = partial pressure of carbon dioxide in arterial blood; propofol = concentration in arterial blood; Sa_{O_2} = oxygen saturation by pulse oximetry; SBP = systolic blood pressure.

** For more details on the stimuli, see www.zlab.mcgill.ca (under Supplements; Voice perception). Accessed January 7, 2006.

†† http://www.bic.mni.mcgill.ca/software/. Accessed October 27, 2005.

‡‡ www.math.mcgill.ca/keith/fmristat/. Accessed October 27, 2005.

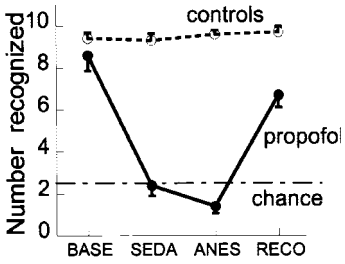

Fig. 2. Recognition memory. Number of items recognized for anesthetized and control subjects exposed to the same stimuli under similar conditions. Data are mean ± SE. Chance level denoted by *dashed line*. ANES = anesthesia; BASE = baseline; RECO = recovery; SEDA = sedation.

Procedures were performed with Statistica 4.1 for Macintosh (Statsoft, Tulsa, OK).

Results

Anesthesia Clinical Parameters

Systolic blood pressure was significantly ($P < 0.01$) lower during anesthesia and recovery compared with baseline. The concentration of propofol during sedation and recovery did not differ significantly ($P > 0.20$; table 1).

Memory for Words

The recognition scores during baseline and recovery were significantly ($P < 0.001$) higher than during sedation and anesthesia, where performance was at chance level (25%; fig. 2). Recognition during baseline was also significantly ($P < 0.02$) higher than during recovery. The control group of nonanesthetized subjects showed a score of greater than 90% for all periods, with no significant differences between periods. The control group had a significantly ($P < 0.001$) higher recognition score than the anesthetized group for all periods except baseline (not significant; $P = 0.62$).

All Sounds Combined versus *Silence*

Robust ($t \geq 5.7$; $P < 0.0001$) bilateral activations in HG and planum temporale (PT) were present during all periods, including anesthesia. VOI measures from individual subjects showed, however, that HG and PT activations decreased significantly ($P < 0.05$) during sedation and anesthesia compared with baseline and recovery (table 2 and fig. 3).

During sedation, significant ($t \leq -6.5$; $P < 0.0001$) negative activations (*i.e.*, silence associated with more activity than sounds) occurred in both lentiform nuclei ($x = -22$, $y = 4$, $z = -7$, and $x = 20$, $y = 6$, $z = -4$; fig. not shown).

Words versus *Scrambled Words*

This contrast yielded significant ($P < 0.01$, uncorrected) activations during baseline in the left PT and superior temporal sulcus (table 3 and fig. 4). During sedation and anesthesia, no activations yielded a t value of 3.2 or above in auditory areas. During recovery, significant activations were present bilaterally in the HG and PT as well as in the superior temporal gyrus and sulcus ($3.2 \leq t \leq 7.4$; $P < 0.01$). The VOIs showed no residual activity during anesthesia (one-sample *t* tests, $P \geq 0.2$).

However, during anesthesia, there was a significant negative activation (*i.e.*, scrambled words eliciting more activity than the normal words) in the right ($t = -4.6$; $P < 0.01$, two-tailed) and left PT ($t = -3.7$; $P = 0.01$, two-tailed; fig. 5).

Vocal versus *Nonvocal Sounds*

This contrast yielded significant ($P < 0.01$ uncorrected) activations during baseline in the PT and bilaterally. During sedation, significant ($t = 3.2$; $P < 0.01$) activations persisted bilaterally in the superior temporal sulcus. These activations did not persist during anesthesia. During recovery, there were significant bilateral activations ($3.2 \leq t \leq 6.0$; $P < 0.01$) in the PT and upper bank of the superior temporal sulcus as expected (table 4 and fig. 6). The VOIs showed no residual activity during anesthesia (one-sample *t* tests, $P \geq 0.2$).

Recovery versus *Baseline*

Because the t maps for the above three contrasts unexpectedly showed greater activation during recovery than baseline, we obtained additional t maps to directly compare recovery with baseline. The results revealed numerous areas, mainly in the temporal cortices, where activation was greater ($3.3 \leq t \leq 7.8$; $P < 0.01$) during recovery (table 5).

Correlation with Recognition Performance

There was a significant ($t \geq 4.6$; $P < 0.01$, corrected) correlation between recognition performance and activation in the right and left PTs across all four conditions, indicating that higher BOLD signal in this region was associated with better recognition (fig. 7).

Discussion

The first significant finding of this study is that propofol reduced but did not abolish BOLD auditory cortical activation. Both primary and secondary auditory cortex remained clearly responsive to auditory stimulation during anesthesia, but with a reduction in magnitude of 42% (HG) and 50% (PT) (fig. 3). These observations show that the state of complete oblivion produced by propofol does not require complete suppression of neural activity in secondary cortical areas.

Our results contrast with those of Heinke *et al.*,[16] who did not observe any speech-related activation during

Table 2. All Sounds–Silence

Anatomical Location	Talairach Coordinates x	y	z	t
Baseline				
Right				
HG*	40	−20	6	12.5
HG	52	−10	4	12.5
PT/HG	42	−30	14	14.3
PT*	60	−26	10	13.3
PT	66	−16	4	13.1
Anterior STG	58	−2	8	12.4
Lateral STG	64	−34	6	10.1
Insula	38	−14	−4	7.6
Left				
HG*	−52	−12	2	13.0
PT*	−42	−34	16	15.1
PT	−64	−18	10	14.7
PT	−62	−32	12	14.6
PT	−56	−24	6	13.1
PT	−64	−14	2	11.6
Insula	−42	2	−14	5.4
Inferior parietal lobule	−62	−38	38	4.9
Precentral gyrus	−60	4	6	4.8
Sedation				
Right				
HG	54	−8	4	6.4
HG	40	−28	8	6.0
PT/HG	60	−20	12	7.8
PT	64	−28	6	6.8
PT	68	−18	6	5.4
Anterior STG	58	2	4	6.4
Left				
PT/HG	−42	−32	16	7.1
PT	−56	−24	2	6.3
PT	−66	−34	8	6.0
Posterior MTG	−52	−50	0	5.6
ITG	−44	−32	−14	6.3
Fusiform gyrus	−34	−54	−6	4.9
Anesthesia				
Right				
HG	38	−26	16	6.5
PT	60	−18	10	9.6
PT	60	−8	4	7.4
PT	40	−32	8	7.4
PT	58	−18	−2	6.0
STG	56	−2	8	9.0
Posterior STG	62	−34	8	6.5
Posterior STG	52	−38	12	5.6
MTG	64	−30	−2	5.0
Inferior parietal lobule	58	−34	44	4.9
Postcentral gyrus	62	−10	20	4.9
Left				
HG	−54	−6	6	7.1
HG	−44	−20	2	6.7
HG	−40	−22	10	6.3
PT/HG	−56	−20	10	6.2
PT	−64	−20	8	6.7
PT	−54	−20	2	6.6
PT	−40	−30	16	6.1
Anterior STG	−44	−14	−2	5.9
Posterior STG	−60	−42	8	5.6
STG	−56	4	4	5.1
STG	−42	−56	22	4.8
Paracentral lobule	−6	−38	50	5.8
Precentral gyrus	−60	2	20	5.5
Superior parietal lobule	−52	−70	36	5.4
Inferior parietal lobule	−58	−32	38	5.2
Isthmus gyrus cinguli	−6	−44	12	4.8
Supramarginal gyrus	−52	−60	42	4.8
Recovery				
Right				
HG	52	−10	6	17.0
PT/HG	42	−28	14	18.9
PT/HG	58	−20	10	17.1
PT	62	−14	4	15.5
PT	62	−32	8	13.9
STG	52	12	−6	5.8
Left				
HG/PT	−42	−32	18	24.0
PT	−64	−16	4	19.3
PT	−64	−22	12	16.3
PT	−62	−30	12	15.4
Anterior STG	−42	2	−18	5.6
Anterior STG	−44	−4	−10	5.5
Inferior parietal lobule	−60	−38	34	8.2

(*Table continues*)

Coordinates in standard stereotaxic space (mm), approximate anatomical location and t value for voxels with $t \geq 4.8$ ($P < 0.01$, corrected). When two voxels within the same anatomical location were separated by 8.0 mm or less, only the voxel with the higher t value was listed to limit the size of the table. Voxels marked by * were selected to extract volume of interest (VOI) values from individual subjects (fig. 3).

HG = Heschl gyrus; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; PT = planum temporale; STG = superior temporal gyrus.

general anesthesia with propofol. Their negative finding is perhaps accounted for by a reduction of the dynamic range of the fMRI signal caused by noise from the scanner.[18,29] Our results are similar to those of Kerssens *et al.*,[15] who reported residual BOLD activations in response to words during 1.0% end-tidal sevoflurane.

The second significant finding is that higher-level processing for speech and voice is abolished during anesthesia. The mean BOLD signal amplitude during anesthesia for speech-specific (fig. 4) and voice-specific (fig. 6) activations was near zero. Cortical areas outside of primary and adjacent regions in the PT, which normally respond in a specific fashion to words[22,30] and voices,[21] did not discriminate between the target and control stimuli during anesthesia. These results indicate that mainly nonspecific cortical activity remains during anesthesia. Similarly, Pack *et al.*[31] observed that single neurons in the middle temporal visual cortical area of macaque monkeys lose the ability to integrate conflicting local motion signals during anesthesia with isoflurane, despite intact directional tuning characteristics.

The observation that scrambled words produced *more* activation that normal words in the PT bilaterally during anesthesia (fig. 5) was unexpected. This finding contrasts with the vast neuroimaging literature[32] that has identified cortical areas that consistently show greater activation after language-specific stimuli than after appropriate control stimuli. The larger activation produced

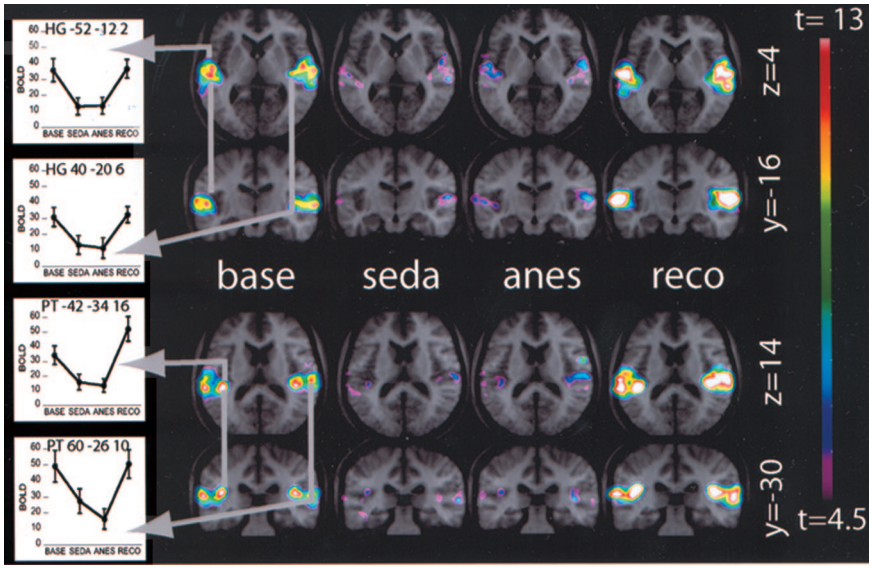

Fig. 3. Group average responses for all sounds–silence. Activation t maps overlaid over average anatomical image in standard stereotaxic space. The *right side* of the images corresponds to the subjects' right side. *Line diagrams* show mean ± SE of signal magnitude (difference in effect size between the two conditions, *i.e.*, sound *vs.* silence) in volume of interest centered on selected voxels (x, y, z coordinates indicated above graph). The y and z values on the *far right* are the Talairach coordinates of the slices; t values are revealed by *color scale*; values above upper limit are shown in *white*. ANES = anesthesia; BASE = baseline; BOLD = blood oxygen dependent level; HG = Heschl gyrus; PT = planum temporale; RECO = recovery; SEDA = sedation.

by scrambled words during anesthesia shows, however, that the anesthetized brain may respond differentially but atypically to complex stimuli depending on their structure. Therefore, the absence of cognitive processing that is the hallmark of general anesthesia does not require the complete suppression of differentiated activity in cortical association areas.

The absence of clear speech-specific activations during sedation does not rule out the possibility that residual activity was present. The preserved ability of the sub-

Table 3. Words–Scrambled Words

Anatomical Location	Talairach Coordinates x	y	z	t
Baseline				
Right				
No activations at t ≥ 3.2				
Left				
PT/STS	−64	−16	0	3.5
PT	−60	−14	2	3.4
Sedation				
No activations at t ≥ 3.2				
Anesthesia				
No activations at t ≥ 3.2				
Recovery				
Right				
HG	62	−10	4	4.9
HG/anterior STG	52	0	0	5.1
PT/HG	54	−8	4	5.7
PT	64	−28	14	4.2
PT	46	−40	16	3.5
Posterior STS*	60	−30	−4	6.0
Anterior STS	60	−14	−6	4.5
Left				
HG/anterior STG	−58	−4	2	5.2
PT/STS*	−66	−12	2	7.4
PT	−62	−16	10	6.2
PT	−68	−34	12	4.6
PT	−60	−42	16	4.2

Coordinates in standard stereotaxic space (mm), approximate anatomical location, and t value for voxels with t ≥ 3.2 ($P < 0.01$, uncorrected). When two voxels within the same anatomical location were separated by 8.0 mm or less, only the voxel with the higher t value was listed to limit the size of the table. Voxels marked by * were selected to extract volume of interest (VOI) values from individual subjects (fig. 4).

HG = Heschl gyrus; PT = planum temporale; STG = superior temporal gyrus; STS = superior temporal sulcus.

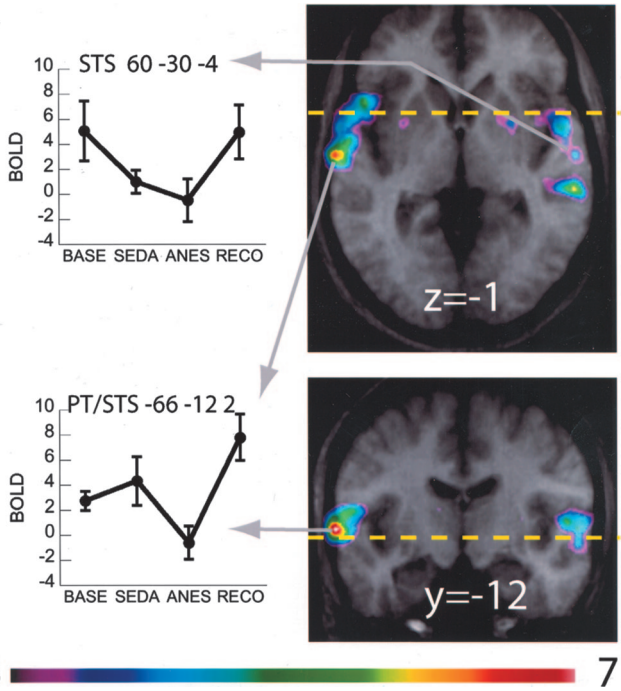

Fig. 4. Group average responses for words–scrambled words during recovery. Activation t maps overlaid over average anatomical image in standard stereotaxic space. The *right side* of the images corresponds to the subjects' right side. *Line diagrams* show mean ± SE of signal magnitude in volume of interest centered on selected voxels (x, y, z coordinates indicated above graph). The y and z values in *white* are the Talairach coordinates of the slices; t values are revealed by *color scale*. The *dashed yellow line* shows the section plane of the other view. ANES = anesthesia; BASE = baseline; BOLD = blood oxygen dependent level; PT = planum temporale; RECO = recovery; SEDA = sedation; STS = superior temporal sulcus.

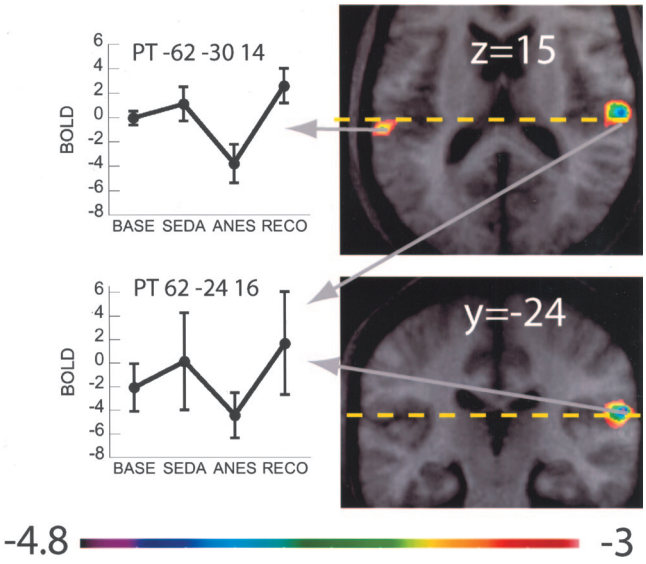

Fig. 5. Group average responses for words–scrambled words during anesthesia showing bilateral negative activations in PT. Activation t maps overlaid over average anatomical image in standard stereotaxic space. The *right side* of the images corresponds to the subjects' right side. *Line diagrams* show mean ± SE of signal magnitude in volume of interest centered on selected voxels (x, y, z coordinates indicated above graph). The y and z values in *white* are the Talairach coordinates of the slices; t values are revealed by *color scale*, which is inverted with *blue* corresponding to highest significance. The *dashed yellow line* shows the section plane of the other view. ANES = anesthesia; BASE = baseline; BOLD = blood oxygen dependent level; PT = planum temporale; RECO = recovery; SEDA = sedation.

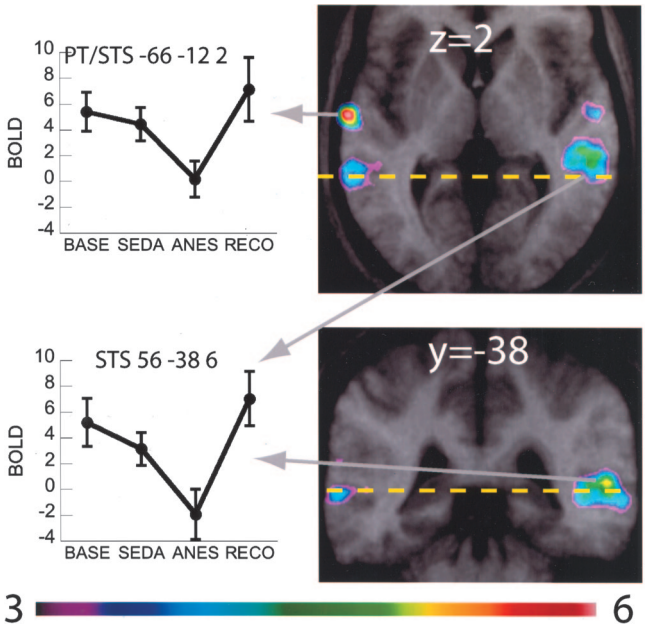

Fig. 6. Group average responses for vocal–nonvocal sounds during recovery. Activation t maps overlaid over average anatomical image in standard stereotaxic space. The *right side* of the images corresponds to the subjects' right side. *Line diagrams* show mean ± SE of signal magnitude in volume of interest centered on selected voxels (x, y, z coordinates indicated above graph). The y and z values in *white* are the Talairach coordinates of the slices; t values are revealed by *color scale*. The *dashed yellow line* shows the section plane of the other view. ANES = anesthesia; BASE = baseline; BOLD = blood oxygen dependent level; PT = planum temporale; RECO = recovery; SEDA = sedation; STS = superior temporal sulcus.

jects to follow verbal commands provides evidence of speech processing during sedation. The lack of significant speech-related activation can be attributed to low signal-to-noise resulting from propofol-induced reduction of signal strength, interference by clinical monitoring devices, and possibly increased motion artifacts. Another factor that may have reduced signal strength is the presentation of only one word (repeated six times) within each block, a strategy that we adopted to facilitate memorization. Blocks made of six different words would have yielded greater activations. On the other hand, the fact that a significant but atypical response to the scrambled words was detected during the fully anesthetized state (fig. 5) suggests that neither insufficient sampling nor movement artifact was a factor during anesthesia, strengthening our conclusion that the normal specificity of auditory cortex to speech and voice is abolished during propofol anesthesia.

Can the absence of speech-specific activations (and explicit memory) during the sedation period be explained by the subject's having fallen asleep? We believe that this explanation is unlikely. First, it is difficult to fall asleep in the cramped and noisy scanner environment. Second, the subjects were closely monitored, and at no time did we have the impression that they were asleep or that we had awakened them. Third, when the subject arrives for testing, we routinely inquire about personal events in the preceding 24 h, including duration and quality of sleep. No subject reported sleep problems. Fourth, natural sleep alone does not abolish auditory activation by complex stimuli.[33,34]

What are the mechanisms by which propofol interferes with higher-level analysis? Potentiation of the γ-aminobutyric acid type A receptor is the most plausible mechanism of action for propofol and other general anesthetics.[35] Anesthesia is associated with decreased spontaneous activity in the primary auditory cortex with a predominance of narrowly frequency-tuned units that reveal tonotopy more clearly than in awake animals.[2,36] Anesthetics seem to reinforce inhibitory mechanisms, thereby decreasing spontaneous activity and suppressing evoked activity of neurons that are synaptically distant from direct thalamic input.[2] Therefore, anesthetics could potentiate γ-aminobutyric acid–mediated inhibition at multiple levels of the ascending auditory pathways,[37] including the auditory thalamus and cortex.[2,38,39] This model would be consistent with our observations.

A third significant finding is that the area most highly correlated with recognition memory was the left PT (fig. 7), although a bilateral effect was observed. This finding is consistent with the role of left perisylvian cortex in speech processing and suggests that successful recogni-

Table 4. Vocal–Nonvocal Sounds

Anatomical Location	Talairach Coordinates x	y	z	t
Baseline				
Right				
PT/STS	70	−12	2	3.6
Posterior STS	62	−38	4	3.2
Left				
Inferior temporal gyrus	−52	−40	−18	3.7
PT/STS	−64	−14	0	3.5
Sedation				
Right				
Middle STS	58	−28	−4	3.2
Left				
PT/STS	−64	−16	4	3.2
Anesthesia				
No activations at t ≥ 3.2				
Recovery				
Right				
HG	60	−4	8	3.9
HG	54	−8	0	3.5
PT/STS	60	−12	2	3.9
Posterior STS*	56	−38	6	5.3
Posterior STS	56	−30	−4	5.2
Posterior STS	46	−34	−2	4.5
Posterior STS	62	−40	0	4.2
Middle STS	56	−16	−4	3.8
Middle STS	48	−14	−16	3.7
Anterior STS	56	−4	−6	3.5
Left				
PT/STS*	−66	−12	2	6.0
PT	−62	−40	16	3.5
Anterior STS	−64	−6	−6	4.6
Posterior STS	−56	−44	6	4.2
Posterior MTG	−64	−50	4	4.1

Coordinates in standard stereotaxic space (mm), approximate anatomical location, and t value for voxels with t ≥ 3.2 ($P < 0.01$, uncorrected). When two voxels within the same anatomical location were separated by 8.0 mm or less, only the voxel with the higher t value was listed to limit the size of the table. Voxels marked by * were selected to extract volume of interest (VOI) values from individual subjects (fig. 6).

HG = Heschl gyrus; MTG = middle temporal gyrus; PT = planum temporale; STS = superior temporal sulcus.

Table 5. Recovery–Baseline

Anatomical Location	Talairach Coordinates x	y	z	t
All sounds–silence contrast, t ≥ 4.8 ($P < 0.01$ corrected)				
Right				
Postcentral gyrus	52	−16	14	6.8
Precentral gyrus	52	−8	10	6.1
STG	60	−14	0	5.3
Insula	44	−10	14	5.0
PT/HG	42	28	14	4.9
Postcentral gyrus	56	−12	16	4.9
STG	56	4	0	4.9
PT	64	−30	8	4.8
Insula	38	−30	20	4.8
Left				
PT	−42	−34	20	7.8
PT	−52	−38	22	7.4
PT	−62	−14	4	6.3
Words–scrambled words contrast, t ≥ 3.2 ($P < 0.01$ uncorrected)				
Right				
PT	64	−16	10	3.9
PT	68	−36	18	3.7
STG	56	4	0	3.5
PT	64	−10	6	3.5
HG	52	0	0	3.5
HG	54	−8	4	3.4
HG	48	−16	10	3.4
MTG	62	−32	2	3.3
STG	62	−32	2	3.3
STG	50	−4	2	3.3
Left				
Transverse temporal gyrus	−56	−18	14	4.8
STG	−68	−12	2	4.2
STG	−48	6	0	4.0
Transverse temporal gyrus	−62	−14	12	3.8
PT	−68	−16	8	3.6
Vocal–nonvocal stimuli contrast, t ≥ 3.2 ($P < 0.01$ uncorrected)				
Right				
MTS	50	−14	−16	3.6
MTS	44	−36	−4	3.4
PT	60	−14	2	3.2
Left				
None				

Coordinates in standard stereotaxic space (mm), approximate anatomical location, and t value for voxels with t ≥ 3.2 ($P < 0.01$, uncorrected).

HG = Heschl gyrus; MTG = middle temporal gyrus; MTS = middle temporal sulcus; PT = planum temporale; STG = superior temporal gyrus; VOI = volume of interest.

tion memory was largely accounted for by the degree to which the stimuli were processed by specialized speech decoding mechanisms at the time of presentation. Because this process was abolished during anesthesia, as indexed by low or absent BOLD signal, later recognition was impossible. The residual activation in primary regions during anesthesia was evidently insufficient to support formation of any memory traces.

The absence of explicit memory during sedation is surprising because we would have predicted a recognition rate near 50% based on the propofol concentration.[40] It is of course possible that implicit memory was present and that our recognition procedure was insufficient to demonstrate it. However, a forced-choice task was used, and responses were indistinguishable from chance, suggesting that little if any memory trace remained. The absence of recognition during sedation may be explained by differences in experimental conditions

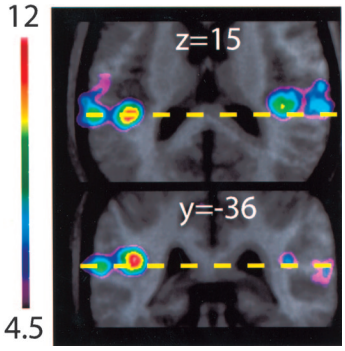

Fig. 7. Group average response showing correlation t map for all sounds–silence as function of recognition memory performance. Activation t maps overlaid over average anatomical image in standard stereotaxic space. The *right side* of the images corresponds to the subjects' right side. The y and z values in *white* are the Talairach coordinates of the slices; t values are revealed by *color scale*. The *dashed yellow line* shows the section plane of the other view.

during encoding (number of words, number of repetitions, depth of processing) or the retention phase (subsequent exposure to two other lists of words and to hypnotic concentration of propofol). Based on the current data, this amnesic effect would seem to be linked to the disruption of perceptual processes, rather than encoding or consolidation processes.

A fourth significant finding is that the activation levels during recovery were much higher than during sedation despite similar propofol concentrations (table 1). We think that the most likely explanation is acute tolerance to propofol, a phenomenon that has also been reported with rats.[41,42] Therefore, the level of BOLD signal activity would seem to constitute a better index of conscious processing than blood concentration of anesthetic agent.

Czisch *et al.*[33] reported that non–rapid eye movement sleep reduces but does not abolish BOLD activations induced in the auditory cortices by complex auditory stimuli (tape recordings of Mark Twain novels), a finding that resembles our observations. By contrast, Portas *et al.*[34] observed no change in auditory cortical activation during non–rapid eye movement sleep using pure tones and the subject's first name. However, they observed reduced activations during sleep in the thalamus and cortical areas, including the prefrontal and left parietal cortex. Auditory stimulation (95-dB clicks) activated bilateral primary, but not associative, auditory cortices in neurovegetative patients,[43] suggesting that the neurovegetative state is associated with a more severe disruption of sensory processing than anesthesia with propofol.

Finally, the current findings serve to illuminate the neural changes associated with pharmacologic alterations of consciousness in humans. The data indicate that one prominent characteristic of loss of consciousness induced by propofol is that specialized, higher-order processing areas that normally respond differentially to certain classes of stimuli no longer do so. Instead, a generalized but attenuated response in primary and adjacent regions persists, as well as a paradoxical response to scrambled words. These data therefore indicate that although not all cortical responses are abolished in the unconscious state, the highly differentiated neural processes whose outcome leads to conscious perception either are deprived of their normal input or are unable to perform their normal computations. The outcome, then, is that the normal pathways for processing that eventually lead to formation of percepts are not operative, which in turn contributes to what we experience as a loss of consciousness. Whether similar events occur with other anesthetic drugs deserves inquiry.

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