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Drug-induced Amnesia Is a Separate Phenomenon from Sedation

Electrophysiologic Evidence

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Background: **Sedative–hypnotic drugs not only increase sedation, but also impair memory as serum concentration increases. These drugs also produce profound changes in the auditory event-related potential (ERP). The ability of various ERP components to predict changes in sedation and memory produced by various drugs was tested.**

Methods: **Sixty-five healthy volunteers randomly received intravenous placebo, midazolam, propofol, thiopental, fentanyl with ondansetron, or ondansetron alone at five different stable target concentrations (three increasing, two decreasing) using a computer-controlled infusion pump to produce varying degrees of sedation without loss of consciousness. ERPs were recorded while volunteer participants detected a deviant auditory stimulus and made a button-press response to a target tone (standard oddball paradigm, 80:20 ratio, to elicit a P3 response). At each target concentration, volunteers learned a list of 16 words. The predictive probabilities (P_k) of various ERP components were determined for word recognition at the end of the day (memory) and log reaction time to the deviant stimulus (sedation).**

Results: **The N2 latency of the ERP consistently predicted log reaction time in all groups (P_k ± SE from 0.58 ± 0.04 to 0.71 ± 0.04). The N2P3 amplitude of the ERP was the best predictor of memory performance for midazolam (P_k, 0.63 ± 0.04), propofol (P_k, 0.62 ± 0.05), and thiopental (P_k, 0.66 ± 0.04). There was a differential ability to predict memory performance from sedation for midazolam and propofol.**

Conclusions: **Midazolam and propofol affect memory differentially from their sedative effects, and these are indexed by specific components of the auditory ERP. These components of the ERP are associated with specific, but not necessarily unique, neuroanatomic structures. Thus, these drugs act by additional mechanisms beyond general central nervous system depression to produce the effects of sedation and memory impairment.**

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THE sedative and amnesic effects of sedative–hypnotic drugs are closely related, as sedation itself produces impairment in memory performance, and both effects vary in the same direction as serum concentration changes.[1,2] There is evidence that separate neuroanatomic regions mediate arousal or attention *versus* memory processes in humans who have not received any drug,[3–6] and these processes can be indexed by specific components of event-related potentials (ERPs).[7] In particular, the P3, the longest and most studied ERP component in relation to memory processes, has been repeatedly shown to relate to subsequent memory. In general, a larger P3 is associated with subsequent remembering.[7–9] This finding can be interpreted as the central nervous system (CNS) attending more to distinct aspects of the stimuli and remembering these in preference to other, less distinctive stimuli.[9] As with memory processes, these ERP components may be localized to certain neuroanatomic structures.[10,11] This provides a neuroanatomic basis for the concept that drug effects on memory and sedation are specific.[12] Curran *et al.*[13] used these properties of the ERP to dissociate the memory *versus* sedative effects of lorazepam, diphenhydramine, and scopolamine. The sedation-independent effect of a drug on memory is often not appreciated. If a drug is given to induce unresponsiveness (hypnosis), no explicit memory can be formed.[14] Consequences of this fact include the current perception of some, for example, that propofol has few or no amnesic properties independent of its hypnotic effects.[15] Few investigations of the memory effects of drug are conducted with the ability to differentiate sedative from amnesic effects while participants are still responsive.

The best method to demonstrate dissociation of sedative from amnesic drug effects is the use of different drugs to produce equivalent sedative, yet differing memory effects.[1,2,12,16] Using this approach, we previously showed that the memory effects of propofol are similar to those of midazolam and are independent of a subjec-

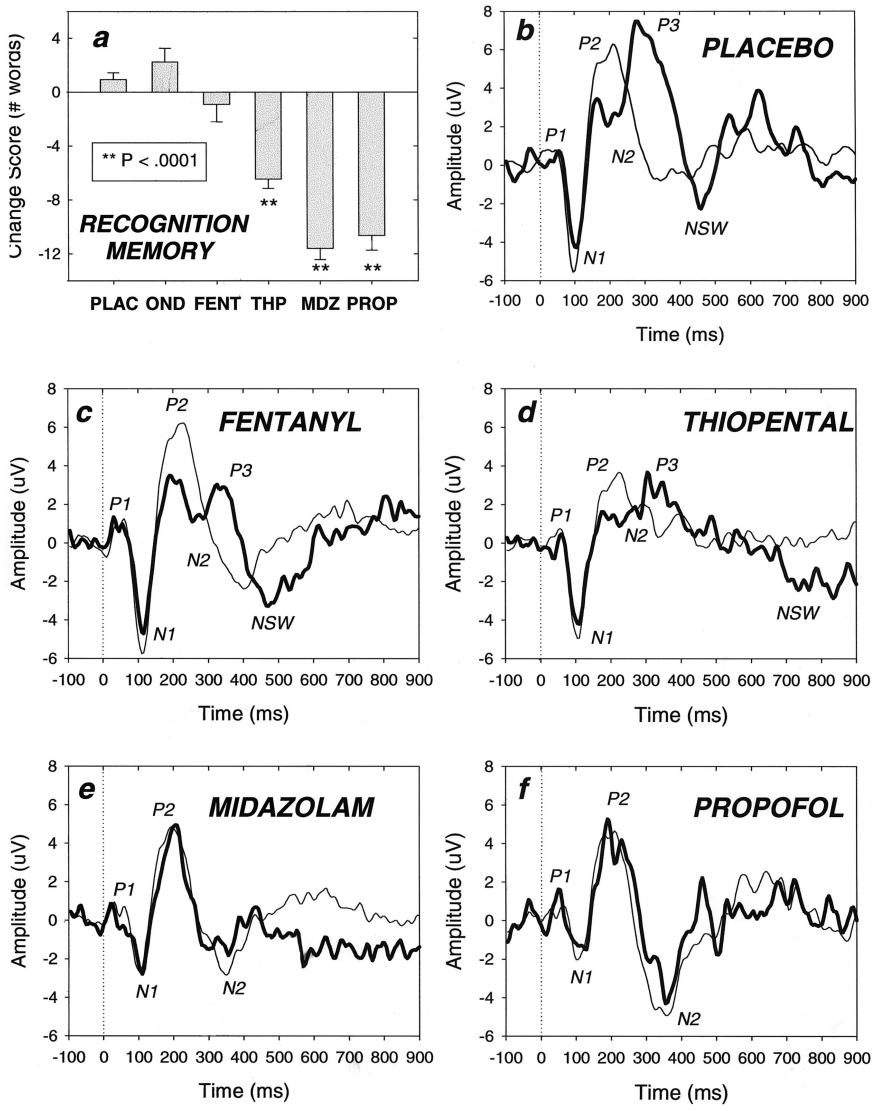

Fig. 1. Effect of the study drugs on memory (*A*) and auditory event-related potentials (ERPs; *B–F*) at maximum concentration. (*B–F*) Grand average waveforms for ERPs to target (thick line) and nontarget (thin line) tones for the Cz electrode are shown. The vertical dotted line at 0 ms indicates the time of stimulus presentation. (*A*) Delayed recognition for words presented at maximum concentration shown as change (mean + SE) from baseline. PLAC = placebo; OND = ondansetron; FENT = fentanyl; THP = thiopental; MDZ = midazolam; PROP = propofol. (*B*) Placebo. The N2 is of smaller amplitude (more positive) for the target tones than for the nontargets, as is usually the case, being partially occluded by the large positive wave (P3), which follows at around 300 ms for the target tones only. The P3 is followed by the negative slow wave (NSW). (*C*) Fentanyl and (*D*) thiopental. Both N2 and P3 to target tones are reduced in amplitude. (*E*) Midazolam and (*F*) propofol. The ERP waveforms are now very similar between target and nontarget tones. As the P3 waveform disappears, the P2 and N2 components may become more visible. The maximal peak amplitudes for N2 are larger (*i.e.*, more negative) in the groups receiving sedative drugs (mean ± SD: −1.6 ± 4.0 μV for placebo *vs.* −3.8 ± 2.1 μV for midazolam, −3.9 ± 5.6 μV for propofol, −2.4 ± 3.0 μV for thiopental, and −3.7 ± 5.1 μV for fentanyl).

tive measure of sedation, the Norris visual analog scale.[16] To index CNS effect, that analysis used measured serum drug concentrations, which can only be obtained retrospectively. The current report presents a new analysis of these memory effects using the ERPs obtained in that study. The auditory ERP is a concurrent, real-time measure of CNS effect of the drugs administered.

The late components of the ERP are visibly affected to a larger extent by midazolam and propofol when compared with thiopental or fentanyl (fig. 1). We hypothesized that this difference is a result of the specific effects of midazolam or propofol on memory *versus* sedation. Although the ERPs were obtained using a go–no-go attention task, which does not specifically target memory processes, there is evidence that some memory processes are engaged and that various ERP components from this paradigm index memory function.[7–9] To explore this effect, we used the method of Smith *et al.*[17] and Dutton *et al.*[18] to relate auditory ERP components to either memory or sedative effects by means of the predictive probability parameter (P_k). Although the previously used Norris visual analog scale is an accepted method of assessing sedation, it is by necessity subjective.[19] In the current analysis we chose to use another, possibly more objective measure of sedation, the logarithm of the reaction time (logRT) to an auditory stimulus in a go–no-go class of task.[20] As before, the memory effect was measured by the ability of volunteers to recognize words previously presented at different target drug concentrations at the end of the study day.[16]

Materials and Methods

This investigation was approved by the institutional review board of Memorial Sloan-Kettering Cancer Center, New York, New York, before accrual of volunteer participants took place. All volunteers were given detailed information about the study, and informed consent was obtained before participation.

Orientation Session

After telephone interview, volunteers were assessed in person for inclusion in the study. This assessment included a brief physical examination. Potential volunteers were excluded if there was evidence of medical, neurologic, or psychiatric problems, substance abuse, or medication use that might interact with the study drugs. Volunteers participated in an orientation session in which the study requirements were fully explained, and all experimental tasks were practiced.

Study Groups. Sixty-five volunteers (39 men, 26 women) aged 21–45 yr participated in a placebo-controlled study of mild, moderate, and maximal sedation levels in a single session. Volunteers were randomized to receive either midazolam (n = 11), propofol (n = 11), thiopental (n = 10), fentanyl with ondansetron pretreatment (n = 10), ondansetron alone (n = 8), or placebo (n = 15). All drugs were administered by computer-controlled continuous intravenous infusion (see Veselis *et al.*[21] for details regarding kinetic data sets and pump performance) to target constant brain concentrations at three increasing and two decreasing levels of target concentration, with the highest concentration achieved designated as "maximum concentration" (see fig. 1 in Veselis *et al.*[16] for more details regarding infusion profile). The highest concentration was chosen based on previous experience to produce deep sedation without unresponsiveness. Blood samples were drawn for later assay of serum concentrations by high-performance liquid chromatography. Serum concentrations were not determined for the ondansetron group. All volunteers fasted from midnight of the previous night. A 5% dextrose ½ normal saline solution was administered intravenously at approximately 125 ml/h to prevent stress from prolonged glucose restriction.

Event-related Potential Recording. Nineteen channels of unipolar electroencephalogram were recorded using the International 10-20 System montage, referenced to linked mastoids, using NeuroScan SynAmps and software (Scan 3.0, NeuroScan Inc., Herndon, VA). Electroencephalographic data were acquired at a sampling rate of 200 Hz with a lowpass filter set at 40 Hz. A notch filter was used to remove 60-Hz artifact. Artifact rejection was conducted offline using various criteria, including a maximum amplitude criterion of ± 100 μV, vertical electrooculogram, and electromyogram signals indicative of movement, and notes regarding artifacts and events were stored with the electroencephalographic data. Pure tone stimuli were presented *via* headphones and were indicated in the electroencephalographic data file by timing marks for *post hoc* ERP analysis.

Auditory stimuli were presented using an "oddball" paradigm, with frequent (80%: 1,000 Hz) and rare (20%: 2,500 Hz) tones presented at intervals of 1.1 s. Rare tones at 2,500 Hz were designated as "targets," and participants pressed a button when they heard one of these tones. Frequent tones at 1,000 Hz (80%) were designated as nontargets, and no response was required. Five-minute trials included 33–43 target tones, from which the ERPs used in this report were derived (some target tones were lost after editing out artifacts from the ERP files). ERPs from target and nontarget tones were analyzed in 1-s epochs surrounding the target tone stimulus (−100 to +900 ms poststimulus). The latency, peak amplitude, and average amplitude of the P1, N1, P2, N2, P3, and negative slow wave ERP components from the target tones only were determined for the Cz electrode using Readpeak software (Christopher Nielsen, Copenhagen, Denmark). Although the Pz electrode is most commonly used in studies of the P3 component, we chose to present data from the more anterior electrode, Cz. We previously demonstrated that drug-induced changes in the electroencephalogram occur primarily in the frontal region with these drugs.[22] The electrode Cz is close to most of the maximal ERP peaks (figs. 2 and 3; a color version of fig. 3 is available in the Web Enhancement [fig. 3A]).

Following conventional procedures, amplitude was determined for each peak as the point with greatest deviation from baseline, and latency was measured as the value in milliseconds corresponding to maximal amplitude. The average amplitude of each peak was determined by averaging the voltage in time windows as follows: P1, 50–80 ms; N1, 80–120 ms; P2, 150–220 ms; N2, 160–350 ms; P3, 250–500 ms; N3, 400–700 ms. Average values for waveforms were used rather than actual peak values (except for N2P3, see below), because when drug is present, it is frequently difficult to identify which peak is present–absent in a given individual. In this situation, Readpeak software can provide a less biased estimate of ERP activity in the given time window than can be obtained by visual identification of a given peak in a given individual. The time windows were selected based on previous literature and examination of grand average waveforms obtained by pooling data across participants for the appropriate groups and conditions.

We found a substantial number of missing data points for the P3 peak amplitude and latency. This was a result of various factors, including the participant being too sedated to perform the tone discrimination task. In many cases the P3 was simply not recognizable because of the persistent α or β activity in the background electroencephalogram. In all of these cases, the P3 amplitude was determined as the average amplitude in the P3 time window (250–500 ms). This value was considered a less biased estimate of the P3 amplitude than a value of zero would have been. However, a latency value could not be accurately determined and was left as a missing value. Thus, there are more missing data for latencies than for amplitudes. This substitution of values was necessary for approximately 10–15% of the data points for the ondan-

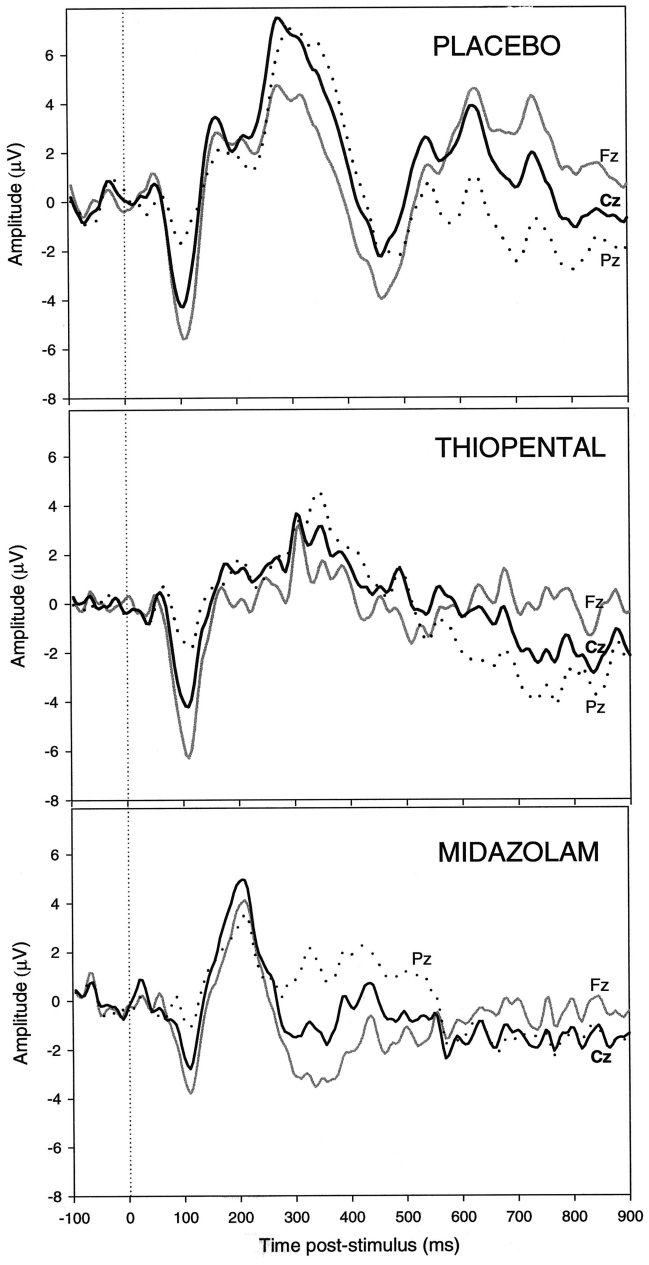

Fig. 2. Event-related potential responses to target tones across the midline of the head, superimposing waveforms from Fz (anterior), Cz (central), and Pz (posterior) electrodes. (*Top*) Placebo waveforms; (*middle*) thiopental waveforms; (*bottom*) and midazolam waveforms (all at maximum concentration).

setron, propofol, and thiopental groups, and for approximately one quarter of the data points in fentanyl and midazolam groups. No datapoints were missing from the placebo group.

N2P3 Amplitude. Although P3 peaks were difficult to identify, N2 peaks were more easily identifiable. The peak-to-peak measurements for N2P3 amplitude demonstrated relatively high P_k for memory effect (see below), and we thus include the N2P3 amplitude in this report as a peak-to-peak measure. If a P3 peak could not be identified, the average P3 value was substituted as the P3 peak value, as explained above. N2 and P3 amplitude average values are referenced to a 100-ms prestimulus baseline. The peak-to-peak measure is independent of the 100-ms prestimulus baseline value. The P_k values calculated using averaged N2 and P3 amplitudes were similar but not as large as peak-to-peak N2P3 values, possibly because of this consideration.

Memory Tests. Volunteers completed a modified Rey Auditory-Verbal Learning Test at each target concentration, approximately 30 min before ERP recording at the same target concentration. Different word lists were used at each concentration in randomized fashion. The task consisted of learning a list of 16 words sequentially presented four times for memorization. Several hours later, after the drug had worn off, participants were required to recognize at the end of the study day any words that were presented on any of the study lists by circling them on an answer sheet that contained presented and nonpresented words (n = 112 and n = 64, respectively; more details are presented in the appendix of Veselis *et al.*[16]).

Reaction Time Task (Oddball Paradigm). Reaction times (RTs) to correctly detected target tones were calculated using the Neuroscan Respwin utility with an accuracy of 5 ms. As is customary, RTs were log-transformed (base 10) before statistical analysis to more closely approximate the normal distribution.

Visual Analog Scale Measure of Sedation (Norris Scale). Sixteen bipolar visual analog scales of sedation were obtained repeatedly at each serum concentration.[19] Four scales were presented on each of four pages. Each was 10 cm in length, and the participant would make a mark along the length of this scale. Completion of the 16 scales took approximately 2–3 min. The order of presentation of pages was randomized between tests, and similar poles alternated between left and right ends of the scale (*e.g.*, weak on right, clumsy on left) to avoid bias in responding. The individual scales were summed into four measures with possible values from 0 to 40 each: Physical Sedation (weak, clumsy, lazy, incompetent), Mental Sedation (drowsy, slow, dreamy, fuzzy), Tranquilization (calm, contented, peaceful, relaxed), and "Other" feelings (bored, hostile, sad, withdrawn). As there were no significant differences between Physical and Mental Sedation, these were averaged together to provide one measure of sedation, Average Sedation, also with a maximal value of 40.

Predictive Probability Analysis. The P_k, a nonparametric test of the ability of one variable to predict another, was used to evaluate the strength of relation between ERP components from target tones and behavioral measures.[18] This test is appropriate even if the data fail to approximate the normal distribution. This parameter accurately measures the predictive ability of one parameter for another regardless of scale units or underlying distribution of data. If perfect prediction is ob-

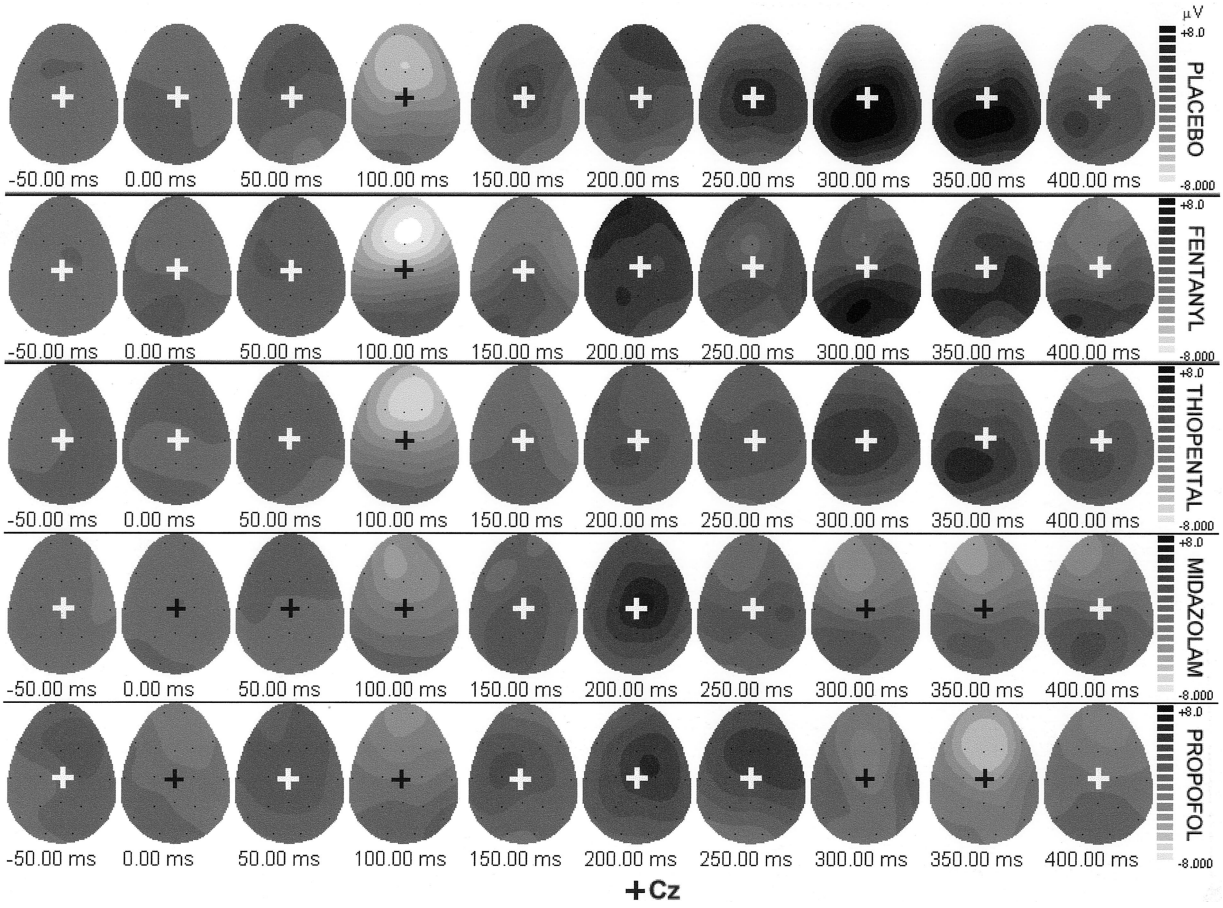

Fig. 3. Topographic distribution of event-related potential amplitudes across the entire head pictured at a given instant at intervals of 50 ms, starting 50 ms before stimulus onset. The left-most two head maps represent normal variation of ERP amplitude. For each head map, anterior is at the top, posterior is at the bottom, and the volunteer's right is on the right. Event-related potential amplitudes are shown as a gray scale, with white indicating −8.0 μV and black indicating +8.0 μV. Cz is indicated by a plus sign. Reference should also be made to the grand average waveforms shown in figure 1 when examining this figure. Note that the high amplitude P3 present in the placebo group is reduced for fentanyl and thiopental and absent (or negative) for midazolam and propofol. Note also that the P3 in volunteers receiving drug is delayed in latency and may occur at 350 ms, if present. (A color version of this figure is available in the Web Enhancement [fig. 3A]).

tained, then the P_k has a value 1 (or 0). If there is no relation between parameters, then the P_k is 0.5. The P_k will be between a value of 0.5 and 1 if one indicator increases as the other parameter does. P_k values between 0.5 and 0 indicate that as one parameter increases, the other decreases. The key statistical test is to determine if the P_k value is significantly different from 0.5, and this is performed using a standard *t* test for proportions. $P < 0.05$ was taken as the level of statistical significance.

PkMACRO, obtained from Dr. Warren Smith (California State University, Sacramento, CA), was used to relate various ERP components to two predicted measures: word recognition by the participant at the end of the study day as a measure of memory ($P_{k\text{MEMORY}}$), and the logRT to target tones as a measure of sedation($P_{k\text{SEDATION}}$). All observations from different dosages of the drug were included in the analysis. After this initial analysis, it was found that the N2 latency was the most predictive of sedation and that the N2P3 amplitude was the most predictive of memory when drug was present.

Combined Event-related Potential parameter CN2P3. A combined ERP parameter was calculated that was to represent the "sedation-independent" amplitude of N2P3. In general, sedation will decrease the amplitude of any ERP component, as well as lengthening the latency of the ERP. Thus, the amplitude of N2P3 would be larger in the absence of the sedative effect, and the correction was empirically calculated by factoring in the increase in latency present with sedation: N2P3 amplitude (microvolts) + N2 latency (milliseconds)/25. The derivation of this parameter was based on similar considerations to those that were used to derive the "single index parameter" recently described by Dutton *et al.*[18] The N2P3 peak-to-peak amplitude was chosen as the best indicator of memory and the N2 latency as the best indicator of sedation. Dutton *et al.* used a corrective

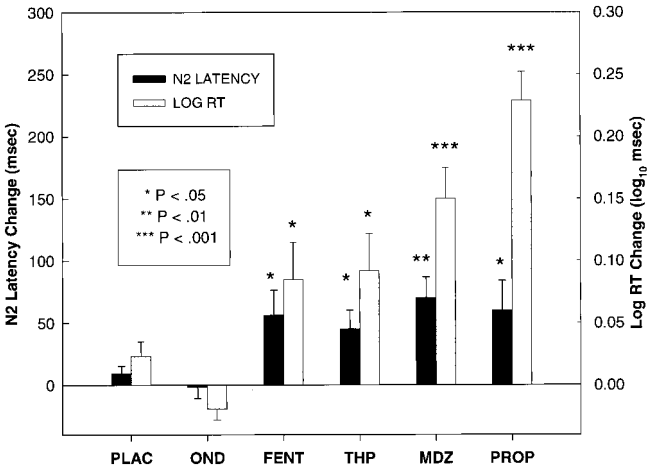

Fig. 4. Change from baseline levels in N2 latency and log reaction time (RT). The increase in RT is greater for midazolam and propofol ($P < 0.001$) than for fentanyl and thiopental ($P < 0.05$), whereas the increase in N2 latency is about the same in all sedative drugs ($P < 0.05$). *P* values indicated are from paired *t* tests on the change scores, maximum concentration minus baseline. PLAC = placebo; OND = ondansetron; FENT = fentanyl; THP = thiopental; MDZ = midazolam; PROP = propofol.

factor of 10 for the latency, working with an ERP component of latency approximately 100 ms. Thus, we chose 25, as we were working with an ERP component of latency of approximately 250 ms.

Determination of "Best" Event-related Potential Predictors: Rank Sum Analysis. The predictive probabilities for each of the ERP components (latency and average amplitude) were compared as a set. To compare the P_k coefficients with each other, the value of 0.50 was subtracted from each P_k value, and the result was expressed as the absolute value. This allows parameters that change in different directions to be directly compared. For instance, increased latency as well as decreased amplitude may predict sedation equally well with P_k values of 0.60 and 0.40. Absolute values were then ranked in order (rank 1 = largest P_k), with tied ranks expressed as the mean rank. The sedative drugs were ranked together (midazolam, propofol, thiopental, and fentanyl for sedation; fentanyl excluded for memory, as it had no memory effect). The rank order of ERP components in order of their predictive probabilities for word recognition (memory) and logRT (sedation) were determined. To test the hypothesis that, independent of drug used, a given ERP parameter was significantly better at predicting memory or sedation, group differences between the P_k values of all drugs combined (fentanyl excluded in the case of memory) of a given ERP component *versus* the best ranked component were tested using z scores, with no correction for multiple comparisons using a PkDIFF macro, also obtained from Dr. Warren Smith (California State University).

Statistical Analysis. Results are reported throughout as mean ± SD unless otherwise indicated. Traditional ERP components were analyzed by testing for differences between study groups by an analysis of variance with drug as a grouping factor. The behavioral variables (memory, Average Sedation, logRT) were tested at maximum concentration by one-way analysis of covariance with baseline scores as a covariate. *Post hoc* comparisons of significant results were performed using the Dunnett one-tailed test, as the anticipated direction of change was for increased sedation, decreased memory, increased ERP latencies, and decreased ERP amplitudes with drug administration. In figures 1 and 4, change from baseline in recognition memory, reaction time, and N2 latency were analyzed by paired *t* test for each group. $P < 0.05$ was taken as the criterion value for statistical significance in all tests.

Results

Subject Characteristics

Mean values for volunteer participants' age and weight can be found in table 1 for each drug group. All volunteers claimed to have slept normally the night before (mean sleep duration, 6.2 ± 0.9 h). No differences were found between drug groups in age, body weight (kilograms), body mass index, sleep, or right hand dominance.

Table 1. Values for Demographic, Memory, and Sedation Variables by Drug Group

	Placebo	Midazolam	Propofol	Thiopental	Fentanyl	Ondansetron
N	15	11	11	10	10	8
Age	27.5 ± 4.8	28.9 ± 6.4	28.7 ± 5.2	28.1 ± 8.2	25.3 ± 2.7	28.0 ± 7.1
Weight (kg)	69.2 ± 10.9	63.1 ± 10.9	70.8 ± 11.7	69.0 ± 11.0	69.1 ± 17.2	71.7 ± 16.0
Max[Conc] (μg/ml)	—	0.137 ± 0.029	1.40 ± 0.18	4.48 ± 1.33	2.24 ± 0.40	—
Learning (words)	14.0 ± 1.3	4.6 ± 3.3*	5.9 ± 3.2*	7.8 ± 3.7*	10.9 ± 2.6*	13.8 ± 1.6
Recognition (words)	14.0 ± 1.5	2.2 ± 1.3*	1.9 ± 1.9*	7.1 ± 2.4*	12.0 ± 2.9*	14.6 ± 1.4
AvgSed	16.2 ± 8.6	27.1 ± 3.3*	18.7 ± 8.6	25.1 ± 6.4*	27.8 ± 7.6*	16.2 ± 6.9
LogRT (hits)	2.605 ± 0.078	2.736 ± 0.086*	2.778 ± 0.061*	2.664 ± 0.092	2.634 ± 0.109	2.642 ± 0.145
Hits (%)	99.8 ± 0.7	65.9 ± 14.9*	86.8 ± 22.5	85.1 ± 18.1	77.6 ± 32.5	89.1 ± 23.7

Values are mean ± SD. For memory and sedation measures, means are given for the time of peak drug concentration (Max[Conc]).

* $P < 0.05$ *versus* placebo group, by Dunnett test (one-tailed).

AvgSed = average of visual analog scale self-rating for mental and physical sedation; learning = number of words learned after four trials from a 16-word list; recognition = number of words recognized at end of study day; LogRT = $\log_{10}$ of reaction time (ms) to correctly detected target tones (hits).

Table 2. Selected Event-related Potential Measures at Peak Drug Concentrations to Target Tones at Cz Electrode by Drug Group (Mean ± SD)

	Placebo	Midazolam	Propofol	Thiopental	Fentanyl	Ondansetron
N	15	11	11	10	10	8
N2 latency (ms)	223.6 ± 31.0	295.5 ± 54.6*	278.5 ± 69.2*	253.1 ± 39.2	278.5 ± 64.0	226.3 ± 47.3
P3 latency (ms)	303.0 ± 55.4	385.0 ± 83.4*	334.3 ± 89.6*	346.3 ± 75.9	346.7 ± 37.6	326.3 ± 51.2
N2 average amplitude (μV)	5.5 ± 5.5	1.0 ± 2.2*	2.3 ± 3.3	2.0 ± 2.1	2.4 ± 3.0	6.8 ± 5.6
P3 average amplitude (μV)	3.7 ± 5.4	−0.6 ± 2.3*	−1.2 ± 2.3*	1.6 ± 2.9	0.04 ± 3.6	4.3 ± 5.7
N2P3 amplitude (μV p-p)	13.6 ± 6.9	6.6 ± 4.6*	9.1 ± 4.9	10.0 ± 4.6	7.8 ± 8.1	11.4 ± 5.2
CN2P3	22.5 ± 6.6	18.4 ± 4.4	20.2 ± 3.8	20.1 ± 3.5	19.0 ± 7.6	20.4 ± 4.9

Amplitude measures are average amplitudes within a specific time window, as described in the text, with the exception of N2P3, which is measured peak-to-peak (p-p). CN2P3 is the combined "sedation independent" measure of N2P3 amplitude corrected by N2 latency/25, as described in the text.

* $P < 0.05$ *versus* placebo group, by Dunnett test (one-tailed).

Memory Performance

All drugs impaired initial learning of the word lists ($P < 0.0001$ by analysis of covariance) compared with volunteers receiving placebo and ondansetron (table 1). Once learned, the material was well retained in the placebo, ondansetron, fentanyl, and thiopental groups, but participants receiving midazolam and propofol had further loss of information when tested by recognition at the end of the study day ($P < 0.0001$ by analysis of covariance). Recognition memory calculated as a change from baseline is shown in figure 1A, and absolute values are given in table 1.

Sedation

The mean values of variables measuring sedation are shown in table 1. It should be noted that the placebo group also had significant increases in the visual analog scale measure of sedation, with the range of scores being somewhat similar to that in the groups receiving a sedative drug. RT was significantly increased for midazolam, propofol, and thiopental compared with placebo ($P <$

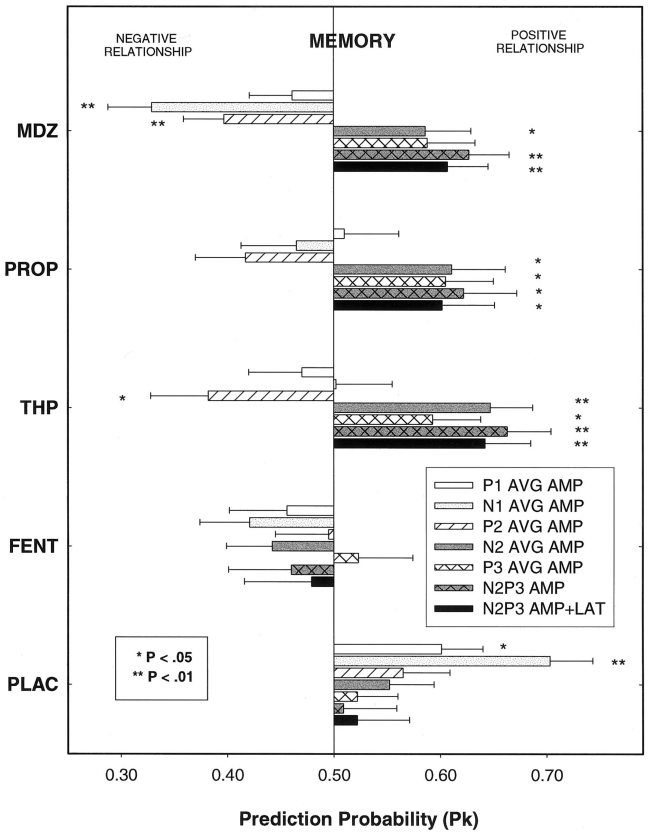

Fig. 5. The ability of amplitude measures derived from the auditory event-related potential to target tones at Cz to predict memory is displayed as the P_k value + SE. MDZ = midazolam; PROP = propofol; THP = thiopental; FENT = fentanyl; PLAC = placebo.

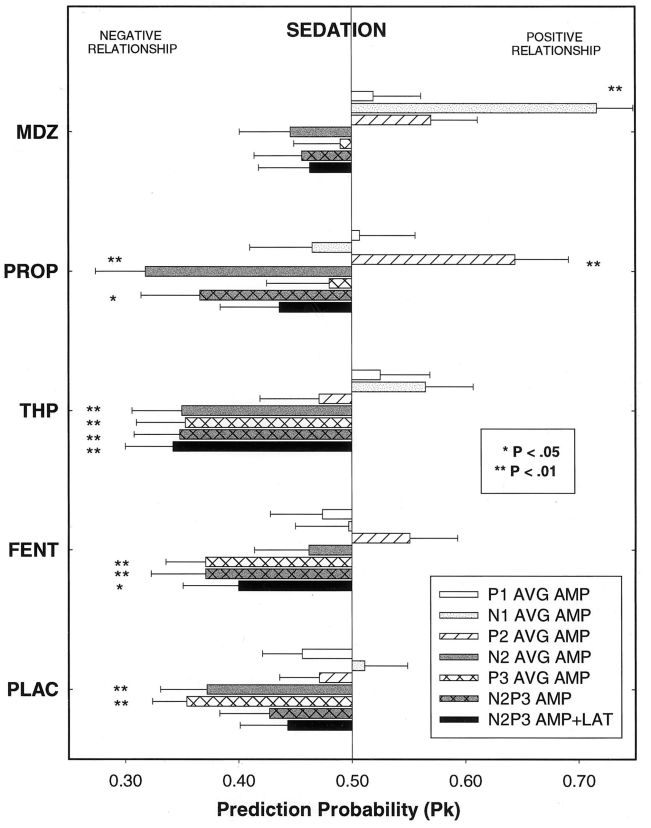

Fig. 6. The ability of amplitude measures derived from the auditory event-related potential to target tones at Cz to predict sedation as measured by logarithm of reaction time is displayed as the P_k value + SE. MDZ = midazolam; PROP = propofol; THP = thiopental; FENT = fentanyl; PLAC = placebo.

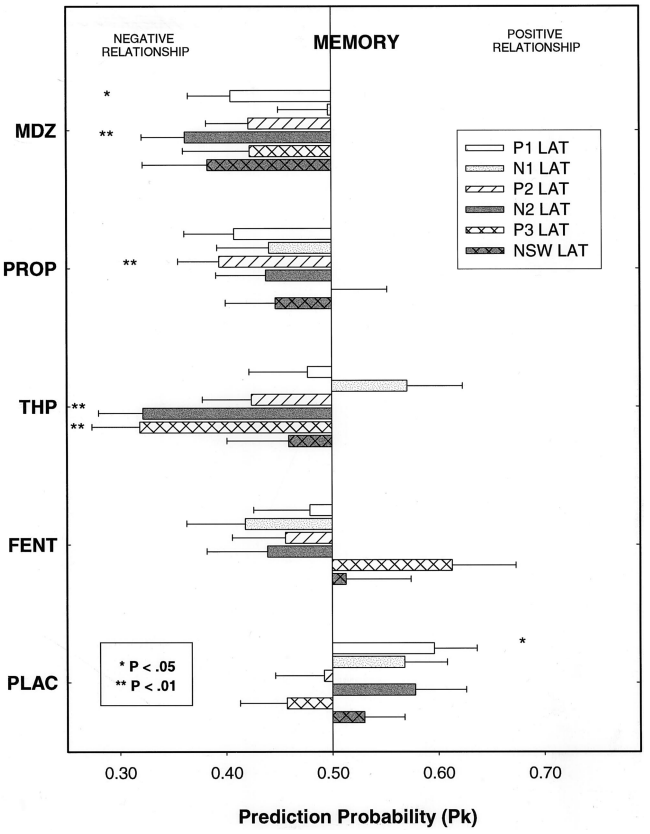

Fig. 7. The ability of latency measures derived from the auditory event-related potential to target tones at Cz to predict memory is displayed as the P_k value + SE. MDZ = midazolam; PROP = propofol; THP = thiopental; FENT = fentanyl; PLAC = placebo.

0.0001 by analysis of covariance; fig. 4). Accuracy of detecting target tones declined for all drugs compared with placebo ($P < 0.001$), but absolute performance levels were not impaired as much as might have been expected for the degree of sedation present (percent correct responses of total target tones: placebo, 100%; propofol, 87%; thiopental, 85%; fentanyl, 78%; midazolam, 66%). The midazolam group, in which volunteers missed one third of all target tones, had significantly worse ($P < 0.05$) performance than all other study groups. Because of high variability on this measure, only the midazolam and thiopental groups responded to significantly fewer tones than placebo. False alarms (responses to nontarget tones) averaged only 3% for the midazolam and propofol groups ($P < 0.05$ *vs.* placebo) and were less than 1% for thiopental, fentanyl, and placebo.

Drug Effects on Event-related Potential Components

Table 2 presents mean latency and amplitude measures for traditional ERP components at maximum concentration and an analysis of variance analysis of drug effects on these. The corresponding grand average waveforms are shown in figures 1B–1F.

Predictive Ability of Event-related Potential Measures for Sedation and Memory Performance

Figures 5–8 graphically demonstrate the ability of particular components from the auditory ERP to target tones to predict memory or sedation. For instance, in figure 5, the $P_{k\text{MEMORY}}$ of the average amplitude of the N2 component (solid dark gray bar), is significantly greater than 0.5 for all drugs other than fentanyl, which had no significant memory effect. This indicates that memory is better when the amplitude of N2 is larger. On the other hand, the $P_{k\text{SEDATION}}$ (fig. 6) of the average N2 amplitude is significantly less than 0.5 in the case of propofol and thiopental, indicating that as sedation increases, the average amplitude of N2 decreases. This relation between memory and sedative effects is evident for the majority of ERP components, indicating that there is a very close relation between memory and sedation measurable in various ERP components. To further quantify the data in figures 5–8, the results of the rank sum analysis are presented in table 3. In general, the group differences between various ERP components were small and not significant in many cases. It should be noted that the combined parameter was almost as predictive of memory as the N2P3 amplitude, but possibly less predictive

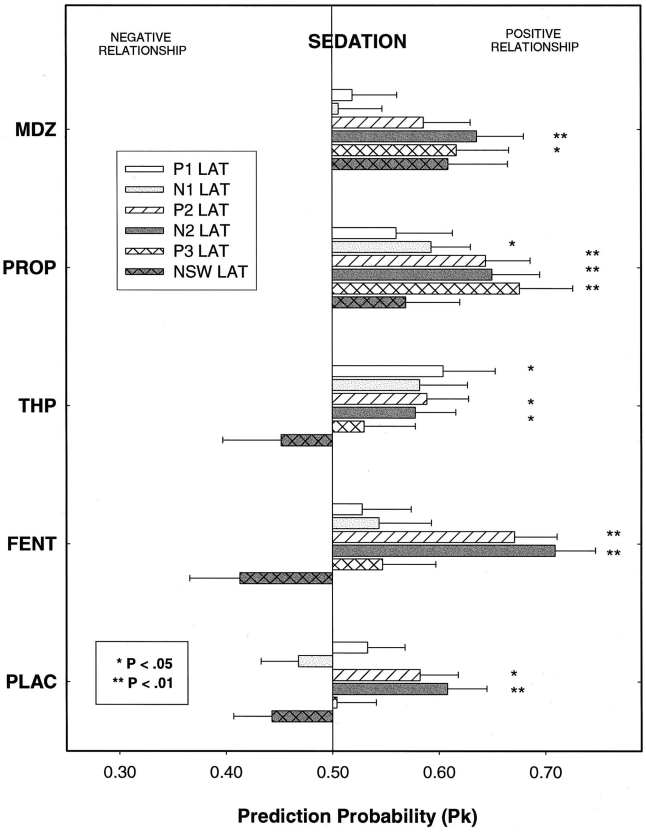

Fig. 8. The ability of latency measures derived from the auditory event-related potential to target tones at Cz to predict sedation as measured by logarithm of reaction time is displayed as the P_k value + SE. MDZ = midazolam; PROP = propofol; THP = thiopental; FENT = fentanyl; PLAC = placebo.

Table 3. Rank Sums of Predictive Probabilities (P_k) for Various ERP Components at Electrode Cz for Drugs with Significant Effects

Rank for Pk	Overall Rank	Amplitude Component	Latency Component
Rank of P_ks of ERP component for memory*	7/36	N2P3	—
	11/36	CN2P3 (0.02, NS)	CN2P3
	12/36	—	N2 (0.02, NS)
	14/36	N2 (0.01, NS)	—
	18/36	P2 (0.01, NS)	—
Rank of P_ks of ERP component for logRT†	10/48	—	N2
	17/48	—	P3 (0.08, $P < 0.01$)
	18/48	N2P3 (0.02, NS)	—
	21/48	CN2P3, P2 (0.05, $P < 0.04$)	CN2P3, P2 (0.05, $P < 0.04$)
	21/48	N2 (0.05, $P < 0.07$)	—

Rank sums of event-related potential (ERP) components for predicting memory or logRT (a measure of sedation). In this analysis, the Pks for amplitude and latency were pooled and were analyzed together for all sedative drugs combined because fentanyl had no memory effect, it was excluded from the memory analysis). Amplitude components are indicated separately from latency components for clarity (except the combined parameter CN2P3, which contains both and is indicated in both amplitude and latency columns). Each component is followed by the group difference of all observations for all drugs combined in predictive probability and *P* value, *versus* the rank 1 component in each cell.

* Midazolam, propofol, thiopental only 12 ERP parameters × 3 drugs; worst rank is 36. † Midazolam, propofol, thiopental, fentanyl 12 ERP parameters × 4 drugs; worst rank is 48.

NS = not significant.

of log RT than N2 latency in comparison with N2P3 amplitude.

In general, the N2 latency was the best predictor of logRT in all groups, including placebo and ondansetron. In our study, when volunteer participants were under the influence of drug, the N2P3 amplitude was the best predictor of subsequent recognition of material presented at that particular drug concentration. However, in the placebo group, amplitude of the early components of the ERP predicted subsequent memory performance, with $P_{k\text{MEMORY}}$ for N1 average amplitude of 0.70 ± 0.04 ($P < 0.001$).

The predictive performance of the combined ERP parameter is presented in table 4, in comparison with the predictive ability of actual measured serum concentrations. It should be noted that, in many cases, the predictive ability of ERP values for memory and sedation are as good as serum concentration itself.

For volunteers receiving ondansetron, $P_{k\text{SEDATION}}$ for the N2 latency was 0.60 ± 0.05 ($P < 0.05$), similar to the other groups. No ERP components related to memory performance for participants receiving ondansetron, even though the distribution of memory scores was similar to participants receiving placebo. For this reason, ondansetron data have been omitted from figures 5–8 to save space. The lack of predictive relation between ERP variables and memory may be related to the fact that the fewest number of participants were in the ondansetron group (8 *vs.* 15 for placebo).

Discussion

Midazolam and propofol, drugs with memory effects independent of sedation as measured using subjective ratings,[16] seem to have a differential effect on the late positive components of the auditory ERP in relation to other drugs with sedative properties and lesser effects on memory, such as thiopental and fentanyl (fig. 1).[23] These late components, including the P3, relate to novelty detection and memory processes.[7,24] Subsequently remembered material is associated with a larger ERP component in this latency range and has been localized to prefrontal regions, close to those exhibiting dose-related decreases in regional cerebral blood flow with midazolam.[7,25–28] Components of the ERP from 50–250 ms relate

Table 4. The Predictive Abilities (Normalized as Absolute Value of $P_k = 0.5$) of Actual Measured Serum Concentrations and the Combined ERP Parameter for Memory or Sedation

	Drug	$P_{k\text{MEMORY}}$ Recognition of Words	$P_{k\text{SEDATION}}$ Log Reaction Time
Measured serum concentration	Propofol	0.75*	0.65*
	Thiopental	0.65*	0.66*
	Midazolam	0.75*	0.69*
	Fentanyl	0.57	0.63*
Combined ERP parameter, CN2P3	Propofol	0.60†	0.56
	Thiopental	0.63*	0.66*
	Midazolam	0.61*	0.54
	Fentanyl	0.48	0.60†

ERP = event-related potential.

* $P < 0.01$, † $P < 0.05$ for significant difference from $P_k = 0.5$.

Table 5. Predictive Abilities of ERP Parameters for Reaction Time *versus* Norris VAS Average Sedation Measures of Sedation

Drug / ERP component	Propofol		Fentanyl		Thiopental		Midazolam	
	LogRT	Norris VAS	LogRT	Norris VAS	LogRT	Norris VAS	LogRT	Norris VAS
N2lat	0.65*	0.46	0.71	0.71	0.58	0.56	0.64	0.64
P3lat	0.68*	0.43	0.55	0.60	0.53	0.52	0.62	0.60
N2P3ampl	0.37*	0.58	0.37	0.36	0.35*	0.44	0.46	0.42
CN2P3	0.41*	0.56	0.40	0.38	0.34*	0.42	0.46	0.42
N2avg	0.32*	0.52	0.46	0.44	0.35*	0.41	0.45	0.39*

The most predictive event-related potential (ERP) components of sedation overall were analyzed (table 3). For each drug, * indicates the measure of sedation demonstrating the highest predictive probability for a given ERP parameter. If the difference between the two predictive probability values for the two measures of sedation is less than or equal to 0.05 (the average value of the standard error of the mean), the P_k values were considered a tie.

VAS = visual analog scale.

to general arousal or attention and may index the sedative effects of drugs.[18] Curran *et al.*[13] dissociated the amnesic from sedative effects of lorazepam by differential effects on early and late ERP components.

In general, the results from this study extend the findings of Curran *et al.*,[13] with various components differentially predicting measures of sedation and memory (table 3). Some ERP components consistently predict memory performance or sedation for each drug and thus have a substantially better ranking than other components, despite the fact that, overall, the differences in P_k values may be small and not necessarily significant. These small and variably significant differences are confirmed by the analysis of variance results in table 2. As in the study by Curran *et al.*,[13] latencies of P1 and N1 were unaffected, while the amplitudes of P3 and N2P3 were decreased significantly by midazolam and propofol. In contrast to the findings of the current study, Curran *et al.* reported that lorazepam or scopolamine did not affect N2 latency and amplitude. Differences between this and the current study include how ERP amplitudes were measured (peak *vs.* average amplitude), measures used to assess sedation (tapping and more complex psychomotor tasks *vs.* reaction time), and memory measures (a continuous recognition task with simultaneous ERP recording *vs.* a repeated presentation of word lists).

The N2 latency was increased by all drugs at the highest concentration (fig. 4), with P_kSEDATION values ranging from 0.59 for thiopental, which had the smallest change in N2 latency, to 0.71 for fentanyl.[29] Close inspection of figure 1 reveals that the maximal peak amplitude of N2 may be larger (*i.e.*, more negative) when drug is present, which is contrary to the generalized decrease in ERP amplitudes seen with sedative–hypnotic drugs. The increase in peak N2 amplitude with sedation may be related to the volunteer's increased "effortful processing" to overcome the increased difficulty of the discrimination task when drug is present.

The N2 is automatically elicited by changes in stimulus properties, and its latency and the reaction time are closely related.[30,31] Decreased arousal or attention will impair the ability to rapidly detect a deviant stimulus and can thus affect N2 latency. The N2 has various subtypes, and the one most commonly observed in the "oddball" paradigm is the N2b.[32,33] Its frontocentral distribution is similar to our findings (fig. 3). The N2b–P3a complex is thought to represent evaluation of stimulus information relevant to attentional focus and response choice.[31]

Increases in reaction time may or may not be synonymous with "sedation." There is currently no well-accepted direct measure of sedation, and different measures can yield different results. Sedation as measured by reaction time was little changed by fentanyl. However, visual analog scale measures showed similar effects of fentanyl to other drugs. Reaction time may have been enhanced by the arousing stimulus of the nausea experienced by 70% of volunteers receiving fentanyl. The opposite pattern was seen with propofol, where the visual analog scale of sedation changed little, but reaction time and N2 latency indicated substantial sedative effect. Other investigators have noted similar discrepancies between different measures of sedation, as well as imprecise perception of participants as to degree of objective impairment.[13,34] A comparison of the best-ranked ERP components (table 3) to predict changes in logRT and Norris visual analog scale was made (table 5). In general, similar predictive abilities were obtained, except in the case of propofol. It may be possible that the subjective perception of sedation during propofol is inaccurate compared with other drugs. As the results from the propofol group are congruous with other drugs when logRT is used, one might argue this is a more objective measure of sedative effect.

We found that the peak-to-peak amplitude of N2P3 was the best predictor for memory impairment, ranging from 0.62 for propofol to 0.66 for thiopental (table 3). Because neither fentanyl nor ondansetron produced impairment of memory, there was no relation between the N2P3 amplitude and memory with these drugs. The of N2P3 amplitude is also predictive of sedation, except in the case of midazolam, where it seems to reflect a memory effect independent of sedation. As N2 latency was consistently predictive of sedation, it was used in an attempt to factor out the sedative effect on the amplitude of the N2P3.[18] The predictive ability for a memory effect is retained for propofol, midazolam, and thiopen-

tal, whereas the ability to predict sedation is retained only for thiopental and fentanyl (figs. 5 and 6). The predictive ability of this combined parameter compared with N2P3 amplitude alone is presented in table 3. These findings, indicative of differential sedative and amnesic effects in the ERP components, are congruous with our previous ones derived from other independent measures.[16] A thorough analysis of all possible linear combinations of various ERP components and P_k values might reveal a memory predictive parameter largely independent of sedation.

Changes in the state of arousal affect memory performance. The N1 component of the ERP, too early to reflect any memory processes, relates to arousal and automatic initial processing of stimuli.[3] The predictive ability of N1 amplitude for memory performance in participants receiving placebo might be explained by higher levels of arousal compared with drug. More cognitive resources were available to perform both the discriminative attention and the memory tasks with less effort. Alternatively, the failure to find the expected relation between later ERP components such as N2 and P3 and memory performance in the placebo group may be a result of the limited range of scores in this group (mean recognition score: 14.0 + 1.5 words from a list of 16 words.)

The results of this study need to be interpreted while keeping in mind certain considerations. Although ERPs were obtained soon after the word memorization task at constant serum concentrations, they were not obtained simultaneously with word encoding. The oddball paradigm used examines the attention paid to a deviant stimulus. Thus, it measures more the ability of the brain to attend to and discriminate stimuli rather than memory processes *per se*. In fact, a dissociation between enhanced memory of distinctive stimuli and the amplitude of the P3 may exist.[9] In future investigations, ERPs should be obtained concurrently with a longer list of stimulus words. The P_k values obtained in this study are less than the desirable values of greater than 0.8 (or < 0.2), such as those reported by Dutton *et al.*[18] In that study, the P_k values derived from ERP components were similar to those from end-tidal anesthetic gas concentrations, which can be considered analogous to measured serum concentrations for intravenous agents. Despite our relatively lower P_k values, these are comparable with the P_k values obtained for measured serum concentrations. Explanations for this finding include the following: (1) the ERPs were not recorded simultaneously with the verbal learning task or with the delayed recognition test; (2) Dutton *et al.* used a well-defined end point, loss of responsiveness, whereas no such similar measure exists for sedation or memory; and (3) the data in this study represent relatively small changes in serum concentration from baseline to maximal sedation, whereas Dutton *et al.* were able to study the much larger ranges associated with full anesthesia (P_k values tend to be higher for larger data ranges).

Multiple comparisons were performed of P_k values against a value of 0.5. Based on previous results, we hypothesized that N2 latency would be the most sensitive to sedation effects and that the P3 or similar ERP component would be the most sensitive to memory effects.[29,35] These hypotheses comprise approximately three to five *a priori* comparisons. Actual *P* values for a two-tailed *t* test are reported in figures 5–8, and those significant at a level less than 0.01 are conservatively appropriate for the number of *a priori* comparisons.

The auditory P3 is generated in distributed brain regions.[10,11,36] The neuroimaging literature demonstrates that memory function is a distributed process that may correspond to the components of the ERP later than 250 ms.[5,37] ERP components before 50–100 ms are produced by neural transmission through the brainstem and thalamus, sites that are prime candidates for the hypnotic (as defined by loss of responsiveness) effects of anesthetics.[38,39] At concentrations of anesthetic associated with responsiveness, this hypnotic effect is manifested as "sedation," measurable in given components of the ERP. At concentrations producing heavy sedation, but not complete unresponsiveness, both propofol and midazolam have the ability to produce oscillations in the 12–14-Hz range[40] similar to previously described thalamocortical oscillations.[41] Midazolam and propofol produce regional decreases in thalamic blood flow at these concentrations,[39,42] and changes in thalamic metabolism have been correlated with changes in arousal with other benzodiazepines.[43] These effects may represent the expression of sedative drug effects *via* thalamic mechanisms at these concentrations.

In conclusion, the differential effect of CNS-active drugs on memory and arousal–attention–sedation can be demonstrated in the ERP. Using ERPs as a measure of CNS effect may be particularly advantageous as objective measures of both memory and sedative effects are obtained simultaneously and in real time. In addition, it is now possible to locate potential generators of particular ERP components with reasonable accuracy in the brain.[11] The findings of this study are in agreement with the hypothesis that sedation, the "hypnotic" effect of anesthetics at lower concentrations than those causing unresponsiveness, may not act exclusively by generalized CNS depression.[38,39,44] The fact that certain CNS structures relate both to arousal or attention and memory processing[45] provides a neuroanatomic basis for the interaction of sedation with memory when drugs are administered. The ability to relate the electrophysiologic changes to the memory and sedative behavioral effects of drugs provides the ability to measure these effects independently without the potentially confounding factor of subjective perception. These identified electrophysiologic changes can then be related to brain images

from positron emission tomography or functional magnetic resonance imaging to accurately localize and quantify the neuroanatomic regions mediating these drug effects.

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