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Visual P2–N2 Complex and Arousal at the Time of Encoding Predict the Time Domain Characteristics of Amnesia for Multiple Intravenous Anesthetic Drugs in Humans

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ABSTRACT

Background: Intravenous anesthetics have marked effects on memory function, even at subclinical concentrations. Fundamental questions remain in characterizing anesthetic amnesia and identifying affected system-level processes. The authors applied a mathematical model to evaluate time-domain components of anesthetic amnesia in human subjects.

Methods: Sixty-one volunteers were randomized to receive propofol (n = 12), thiopental (n = 13), midazolam (n = 12), dexmedetomidine (n = 12), or placebo (n = 12). With drug present, subjects encoded pictures into memory using a 375-item continuous recognition task, with subsequent recognition later probed with drug absent. Memory function was sampled at up to 163 time points and modeled over the time domain using a two-parameter, first-order negative power function. The parietal event-related P2–N2 complex was derived from electroencephalography, and arousal was repeatedly sampled. Each drug was evaluated at two concentrations.

Results: The negative power function consistently described the course of amnesia (mean $R^2 = 0.854$), but there were marked differences between drugs in the modulation of individual components ($P < 0.0001$). Initial memory strength was a function of arousal ($P = 0.005$), whereas subsequent decay was related to the reaction time ($P < 0.0001$) and the P2–N2 complex ($P = 0.007/0.002$ for discrete components).

Conclusions: In humans, the amnesia caused by multiple intravenous anesthetic drugs is characterized by arousal-related effects on initial trace strength, and a subsequent decay predicted by attenuation of the P2–N2 complex at encoding. The authors propose that the failure of normal memory consolidation follows drug-induced disruption of interregional synchrony critical for neuronal plasticity and discuss their findings in the framework of memory systems theory.

What We Already Know about This Topic

- Long-term memory depends on the strength of the original memory trace and on the natural decay of that trace over time
- The effects of anesthetics on these processes are not established

What This Article Tells Us That Is New

- In 61 volunteers, memory trace strength was related to state of arousal and decay of that trace to reaction time and the P2–N2 complex of the posterior parietal event-related potential
- Dexmedetomidine affected memory primarily by affecting memory trace strength, whereas propofol and midazolam marked affected decay of that trace

INTRAVENOUS anesthetic drugs are able to cause anterograde amnesia at brain concentrations well below those required to induce unconsciousness.[1,2] This implies that certain neural processes critical to normal memory function are more susceptible to these agents than are those necessary for consciousness. *In vitro* studies have identified several drug actions that could plausibly be involved, including

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the inhibition of long-term potentiation (LTP),[3–7] interference with extracellular signal-regulated protein kinase function,[8,9] modulation of hippocampal protein expression,[10] and suppression of arousal systems.[11,12] However, fundamental questions remain as to what significance any of these effects has on human memory *in vivo*, and the degree to which this diverse group of drugs converges on a common amnestic pathway.

One approach to evaluate memory function in humans is to mathematically model what happens to memories over time. In normal memory function, a trace is established rapidly and then progressively decays. Previous studies show that this temporal course can be described by a negative power function,[13–16] approximated under typical assumptions by the simple equation

$$m_t = \lambda t^{-\psi},$$

where m is the memory strength at time t, λ describes the strength of the initial memory trace, and ψ describes the subsequent rate of decay of that trace (appendix). It follows that any intervention that alters memory function, such as an amnestic anesthetic drug, will modulate these parameters.

Our study is centered on the principle that the pattern of mathematical modulation is a function of the underlying mechanism(s) of amnesia. Much as Fourier transformation is used to separate a complex waveform into component frequencies, this principle enables nonlinear memory decay to be quantitatively dissociated into simpler subcomponents. Therefore, our first objective was to experimentally determine and compare how intravenous anesthetics modulate the mathematical form of memory decay. The null hypothesis was that there is no difference between drugs in modulation of λ and ψ at equivalent absolute levels of memory loss. Our second objective was to determine whether components of the mathematical model could be linked to neurophysiologic or neurobehavioral drug effects. Specifically, we investigated three variables that all require the functional integration and connectivity of distributed neural systems: (1) the level of tonic arousal, which is known to modulate selective and sustained attention and attentional effort; (2) reaction time, which is associated with interregional phase coherence at multiple oscillatory frequencies[17,18]; and (3) the P2 and N2 components of the posterior parietal event-related potential (ERP). Although several early components of the ERP are believed to emerge from a reset of oscillatory activity by a visual event, the P2–N2 complex was chosen because of its association with θ (3–8 Hz) synchrony,[19–22] with the advantage of being far more reliably obtained than direct measures of phase coherence. The importance of θ phase appears repeatedly in the memory literature and has been linked to successful memory function,[23–26] memory trace decay,[27] and memory-related hippocampo-cortical feedback loops.[28–31] It is critical to the induction of LTP,[32] a neuroplastic process widely regarded as a key underlying mechanism for memory function and is also modulated by halogenated volatile anesthetics *in vivo*.[33] Although the P2–N2 complex in no way represents a direct measure of θ synchrony, it is an informed starting point for investigating the relationship between a drug's amnestic potential and the system-level effects on connectivity.

We studied drugs from three distinct classes of γ-aminobutyric acid (GABA)ergic agonist: thiopental (barbiturate), propofol (alkylphenol), and midazolam (benzodiazepine). Although these drugs share the GABA subtype-A receptor as a principal target, human neuroimaging and electrophysiology studies have revealed marked differences between them in regional activation patterns during memory tasks[34–36] and also in amnestic potency when the sedative effect of the drug is held constant.[2] We also studied dexmedetomidine, which binds to α_{2A}-adrenoreceptors in the locus coeruleus and decreases activity in a widespread network of cortical and subcortical noradrenergic pathways associated with tonic arousal and vigilance,[37,38] but it is not known to have a specific amnestic effect unrelated to sedation. All four active drugs were dosed to target a common level of end-amnesia (*i.e.*, all subjects receiving an active drug would ultimately forget the same amount of material). Two amnestic levels were assessed by having each subject perform the experimental procedure at two sequential steady-state concentrations.

Materials and Methods

Subjects

Sixty-seven healthy, right-handed volunteers were recruited from the general community and remunerated for their participation. Subjects provided written consent, and the study was approved and monitored by the Institutional Review Board of Memorial Sloan–Kettering Cancer Center (New York, New York). Subjects were fluent in English, had a minimum of a high school education, had no current medical or psychiatric comorbidity, and had no history of recreational drug abuse, head injury, or psychiatric disorder. Subjects were excluded if they had relevant allergies, a family history of porphyria, or a body mass index exceeding 30 kg/m^2. Pregnant patients were excluded through assessment of plasma β-human chorionic gonadotropin. Several days before the study, subjects attended an orientation session, during which they practiced abbreviated versions of the memory experiments.

Drugs and Drug Delivery

Subjects were randomly allocated using computerized random number generation (Excel software, Microsoft Corp., Redmond, WA) to receive propofol ($n = 13$), thiopental ($n = 14$), midazolam ($n = 13$), dexmedetomidine ($n = 15$), or a placebo ($n = 12$) mimicking one of the active drugs. Both subject and investigator were blinded to the drug allocation. To determine the target drug concentrations, data from previous studies[1,2] were used to provide estimates for the concentrations required to bracket a 50% retention rate for visual stimuli after 4 h (without correction for false alarms): the low

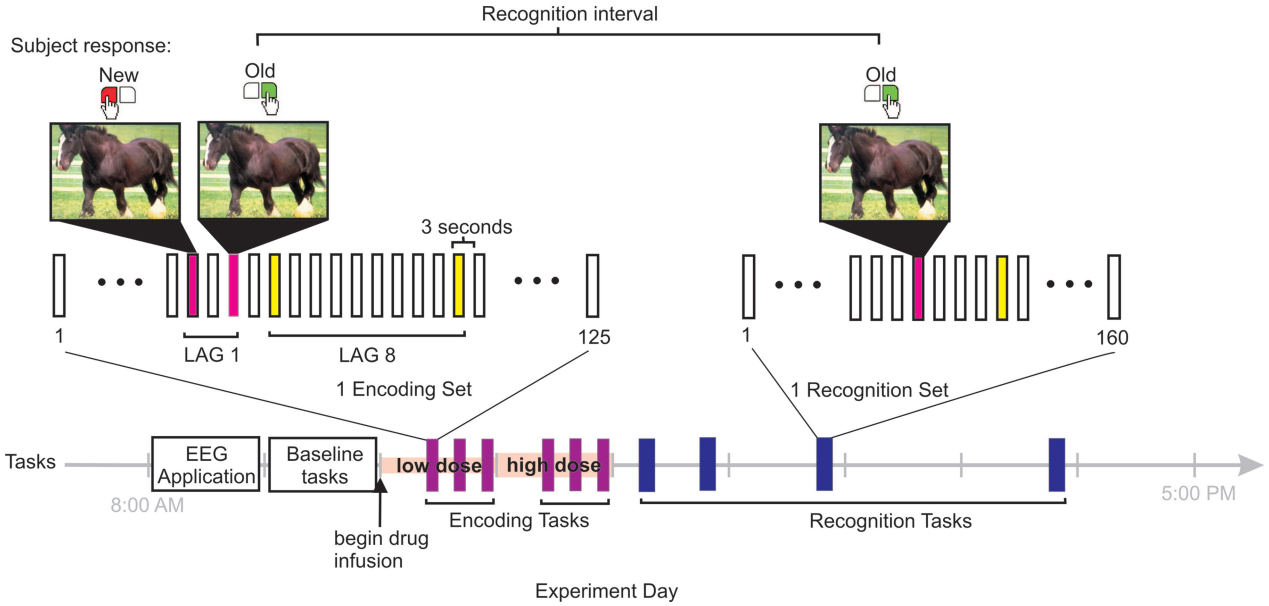

Fig. 1. Study profile. The master timeline for the experiment is shown at the base of the figure, with a profile of the specific tasks expanded in the upper portion. The central elements are a sequence of Encoding Tasks (*purple bars*) performed with the drug equilibrated at the target concentration, followed by a series of Recognition Tasks (*blue bars*) performed after the drug infusion was stopped. Items appeared twice during the Encoding Task sequence and were defined to have been encoded if they were correctly recognized at the second presentation. Memory for the item was subsequently tested within one of the Recognition Tasks. Sequencing within the 12 Encoding Task–Recognition Task permutations permitted the probing of memory performance at 160 time intervals. EEG = electroencephalography.

drug level was the estimate for 60% retention, and the high drug level was the estimate for 40% retention.

Drugs were delivered *via* a catheter inserted into a vein on the left hand, with 5% dextrose–0.45% NaCl solution used as a carrier. A Harvard 22 syringe pump (Harvard Apparatus, Inc., Holliston, MA) was controlled by STANPUMP pharmacokinetic software** installed on a laptop computer. Cognitive experiments commenced only after the pharmacokinetic model predicted equilibration at the effect site (brain), which took approximately 15 min.

Exclusions and Stopping Point

Six subjects were excluded from analysis. Four subjects (one propofol, one thiopental, and two dexmedetomidine) were excluded because a technical malfunction resulted in the loss of greater than 25% of response data. One subject (midazolam) was excluded because the subject recognized less than 20% of the presented material at both drug levels. One subject (dexmedetomidine) failed to complete the study after fainting during the insertion of the intravenous catheter. Exclusions were determined according to criteria established before commencing the study. Enrollment continued until at least 12 nonexcludable subjects were in each group.

Materials

All stimuli were color photographs taken from the International Affective Picture System.[39] For the experiment, images were assigned to one of three sets: 160 were used in Encoding Set 1, 160 in Encoding Set 2, and 320 used as recognition foils. Images were presented using STIM^2 software (Compumedics Neuroscan, Charlotte, NC) on a 17-inch liquid crystal display monitor placed at eye level at a distance of 1.2 m. Each item was presented for 2,000 ms and followed by a 1,000-ms blank screen, for a total interstimulus interval of 3,000 ms.

Experimental Procedure

The experimental sequence is depicted in figure 1. After arrival (8:00 AM), gold cup electroencephalography leads were applied, the intravenous catheter was placed, and baseline measurements were performed. Drug infusion was then commenced (10:00 AM), and after equilibration, the Low-dose Encoding Task was performed using images from one of the Encoding Sets described earlier. The total sequence was 375 items long and was divided into three blocks of 125, each separated by a 5-min rest. All 160 images in the Encoding Set were repeated during the sequence: (1) 70 were repeated following one intervening item (Lag 1, 6-s probes); (2) 70 were repeated following eight intervening items (Lag 8, 27-s probes); and (3) 20 images were repeated following 20 intervening items (Lag 20, 63-s probes). Some additional images were used to fill gaps in the sequence. The subject's task was to indicate using a mouse whether the item was being presented for the first time (new) or was a repeated item (old). Once this sequence was completed, the drug concentration was increased to the higher level (11:00 AM), and the High-dose Encoding Task was performed. The sequencing for this

** Freely available from the WorldSIVA Open TCI Initiative at http://opentci.org/doku.php. Accessed March 2, 2010.

task was identical to the low-drug task, but it used the images from the other Encoding Set. The drug infusion was then stopped (12:00 PM). Four Recognition Tasks were performed exactly 15, 45, 105, and 225 min after stopping drug. Each Recognition Task contained 160 stimuli: (1) 40 from the Low-dose Encoding Task; (2) 40 from the High-dose Encoding Task; and (3) 80 novel images. Subjects were provided a light lunch during the course of the afternoon, but they were not permitted to have caffeinated beverages.

To sample memory performance at approximately 10 min, which was shorter than that could be achieved with the first Recognition Task, the Lag 20 images were treated differently. All Lag 20 images had their first two presentations (the initial new and old pair) placed within the first block of the Encoding Task. A third presentation was then placed in the second block of the Encoding Task, and this functioned as the recognition probe for that image. These images were again presented in both the third block of the Encoding Task and in the Recognition Task, but these subsequent presentations functioned as fillers and were not part of the analysis.

Calculation and Statistical Analysis of the Memory Decay Function

An image was included in the calculation of the decay function only if it was demonstrably attended to and encoded. We defined encoding to have occurred if an image was appropriately identified as old when presented for the second time in the Encoding Task. The subsequent recognition for all such items was traced, and the exact time interval between encoding and recognition (recognition interval) was calculated using the computer time stamp. The value for each item was adjusted by subtracting the false-positive rate for the specific Recognition Task in which the item was presented.

The data were next clustered into 13 points. Twelve clusters were established by average weighting all Lag 1 and Lag 8 items that belonged to a specific Encoding Task—Recognition Task permutation. The thirteenth point was derived from the third presentation of the Lag 20 items, which was embedded within the Encoding Task as described earlier. Subjectwise clusters were averaged to generate the groupwise values.

Two statistical methods were then applied to the memory decay function. First, the Marquardt–Levenberg nonlinear regression algorithm was used to derive discrete values for λ and ψ in each drug and dose combination. This is the conventional approach for modeling memory decay functions,[13,15] and provided the point values required for the subsequent correlational analyses. However, this model is compromised for statistical comparison between the groups. Instead, to provide the strongest statistical comparison of drug effects on λ and ψ, we used Kristensen's nonlinear mixed-effects model,[40] which incorporates subject-specific variability and accommodates the repeated measures study design. Here, the initial decay function is extended to form the following equation:

$$m_{tij} = [\lambda_i + \mu_{ij}] \times t^{-(\psi_i + \xi_{ij})},$$

where subscript i indicates the treatment group, and subscript j the individual subject. Thus, the terms μ_{ij} and ξ_{ij} characterize the individual variation in initial signal strength and rate of forgetting, respectively. This model was calculated using the nlme package in the statistical computer language R.†† Drug and drug level were incorporated as fixed factors, and the individual subject was incorporated as a random factor. All other statistical calculations were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL). Hypothesis testing was two-tailed in all cases, and the results were quoted as significant for P values less than 0.05.

Assessment of Tonic Arousal

Subjects completed the Positive and Negative Affect Schedule[41] at baseline and at the beginning and end of each Encoding Task. Affective dimensions were rated on a scale of 1 ("very slightly or not at all") through 5 ("extremely"). Self-reported sedation–arousal scores were calculated from the averaged responses for the alert, attentive, and active items, using both schedules completed at each drug level.

Event-related Potentials

The electroencephalogram was obtained in 55 of the 61 subjects included in the behavioral analysis. The electroencephalogram was not recorded in the remaining six subjects (one propofol, one thiopental, one midazolam, and three dexmedetomidine) because of technical problems. Nineteen channels were sampled at 1 kHz using Synamps amplifiers and Scan software (Compumedics Neuroscan). Data were referenced to the left mastoid during acquisition but re-referenced to linked mastoids for analysis. Offline, the electroencephalogram was epoched to 2,500 ms, with a 199-ms prestimulus baseline. Electrooculography artifacts were attenuated using the Neuroscan regression algorithm, and residual artifacts were removed through automated rejection followed by visual inspection. ERPs were obtained from baseline correction and averaging according to item criteria.

The amplitude and latency of the P2 and N2 components of the ERP at the Pz electrode were determined. Because the time interval between first and second presentations is known to influence θ synchrony,[27] which was critical to our interest in the P2–N2 complex, we evaluated only the second presentation of the Lag 8 (27 s) probes. After filtering, the identification of the P2 and N2 peaks was performed at the level of the individual subject through two independent visual inspections, and the group value was derived from subject averaging.

Visual Verbal Learning Test

It is not possible to encode material in the presence of drug and then study early recognition without some residual drug being

†† R Development Core Team: R: A language and environment for statistical computing. Vienna, Austria, R Foundation for Statistical Computing, 2008. Available at: http://www.r-project.org. Accessed March 2, 2010.

Table 1. Subject Characteristics

Drug	Included Subjects	Age, yr	Gender (M/F)	BMI, kg/m^2
Propofol	12	26.0 (6.6)	8/4	23.1 (2.8)
Thiopental	13	29.7 (8.3)	10/3	24.9 (2.9)
Midazolam	12	27.4 (8.0)	7/5	22.9 (3.1)
Dexmedetomidine	12	31.8 (10.7)	7/5	23.2 (3.2)
Placebo	12	30.1 (5.5)	7/5	23.3 (2.3)

There was no significant difference between groups with respect to age, gender distribution, or body mass index (BMI). Only subjects ultimately included in the analysis are listed. Values are presented as mean (SD).

present. Thus, a test was required to determine whether the anesthetic drugs had any retrograde effect on the recognition of material learned before the drug is administered.

A visual modification of the Rey Auditory Verbal Learning Test[42] was developed. The learning phase occurred just before the initial drug administration. Subjects were shown a primary list of 16 emotionally neutral words on a computer screen. Each word was presented for 1,500 ms and followed by a blank screen for 500 ms using the STIM^2 software. Immediately after the presentation, subjects were given 30 s to name any words that they could recall. This procedure was performed four consecutive times. Subjects were then shown a secondary list of 16 words and again given 30 s to name any words that they could recall. This list was shown only once. Thus, it was expected that the primary list would be more strongly learned than the secondary list. To counterbalance any effect of individual words, three versions of the test were created and assigned randomly.

Recognition occurred during the drug infusion. Subjects performed a forced-choice task in which they were presented word pairs for 2,500 ms followed by a blank screen for 500 ms. One word was taken from either the primary or the secondary list (old), and the other was a novel foil (new). The task was to identify the old word. At each of the two drug levels, eight words from each of the primary and secondary lists were probed.

Results

Subject Characteristics

There was no significant difference between the treatment groups in subject demographic characteristics (table 1). The average age for the 61 subjects included in the analysis was 29.0 yr (SD 8.0; range, 18–50 yr). Male:female ratio was 39:22. The average body mass index was 23.5 kg/m^2 (SD 2.9; range, 17.2–29.8 kg/m^2).

Task Integrity

To assess the ability of subjects to adequately attend to and perform the Encoding Task, we evaluated performance accuracy for the initial presentations of the Lag 1 (6 s) probes (table 2). Overall accuracy in identifying the initial presentation as new was 91.6% (SD 7.8), whereas accuracy in identifying the second presentation as old was 90.2% (SD 9.9). All of the active drugs caused diminished accuracy at the high drug level, resulting in a statistically significant drug:level interaction for both new ($F_{4,55} = 4.98$, $P = 0.002$) and old ($F_{4,55} = 3.404$, $P = 0.015$) items. There was no overall accuracy bias toward either new or old items ($t_{120} = -1.853$, $P = 0.066$). Further, accuracy for an item's first (new) presentation did not influence the accuracy for its second (old) presentation ($t_{114} = 0.350$, $P = 0.727$), suggesting that miscategorization had no significant effect on learning from item exposure.

Table 2. Task Performance Measures and Key Decay Model Parameters

			Task Performance Measures (6-s Probes)				Power Decay Model			
Drug	Pharmacokinetic Model	Target Concentration	New Accuracy (%)	Old Accuracy (%)	New Reaction Time (ms)	Old Reaction Time (ms)	λ	ψ	R^2 Value	t at $m_t = 1$ (min)
Propofol	Schnider	0.45 μg/ml	95.4 (3.4)	95.4 (4.3)	955 (232)	802 (158)	1.401	0.179	0.763	6.6
		0.90 μg/ml	86.3 (8.7)	88.1 (11.5)	1098 (192)	900 (159)	1.586	0.326	0.890	4.1
Thiopental	Shafer	1.5 μg/ml	94.7 (5.7)	93.4 (7.9)	935 (133)	778 (146)	1.499	0.195	0.926	8.0
		3.0 μg/ml	89.0 (8.6)	85.9 (14.1)	1016 (123)	821 (153)	1.285	0.221	0.870	3.1
Midazolam	Greenblatt	20 ng/ml	91.9 (5.5)	87.4 (11.4)	981 (187)	889 (192)	1.502	0.258	0.881	4.8
		35 ng/ml	85.1 (12.8)	78.7 (10.2)	1046 (153)	946 (166)	1.170	0.296	0.801	1.7
Dexmedetomidine	Markku	0.20 ng/ml	95.1 (2.6)	93.3 (5.0)	906 (108)	779 (88)	1.492	0.203	0.875	7.2
		0.40 ng/ml	85.7 (7.4)	87.2 (7.9)	979 (147)	810 (144)	1.132	0.200	0.830	1.9
Placebo	—	—	95.7 (1.8)	95.5 (4.5)	850 (178)	784 (194)	1.346	0.143	0.838	8.0
		—	96.4 (3.0)	96.4 (3.3)	874 (96)	752 (128)	1.226	0.113	0.868	6.1

New and old accuracy measures represent performance in correctly categorizing the first (new) and second (old) presentations within the Encoding Task for those probes separated by 6 s. t at $m_t = 1$ is the predicted time at which memory decay would become behaviorally detectable. Data are presented as mean (SD).

Although all active drugs caused an unavoidable degree of globally impaired task performance at the higher dose, overall performance remained generally high and unbiased. The exclusion of miscategorized items from further analysis provided control against dynamics in task integrity.

Applicability of the Negative Power Function in Describing Drug-induced Amnesia

Using the Marquardt–Levenberg nonlinear regression algorithm, the range of R^2 values for the negative power function model $m_t = \lambda t^{-\psi}$ was 0.763–0.926 (mean 0.854; SD 0.047; table 2). The model satisfied the axiomatic condition that behavioral memory performance was intact in the initial state (*i.e.*, $m_t \geq 1$ as $t \rightarrow 0$), which was required because the analysis included only images that had been correctly identified as "old" in the Encoding Task. The model predicted that memory decay would become behaviorally detectable (*i.e.*, $m_t < 1$) in the range of 1.7–8.0 min after encoding, depending on the drug and dose condition (see appendix for a discussion of the limitations of the two-parameter model in predicting this value).

We also attempted to fit the data to multiple exponential, logarithmic, and multiphased linear decay models. When constrained to satisfy the axiomatic condition described earlier ($m_{t \rightarrow 0} \geq 1$), we found that all alternate models either failed or had markedly increased unexplained variance relative to the power model. The negative power function, thus, seems to robustly describe both the nondrug state and the pharmacologic modulation of memory for drug–dose combinations studied.

Assessment of Equiamnestic Dose Targeting

To determine whether the target drug concentrations had resulted in approximately equal levels of end-amnesia, we analyzed the three terminal clusters in each decay function. For subjects receiving an active drug, the mean recognition rate (corrected for false alarms) at the low drug concentration was 0.429 (SEM 0.020). By repeated measures ANOVA (repeated cluster measurements per subject), the differences between drugs was not quite statistically significant ($F_{3,45} = 2.745$, $P = 0.054$).‡‡ At the high drug concentration, the mean recognition rate was 0.304 (SEM 0.020), with no significant difference between drugs ($F_{3,44} = 1.670$, $P = 0.187$). By comparison, the mean recognition rate in the placebo group at the low drug level was 0.592 (SEM 0.037) and at the high drug level was 0.629 (SEM 0.036), with no significant difference between the two levels ($F_{1,11} = 0.577$, $P = 0.463$). We concluded that at each of the two drug levels, the target drug concentrations had resulted in degrees of end-amnesia that, although not perfectly equal, were sufficiently equivalent to enable direct comparison between the drugs for the principally qualitative purposes of the study.

‡‡ This near-significant result derives from recognition performance in the following order: thiopental > propofol ≅ dexmedetomidine > midazolam.

Comparison of λ and ψ across Individual Drug and Dose Conditions

Coefficient λ. There was a strong independent effect of drug ($F_{4,1493} = 14.006$, $P < 0.0001$) and also a strong independent effect of drug level ($F_{1,1493} = 33.212$, $P < 0.0001$). Significant fixed effects were identified for the midazolam: level interaction (-0.513, $t_{1493} = -2.465$, $P = 0.014$) and for the dexmedetomidine:level interaction (-0.476, $t_{1493} = -2.638$, $P = 0.008$), with λ significantly decreasing at the higher drug concentration. There was also a significant fixed effect for the propofol:level interaction (0.889, $t_{1493} = 3.489$, $P = 0.001$), which is notable because of a paradoxical increase in λ at the higher drug concentration.

Coefficient ψ. There was a significant independent effect of drug ($F_{4,1493} = 2.759$, $P = 0.027$) and a strong interactive effect of drug and drug level ($F_{4,1493} = 13.910$, $P < 0.0001$). However, there was no independent effect of drug level ($F_{1,1493} = 1.900$, $P = 0.168$). Significant fixed effects were identified for the independent effect of midazolam (0.110, $t_{1493} = 2.648$, $P = 0.008$) and for the interactive effect of propofol with increasing level (0.258, $t_{1493} = 6.597$, $P < 0.0001$).

Thus, we reject the null hypothesis that there is no difference between drugs in modulation of λ and ψ at equivalent levels of memory loss. The decay curves and coefficients for each drug and dose condition are shown in figure 2.

Neurobehavioral and Event-related Potential Correlates of λ and ψ

We next examined whether the modulation of λ or ψ could be correlated with neurobehavioral (fig. 3) and neurophysiologic (fig. 4) events at the time of encoding. For these analyses, we used the groupwise coefficients listed in table 2 and evaluated the relationships using the general linear model.[43] Here, in accommodating the repeated-measures design, *t* and *r* statistics represent partial coefficients after the variance because the paired grouping has been removed.

Self-reported Arousal. Overall, there was a strong relationship between self-reported arousal and λ ($r = 0.832$, $t_7 = 3.965$, $P = 0.005$; fig. 3A). The within-group relationship was highly conserved for placebo, thiopental, midazolam, and dexmedetomidine, but not for propofol. There was no relationship between arousal and ψ ($t_7 = -0.060$, $P = 0.953$ fig. 3B).

Reaction Time. Reaction time was defined as the time from stimulus onset to button response. There was a very strong relationship between increasing average reaction time and higher levels of ψ ($r = 0.949$, $t_7 = 7.946$, $P < 0.0001$; fig. 3D). When the responses for the first (new) and second (old) stimulus presentations were treated separately, the relationship remained robust for both new images ($r = 0.908$, $t_7 = 5.734$, $P = 0.001$; fig. 3F) and old images ($r = 0.941$, $t_7 = 7.345$, $P =$

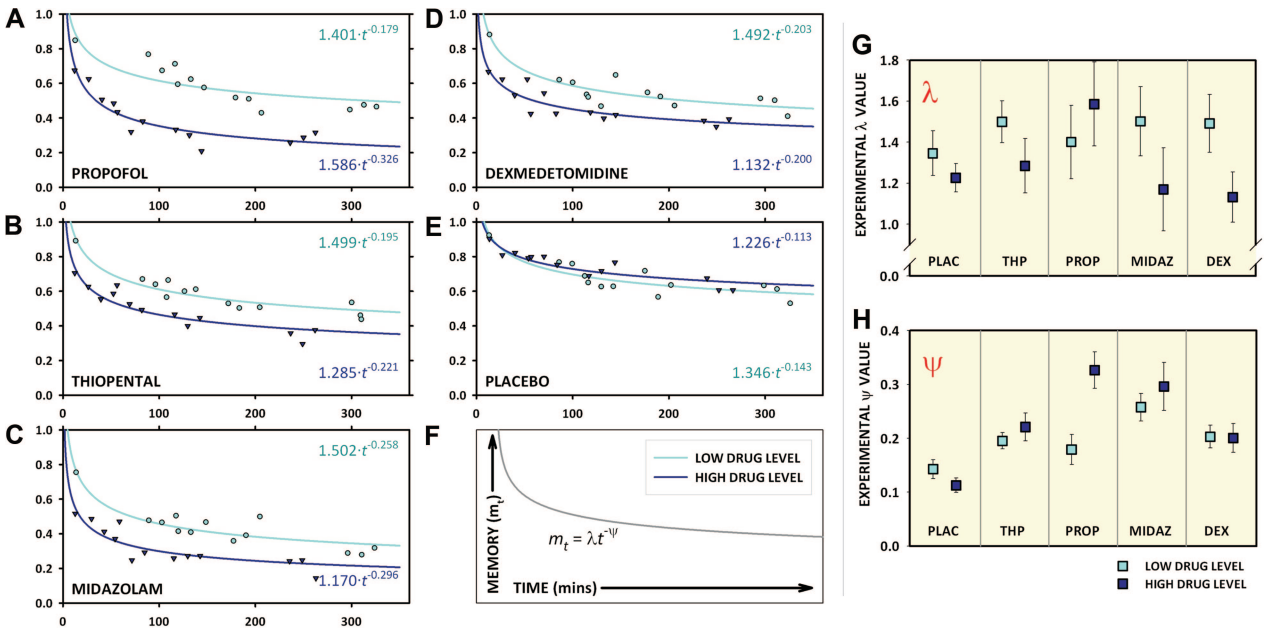

Fig. 2. Memory decay curves and estimates for λ and ψ by drug and dose condition. (*A–F*) The power decay curves for each of the drug-dose combinations. The *abscissa* represents the duration from the final encoding exposure to the subsequent recognition exposure (the recognition interval). For each curve, recognition data were corrected for false positives, clustered into 13 time points, and then fit to the equation $m_t = \lambda t^{-\psi}$ using Marquardt–Levenberg nonlinear regression. The specific equations describing each curve are shown in the upper and lower right corners of panels *A–F*. (*G* and *H*) The values for λ and ψ are shown, with *error bars* representing the SEM for the estimate derived from the nonlinear regression. However, statistical comparison of the decay functions was performed using a more robust nonlinear mixed effects model.[40] For λ, independent effects were established for drug ($P < 0.0001$) and level ($P < 0.0001$), and significant fixed effects seen for the midazolam:level interaction ($P = 0.014$), the dexmedetomidine:level interaction ($P = 0.008$), and the propofol:level interaction ($P = 0.008$). For ψ, independent effects were established for drug ($P = 0.027$) and drug level interaction ($P < 0.0001$), whereas fixed effects were established for midazolam ($P = 0.008$) and propofol:level interaction ($P < 0.0001$). DEX = dexmedetomidine; MIDAZ = midazolam; PLAC = placebo; PROP = propofol; THP = thiopental.

0.0002; fig. 3F). There was no relationship between average reaction time and λ ($t_7 = 0.136$, $P = 0.895$; fig. 3C). Notably, although reaction time is often associated with sedation, in this study, there was no significant relationship between the average reaction time and the arousal score ($t_7 = -0.919$, $P = 0.389$; fig. 3E).

ERP Correlates. There was a strong inverse relationship between the amplitude of the P2 component and ψ ($r = -0.817$, $t_7 = -3.743$, $P = 0.007$; fig. 4B). There was a positive relationship between the latency of the P2 component and ψ, but this did not quite achieve statistical significance ($r = 0.661$, $t_7 = 2.331$, $P = 0.053$). There was a strong relationship between the latency of the N2 component and ψ ($r = 0.867$, $t_7 = 4.610$, $P = 0.002$; fig. 4C). The inverse relationship between N2 amplitude and ψ did not achieve significance ($r = -0.547$, $t_7 = -1.728$, $P = 0.128$). No relationship could be established between any of the components evaluated and the coefficient λ.

Secondary Analyses

Drug Effect on Recognition of Previously Encoded Material. We found no evidence that any of the drugs had any retrograde or recognition process effect within the time window studied (fig. 5). At the low drug level, mean correct recognition was 7.74 (SD 0.55, $F_{4,56} = 0.368$, $P = 0.830$) for the primary list and 6.56 (SD 1.10, $F_{4,56} = 1.47$, $P = 0.225$) for the secondary list. At the high drug level, mean correct recognition was 7.51 (SD 0.68, $F_{4,56} = 0.396$, $P = 0.811$) for the primary list and 5.95 (SD 1.30, $F_{4,56} = 2.176$, $P = 0.085$) for the secondary list.

Memory Performance in the First Minute after Encoding. Because the probe pairs for each of the three intervals (6, 27, and 63 s) were interleaved and balanced throughout the Encoding Task, performance confounders such as sedation, fatigue, false response bias, interference, or sequence effects were distributed equally. Thus, any difference in performance for probes separated by 27 or 63 s relative to those separated by 6 s was a function of the time interval and hence a memory effect. Recognition of the second (old) presentation was calculated as a ratio of recognition at 6 s. For the 27-s probes, two-way repeated measures ANOVA with factors of drug and level found no significant effect of drug ($F_{4,120} = 0.990$, $P = 0.416$), level ($F_{1,120} = 0.0475$, $P = 0.828$), or drug:level interaction ($F_{4,120} = 0.785$, $P = 0.537$). Similarly, for the 63-s probes, there was no significant effect of drug ($F_{4,120} = 0.241$, $P = 0.915$), level ($F_{1,120} = 0.0116$, $P = 0.914$), or drug:level interaction ($F_{4,120} = 0.544$, $P = 0.704$). Results are shown in figure 6.

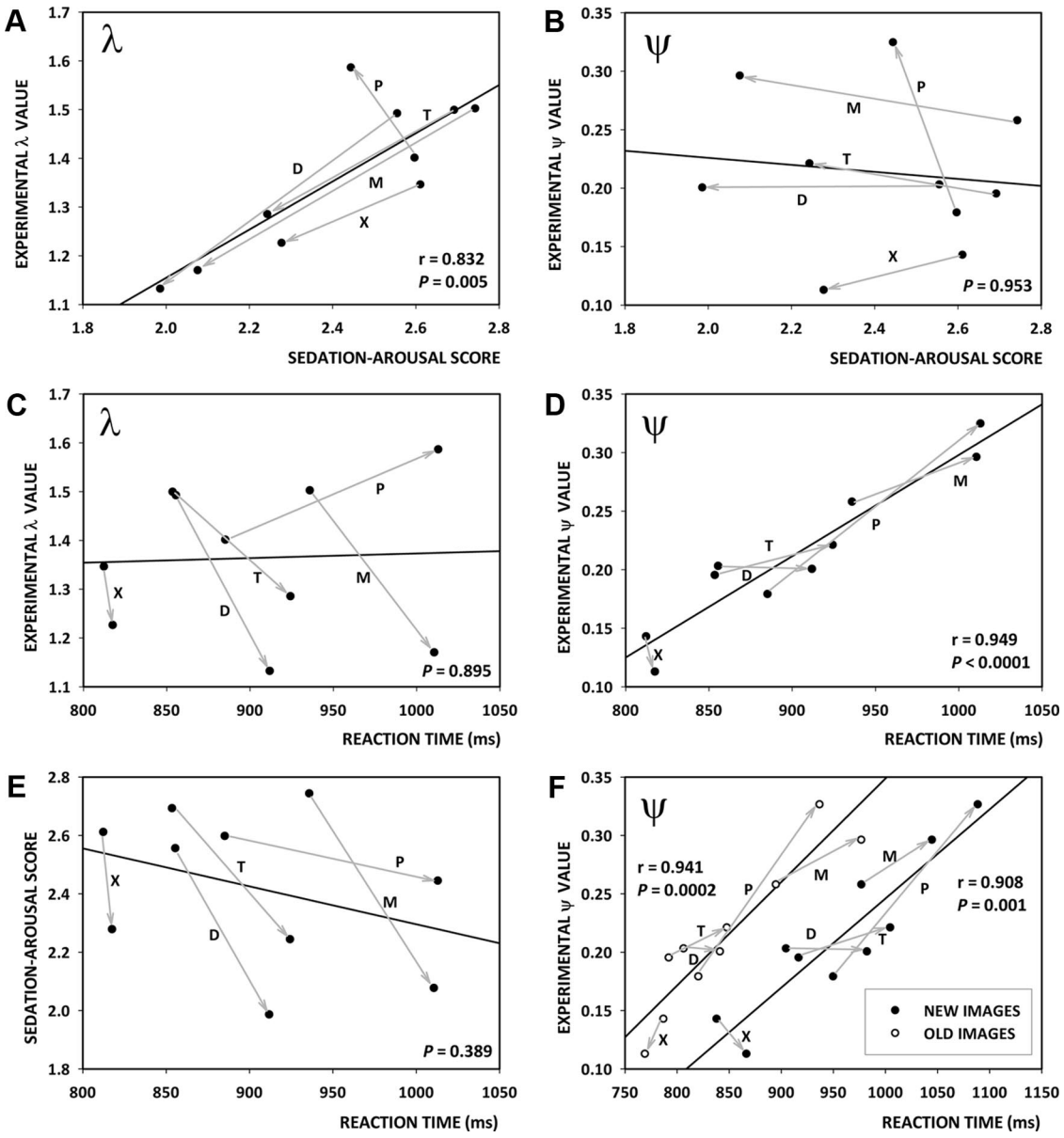

Fig. 3. Correlation of λ and ψ with measures of arousal and reaction time. (*A–F*) The point values for the coefficients λ or ψ (taken from fig. 2) are compared with measures of arousal and reaction time. In each case, the *gray lines* link the two drug levels, directed from low to high drug level. There was a strong relationship between arousal and λ ($P = 0.005$, *A*), but not with ψ ($P = 0.953$, *B*). Reaction time was instead strongly linked to ψ ($P < 0.0001$, *D*), but not to λ ($P = 0.895$, *C*). When new and old presentations of the images were considered separately, the ψ correlation remained strong for both ($P = 0.001$ and $P = 0.0002$, *F*). There was no significant relationship between reaction time and arousal ($P = 0.389$, *E*). Drugs are labeled as follows: D = dexmedetomidine; M = midazolam; P = propofol; T = thiopental; X = placebo.

Discussion

Our objective was to apply a mathematical model to characterize how several intravenous anesthetics modulate the establishment and decay of episodic memory for visual stimuli. We found that although the basic mathematical form of memory decay—the negative power function $m_t = \lambda t^{-\psi}$—is consistently preserved, there are marked differences between the drugs in the way they modulate the function. We concurrently established that each mathematical parameter could be correlated with neurophysiologic and neurobehavioral events with remarkable precision: the strength of the initial memory trace is a function of tonic arousal, whereas the rate of decay of an established memory is accelerated with the loss of the P2–N2 complex at encoding and a prolongation of reaction time. Although anesthetic amnesia is evidently a heterogeneous phenomenon, the underlying mechanisms may converge on only a very limited number of system-level functions. Although it may take several minutes for the amnesia to become behaviorally detectible, it seems that the fate of the memory trace is largely determined at the moment of exposure.

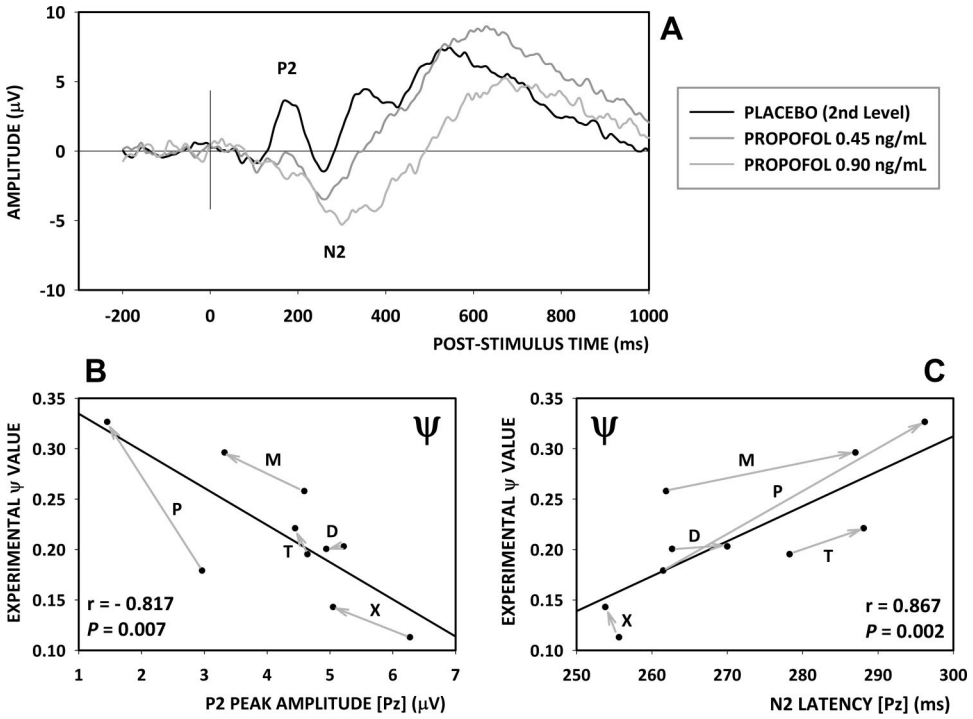

Fig. 4. Correlation of λ and ψ with the parietal event-related P2–N2 complex. (*A*) The grand average waveforms obtained at the Pz electrode for the placebo group at the second level and for the propofol group at both drug levels, demonstrating the progressive changes in P2 and N2 amplitude and latency with increasing drug level are shown. (*B*, *C*) The relationship between the point values for ψ (taken from fig. 2) and group (not grand) average components. Relationships were evaluated using the general linear model.[43] There was a strong relationship between ψ and P2 amplitude ($P = 0.007$, *B*) and N2 latency ($P = 0.002$, *C*). No event-related potential relationships could be established with λ. *Gray lines* link the two drug levels, directed from the low to high drug level. Drugs are labeled as follows: D = dexmedetomidine; M = midazolam; P = propofol; T = thiopental; X = placebo.

Dexmedetomidine closely approximates an archetypal sedative-only drug. It causes a dose-dependent decrease in the strength of the initial memory trace, which parallels a decrease in tonic arousal. If anything, it has only minimal effect on the rate of decay, which does not seem to change with dose and which corresponds to a modest loss of P2–N2 and increased reaction time. Although dexmedetomidine will cause memory impairment because of weakened encoding, those memories that are established seem to subsequently behave in a largely normal fashion—an observation that would suggest caution in its use as a sole sedative agent in clinical settings where amnesia is required.

In contrast, the amnestic effect of propofol is characterized by robust encoding followed by a marked acceleration in decay of the established memory. The effect is dose-dependent and is associated with an equally marked loss of P2–N2 and increased reaction time. Although subjects receiving propofol did report sedation, this did not translate into weakened establishment of the memory trace. These findings are consistent with our previous studies using propofol, in which we demonstrated intact acquisition of material into long-term memory[44] and normal encoding-related activation of left inferior prefrontal cortex.[45] However, the design of the current study allowed us to observe a paradoxical augmentation in initial trace strength at the doses studied. Although this result stands out as the sole exception to the arousal → encoding | P2–N2 → decay rule, it should not be dismissed (if it were artifact, the ψ value should reciprocally shift and fail to conform to the rule, which we did not observe). Propofol, like many other anesthetics, can cause paradoxical excitation phenomena at low doses. Mathematical network modeling shows that this can result from a membrane-level interaction of GABA subtype-A current and intrinsic membrane slow potassium current, with the consequence being a large scale loss of interneuronal synchrony,[46] whereas work in patients with pathologic disorders of consciousness whose cognitive function is improved by GABAergic drugs suggests that the mechanism involves suppression of inhibitory control signals regulating thalamocortical function.[47] Whatever the specific mechanism, our results suggest that the perceived loss of arousal produced by propofol possesses features not shared by the other drugs.

The profile of midazolam is that of a mixed sedative-amnestic, with clear effects on both the establishment of memory and its subsequent decay that adhere closely to the arousal → encoding | P2–N2 → decay rule. We found that the accelerated decay was the dominant effect at the low dose, whereas increasing the concentration to the high dose acted principally by causing a marked decrease in arousal, with relatively little additional effect on decay. This dose-depen-

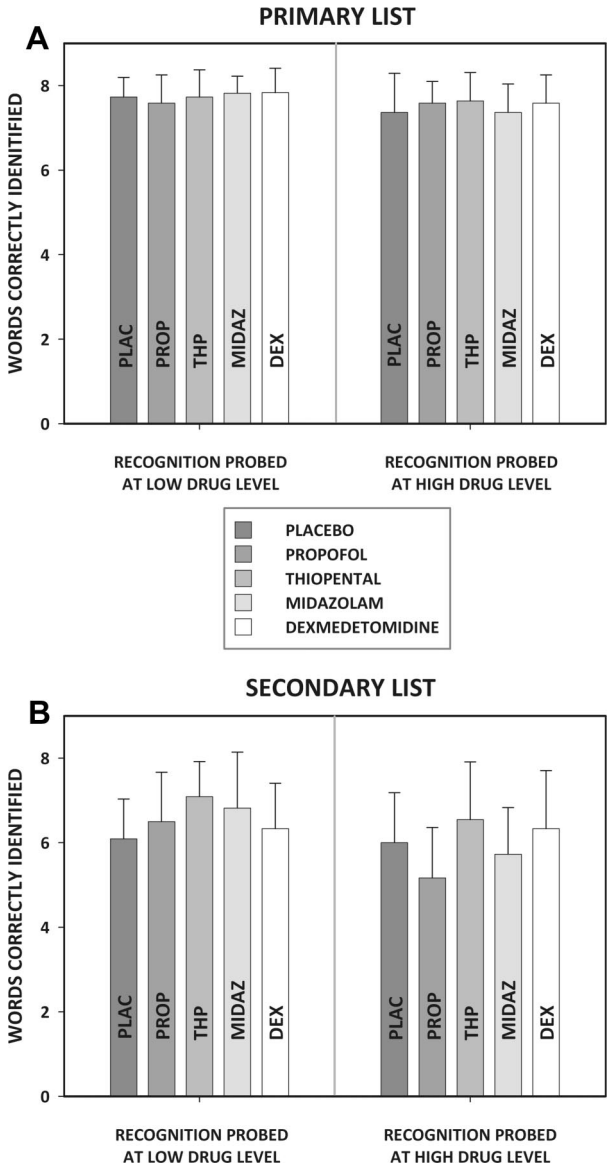

Fig. 5. Drug effect on the recognition of previously encoded material. Subjects learned two lists of 16 words before receiving drug: a primary list was strongly learned through four repetitions, and a secondary list more weakly learned through only a single repetition. Later, during the drug infusion, subjects performed forced-choice tasks to test recognition of the learned words. (*A*) The results for probed recognition of the primary list, and (*B*) the results for the secondary list. One-way analysis of variance was performed on each of the four-word list:drug level combinations to evaluate the effect of drug. There was no significant effect of any drug on the recognition of either strongly or weakly learned words. *Error bars* represent SEM. DEX = dexmedetomidine; MIDAZ = midazolam; PLAC = placebo; PROP = propofol; THP = thiopental.

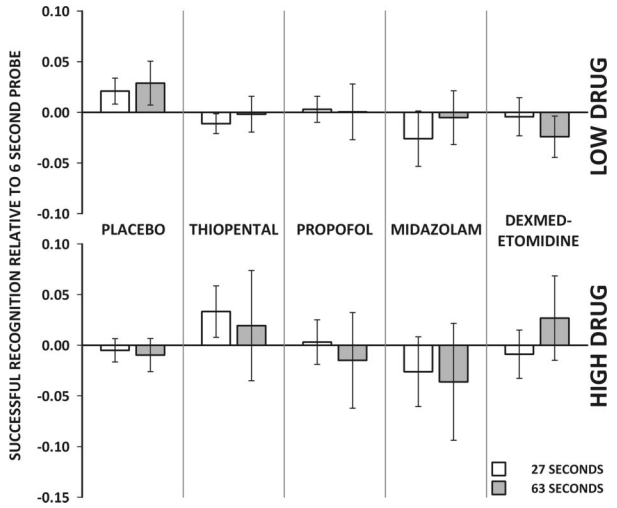

Fig. 6. Memory performance in the first minute after encoding. In the Encoding Task, image pairs were presented 6, 27, or 63 s apart. Recognition of the second (old) presentation of the 27 and 63 s probes is shown as a ratio of recognition at 6 s. Random confounders such as fatigue or sequence effects are equally distributed, and thus differences would reflect a true memory effect. At 27 s, there was no significant effect of drug ($P = 0.416$), level ($P = 0.828$), or drug:level interaction ($P = 0.537$). Similarly, at 63 s, there was no effect of drug ($P = 0.915$), level ($P = 0.914$) or drug:level interaction ($P = 0.704$). Although our other results imply that the events leading to memory decay were established at the time of encoding, no effect on performance was detectible in the first minute. *Error bars* represent SEM.

dent selectivity supports the picture that the two effects are mechanistically dissociated. Further, the tapering effect of increasing dose on decay suggests that there may be a ceiling phenomenon with respect to a drug's ability to accelerate decay.

We were not able to establish a statistically significant characterization of thiopental, but this should not negate a cautioned discussion of the observed trend—our decision to study multiple drugs at two levels incurs a strong multiple comparisons paradox, and the results for thiopental would have achieved significance had we investigated fewer drugs. The profile of thiopental most closely resembles that of dexmedetomidine, with the dominant effect being an arousal-related decrease in the strength of the initial memory trace. In contrast to the other two GABAergic drugs, only a modest effect on the rate of decay and P2–N2 was observed. This finding confirms previous studies demonstrating that the memory effect of thiopental is predominantly related to sedation,[2,36,44] and the marked difference between thiopental and propofol is supported by neuroimaging showing clear differences in the regional cerebral blood flow patterns induced by these two drugs at doses similar to the higher drug level studied here.[35]

The measures of reaction time and the parietal P2–N2 complex can offer only limited mechanistic information. However, the dramatic consistency in the relationship between these measures and the rate of memory decay—valid across all studied drugs—does strongly imply that accelerated trace decay is the product of a specific loss of function that leads to the failure of a memory to consolidate. As recent priming experiments have demonstrated that reaction time is related to interregional synchrony,[18] what functionally connects these two measures is that they both represent a loss of synchronous cooperativity across distributed networks.

In this regard, the extremely close relationship between the P2–N2 complex and the accelerated decay is particularly intriguing because of the potential relationship between P2–N2 and θ synchrony.[19–22] θ phase is known to be critical to the induction of LTP,[32] and *in vivo* studies demonstrate that hippocampal θ coherence is associated with successful learning.[48–50] In this study, we were only able to obtain cortical signals, but there is substantial evidence that cortical and hippocampal rhythms are phase-related to the recruitment of transient hippocampal-cortical feedback loops.[28,29,31] Thus, we speculate that the P2–N2 changes we observed may involve a loss of θ synchrony across a distributed cortical–subcortical network, which includes the hippocampus.

As such, we hypothesize that a key mechanism underlying the effect of anesthetic drugs on the long-term stability of memory—measured here by the rate of decay—is related to neurophysiologic events occurring at the time of encoding and likely involves the loss of phase coherence necessary for the induction of synaptic plasticity across a distributed network. This represents a somewhat novel understanding of how drug effects on plasticity, and on LTP, in particular, might lead to behavioral amnesia in humans. Because both propofol[3,5–7] and midazolam[4] have been shown to inhibit LTP in hippocampal slices *via* actions related to their GABA subtype-A activity, it has been tempting to presume that amnesia follows direct modulation of the molecular mechanisms underlying LTP. However, this model is problematic because of the failure to observe retrograde amnesia in humans either in this or previous studies.[1,44,51] If, as is suggested by the *in vitro* studies, the drugs inhibit some aspect of LTP beyond its induction, this should inhibit consolidation of recent memories and lead to a retrograde memory effect, which is clearly not observed. In contrast, by proposing that the memory trace instead fails to propagate because of events associated with its initiation, our hypothesis predicts an exclusively anterograde amnesia, consistent with the human studies. This does not imply that all downstream processes associated with memory consolidation will fail, and our conclusion should not, for example, be regarded as inconsistent with findings that messenger RNA for activity-related cytoskeletal-associated protein is found in the hippocampus of amnestic rats receiving propofol, even though the actual protein is not produced.[10] We suggest only that the critical step leading to consolidation failure is ultimately linked to its induction.

We found reaction time to be a poor absolute measure of sedation in the presence of anesthetic drugs, in contrast to the relationship established in numerous previous nondrug experimental paradigms. Instead, we found it to be very closely correlated to the rate of decay and θ-phase ERP changes. As expected, reaction time for old images was faster than for new images. However, in contrast to the global changes in reaction time, this old–new gap, which represents a form of priming memory effect, was preserved as a constant (resulting in the parallel lines seen in fig. 3C). Thus, although the reaction time → decay effect appears strongly related to memory function in the time frame of minutes to hours, we did not find it to be related to memory function in time frames measured in seconds.

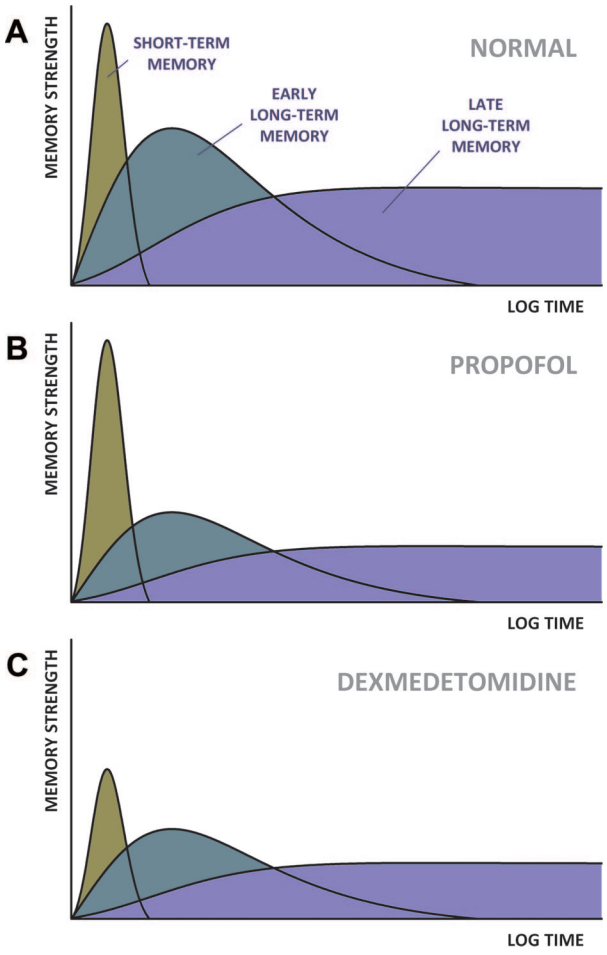

Fig. 7. A parallel memory systems model of anesthetic amnesia. (*A*) Schematic demonstration of the principles of the parallel systems framework: the temporal course of memory results from consolidation in parallel systems operating in different time domains. We propose that propofol permits robust short-term performance, but performance rapidly decays as selective effects on long-term domains are unmasked (*B*). In contrast, dexmedetomidine causes diffuse, nonselective attenuation, resulting in a memory that is weak but which transitions across the time domains with relative normality (*C*). Modified from McGaugh[52] (McGaugh JL: Memory—a century of consolidation. Science 2000; 287:248–51), with permission from the American Association for the Advancement of Science.

When brought together, our findings can be viewed within the framework of memory system theories proposing that short- and long-term memory stores, although behaviorally perceived as sequential and continuous, are mechanistically independent and parallel.[52] In this context, our results and hypothesis suggest that the drug effects on memory systems in different time domains may be dissociable (fig. 7). In the case of propofol, a robust short-term system permits intact initial learning, but as this trace decays, the failure of consolidation in parallel long-term systems is unmasked,

leading to the behavioral picture of rapid decay (fig. 7B). In contrast, dexmedetomidine has a nonselective effect attenuating all systems, and the picture is that of a memory which is weak, but which transitions normally across the time domains (fig. 7C).

Although we included many controls, we acknowledge that our experimental design was complex and incurred methodologic limitations, which must be noted. First, we note that there is no available method for monitoring the serum concentration of the study drugs in real time, and thus titration to a desired serum concentration is not possible in individual subjects. The STANPUMP pharmacokinetic models provide the best available method for achieving a targeted concentration, but they inevitably have associated variance. Second, we recognize that the equiamnestic dose targeting, although not statistically rejected, was imperfect. Third, we note that there is no available method for rapid removal of the study drugs. Thus, during the recognition phase of the study, there was inevitably a steadily decreasing concentration of residual drug present. We used the Visual Verbal Learning Test as a control to evaluate whether the presence of drug had any independent effect on recognition processes and found none. However, the sensitivity of the Visual Verbal Learning Test to detect such an effect is limited, and although we are confident that residual drug does not markedly impair recognition, we cannot discount the possibility that subtle changes may occur. Despite these limitations, we believe that the marked statistical significance seen in multiple aspects of the study makes it highly unlikely that the core conclusions are the result of experimental artifact.

Further, although the dominant form of the P2–N2 complex may emerge from θ synchrony, it must be emphasized that it is both an untransformed and indirect measure, and so it should be regarded as an imperfect and preliminary evaluator of the relationship between anesthetic amnesia and θ activity. A full and precise understanding of how anesthetic drugs affect memory-related synchronous activity across cortical and subcortical regions poses profound methodologic challenges and will require extensive future study. Our results should be interpreted only to the extent that they provide sufficient evidence to introduce a framework to guide future study.

By demonstrating that a well-described mathematical model of human memory used in the neurocognitive sciences can be applied in the setting of drug-induced amnesia, this study introduces a novel framework for understanding the effects of anesthetic drugs on memory processes in humans. We have demonstrated that this method can derive powerful, quantitative descriptors of memory function that can be used to study the relationship between behavior and underlying mechanisms. Viewed reciprocally, we also suggest that careful characterization of anesthetic amnesia in this way provides a valuable tool for the study of normal memory function and pathologic states of amnesia.

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Appendix: Elaborating the Mathematical Form of Amnesia

Attempts to develop a mathematical model for what happens to memories over time date to 1885, when Herman Ebbinghaus used seven data points extending over 750 h to demonstrate that memory decay is characterized by a very rapid initial decline, followed by a more gradual loss. The model used in our study is derived from the *Wickelgren Power Law*, first published by Wickelgren[14] in 1974. Wickelgren viewed memories as being established with an initial degree of strength and an initial degree of fragility, both of which decline over time. In this model, memory consolidation does not involve any augmentation of trace strength, but instead it results from a reduction in fragility. Wickelgren's most complete description of the power law contains both power and exponential elements:

$$m_t = \phi(1 + \beta t)^{-\psi} e^{-\pi t} \quad (1)$$

The exponential term $e^{-\pi t}$ expresses the characteristics of memory decay caused by interference, which results from interpolated material being highly similar to the learned items. In our experimental paradigm, as with most others used to evaluate memory curves, the stimuli are contextually rich and semantically diverse, and under these conditions, the parameter $\pi \rightarrow 0$. As such, the power law is approximated by the following equation:

$$m_t = \phi(1 + \beta t)^{-\psi}, \quad (2)$$

where ϕ represents the initial degree of learning, and β is a scaling constant derived from the differential equations describing trace fragility. Equation A2 is certainly simpler than equation A1 but to deal with the inherent variance associated with real experimental data sets of limited size, a two-parameter model is preferred. To develop this, equation A2 is first reexpressed as follows:

$$m_t = (\phi + \phi\beta t)^{-\psi} \quad (3)$$

It can be seen that as t increases (*i.e.*, as memory is examined at greater and greater time points), the term $\phi\beta t$ greatly exceeds the term ϕ. At the time intervals studied in our experiment, the term ϕ is comparatively insignificant and can be ignored. Thus, we are left with the following equation:

$$m_t = \phi\beta t^{-\psi} \quad (4)$$

By replacing the two parameters $\phi\beta$ with a single parameter λ, we arrive at the two-parameter power decay model used in our experiment:

$$m_t = \lambda t^{-\psi} \quad (5)$$

The term λ is, thus, a reasonable relative measure of the initial degree of learning when it is derived from data obtained at high values of t, as is the case in our experiment. The limitation of the two-parameter model occurs as $t \rightarrow 0$, when the approximations become progressively less valid, and the function is ultimately undefined at 0. These concerns are largely insignificant for the time

intervals studied in the current study, although could account for a very limited amount of variance in the estimates for t at $m_t = 1$ (table 2).

References

1. Pryor KO, Veselis RA, Reinsel RA, Feshchenko VA: Enhanced visual memory effect for negative *versus* positive emotional content is potentiated at sub-anaesthetic concentrations of thiopental. Br J Anaesth 2004; 93:348–55
2. Veselis RA, Reinsel RA, Feshchenko VA, Wronski M: The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. ANESTHESIOLOGY 1997; 87:749–64
3. Nagashima K, Zorumski CF, Izumi Y: Propofol inhibits long-term potentiation but not long-term depression in rat hippocampal slices. ANESTHESIOLOGY 2005; 103:318–26
4. Evans MS, Viola-McCabe KE: Midazolam inhibits long-term potentiation through modulation of $GABA_A$ receptors. Neuropharmacology 1996; 35:347–57
5. Wei H, Xiong W, Yang S, Zhou Q, Liang C, Zeng BX, Xu L: Propofol facilitates the development of long-term depression (LTD) and impairs the maintenance of long-term potentiation (LTP) in the CA1 region of the hippocampus of anesthetized rats. Neurosci Lett 2002; 324:181–4
6. Takamatsu I, Sekiguchi M, Wada K, Sato T, Ozaki M: Propofol-mediated impairment of CA1 long-term potentiation in mouse hippocampal slices. Neurosci Lett 2005; 389:129–32
7. Wang W, Wang H, Gong N, Xu TL: Changes of K^+-Cl^- cotransporter 2 (KCC2) and circuit activity in propofol-induced impairment of long-term potentiation in rat hippocampal slices. Brain Res Bull 2006; 70:444–9
8. Kozinn J, Mao L, Arora A, Yang L, Fibuch EE, Wang JQ: Inhibition of glutamatergic activation of extracellular signal-regulated protein kinases in hippocampal neurons by the intravenous anesthetic propofol. ANESTHESIOLOGY 2006; 105:1182–91
9. Fibuch EE, Wang JQ: Inhibition of the MAPK/ERK cascade: A potential transcription-dependent mechanism for the amnesic effect of anesthetic propofol. Neurosci Bull 2007; 23:119–24
10. Ren Y, Zhang FJ, Xue QS, Zhao X, Yu BW: Bilateral inhibition of gamma-aminobutyric acid type A receptor function within the basolateral amygdala blocked propofol-induced amnesia and activity-regulated cytoskeletal protein expression inhibition in the hippocampus. ANESTHESIOLOGY 2008; 109:775–81
11. Sukhotinsky I, Zalkind V, Lu J, Hopkins DA, Saper CB, Devor M: Neural pathways associated with loss of consciousness caused by intracerebral microinjection of GABA A-active anesthetics. Eur J Neurosci 2007; 25:1417–36
12. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M: The sedative component of anesthesia is mediated by GABA(A) receptors in an endogenous sleep pathway. Nat Neurosci 2002; 5:979–84
13. Wixted JT, Carpenter SK: The Wickelgren power law and the Ebbinghaus savings function. Psychol Sci 2007; 18:133–4
14. Wickelgren WA: Single-trace fragility theory of memory dynamics. Mem Cognit 1974; 2:775–80
15. Wixted JT: On Common Ground: Jost's (1897) law of forgetting and Ribot's (1881) law of retrograde amnesia. Psychol Rev 2004; 111:864–79
16. Wixted JT, Ebbesen E: On the form of forgetting. Psychol Sci 1991; 2:409–15
17. Jacobs J, Hwang G, Curran T, Kahana MJ: EEG oscillations and recognition memory: Theta correlates of memory retrieval and decision making. Neuroimage 2006; 32:978–87
18. Ghuman AS, Bar M, Dobbins IG, Schnyer DM: The effects of priming on frontal-temporal communication. Proc Natl Acad Sci U S A 2008; 105:8405–9
19. Freunberger R, Klimesch W, Doppelmayr M, Holler Y: Visual P2 component is related to theta phase-locking. Neurosci Lett 2007; 426:181–6
20. Kamarajan C, Rangaswamy M, Chorlian DB, Manz N, Tang Y, Pandey AK, Roopesh BN, Stimus AT, Porjesz B: Theta oscillations during the processing of monetary loss and gain: A perspective on gender and impulsivity. Brain Res 2008; 1235:45–62
21. Karakas S, Erzengin OU, Basar E: The genesis of human event-related responses explained through the theory of oscillatory neural assemblies. Neurosci Lett 2000; 285:45–8
22. Karakas S, Erzengin OU, Basar E: A new strategy involving multiple cognitive paradigms demonstrates that ERP components are determined by the superposition of oscillatory responses. Clin Neurophysiol 2000; 111:1719–32
23. Klimesch W, Doppelmayr M, Russegger H, Pachinger T: Theta band power in the human scalp EEG and the encoding of new information. Neuroreport 1996; 7:1235–40
24. Klimesch W, Doppelmayr M, Schimke H, Ripper B: Theta synchronization and alpha desynchronization in a memory task. Psychophysiology 1997; 34:169–76
25. Summerfield C, Mangels JA: Coherent theta-band EEG activity predicts item-context binding during encoding. Neuroimage 2005; 24:692–703
26. Klimesch W, Doppelmayr M, Stadler W, Pollhuber D, Sauseng P, Rohm D: Episodic retrieval is reflected by a process specific increase in human electroencephalographic theta activity. Neurosci Lett 2001; 302:49–52
27. Klimesch W, Hanslmayr S, Sauseng P, Gruber W, Brozinsky CJ, Kroll NE, Yonelinas AP, Doppelmayr M: Oscillatory EEG correlates of episodic trace decay. Cereb Cortex 2006; 16:280–90
28. Siapas AG, Lubenov EV, Wilson MA: Prefrontal phase locking to hippocampal theta oscillations. Neuron 2005; 46:141–51
29. Young CK, McNaughton N: Coupling of theta oscillations between anterior and posterior midline cortex and with the hippocampus in freely behaving rats. Cereb Cortex 2009; 19:24–40
30. DeCoteau WE, Thorn C, Gibson DJ, Courtemanche R, Mitra P, Kubota Y, Graybiel AM: Learning-related coordination of striatal and hippocampal theta rhythms during acquisition of a procedural maze task. Proc Natl Acad Sci U S A 2007; 104:5644–9
31. Jones MW, Wilson MA: Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. PLoS Biol 2005; 3:e402
32. McCartney H, Johnson AD, Weil ZM, Givens B: Theta reset produces optimal conditions for long-term potentiation. Hippocampus 2004; 14:684–7
33. Perouansky M, Hentschke H, Perkins M, Pearce RA: Amnesic concentrations of the nonimmobilizer 1,2-dichlorohexafluorocyclobutane (F6, 2N) and isoflurane alter hippocampal theta oscillations *in vivo*. ANESTHESIOLOGY 2007; 106:1168–76
34. Veselis RA, Reinsel RA, Beattie BJ, Mawlawi OR, Feshchenko VA, DiResta GR, Larson SM, Blasberg RG: Midazolam changes cerebral blood flow in discrete brain regions: An H2(15)O positron emission tomography study. ANESTHESIOLOGY 1997; 87:1106–17
35. Veselis RA, Feshchenko VA, Reinsel RA, Dnistrian AM, Beattie B, Akhurst TJ: Thiopental and propofol affect different regions of the brain at similar pharmacologic effects. Anesth Analg 2004; 99:399–408
36. Veselis RA, Reinsel RA, Feshchenko VA: Drug-induced amnesia is a separate phenomenon from sedation: Electrophysiologic evidence. ANESTHESIOLOGY 2001; 95:896–907

37. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M: The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. ANESTHESIOLOGY 2003; 98:428–36
38. Aston-Jones G, Rajkowski J, Cohen J: Role of locus coeruleus in attention and behavioral flexibility. Biol Psychiatry 1999; 46:1309–20
39. Lang PJ, Bradley MM, Cuthbert BN: International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6. Gainsville, University of Florida, 2005
40. Kristensen M, Hansen T: Statistical analyses of repeated measures in physiological research: A tutorial. Adv Physiol Educ 2004; 28:2–14
41. Watson D, Clark LA, Tellegen A: Development and validation of brief measures of positive and negative affect: The PANAS scales. J Pers Soc Psychol 1988; 54:1063–70
42. Rey A: L'Examen Clinique en Psychologie. Paris, Presse Universitaire de France, 1964
43. Bland JM, Altman DG: Calculating correlation coefficients with repeated observations: Part 1—correlation within subjects. BMJ 1995; 310:446
44. Veselis RA, Reinsel RA, Feshchenko VA, Johnson R Jr: Information loss over time defines the memory defect of propofol: A comparative response with thiopental and dexmedetomidine. ANESTHESIOLOGY 2004; 101:831–41
45. Veselis RA, Pryor KO, Reinsel RA, Mehta M, Pan H, Johnson R Jr: Low-dose propofol-induced amnesia is not due to a failure of encoding: Left inferior prefrontal cortex is still active. ANESTHESIOLOGY 2008; 109:213–24
46. McCarthy MM, Brown EN, Kopell N: Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol-induced paradoxical excitation. J Neurosci 2008; 28:13488–504
47. Schiff ND, Posner JB: Another "Awakenings." Ann Neurol 2007; 62:5–7
48. Mormann F, Fell J, Axmacher N, Weber B, Lehnertz K, Elger CE, Fernandez G: Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. Hippocampus 2005; 15:890–900
49. Rizzuto DS, Madsen JR, Bromfield EB, Schulze-Bonhage A, Seelig D, Aschenbrenner-Scheibe R, Kahana MJ: Reset of human neocortical oscillations during a working memory task. Proc Natl Acad Sci U S A 2003; 100:7931–6
50. Tesche CD, Karhu J: Theta oscillations index human hippocampal activation during a working memory task. Proc Natl Acad Sci U S A 2000; 97:919–24
51. Ghoneim MM, Block RI: Immediate peri-operative memory. Acta Anaesthesiol Scand 2007; 51:1054–61
52. McGaugh JL: Memory—a century of consolidation. Science 2000; 287:248–51