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A Neuroanatomical Construct for the Amnesic Effects of Propofol

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Background: **This study was designed to identify neuroanatomical locations of propofol's effects on episodic memory by producing minimal and maximal memory impairment during conscious sedation. Drug-related changes in regional cerebral blood flow (rCBF) were located in comparison with rCBF increases during a simple word memory task.**

Methods: **Regional cerebral blood flow changes were assessed in 11 healthy volunteers using $H_2{}^{15}O$ positron emission tomography (PET) and statistical parametric mapping (SPM99) at 600 and 1,000 ng/ml propofol target concentrations. Study groups were based on final recognition scores of auditory words memorized during PET scanning. rCBF changes during propofol administration were compared with those during the word memory task at baseline.**

Results: **Nonoverlapping memory effects were evident: low (n = 4; propofol concentration 523 ± 138 ng/ml; 44 ± 13% decrement from baseline memory) and high (n = 7; 829 ± 246 ng/ml; 87 ± 6% decrement from baseline) groups differed in rCBF reductions primarily in right-sided prefrontal and parietal regions, close to areas activated in the baseline memory task, particularly R dorsolateral prefrontal cortex (Brodmann area 46; x, y, z = 51, 38, 22). The medial temporal lobe region exhibited relative rCBF increases.**

Conclusions: **As amnesia becomes maximal, rCBF reductions induced by propofol occur in brain regions identified with working memory processes. In contrast, medial temporal lobe structures were resistant to the global CBF decrease associated with propofol sedation. The authors postulate that the episodic memory effect of propofol is produced by interference with distributed cortical processes necessary for normal memory function rather than specific effects on medial temporal lobe structures.**

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THE effects of certain anesthetic drugs on memory seem to be specific and separate from their sedative hypnotic effects.[1] Recently there has been an explosion of knowledge regarding human memory systems, based on imaging studies using regional changes in cerebral blood flow or oxygen content.[2–5] These investigations have revealed not only the importance of medial temporal lobe (MTL) structures in memory processes, confirming previous findings from anatomical studies,[6] but also the importance of distributed cortical processes working coherently as a network.[3,7,8] Memory function can be divided into independent processes based on temporal and content criteria. A basic division exists between explicit, episodic memory, wherein a specific context of an event can be remembered (*e.g.*, what one had for dinner last night), and implicit memory, demonstrable only indirectly (*e.g.*, faster recognition of previously presented stimuli that were not perceived or recalled, such as words presented during certain depths of anesthesia). Propofol produces specific impairment of episodic memory, similar to midazolam and other benzodiazepines.[9] Before material enters long-term memory, it is held and manipulated in working memory, a group of interrelated cognitive processes that are widely distributed among different cortical regions.[10,11]

The differential amnesic and sedative and hypnotic effects of certain anesthetic drugs can be demonstrated using behavioral[9] and electrophysiologic criteria.[12,13] Our hypothesis is that these effects are likely mediated in certain neuroanatomical regions or networks of the brain that subserve these behaviors. The focus of the current investigation is on the impairment of episodic memory by propofol. A substantial body of literature indicates that anesthetic drugs have regional effects on cerebral blood flow and metabolism, frequently in regions of the brain whose known functional effects are congruent with the clinical effects of the drug studied (for example, the hypnotic effect of anesthetics and the thalamus).[14,15] Recent evidence demonstrates that the neuroanatomical substrate of drug action can be identified by regional changes in hemodynamics.[16]

This study was designed to more clearly identify potential neuroanatomical substrates associated with memory impairment produced by propofol. Based on substantial experience from previous studies, two target doses of propofol were chosen to result in mild and almost maximal memory effect, with less sedative effect

than in our previous regional cerebral blood flow (rCBF) imaging study using midazolam.[9,17] Subjects were assigned to a mild or maximal memory effect based on word recognition scores on a simple verbal memory task performed during positron emission tomography (PET) imaging. The interaction between changes in rCBF and level of drug effect more clearly identifies specific regions of the brain affected by the change in drug effect.[18] Regions of the brain demonstrating a significant interaction between rCBF changes and level of memory effect from propofol were identified. We hypothesized that these regions would be involved in the expression of the amnesic effects of propofol. To determine if these regions were related to the amnesic rather than the sedative effects of propofol, the locations of these regions were compared with those activated during the same memory task at baseline.

Materials and Methods

This investigation was approved by the Hospital Institutional Review Board and Radiation Safety Committee of Memorial Sloan Kettering Cancer Center, New York, New York. Informed consented was obtained in writing before accrual of subjects took place.

Subjects

Eleven normal right-handed volunteers (7 men, 4 women) were recruited through flyers and paid for their participation. On responding to the flyer, volunteers were interviewed extensively by telephone, and a detailed medical history was taken. Exclusion criteria included use of psychoactive medication; history of recreational drug abuse; head trauma resulting in loss of consciousness; neurologic, cardiovascular, or respiratory disease; claustrophobia; hypertension; peripheral vascular disease; hearing deficit; carpal tunnel syndrome; or allergy to eggs. Selected volunteers ranged in age from 20 to 36 yr (mean ± SD, 26.6 ± 5.8 yr) and weighed between 51.5 and 122 kg (78.0 ± 18.7 kg). All volunteers had received some college education, were right-handed, and native English speakers with normal vocabulary ability. All volunteers reported sleeping normally the night before, although two reported sleeping fewer than 5 h.

Recruitment and Orientation Session

A comprehensive medical history was taken during the initial telephone interview. At the orientation session, detailed information on study procedures was given. Tests of handedness (Edinburgh Handedness Inventory[19]) and vocabulary (score above median for age group on the vocabulary subtest of Wechsler Adult Intelligence Scale–Revised) were administered, followed by a brief physical examination. The session concluded with practice on the study tasks.

Procedure on Positron Emission Tomography Study Day

Subjects arrived at approximately 8 AM, being *non per os* since midnight. Subjects were monitored with electrocardiograph (ECG) and pulse oximeter. Venous and radial arterial catheters were inserted before transfer to the PET suite. D5½NS at approximately 100 ml/h was administered intravenously. The volunteer's time in the PET scanner was approximately 3 h, including time for positioning and calibration scans. After completion of PET scanning, the arterial catheter was removed, and the volunteer was returned to the Neuroanesthesia Laboratory, where the intravenous agent was discontinued after the volunteer was given a light lunch. The word recognition test was administered shortly before discharge some hours later.

Experimental Tasks Performed during Positron Emission Tomography Scanning

Three experimental tasks were performed twice before and after propofol infusion, consisting of (1) Resting Baseline (R): unstimulated, eyes closed, no task; (2) Memory Task (M): a list of 30 words was played through headphones at a rate of one word every 4 s; the subject was instructed to remember as many as possible; (3) Nonsense Stimuli (N): the same words were played backwards, at the same rate; subjects were instructed not to try to make sense of the words. The nonsense condition was to act as a control for auditory stimulation associated with the word memory task. The three conditions were randomized across subjects. To control for order effects in a given subject, a complete sequence of three tasks was obtained before repeating the sequence, for example, M, N, R, M, N, R. The sequence stayed the same for the subsequent drug condition in a given subject. Different word lists were used for the baseline and drug memory tasks, and the order was counterbalanced across subjects. During the interval between PET scans, subjects were allowed to listen to music of their choice through headphones.

Study Groups

Eleven volunteers were randomly assigned to receive propofol infusion by CACI (Computer Assisted Continuous Infusion; software kindly provided by Dr. Peter Glass, Professor and Chairman, Department of Anesthesiology, State University of New York at Stony Brook, Stony Brook, New York) to target either "low," 600 ng/ml, or "high," 1,000 ng/ml concentrations, associated with a predicted 50% and 90% decrement in auditory verbal memory.[9,20] After 10 min, following predicted equilibration between serum and effect site concentrations, PET scanning was resumed.

Arterial blood samples were obtained immediately after every other scan for arterial blood gas and propofol assay. Propofol concentrations were determined by

high-performance liquid chromatography with fluorescence detection.[20]

For purposes of analysis, subjects were assigned to a low or high memory effect based on recognition of visually presented words at the end of the study day. An equal number of distractor words were presented along with target words, and subjects were instructed to circle the words they recognized (no forced choice).

Neuropsychologic State during Positron Emission Tomography Scanning

Volunteers were scanned with eyes closed, wearing RadioShack Optimus in-ear stereo earphones (RadioShack Corp., Fort Worth, TX) for delivery of auditory stimuli during PET scanning. Subjects were wearing an electroencephalograph (EEG) "electro-cap" (Electro-Cap International, Eaton, OH) and had their heads resting on a foam finger mat for comfort. A U-shaped, foam-lined plastic holder with no mask held the head stationary. Both groups were instructed to remain awake during PET scanning. However, one subject in the low effect group and two subjects in the high effect group were noted to have dozed off during at least one presentation of the word list. All subjects responded to verbal stimulation immediately after acquisition of PET images.

Positron Emission Tomography Scanning

Two PET scans were obtained in each condition, before and after propofol, for a total of 12 scans. Every 12 min, 10 mCi of intravenous $H_2{}^{15}O$ was delivered at a constant rate over 20 s *via* an infusion pump. Scans were obtained on a GE Advance scanner (GE Medical Systems, Waukesha, WI) in the three-dimensional "septa out" mode. The resolution of the PET camera in this mode is approximately 5.2 mm in all dimensions. Four 30-s frames were obtained during each scan, but only the first three frames were analyzed as the majority of uptake of tracer into the brain occurs in the first 90 s. The images were reconstructed using filtered back projection and standard clinical protocols and were stored as "counts" images (counts of coincidence events expressed as nCi/ml). Images were converted to Analyze format before statistical analysis.

Data Analysis

Behavioral and Demographic Variables. Performance data and subject-related information are presented throughout as mean ± SD. Groups were compared by *t* test. Statistical significance was set at $P < 0.05$.

Statistical Analysis of Positron Emission Tomography Images. Positron emission tomography images were analyzed using statistical parametric mapping (SPM) with SPM99 (Wellcome Institute of Cognitive Neurology, London, UK; implemented in Pro Matlab v. 5.3 (Mathworks, New York, NY). Images were realigned to the first scan and normalized into Montreal Neurologic Institute (MNI) brain image space. A 15-mm FWHM Gaussian smoothing kernel was used to accommodate interpersonal variations in gyral anatomy and facilitate intersubject averaging with a resultant smoothness of 16.9 × 19.6 × 20.7 (x, y, z) mm. Mean global CBF was normalized to 50 ml·100 g^{-1}·min^{-1}. Statistical analysis used a proportional scaling model, which allows a differing relationship between regional CBF effect, depending on global CBF. A significant regional change in the SPM image was defined as a minimum of 20 voxels, with a height threshold corresponding to a T of 3.17 ($P < 0.001$ uncorrected). T values above 4.6 represent probability values corrected to $P < 0.05$ for multiple comparisons over the entire imaged brain space. This protects against multiple comparisons when no *a priori* hypothesis regarding location of effect is appropriate. This criterion is too stringent if a hypothesis is restricted to a smaller region of brain. In certain analyses, findings with lower T values are reported because one *a priori* hypothesis was that rCBF decreases induced by propofol were similar in location to memory task-related activations. Also of interest are changes in rCBF in the MTL structures. No specific corrections were made to obtain the probability values appropriate to a given neuroanatomical region. Rather, rCBF changes exhibiting T values less than 4.6 are reported.

Statistical parametric mapping contrasts were constructed to identify regions of the brain demonstrating relative rCBF changes comparing study groups. rCBF changes related to the *change* in propofol effect between study groups were more specifically identified using an interaction analysis between rCBF changes and study group. Subjects were in three different behavioral states (Resting, listening to Nonsense words, and Memory task) during PET imaging. Analyzing these as a block identified regions exhibiting similar changes in rCBF caused by propofol administration regardless of task (initial results of rCBF changes in congruent states before and after drug are qualitatively similar[21]). Comparing rCBF increases in the memory *versus* resting tasks identified brain regions activated by the memory task. Although the nonsense word task was to act as a control task for auditory stimulation for memory task-related activations, the comparison of Memory task *versus* Nonsense produced somewhat different results than Memory task *versus* Resting. Thus, both sets of results are reported in table 1, but only the Memory task *versus* Rest is presented graphically.

SPM99 provides x, y, z coordinates based on an average magnetic resonance image (MRI) derived from 152 normal structural MRI scans from MNI, Montreal, Canada (the MNI coordinate system). To locate the neuroanatomical structures associated with these coordinates using the standard Talairach atlas, transformation of these coordinates was performed according to details provided by the Medical Research Council Cognition and

Table 1. Locations of rCBF Changes of Interest (Talairach Atlas)

Talairach Region (BA)	Comments	T Value	x	y	z
Interaction (IX) analysis, rCBF decreases (Fig 4)					
Superior frontal g BA 10		5.88	24	58	25
Mid temporal g BA 21	Auditory activation	5.37	67	−33	−8
Brainstem		5.20	8	22	−26
Superior frontal g BA 10	Similar to midazolam	5.05	−28	52	23
Mid frontal g BA 46	**DLPFC**	**5.03**	**51**	**38**	**22**
Inferior parietal l BA 40		**4.98**	**61**	**−44**	**45**
Inferior frontal g BA 47		**4.90**	**50**	**23**	**1**
Memory task rCBF increases *versus* Rest condition (Fig 5)					
Mid temporal g BA 21	Auditory activation	6.42	−63	−37	0
Mid temporal g BA 21	Auditory activation	5.76	65	−24	−6
Mid frontal g BA 9	**DLPFC**	**4.37**	**50**	**29**	**28**
Cerebellum		4.07	50	−67	−26
Inferior parietal l BA 40		**4.02**	**50**	**−52**	**47**
Superior frontal g BA 10		3.80	30	60	−10
Hippocampus		**3.78**	**36**	**25**	**−6**
Inferior frontal g BA 45	Similar to midazolam	3.65	−40	22	4
Cerebellum		3.60	−4	−83	−19
Medial frontal g BA 8/32		3.57	0	29	35
Inferior parietal l BA 40		3.56	−48	−50	54
Medial frontal g BA 6		3.56	2	14	55
	Off atlas	3.31	24	−68	−43
Memory task rCBF increases *versus* Nonsense Word condition					
Cerebellum		4.17	4	−80	−16
Mid frontal g BA 46	**DLPFC**	**4.01**	**50**	**36**	**26**
Parahippocampal g BA 27	Similar to midazolam	3.78	17	−29	−4
Superior parietal l BA 7		**3.48**	**40**	**−65**	**55**
Cerebellum		3.44	−48	−56	−29
Putamen	Similar to midazolam	3.43	−20	10	11
Cerebellum		3.31	28	−61	−22
Interaction analysis, relative rCBF increases (Fig 6)					
Sulcus precentral g BA 6		5.70	63	−6	32
Sulcus BA 5/7		5.56	18	−34	53
Cingulate gyrus BA24		5.36	14	−6	43
Sulcus inferior frontal g BA 44/6		5.34	−51	−6	30
Cingulum		5.16	−14	0	31
Superior temporal g BA 42	? Artifact	5.09	71	−15	10
Transverse temporal gyrus BA 41		5.00	48	−25	12
rCBF increases close to medial temporal lobe (MTL; Fig 6)					
Brainstem		4.30	−22	−27	−27
Cerebellum/Fusiform g BA 19	Similar to midazolam	4.26	−14	−53	−7
Cerebellum/Fusiform g BA 19		4.23	16	−51	−9
Inferior temporal g BA 20	Similar to midazolam	3.72	36	−21	−33
Parahippocampal g BA 36	Similar to midazolam	3.67	36	−32	−19

Boldface = similar cortical locations affected by propofol and memory task. A region in the dorsolateral prefrontal cortex (DLPFC) seemed to be consistently affected in different comparisons; **Midazolam** = similar effects at similar locations in [18] are noted.

g = gyrus, l = lobule, BA = Brodmann's Area; T value > 4.6 ($P < 0.05$ corrected for multiple comparisons over total brain space); T value > 3.17 ($P < 0.001$ height threshold at a single voxel).

Brain Sciences Unit (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html, last accessed February 28, 2002). Coordinates of interest are reported using Talairach locations in table 1.

Results

Study Groups

Subjects fell into two nonoverlapping groups based on the number of words recognized at the end of the study day. Of the 30 words presented once during PET scanning, the high and low effect groups recognized 2.7 ± 1.4 words and 14.5 ± 2.4 words, respectively, $P < 0.001$; fig. 1). At baseline, subjects in the low effect group had significantly better recognition scores of words presented before propofol infusion than did subjects in the high effect group (26.3 ± 2.5 and 19.9 ± 4.4 for low and high groups, $P < 0.05$). Assignment to low (n = 4) and high (n = 7) memory effect for analysis was congruous with original randomization except in three

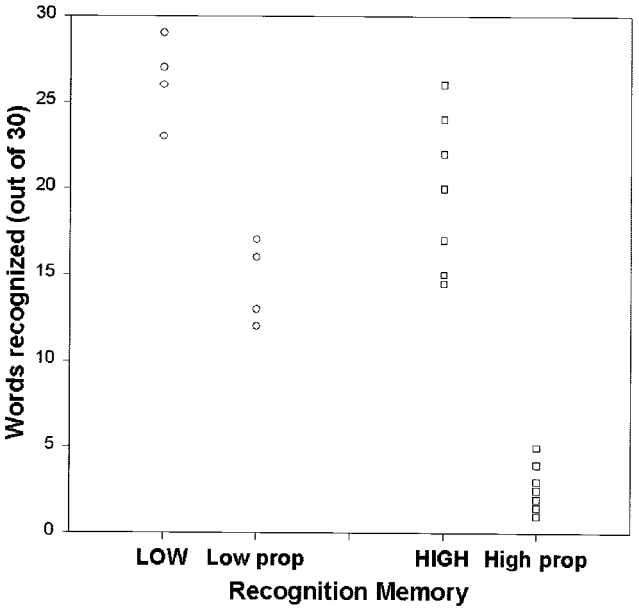

Fig. 1. Words recognized by subjects at the end of the study day. Thirty words were presented during positron emission tomography (PET) scanning in baseline (LOW and HIGH) and drug (prop) conditions. Subjects were grouped into low and high effect groups based on recognition score for words presented in the drug condition.

subjects. Two were reassigned to a high memory effect from the original low propofol target dose of 600 ng/ml. One subject had a measured propofol concentration of 600 (two words recognized), whereas the other had a concentration of 750 ng/ml (three words recognized). Neither of these subjects was noted to be dozing during word presentation. One subject originally assigned to the high target concentration of 1,000 ng/ml had a measured propofol concentration of 420 ng/ml (17 words recognized). Measured propofol concentrations were 523 ± 138 and 829 ± 246 ng/ml for the low and high groups, respectively ($P < 0.05$). There were minor, nonsignificant changes in $PaCO_2$ with propofol administration, from 38.4 ± 3.1 to 40.8 ± 2.8 mmHg in the low effect group and 39.4 ± 4.4 to 41.9 ± 3.9 mmHg in the high effect group. There were no significant differences in other demographic variables, which included age, weight, weight above ideal weight, educational level, and hours slept the previous night.

Regional Cerebral Blood Flow Decreases Related to Change in Propofol Effect

As decreases of rCBF by propofol are of primary interest in examining cognitive impairments, the regions showing significant decreases in rCBF beyond any changes in global CBF are shown in figures 2 and 3 for the two different study groups. The right lower corners of these and subsequent figures refer to the statistical design matrix used in the SPM analysis (this information is available on the ANESTHESIOLOGY web site at http://www.anesthesiology.org). At low effect, primarily left-sided changes are seen. These become widespread over prefrontal, posterior parietal and temporal and cerebellar regions as propofol effect increases. More speci-

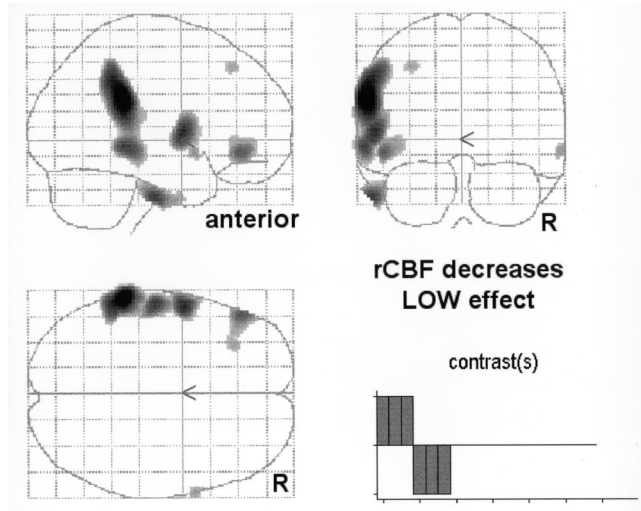

Fig. 2. Regional cerebral blood flow (rCBF) decreases during propofol administration in comparison with baseline for subjects demonstrating a low memory effect. In this and subsequent figures, rCBF change "blobs" are shown in relation to a transparent, "glass" brain. The blobs are "floating" in this outline. Thus, a blob on the far side of the brain can still be seen from the near side. The darkness of a voxel represents increasing statistical significance. To accurately determine where a blob is in three-dimensional space, all three figures must be examined in conjunction. For interested readers, the lower right figure should be compared with the SPM statistical design matrix (available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org), and represents the specific contrast used. A positive voxel is displayed only if T value is greater than 4.6 ($P < 0.05$, corrected for multiple comparisons over the total brain space).

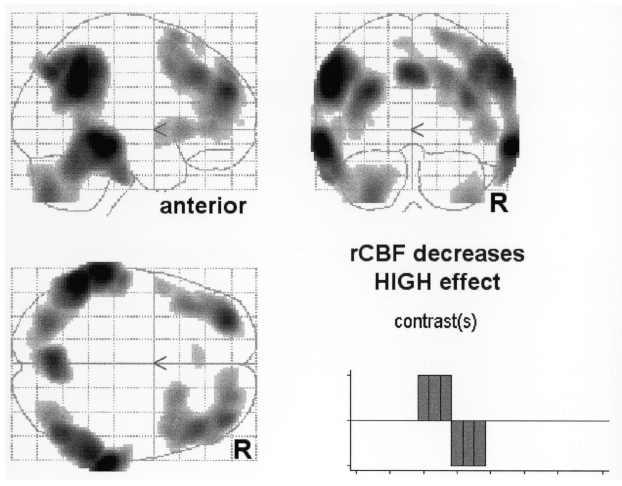

Fig. 3. Regional cerebral blood flow (rCBF) decreases during propofol administration compared with baseline for subjects demonstrating a high memory effect. Note that the primarily unilateral changes in the low effect group become generalized over prefrontal, parietal, and cerebellar regions. A positive voxel is displayed only if T value is greater than 4.6 ($P < 0.05$, corrected for multiple comparisons over the total brain space). The lower right figure represents the specific contrast used.

fically, regions of the brain affected by the increase in propofol effect are located in the right prefrontal, parietal, and temporal regions (fig. 4 and table 1).

Regional Cerebral Blood Flow Increases Related to Word Memorization

The comparison of the memory condition *versus* rest for all subjects at baseline is shown in figure 5. During propofol infusion, a region in the right dorsolateral prefrontal cortex (DLPFC) in the middle frontal gyrus (Talairach coordinates 51, 38, 22, BA 46) is noted to exhibit significant rCBF decreases (fig. 4) and memory-related rCBF increases, regardless of comparison with resting (fig. 5) or nonsense conditions (table 1). Significant bilateral temporal activation is produced by hearing word stimuli (Memory task *vs.* Rest comparison; fig. 5).

Regional Cerebral Blood Flow Increases Related to Change in Propofol Effect

These regions of the brain represent locations where rCBF is relatively unchanged in relationship to the global decrease in CBF associated with sedative doses of propofol (fig. 6).[17,18] Table 1 lists coordinates that survive correction for multiple comparisons over the total brain image space. Of particular interest are regions close to the MTL. These locations are noted separately in table 1, as the statistical significance of these regions range in T values from 3.67 to 4.3 and do not survive correction for multiple comparisons over the total brain image space. However, they would likely be significant if only MTL structures were considered. Because of some inaccuracies in neuroanatomical location in this region, based on differing atlases and subject variation, the closest MTL location within approximately 1 cm to the cerebellar and brainstem structure is indicated as well.

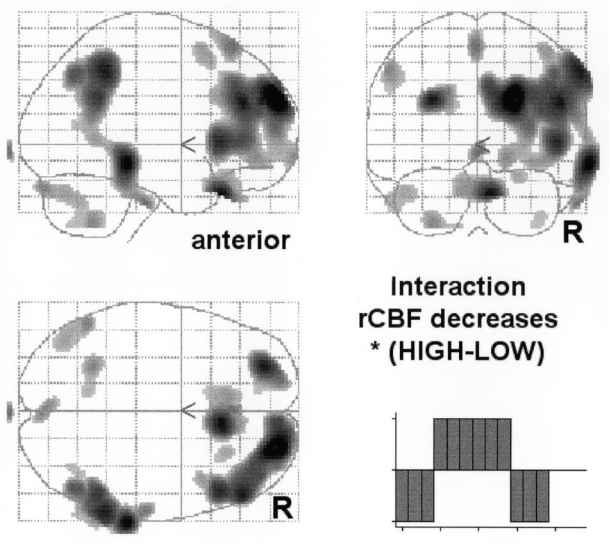

Fig. 4. Interaction analysis of data presented in figures 3 and 4. All voxels with T values greater than 3.17 ($P < 0.001$ uncorrected for multiple comparisons) are shown. Coordinates reported in table 1 represent those locations that survive correction for multiple comparisons over the total brain image space (T > 4.6). Most of the incremental changes are right sided, as expected from the left-sided distribution of rCBF decreases in the low effect group. The lower right figure represents the specific contrast used.

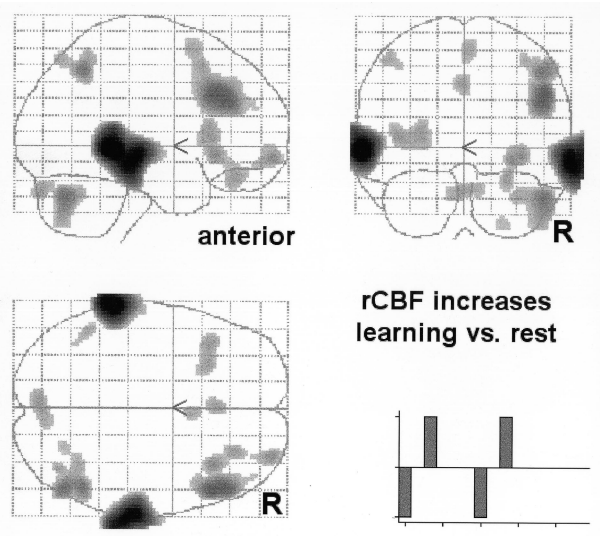

Fig. 5. Memory task-related increases in regional cerebral blood flow (rCBF) during the word memory task for all subjects at baseline, before drug administration. Note the strong bilateral auditory activation from the word stimuli, as compared with the unstimulated Resting condition. Voxels with T values greater than 3.17 are shown ($P < 0.001$ uncorrected for multiple comparisons). None of the memory task-related activations survive correction for multiple comparisons at the $P < 0.05$ level for total brain space. However, several activations are close to the interaction analysis for decreases in rCBF (fig. 4). These are indicated in table 1. Comparison of memory task-related rCBF activations with the Nonsense word condition is not graphically presented, but coordinates of interest are listed in table 1. The lower right figure represents the specific contrast used.

Discussion

The primary finding of this study is that propofol specifically affects prefrontal and posterior parietal brain regions at a time when the impairment in episodic memory becomes maximal. The memory effect in the low effect group, although clearly a decrement from baseline performance, is of small magnitude, as it is still within the range of the lowest level of performance for the volunteer subjects at baseline. It is possible that some of the memory effect in the low effect group may be from interference from hearing the second word list. An improved study design may incorporate a control group, with counterbalancing of conditions on different study days, although replicability of rCBF measurements and coregistration of brain images becomes an issue in this type of design.

By design, the primary behavioral change occurring between high and low effect groups is the change in memory. The similar locations of rCBF decreases pro-

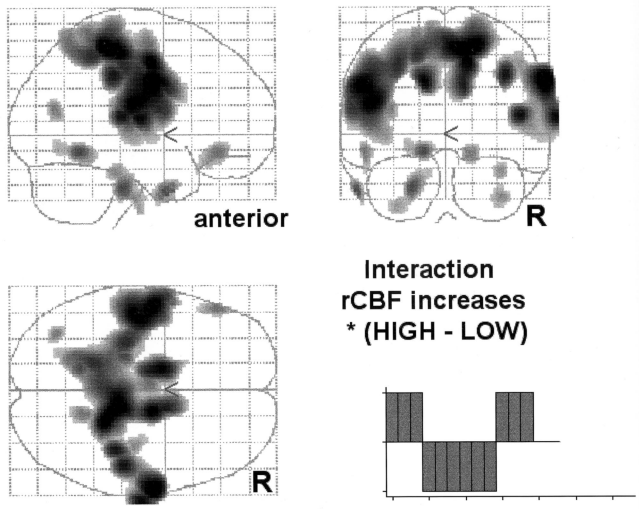

Fig. 6. Interaction analysis of regional cerebral blood flow (rCBF) increases and study group. All voxels with T values greater than 3.17 ($P < 0.001$ uncorrected for multiple comparisons) are shown. Of particular interest are structures in the medial temporal lobe (MTL) region, and specific locations are reported in table 1. The lower right figure represents the specific contrast used.

duced by propofol and rCBF increases during performance of the memory task at baseline indicate that many regions affected by propofol are related to memory function. Although sedation was increasing at this time, based on measured serum concentrations during PET scanning, it is approximately half of that in our previous rCBF imaging study with midazolam where thalamic blood flow was decreased.[17] No identifiable decreases in thalamic rCBF were demonstrable at this dose of propofol, indirectly supporting the hypothesis that the thalamus is a key target of the hypnotic effect of anesthetics.[14,22–24]

The right DLPFC, in particular, is affected by an increase in propofol effect, as well as being activated during the memory task, regardless of comparison with Resting or Nonsense word control tasks (indicated by boldface and DLPFC in table 1). Although many verbally related memory processes have been localized in the left hemisphere, recent evidence identifies the importance of the right DLPFC in memory tasks using auditory presentation of material.[25] The memory task-induced activations in rCBF were less significant than corresponding changes in rCBF related to propofol administration. This is likely to be related to inhomogeneity of processes subjects used in memorizing the word list. Unfortunately, we did not prospectively determine or control which strategies subjects used to memorize the word list. However, in seven subjects (four in the low effect group and three in the high effect group), study notes indicate that a large variety of methods were used, including visualizations, associating words, first letter mnemonics, grouping into categories, making sentences using the words, and repetition using chunking. Subjects in the low effect group tended to use a strategy of forming associations between words, whereas those in the high effect group more often used a strategy of simple repetition or "chunking" adjacent words. These strategies were most often rated as "somewhat" effective before drug administration and "not very" effective afterward. Listening to nonsense words may not have been an appropriate control for auditory stimulation because unconscious semantic processing of a word-like stimulus may have occurred even though subjects were told not to attempt to decode the nonsense words. Thus, some aspects of verbal and memory processing may have been subtracted out in the Memory task *versus* Nonsense words comparison.

The locations identified in the prefrontal and parietal cortices correspond closely to those identified as important in working memory processes.[11,26] Working memory temporarily stores and manipulates information for purposes of higher cognitive activity, one of those being learning. There is substantial evidence that working memory processes are engaged during memorization of verbal material, particularly subvocal rehearsal of material in the phonologic loop.[10,27] Diminished capacity for verbal information is a notable effect of propofol and other amnesic drugs.[28] In the case of auditory verbal working memory, the storage buffer is likely located in Wernicke's area, accessed by the phonologic loop localized to Broca's area in the prefrontal lobe. In the low effect condition, left-sided decreases in rCBF may indicate a preferential impairment of verbal memory processes at low doses. Increases in working memory load are associated with incremental right-sided activations in prefrontal and parietal regions, where many of the dose-related rCBF decreases were seen in this study as memory became further impaired.[29] In our previous study with midazolam, an older PET scanner with a limited field of view was used. Because we wanted to ensure inclusion of MTL structures in this initial study, the top of the cerebrum was not imaged. Thus, it is unknown if midazolam produces reductions in parietal rCBF similar to those of propofol.

Working memory processes, distributed over different brain regions, need to function as a whole in the service of working memory.[30] Each brain region must integrate information from the other brain regions involved. Varela *et al.*[31] have proposed that this "large scale integration" is achieved by synchronous EEG activity. Activity in the lower EEG frequencies (α, θ, β) is involved with cognition, whereas higher frequency γ activity is involved in perception and consciousness. This theory fits well with the recent findings of John *et al.*[23] regarding the collapse of γ coherence across the brain at the point of loss of consciousness. If EEG activity is examined carefully over time in relation to the onset of amnesia for verbally presented material, a spectrally broad distribution of β EEG activity begins at this time

point.[32,33] Normal resting α activity is greatly decreased when this occurs. Rather than representing a nonspecific "pharmacologic" effect of these drugs, these EEG changes may represent interference with normal synchronous EEG processes necessary for memory function, which is distributed widely over the cortical surfaces. The effects of propofol on rCBF in discrete, but distributed, cortical regions support further investigation of EEG effects occurring during the onset of drug-induced amnesia.

The interaction between changes in rCBF with drug effect can also identify regions of the brain "resistant" to the global decreases in CBF associated with this dose of propofol. This effect is estimated to be about 5–10% from predrug levels.[17,24] Regions located close to or in the MTL[‖] seem to be resistant to the CBF decreases induced not only by propofol, but also by midazolam sedation (see table 1).[18] These findings seem incongruous as MTL structures are critical to episodic memory formation. However, amnesic drugs may not act at the MTL to impair memory processes. The findings of this study implicate dysfunction of cortically distributed processes by these drugs to produce episodic memory impairment. It is possible that certain MTL structures (*e.g.*, hippocampus) are involved in these distributed cortical processes but may have been too small to be reliably imaged in this study. Of note, MTL structures are important during retrieval of information and during encoding.[34,35] Semantic retrieval processes have been recently localized to the parahippocampal gyrus; semantic retrieval is a function that benzodiazepines do not affect.[36–38]

In conclusion, during a time when ablation of episodic memory becomes maximal, an increase in propofol effect is associated with decreases in rCBF in right-sided prefrontal and posterior parietal regions. These neuroanatomical regions are similar to those activated during a simple verbal memory task and previously reported working memory processes. MTL structures seem resistant to the effects of propofol and midazolam. These findings lead us to hypothesize that propofol and midazolam interfere with episodic memory function by inhibition of the distributed cortical processes necessary for normal memory function rather than by specific or isolated impairment of MTL function. The collapse of the cognitive "brainweb"[31] needed for normal memory function may be temporally indexed by dramatic changes in EEG activity at this time. The findings from this study point to more specific goals for the study of amnesic sedative drugs. In particular, despite evidence of normal "short-term" memory function as assessed by digit span and recency effects in the presence of benzodiazepines, further elucidation of the interaction of amnesic drugs and working memory processes is necessary, particularly in relation to EEG changes occurring during this time.

[‖] Some of these findings, when mapped to the standard Talairach atlas, are located in the cerebellum, a larger structure in relation to the MTL. Using the Talairach atlas rather than averaged individual MRI structural scans, not obtained in this study, can lead to significant errors, particularly in medial, deep, small structures given the resolution of current PET techniques.

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