Investigation of Slow-wave Activity Saturation during Surgical Anesthesia Reveals a Signature of Neural Inertia in Humans

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ABSTRACT

Background: Previously, we showed experimentally that saturation of slow-wave activity provides a potentially individualized neurophysiologic endpoint for perception loss during anesthesia. Furthermore, it is clear that induction and emergence from anesthesia are not symmetrically reversible processes. The observed hysteresis is potentially underpinned by a neural inertia mechanism as proposed in animal studies.

Methods: In an advanced secondary analysis of 393 individual electroencephalographic data sets, we used slow-wave activity dose-response relationships to parameterize slow-wave activity saturation during induction and emergence from surgical anesthesia. We determined whether neural inertia exists in humans by comparing slow-wave activity dose responses on induction and emergence.

Results: Slow-wave activity saturation occurs for different anesthetics and when opioids and muscle relaxants are used during surgery. There was wide interpatient variability in the hypnotic concentrations required to achieve slow-wave activity saturation. Age negatively correlated with power at slow-wave activity saturation. On emergence, we observed abrupt decreases in slow-wave activity dose responses coincident with recovery of behavioral responsiveness in ~33% individuals. These patients are more likely to have lower power at slow-wave activity saturation, be older, and suffer from short-term confusion on emergence.

Conclusions: Slow-wave activity saturation during surgical anesthesia implies that large variability in dosing is required to achieve a targeted potential loss of perception in individual patients. A signature for neural inertia in humans is the maintenance of slow-wave activity even in the presence of very-low hypnotic concentrations during emergence from anesthesia.
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IT is still unclear when an individual patient experiencing clinical anesthesia stops perceiving the external world and surgery-related stimulation.[1,2] Previously, we used simultaneous electroencephalography (EEG) and functional magnetic resonance imaging during an ultraslow propofol anesthesia-induced loss of consciousness to track healthy individuals' responses to external stimuli.[3] We found that after loss of behavioral responsiveness, each individual's slow-wave activity (0.5 to 1.5 Hz)—a characteristic waveform seen in sleep and anesthesia[4]—rose to saturation but then remained constant despite increasing anesthetic concentrations. Simultaneous functional magnetic resonance imaging showed that, at the point of slow-wave activity saturation (SWAS), stereotypical thalamocortical responses to nociceptive and auditory inputs were abolished.

Furthermore, we observed a significant correlation between individuals' maximum slow-wave power and their prefrontal cortex gray matter volume, suggesting a direct neurobiologic relationship between SWAS and the number

What We Already Know about This Topic

- During anesthetic administration, slow-wave activity in the 0.5- to 1.5-Hz range increases after loss of consciousness and reaches a maximum (slow-wave activity saturation). Therefore, slow-wave activity saturation may be of utility as an individualized clinical indicator to titrate anesthetics to loss of perception.
- Slow-wave activity saturation was measured in patients undergoing general anesthesia with intravenous and volatile anesthetics, with supplementation with opiates and muscle relaxants.

What This Article Tells Us That Is New

- Slow-wave activity saturation was observed on induction under both propofol and sevoflurane anesthesia. Simultaneous administration of opiates, but not muscle relaxants, reduced the concentration of anesthetic required for slow-wave activity saturation.
- Anesthetic dose required to induce slow-wave activity saturation was different during induction and emergence, indicating a certain neural inertia on transition to return of consciousness. Interestingly, abrupt changes in slow-wave activity were more often associated with confusion and delirium after emergence.

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of oscillating cortical neurons—the underpinning basis of slow waves.[5] We hypothesized that SWAS is an important individualized electrophysiologic endpoint that is a manifestation of perception loss to incoming stimuli and as such reflects isolation from the external world. Therefore, SWAS provides a potential brain-based target that would allow optimum anesthetic dosing for perception loss in each individual patient, thus reducing the risk of mortality and morbidity from over- and underanesthesia, particularly in elderly and vulnerable patients.[6,7]

Here, we aimed to determine whether SWAS occurs in the less well controlled, clinical environment. We have developed robust analytical methods to parameterize slow-wave activity dose-response relationships on an individual basis using electroencephalographic data from our previous experimental study and three additional clinical studies.[3,8–10] We aimed to determine whether SWAS occurs for both intravenous and volatile general anesthetics (VGA) on induction to and exists before emergence from anesthesia. We also examined how clinically used coinduction agents, such as opioid analgesia and neuromuscular blockades, influence the SWAS parameters. Because both gray matter volume/density[11] and anesthetic dose requirement[12] decrease with age, we hypothesized *a priori* that the SWAS parameters for induction and emergence would show similar decreases with age in the adult population.

It has long been thought that induction and emergence from anesthesia are not reversible and symmetric processes[13]; however, there is little evidence in humans to support this.[14] Recently, the concept of neural inertia has been suggested to explain the hysteresis observed in anesthetic dose responses between induction and emergence.[15] The authors proposed that neural inertia acts to "resist behavioral state transitions between unconscious and conscious states." Specifically, they demonstrated that hysteresis of the anesthetic dose associated with behavioral responsiveness in animals is not simply due to pharmacokinetic differences and can be genetically modulated. Importantly, while the authors hypothesized that this effect has a neural origin, they do not provide direct evidence of this phenomenon.

We aimed to determine whether neural inertia exists in humans by comparing brain-based differences in the slow-wave activity dose-response relationships on induction and emergence. Furthermore, we aimed to identify clinically relevant variables that predict whether an individual is likely to experience neural inertia and show how this can influence short-term confusion/delirium on emergence from anesthesia.

Materials and Methods

Data Collection

We analyzed electroencephalographic data from adults aged 18 to 90 yr collected in four separate studies with the following information: raw EEG, end-tidal volatile anesthetic gas concentrations and/or estimated propofol concentrations, time of loss and/or recovery of behavioral responsiveness (L/ROBR), and patient demographics. The studies were an experimental 32-channel propofol healthy volunteer (N = 16) study that provided the initial description of SWAS[3] (study 1), a presurgery sevoflurane patient (N = 21) study[8] (study 2), a desflurane-fentanyl infusion patient (N = 102) study[9] (study 3), and a routine clinical care patient (N = 254) study[10] (study 4). Research ethical committee approval was previously obtained for each of the studies separately. Full data collection details for all studies are provided in the Supplemental Digital Content (http://links.lww.com/ALN/B503). EEG data for the clinical studies were collected using depth of anesthesia monitors and a standard prefrontal montage (Fp7-Fz). Multichannel EEG data were initially collected using a FCz reference but later rereferenced to common average.

Sigmoid Fitting of Slow-wave Activity Saturation

A standardized preprocessing and analysis procedure was applied to each individual electroencephalographic data set on induction and emergence and at various electrode positions for the multichannel data using Matlab R2013a (Mathworks, USA; see appendix for full details). Preprocessing included down-sampling to 125 Hz, 0.25- to 45-Hz band-pass filtering using a Butterworth filter, remove blink and eye-movement artefacts using a Whittaker filter, generation of a short-term Fourier transform spectrograms, and extraction of mean power in the 0.5- to 1.5-Hz frequency band. The time series of the estimated effect site concentrations (C_e) of propofol, opioids, and volatile anesthetic drugs were calculated using standard population-based pharmacokinetic models.[16–19]

We then fitted a parametric sigmoid curve using Bayesian inference to identify SWAS for each individual electroencephalographic data set (see appendix). We confirmed the presence of SWAS by determining whether a plateau in the slow-wave activity drug dose-response curve was observed before maximum anesthetic dosing (fig. 1). We formally defined SWAS as the power and concentration that corresponded to 95% of the slow-wave activity posterior distribution around the slow-wave activity plateau. The following statistics were used to characterize the individual SWAS responses:

1) Absolute slow-wave activity power at saturation (P_{SWAS});
2) Concentration required to achieve SWAS (Ce_{SWAS});
3) Absolute slow-wave activity power at baseline ($P_{Baseline}$);
4) Gradient of the sigmoid curve; and
5) SWAS-response gap.

Because induction and emergence were modeled as two separate processes (fig. 1, B and C), these statistics have slightly different interpretations in each context. For induction,

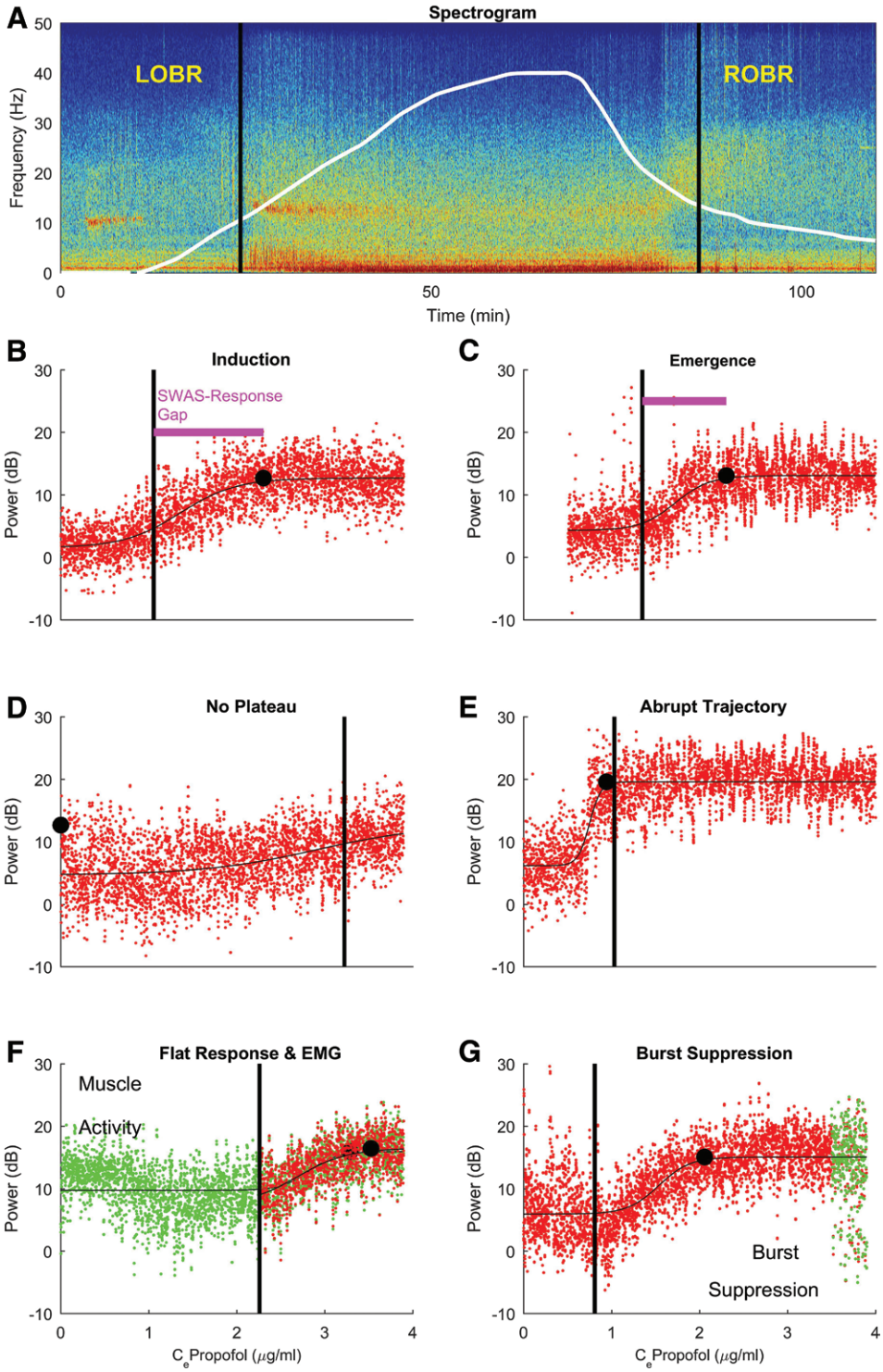

Fig. 1. Estimation of slow-wave activity saturation. (*A*) An individual electroencephalogram time-frequency spectrogram recorded at P7 electrode in study 1, with the propofol effect site concentration (C_e) time course shown in *white* to maximum of 4 μg/ml. (*B*, *C*) Corresponding slow-wave activity (SWA) anesthetic dose-response curves are shown for induction (*B*) and emergence (*C*). Loss and recovery of behavioral responsiveness (LOBR and ROBR) are shown as *black vertical lines* throughout. SWA data is in *red*, the *thin black line* is the sigmoid curve fit, and the *black dot* indicates slow-wave activity saturation (SWAS). (*D–G*) Practical issues related to SWAS estimation. Artefactual data are highlighted in *green* where present. (*D*) Graded pattern but no plateau, because the anesthetic dose administered was not sufficient to achieve SWAS within this individual. (*E*) An abrupt slow-wave trajectory that indicates neural inertia on emergence from anesthesia. It is characterized by the persistence of saturation followed by an abrupt drop in slow-wave activity coincident with the recovery of behavioral responsiveness and formally defined by a small SWAS-response gap (shown as a *pink line*). (*F, G*) Examples with electromyographic (EMG)/movement and burst suppression artefactual disturbance, respectively.

$P_{baseline}$ refers to the slow-wave activity baseline preceding anesthetic administration, *i.e.*, slow-wave activity in the awake state. For emergence, this relates to the slow-wave activity level after the initial ROBR *i.e.*, slow-wave activity associated with the (partially) awake state. The estimation of SWAS and its relationship with loss or recovery of behavioral responsiveness ($Ce_{L/ROBR}$) is captured by the SWAS-response gap. On emergence, a gentle gradient implies a smoothly changing brain state and good predictability of ROBR.

Statistical Analysis

The SWAS fitting outcome was expressed as the percentage of data sets with successful and unsuccessful fits. A successful fit indicates that a plateau in the slow-wave activity dose-response curve could be identified. Failed/unsuccessful fits were further subcategorized as either "no plateau" (fig. 1D) or "flat response and electromyographic (EMG)" (fig. 1F). Summary statistics are used to characterize the variability of the SWAS parameters for the successful individual fits. These values are presented as mean ± SD across volunteers for each study unless otherwise specified. After checking for normality (or after the appropriate transformation), paired *t* tests were used for within-subject comparisons and unpaired *t* tests for between-group comparisons. For multiple groups, we used one- or two-way ANOVA as appropriate. Chi-square tests were used for comparison of categorical data. Significance was set at $P < 0.05$ unless otherwise stated.

We hypothesized *a priori* that at SWAS we would observe a negative correlation between power at SWAS and age. Therefore, P_{SWAS} was compared for induction across all four studies using general linear model analyses of covariance with age as a covariate. Average values for the frontal electrodes were used for study 1. To assess the influence of coinduction agents, cumulative distribution functions of Ce_{SWAS} on induction were generated using the "ksdensity.m" Matlab function (Mathworks) with a smoothing of 0.001 for all three studies. For study 1, this corresponded to average concentration for all channels. Independent *t* tests were performed on all SWAS parameters on induction for studies 3 and 4, using repeated-measures ANOVAs with Tukey–Kramer multiple-comparison corrections (controlling for age and drug type) to identify significant differences between cases with and without muscle relaxant administration.

Experimental Data: Effect of Channel Location and Neural Inertia. We specified frontal channels as Fp1, Fp2, F3, F4, F7, F8, and Fz; central channels as C3, C4, Cz, Cp1, CP2, FC5, and FC6; and parietal channels as P3, P4, P7, P8, and Pz. The data were averaged for each group of regional channels for each subject. After checking for normality, a two-way repeated-measures ANOVA was applied with channel location (between-region variable) and induction-*versus*-emergence (within-subject variable) as the explanatory variables.

Associations between Slow-wave Activity Saturation Parameters and Demographic Variables. Studies 3 and 4 were used to explore how age and other demographic variables might influence or predict the SWAS parameters. Bivariate correlations between age, gender, operation duration and type, volatile and opioid effect-site concentrations, and the SWAS parameters were quantified using Pearson's correlation coefficients (*r*) for continuous variables.

Predicting Graded and Abrupt Emergence Trajectories. After examination of the slow-wave activity dose-response patterns from study 1, it was clear that subcategorization of the slow-wave activity output on emergence was required before statistical comparisons. An abrupt slow-wave emergence pattern was defined as when the slow-wave activity power was maintained by an individual as the hypnotic drug concentration decreased (usually to well below traditional waking minimum alveolar concentration [MAC]), followed by an abrupt decrease in slow-wave activity with a steep gradient around the point of ROBR. For study 1, the criteria for an abrupt trajectory was a SWAS-response gap less than 0.4 μg/ml. For the clinical studies, abrupt trajectories were defined by a SWAS-response gap less than 0.05 MAC (and only positively diagnosed in the absence of significant EMG movement artifact; *i.e.*, only when EMG power was less than 20 dB).

We then performed a *post hoc* multivariate logistic regression to determine which putative demographic and drug factors might determine whether a particular patient has a graded or an abrupt response on emergence from anesthesia. We focused on explanatory factors that could be plausibly predictive and therefore only included factors that could be estimated before or early in emergence. These were age, gender, duration and severity of operation, type of VGA, P_{SWAS} on induction, and P_{SWAS}, VGA, and fentanyl concentrations at start of emergence. We excluded Ce_{SWAS} from the model because, although by far the strongest predictor, it essentially defines the abrupt pattern and is only accessible after emergence has completed.

Assessment of Confusion and Delirium. Patients in study 4 were assessed for delirium (using the confusion assessment method for the intensive care unit [CAM-ICU][20]) and pain (using a 0 to 10 numerical rating scale [NRS]) in the post-anesthesia unit 15 min after waking. High levels of pain (*i.e.*, the presence of moderate or severe pain) were defined as NRS greater than 4. Because patients could fail the CAM-ICU test if they were sleepy or confused, we investigated the separate components. They were classed as being "confused" if they had an unexplained agitation (CAM-ICU Richmond Agitation-Sedation Scale component greater than 0, in the absence of moderate or severe pain *i.e.*, NRS greater than 4) or they failed the disordered thinking component of the CAM-ICU test. Fisher's exact test was used *post hoc* to investigate statistical differences in the incidence of high pain, confusion, sleepiness, and pass/fail on the CAM-ICU between individuals with abrupt and graded slow-wave emergence trajectories.

Results

We successfully identified SWAS on induction of anesthesia in 92% of individuals across all four studies (table 1). We confirmed that SWAS occurs for different classes of

Table 1. Slow-wave Activity Saturation Fitting on Induction of Anesthesia

Induction	Study 1	Study 2	Study 3	Study 4
Study name	Volunteer propofol	Presurgery sevoflurane	Desflurane-fentanyl	Routine clinical care
Induction agent	Propofol	Sevoflurane	Propofol	Propofol
Infusion rate	Slow	Rapid	Rapid	Rapid
Coinduction agents	No	No	Yes	Yes
Age, mean (range)	29 (18–43)	38 (18–63)	42 (17–67)	59 (18–90)
Gender, M:F	8:8	3:18	24:78	129:125
Data sets, No.	16	21	102	254
Successful fits	16 (100%)	18 (86%)	97 (95%)	230 (91%)
Failed fits	0 (0%)	3 (14%)	5 (5%)	24 (9%)
No plateau	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Flat response and EMG	0 (0%)	2 (9%)	5 (5%)	24 (9%)
SWAS parameters				
P_{SWAS}, dB	19.3 ± 3.8	22.3 ± 4.0	22.1 ± 4.9	20.5 ± 4.4
Ce_{SWAS}	2.7 ± 0.5 (μg/ml)	0.6 ± 0.3 (MAC)	1.4 ± 0.6 (μg/ml)	0.9 ± 0.3 (μg/ml)
$P_{baseline}$, dB	9.2 ± 3.2	6.9 ± 8.5	6.8 ± 2.9	4.1 ± 10.1
Gradient, degree	83.0 ± 6.0	86.2 ± 1.9	89.4 ± 0.8	89.4 ± 1.6

The SWAS fitting outcome is expressed as the number (and percentage) of participants for induction of anesthesia in the experimental and clinical electroencephalographic studies. Failed fits were subcategorized as either no plateau (fig. 1D) or flat response and electromyographic (fig. 1F). Concentration required to achieve SWAS is measured in minimum alveolar concentration for study 2 and μg/ml for the other studies. SWAS parameters represent the means and SD across participants. For study 1, SWAS parameters refer to average data collected from the frontal electrodes.

Ce_{SWAS} = concentration required to achieve SWAS; EMG = electromyographic; F = female; M = male; MAC = minimum alveolar concentration; $P_{baseline}$ = slow-wave activity power at baseline; P_{SWAS} = slow-wave activity power at saturation; SWAS = slow-wave activity saturation.

anesthetic agent, *i.e.*, for inhalational sevoflurane (86% successful fits) as well as intravenous propofol anesthesia (100% successful fits). For sevoflurane, one patient was not administered high sevoflurane levels (maximum 1 MAC) and did not achieve a slow-wave activity plateau (fig. 1D, no plateau example). Two other patients had a high $P_{baseline}$ caused by excessive muscle artifacts (or movement) that precluded accurate estimation of SWAS.

The average SWAS parameters for sevoflurane were comparable to those for intravenous propofol. The mean Ce_{SWAS} for sevoflurane is approximately 0.7 MAC and ranges across volunteers from 0.24 to 0.9 MAC. The mean propofol Ce_{SWAS} for study 1 is at the lower end of the concentrations used for total intravenous anesthesia.

We were able to identify SWAS in the clinical data sets (successful fits, study 3: 95% and study 4: 91%), allowing us to confirm that SWAS occurs in routine clinical anesthesia and the operating room environment. The only failed fits on induction in the clinical studies were due to excessive preinduction movement artifacts.

Opioids potentiate hypnotic agents so that reduced concentrations are required to achieve loss of behavioral responsiveness when these drugs are delivered in combination.[21] Similarly, when clinical coinduction agents were used, Ce_{SWAS} was approximately halved compared with study 1 (table 1). We found that 50% of individuals achieved SWAS at a propofol Ce_{SWAS} of at least 0.82 μg/ml for a rapid infusion (study 4) compared with 2.7 μg/ml for an ultraslow infusion (fig. 2). There were no statistically significant differences in the SWAS parameters between the patients in study 4 receiving muscle relaxants (N = 145) and those who did not (N = 85).

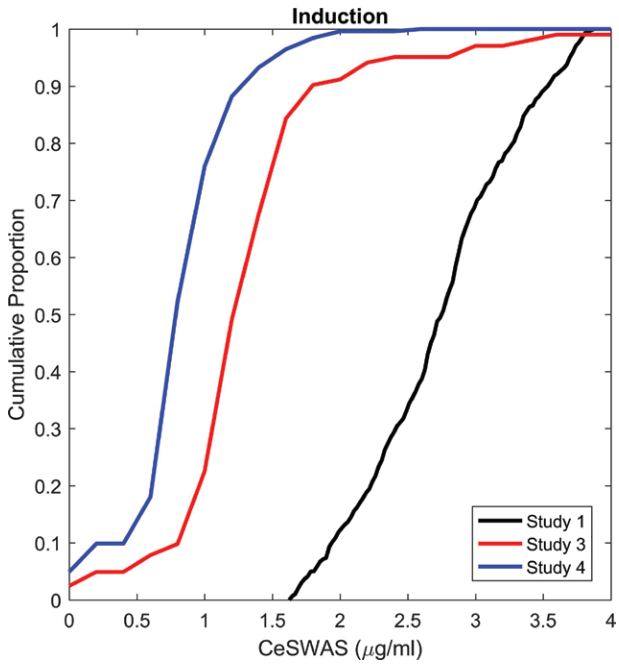

Fig. 2. Opioid analgesia reduces hypnotic concentration required to achieve slow-wave activity saturation. Cumulative distribution function of the concentration required to achieve slow-wave activity saturation (Ce_{SWAS}) on induction of propofol anesthesia. The introduction of opioids (and muscle relaxants) during the clinical administration (studies 3 and 4) potentiates the hypnotic component so that less propofol is required to achieve slow-wave activity saturation across participants than in the experimental study (study 1).

Despite these observed differences in Ce_{SWAS}, we found that P_{SWAS} was largely consistent across the four separate electroencephalographic studies. Frontal P_{SWAS} values for

the experimental study were significantly smaller when compared with the clinical studies using a standard prefrontal montage (Fp7-Fz) ($P < 0.01$, general linear model analyses of covariance with age as a covariate). However, we note that the experimental study also used high-impedance magnetic resonance imaging–compatible EEG electrodes and different referencing arrangements compared with the other studies.

No significant difference in P_{SWAS} was found across the three clinical studies when age was included as a covariate. In particular, no significant differences were found between P_{SWAS} for sevoflurane (study 2) and P_{SWAS} for propofol (studies 3 and 4) using similar electroencephalographic recording equipment. When age was not accounted for, P_{SWAS} was smaller for the older cohort in study 4 when compared with study 3 ($P < 0.05$, ANOVA Tukey–Kramer multiple-comparison Test). Overall, this demonstrates that (for a given recording system) P_{SWAS} is not determined by the hypnotic agent used (or any accompanying coinduction agents) but is potentially intrinsic to the individual, suggesting a sound neurobiologic basis for SWAS. This is consistent with our previous study that identified a significant positive correlation between P_{SWAS} and gray matter volume,[3] because the latter is known to be negatively correlated with age.

We were able to identify SWAS at all 31 electrodes for both induction and emergence in study 1 (table 2). Of a total of 496 channels, the SWAS model only failed to fit in 36 channels for induction (18 from one subject) and 58 channels during emergence (48 from two subjects). Central channels had more successful fits on induction and emergence across all individuals and channels. Frontal channels had more failed fits due to movement and blink artifacts ($P = 0.008$, chi-square test). Central channels also had a less-steep sigmoid gradient on emergence ($P < 0.05$, Tukey–Kramer multiple-comparison test). Slow-wave activity power was significantly different between channels both at SWAS and baseline. In line with previous descriptions of the anteriorization of EEG during general anesthesia,[3,4] it was largest in frontal channels and smallest in central channels.

Study 1 is the only data set with the same anesthetic agent for induction and emergence within an individual. Due to the ultraslow induction, the propofol concentration time courses for induction and emergence are similar, with the obvious proviso that they are derived from population pharmacokinetic models. Despite this, we found that the Ce_{SWAS}, $P_{baseline}$, gradient, and SWAS-response gap were significantly different between induction and emergence ($P < 0.001$; table 2). However, there was no significant difference in P_{SWAS}, adding credence to our hypothesis that SWAS (or more specifically P_{SWAS}) is intrinsic for an individual.

On average, SWAS occurred at propofol concentrations of approximately 1 μg/ml greater than those associated with behavioral unresponsiveness (table 2). When examined on an individual basis, we did not observe any consistent hysteresis in Ce_{LOBR} and Ce_{ROBR} (vertical red and blue lines in figs. 3 and 4, A). However, we did observe a marked hysteresis in Ce_{SWAS} across volunteers (fig. 4, B). In approximately half the subjects (*i.e.*, the lower eight subjects in fig. 3), Ce_{SWAS} on emergence occurred at lower concentrations than Ce_{SWAS} on induction and was often very close to the return of responsiveness.

We believe these more abrupt (rather than graded) slow-wave emergence trajectories indicate the presence of neural inertia in humans, an effect only previously observed in animals.[15] Abrupt slow-wave emergence trajectories (as defined by a SWAS-response gap less than 0.4 ug/ml) occurred across the brain. There was no statistical difference in the classification of abrupt or graded slow-wave emergence trajectory between channel regions ($P = 0.14$, chi-square test).

Successful SWAS fits for emergence were achieved in 94% of the experimental cases but only approximately 70% of clinical cases, with approximately a third of these having abrupt slow-wave trajectories (table 3; fig. 5). Unsuccessful SWAS fits were equally distributed between "no plateau" and "flat response and EMG" cases.

The mean Ce_{SWAS} on emergence for studies 3 and 4 both fall within accepted ranges for surgical anesthesia. Again,

Table 2. Variability of Slow-wave Activity Saturation across the Brain for Induction and Emergence

	Induction			Emergence		
$Ce_{L/ROBR}$ (μg/ml)	1.5 ± 0.7			1.4 ± 0.6		
Channel Region	Frontal	Parietal	Central	Frontal	Parietal	Central
Successful fits, %*	87.5	93.8	94.6	80.4	87.4	89.3
P_{SWAS}, dB*	19.3 ± 3.8	16.5 ± 3.3	15.3 ± 3.5	19.9 ± 4.0	16.8 ± 2.8	15.4 ± 3.6
Ce_{SWAS}, μg/ml†	2.7 ± 0.5	2.7 ± 0.5	2.7 ± 0.5	2.1 ± 0.7	1.9 ± 0.6	1.9 ± 0.6
$P_{baseline}$, dB†‡	9.1 ± 3.2	6.3 ± 2.5	4.1 ± 2.5	8.6 ± 2.6	5.4 ± 2.0	4.0 ± 2.1
Gradient, degree*†	83.0 ± 6.0	83.9 ± 3.0	84.1 ± 2.5	83.4 ± 7.5	86.2 ± 4.0	86.6 ± 3.3
SWAS-RG, μg/ml†	1.2 ± 0.5	1.1 ± 0.3	1.2 ± 0.5	0.7 ± 0.6	0.5 ± 0.5	0.5 ± 0.5

Summary statistics across channel locations for induction and emergence from anesthesia in the experimental study. SWAS parameters are presented as means ± SD of seven frontal, seven parietal, and five central channels for 16 healthy volunteers. After checking for normality, SWAS parameters were analyzed using two-way repeated-measures ANOVA with channel location (between-region variable) and induction *versus* emergence (within-subject variable).

*Significant difference between frontal region and the rest ($P < 0.01$). †Significant difference between induction and emergence ($P < 0.001$). ‡Significant difference between all regions ($P < 0.001$).

$Ce_{L/ROBR}$ = loss or recovery of behavioral responsiveness; Ce_{SWAS} = concentration required to achieve SWAS; $P_{baseline}$ = slow-wave activity power at baseline; P_{SWAS} = slow-wave activity power at saturation; SWAS = slow-wave activity saturation; SWAS-RG = SWAS-response gap.

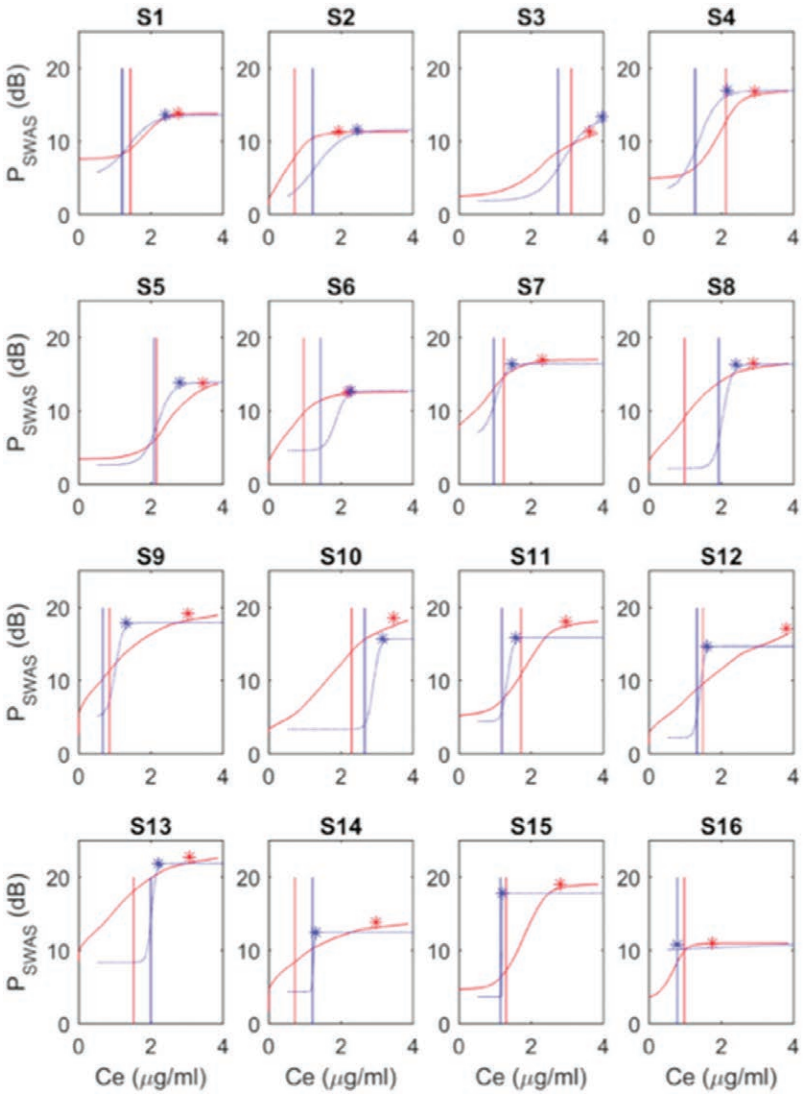

Fig. 3. Experimental evidence for neural inertia in humans. Sigmoid regression of absolute slow-wave activity power as a function of the estimated propofol concentration (C_e) for induction (*red*) and emergence (*blue*) for each individual in study 1. *Asterisks* indicate the point of slow-wave activity saturation, with the *vertical lines* indicating loss (*red line*) and recovery (*blue line*) of behavioral responsiveness. Subjects (S1–S16) are ordered based on the emergence gradient, from gentlest to steepest. Note that subject 3 (S3) barely achieved saturation in this channel, and subject 16 (S16) had a completely abrupt response on emergence, *i.e.*, they recovered behavioral responsiveness directly from slow-wave activity saturation. Examples relate to the P7 electrode. P_{SWAS} = slow-wave activity power at saturation.

we observed a wide interindividual variation with Ce_{SWAS}, ranging from 0.05 to 1.6 MAC for study 3 and 0.03 to 1.3 MAC for study 4 (fig. 5B). We found that P_{SWAS} on induction and emergence were correlated across all of the studies (R^2 = 0.51, P < 0.001; fig. 6). However, in contrast to the experimental study, P_{SWAS} on emergence after surgery was significantly lower than P_{SWAS} on induction (of the order of 4 to 5 dB) in both clinical studies (P < 0.001, paired t test, fig. 5, C and D for study 4). The gradient on emergence was steeper compared to induction in the clinical studies (P < 0.001, paired t test).

Because many of the correlations within the two clinical data sets (studies 3 and 4) were broadly comparable, we decided to focus on the larger study 4 data set. Age was strongly negatively correlated (r ~ –0.6, P < 0.001) with P_{SWAS} on induction and emergence, and with Ce_{SWAS} on emergence (fig. 7; table 4). From figure 7, it is clear that older individuals are more likely to have abrupt slow-wave emergence trajectories than graded emergence trajectories.

There was a good discrimination between the two slow-wave emergence trajectories. Graded responders had significantly higher P_{SWAS} (19.5 ± 3.4 *vs.* 14.0 ± 4.4 dB, P < 0.001) and were younger (48.0 ± 17.3 *vs.* 61.3 ± 16.9 yr, P < 0.001) than those with abrupt slow-wave emergence trajectories. They had also experienced shorter (111 ± 69 *vs.* 137 ± 73 min, P = 0.005) and less severe operations (74% minor operations for graded *vs.* 48% minor for abrupt, P = 0.006). Graded responders were more likely

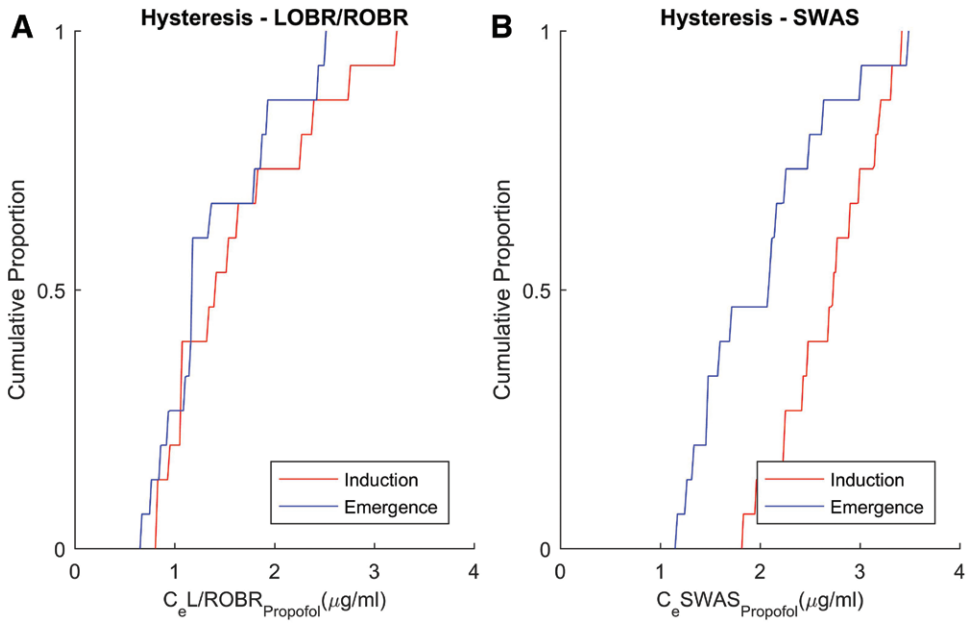

Fig. 4. Hysteresis of slow-wave activity saturation but not behavioral responsiveness. Cumulative distribution functions of the concentrations associated with (*A*) loss and recovery of behavioral responsiveness (LOBR and ROBR) and (*B*) slow-wave activity saturation (SWAS) on induction and emergence from propofol anesthesia. A comparison for 50% of volunteers indicates a significant hysteresis in the concentration required to achieve slow-wave activity saturation (Ce_{SWAS}) but not for behavioral responsiveness. The data in (*B*) correspond to the mean Ce_{SWAS} for all 31 electroencephalogram channels for each of the 16 individuals who participated in study 1.

Table 3. Slow-wave Activity Saturation on Emergence from Anesthesia

Emergence	Study 1	Study 3	Study 4
Anesthetic agent	Propofol	Desflurane	Mixed
Coinduction agents	No	Yes	Yes
Type of surgery	N/A	Gyn: 54; Gen: 37; Orth: 11	Gyn: 129; Gen: 121; Orth: 4; Vasc: 66; Urol: 30; Other: 4
Severity grading of surgery	N/A	1: 0; 2: 51; 3: 51; 4: 0	1: 51; 2: 102; 3: 83; 4: 18
Data sets, No.	16	102	254
Successful fits	15 (94%)	71 (71%)	175 (69%)
Graded response	14 (88%)	50 (49%)	110 (43%)
Abrupt response	1 (6%)	21 (20%)	65 (26%)
Failed fits	1 (6%)	31 (31%)	79 (30%)
No plateau	1 (6%)	16 (16%)	42 (16%)
Flat response and EMG	0 (0%)	15 (15%)	37 (14%)
SWAS parameters			
P_{SWAS}, dB	19.9 ± 4.0	18.1 ± 3.7	16.7 ± 4.8
Ce_{SWAS}	2.1 ± 0.7 (μg/ml)	0.65 ± 0.39 (MAC)	0.47 ± 0.33 (MAC)
$P_{baseline}$, dB	8.6 ± 2.6	8.1 ± 4.4	6.5 ± 5.9
Gradient, degree	83.4 ± 7.5	87.7 ± 2.9	87.8 ± 6.4

SWAS fitting outcome is subcategorized as graded or abrupt based on the slow-wave emergence trajectory gradient. SWAS parameters represent the means ± SD across participants. The table describes the hypnotic agent, whether any coinduction agents were present, and the surgery details.

Ce_{SWAS} = concentration required to achieve SWAS; EMG = electromyographic; Gen = general surgical; Gyn = gynecologic; MAC = minimum alveolar concentration; N/A = not applicable; Orth = orthopedic, $P_{baseline}$ = slow-wave activity power at baseline; P_{SWAS} = slow-wave activity power at saturation; Urol = urologic; SWAS = slow-wave activity saturation; Vasc = vascular.

to have received sevoflurane rather than desflurane VGA (58 *vs.* 41%, $P = 0.002$). In general, the differences were more pronounced in study 4, presumably reflecting the more standardized operations and anesthesia delivery used in study 3.

Using a multivariate logistic regression model to predict whether a patient having surgical anesthesia is likely to have a graded or abrupt emergence trajectory, we found that age, P_{SWAS} on emergence, and VGA type all contributed significantly (with Wald $P < 0.001$):

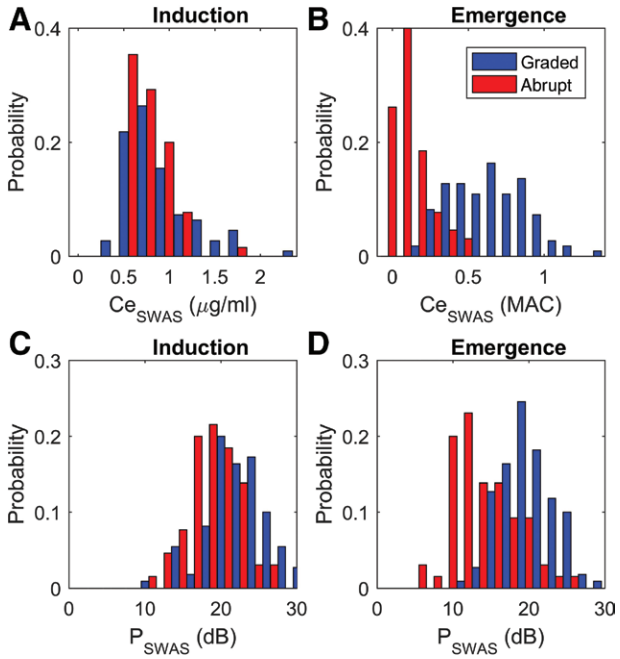

Fig. 5. Slow-wave activity saturation parameters reveal clear separation of graded and abrupt slow-wave emergence trajectories. (*A–D*) Probability distribution of concentration required to achieve slow-wave activity saturation (Ce_{SWAS}) and slow-wave activity power at saturation (P_{SWAS}) on induction and emergence. Clear bimodal distributions in Ce_{SWAS} and P_{SWAS} on emergence can be observed for the graded (*red*) and abrupt (*blue*) slow-wave trajectories. The data are presented for the N = 175 patients in study 4 that had successful slow-wave activity saturation fits on both induction and emergence. Ce_{SWAS} is in μg/ml for induction and minimum alveolar concentration (MAC) for emergence due to the different hypnotic anesthetic agents used.

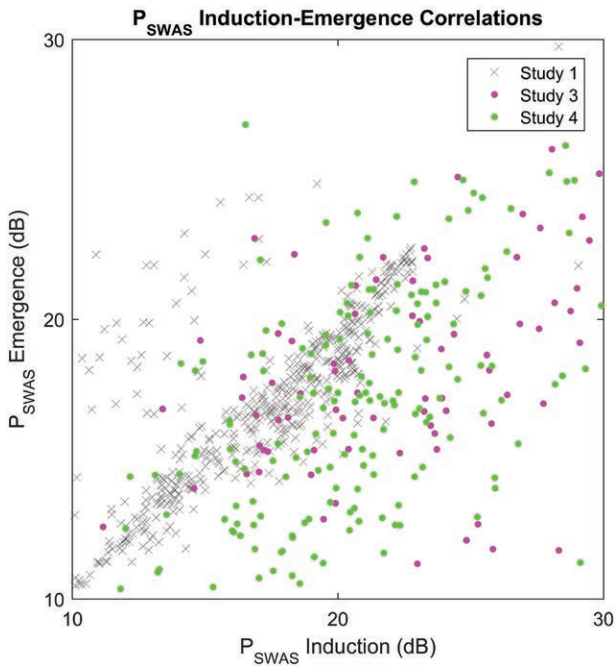

Fig. 6. Power at slow-wave activity saturation (P_{SWAS}) is highly correlated between induction and emergence. The data are presented for the individuals that had successful fits on both induction and emergence for studies 1 (*gray crosses*; all 31 electroencephalogram channels), 3 (*blue dots*), and 4 (*red dots*).

$$LnOdds(abrupt/graded) = 4.31 - 0.28P_{SWAS\_E} - 1.6(VGA = Sevoflurane) + 0.42age(decade)$$

With reference to a graded emergence, the odds ratios for an abrupt response are: 0.75/dB P_{SWAS} on emergence, 0.20 (VGA = sevoflurane), and 1.5 per decade in age. The model had an overall classification accuracy of 78.4%.

We found that the slow-wave activity emergence patterns correlated strongly with the cognitive state in the early postoperative period. Patients with abrupt slow-wave emergence trajectories experienced increased confusion levels 15 min after waking compared to those with graded trajectories (Fisher's exact test, $P < 0.001$). Only 2 of the 110 patients who had a graded emergence were confused (*i.e.*, less than 2%). In contrast, 18% (12 of 65) of patients who had an abrupt emergence trajectory were confused. The incidence of delirium was also higher in patients with abrupt slow-wave emergence trajectories compared with graded responders (14 of 110 *vs.* 17 of 65 patients; CAM-ICU total, Fisher's exact test, $P = 0.02$). No significant differences between the slow-wave emergence trajectories were found in pain levels ($P = 0.59$) or alertness state ($P = 0.4$).

Discussion

Neurobiologic Basis of Slow-wave Activity Saturation

Slow-wave activity is a manifestation of slow ~1 Hz cortical oscillations between a high firing, so-called UP (or active) state, and a quiescent DOWN (or silent) state.[22] We previously provided evidence that saturation of slow-wave activity indicates an individualized state of perception loss, and the peak of slow-wave activity power was correlated with prefrontal cortical gray matter volume across subjects, suggesting maximal involvement of these cortical neurons due to anesthetic-induced increases in corticothalamic hyperpolarization.[3] Here, we have demonstrated that SWAS occurs clinically on induction of anesthesia in 92% cases, for both volatile and intravenous anesthetic agents (table 1). The coadministration of fentanyl markedly left-shifts the concentration required to achieve SWAS, effectively highlighting the potentiation of hypnotic agents by opioids (fig. 2).

When parameterized using dose-response models, SWAS demonstrates negative correlations with age (fig. 7). Because age is known to be negatively correlated with gray matter volume,[11] our previous work[3] suggested that such a relationship with age should exist. Similar adult age-dependent slow-wave activity amplitude decreases (but not saturation *per se*) have been observed during propofol and sevoflurane anesthesia[23] and

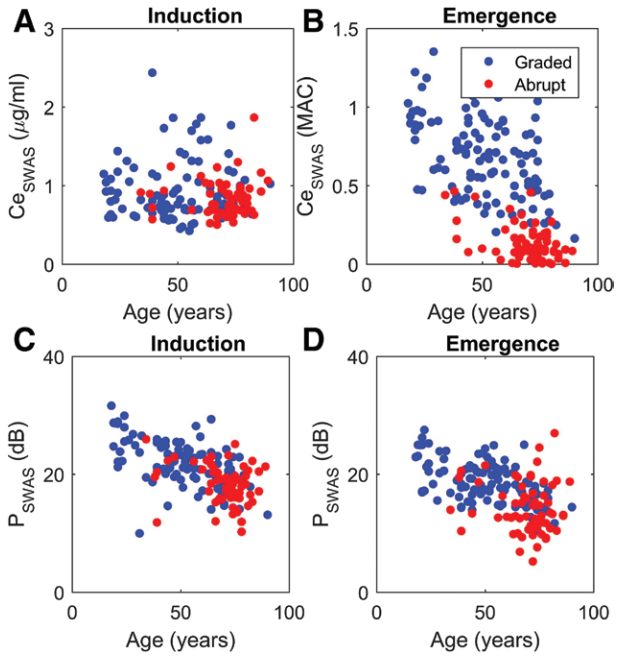

Fig. 7. Older individuals have lower slow-wave activity saturation parameters on induction and emergence. For both induction and emergence, (*A–D*) detail the correlation of the concentration required to achieve slow-wave activity saturation (Ce_{SWAS}) and slow-wave activity power at saturation (P_{SWAS}) with age (in yr). Individuals with graded and abrupt slow-wave trajectories on emergence are shown in *red* and *blue*, respectively. The data are presented for the N = 175 patients in study 4 who had successful slow-wave activity saturation fits on induction and emergence.

during natural sleep. In the latter case, this has also been linked with age-related reductions in neuronal numbers and synaptic density.[24] These data lend support to the idea that the SWAS observed during anesthesia has a sound neurobiologic basis and potentially represents a phenotype of an underlying trait.

In further support of this neurobiologic basis, we found that the power at SWAS was not significantly different between experimental induction and emergence from anesthesia (table 2). Additionally, power at SWAS on clinical induction of anesthesia was not significantly different between studies when the previously mentioned age-related variability was accounted for (table 1). During clinical anesthesia, we also demonstrated that power at SWAS on emergence was highly correlated with but reduced compared to that on induction (fig. 6), possibly indicating modification of synaptic scaling through changes in glial adenosine triphosphate handling and interleukin-1[25] due to the inflammatory and stressful effects of surgery.

The goal of surgical anesthesia is to achieve loss of perception/awareness and no pain by targeting anesthetic drug dosing for each individual patient. Despite recent advances in our understanding of the neuroscientific basis of consciousness at a systems-level, a reliable brain-based indicator of unconsciousness under clinical anesthesia is still required.[2] Importantly, our data presented here further indicate that SWAS is potentially a useful *individualized* biomarker to guide anesthetic drug dosing. Assuming based on our previous work that SWAS indicates true perception loss,[3] the variability in the concentration required to achieve SWAS (fig. 5) implies that approximately 50% of patients receive twice as much anesthesia as they need, and 20% of patients will not achieve full unconsciousness when given a typical clinical anesthetic of approximately 0.7 MAC.

Evidence of Neural Inertia in Humans

Our findings are in support of the neural inertia framework proposed by Friedman *et al.*[15] but have revealed important cross-species differences. Unlike Friedman *et al.*, we did not observe any hysteresis in the average dose associated with behavior in study 1. However, importantly, we did observe clear hysteresis in our brain-based measure of SWAS (fig. 4) that potentially indicates a different arousal state where perception to incoming stimuli is lost.[3] At an individual level, the observed slow-wave activity dose responses during induction are often markedly different to that during emergence. This was most notable in those subjects who had an abrupt (rather than graded) change in the brain's slow-wave activity

Table 4. Age Is Negatively Correlated with Power at Slow-wave Activity Saturation on Induction and Emergence

		Age	P_{SWAS_I}	Ce_{SWAS_I}	P_{SWAS_E}	Ce_{SWAS_E}
Age	*r*		**−0.580**	−0.058	**−0.530**	**−0.681**
	P		**< 0.001**	0.471	**< 0.001**	**< 0.001**
P_{SWAS_I}	*r*	**−0.580**		**0.193**	**0.574**	**0.537**
	P	**< 0.001**		**0.015**	**< 0.001**	**< 0.001**
Ce_{SWAS_I}	*r*	−0.058	**0.193**		0.086	0.149
	P	0.471	**0.015**		0.281	0.062
P_{SWAS_E}	*r*	**−0.530**	**0.574**	0.086		**0.550**
	P	**< 0.001**	**< 0.001**	0.281		**< 0.001**
Ce_{SWAS_E}	*r*	**−0.681**	**0.537**	0.149	**0.550**	
	P	**< 0.001**	**< 0.001**	0.062	**< 0.001**	

Pearson's correlations between age (in yr) and the SWAS parameters for study 4. Age was strongly negatively correlated ($r \sim -0.6$, $P < 0.001$) with slow-wave activity power at saturation on induction (P_{SWAS_I}) and emergence (P_{SWAS_E}), and with the concentration required to achieve SWAS on emergence (Ce_{SWAS_E}). Significant correlations at the level of $P < 0.05$ are indicated with boldface.

Ce_{SWAS_I} = concentration required to achieve SWAS on induction; SWAS = slow-wave activity saturation.

that temporally coincided with recovery of the individual's behavioral responsiveness (fig. 3).

Clinically, we identified that approximately a third of patients experience abrupt slow-wave emergence trajectories after surgery (table 3). The clear bimodal distributions for Ce_{SWAS} and P_{SWAS} (fig. 5) for the abrupt or graded slow-wave emergence trajectories are indicative of two types of emergence with different associated neural processes. We were able to accurately predict the type of slow-wave emergence trajectory in 78% of the individuals using clinically relevant parameters known before emergence. Our data suggest that a patient over 60 yr of age (fig. 6) experiencing desflurane anesthesia with a P_{SWAS} less than 16 dB at the start of emergence (fig. 5D) is significantly more likely to have an abrupt slow-wave emergence trajectory. It is evident that the patient is "stuck" in this unconscious state when they continue to maintain their SWAS level until volatile general anesthetic concentrations are decreased to low levels less than 0.3 MAC.

We suggest that individuals with abrupt slow-wave trajectories experience a high degree of neural inertia, because it is evident that (through the assessment of SWAS) the individual's brain is resisting recovery of consciousness. As such, we believe these abrupt slow-wave trajectories are an archetypal indicator of neural inertia in humans, because they reveal an inherent resistance of the central nervous system to enter a wakeful state even when the brain concentrations of hypnotic drug have decreased to virtually zero. Based on our findings, we therefore propose a more general definition of neural inertia as "a tendency of the central nervous system to resist transitions between conscious and unconscious states." This definition could include various different brain state transitions as inferred by electroencephalographic methods, functional brain imaging, and/or behavior.

Importantly, our findings fit well with other investigations of electroencephalographic changes on emergence from anesthesia. When individual emergence trajectories were characterized in alpha–delta frequency space by Chander *et al.*,[26] approximately 30% of cases were found to have a high level of delta power that continued through to just before the recovery of responsiveness—similar to the incidence of abrupt trajectories in our study. Lee *et al.*[27] also found two different modes of emergence when examining the connection strength component of global efficiency using graph theory. Although they did not explore frequency band specific changes, our data indicate that these individualized changes in slow-wave dose response could contribute to the gradual and abrupt network-level changes they observed. In light of recent findings in rodents that a series of metastable states exist on recovery from anesthesia that may give rise to this neural inertia,[28] our findings also have wider-reaching implications for recovery in disorders of consciousness patients.

Finally, we provide preliminary evidence that individuals with abrupt slow-wave emergence trajectories have more short-term delirium and confusion on recovery from anesthesia. This suggests a link between abrupt slow-wave emergence trajectories and disruption of high-level cognitive functioning. Given that these patients are also more likely to be older and have a lower power at SWAS, this opens up exciting future directions for the continued exploration of the SWAS biomarker and its neurobiologic and clinical significance.

Study Limitations and Application to Depth of Anesthesia Monitoring

Preliminary evidence we present here suggests that understanding the cause of neural inertia and preventing its occurrence may help reduce short-term postoperative confusion and delirium on recovery from anesthesia. However, further work and larger sample sizes will be required to fully elucidate this link. In the short-term, the accuracy of predicting individuals at risk of neural inertia and abrupt slow-wave emergence trajectories could be increased with improved artifact rejection algorithms and SWAS model refinements, particularly because failed SWAS fits due to increased movement are more likely to occur in those with abrupt slow-wave trajectories.

With a view to clinical depth of anesthesia monitoring, the multichannel data set indicates that central recording channels rather than the typically used frontal channels could further reduce failed fits due to muscle artifacts/movement. A further advantage is that the sigmoid gradient is comparatively more gradual in these channels, allowing more advance warning of the patient's recovery of behavioral responsiveness. On emergence we also found equal numbers of failed fits because the model could not identify a plateau in slow-wave activity. We believe the main contributing factor here is the reduction of volatile anesthetic concentrations toward the end of surgery to facilitate a quick recovery of the patient, as is common clinical practice.

Conclusions

Our individualized electroencephalographic marker of perception loss, SWAS, is readily measurable during induction and emergence of clinical anesthesia, and its magnitude negatively relates to age. Furthermore, we have shown that SWAS can be observed across the commonly used γ-aminobutyric acid–mediated anesthetic drugs, in the presence of coinduction agents, and at various locations across the brain. The concentration of hypnotic drugs required to achieve SWAS varies widely between patients, which would suggest that a large percentage of patients are actually under- or overdosed with conventional, population-based, clinical anesthesia dosing regimens. Finally, SWAS on emergence revealed evidence of neural inertia in humans and a potential link between its occurrence and confusion/delirium shortly after recovery from anesthesia.

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Competing Interests

Patent applications were filed by Oxford University Innovation, the technology transfer company of the University of Oxford (formerly Isis Innovation; Oxford, United Kingdom), on perception loss detection. Drs. Warnaby, Jbabdi, and Tracey are listed as inventors. The other authors declare no competing interests.

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Appendix

Preprocessing and Model Description Details

First, a standardized signal processing procedure was applied to each individual electroencephalographic data set using Matlab R2013a (Mathworks, USA). In the period before anesthesia, induction blink and eye-movement artefacts were reduced using a Whittaker filter. The smoothed spectral power in decibels was obtained using the short-term Fourier transform "spectrogram.m" function (window = 4 s, overlap = 3 s, 0.25-Hz resolution) for each electroencephalographic data set over a frequency range from 0.25 to 50 Hz (fig. 1A). The slow-wave activity time series was obtained by extracting the mean power in the 0.5- to 1.5-Hz frequency band. The time series of the estimated effect site concentrations (C_e) of propofol, opioids, and volatile anesthetic drugs were calculated using standard population-based pharmacokinetic models.[16–19] The C_e for propofol and opioids were derived using the time and dose of intravenous administrations. The C_e values for volatile agents were calculated using the end-tidal concentrations assuming a $t_{1/2}$Keo of 135 s,[29] and expressed as minimum alveolar concentration (MAC) uncorrected for age. Morphine administration was converted to fentanyl equivalent C_e.

Second, a sigmoid curve was fitted to the slow-wave activity data using Bayesian inference. We modeled slow-wave activity as a function of the estimated effect site concentration of hypnotic concentration C_e using a logistic function,

$$SWA(C_e) = \frac{s-r}{1+\exp(-[Ce-t]/u)} \quad (1)$$

where {*r, s, t, u*} are free parameters that are fitted to the data. These free parameters were estimated using a custom Matlab implementation of the Metropolis Hastings algorithm, which allows us to sample from the joint posterior distribution on the free parameters. A flat prior distribution was chosen for all parameters, and the likelihood function was built up assuming Gaussian white noise with unknown variance and a Jeffrey's prior on the variance that allows us to integrate it out analytically. This inference method was chosen because it is relatively robust to artefacts and outliers.

The concentration of slow-wave activity saturation (SWAS) was defined as the concentration that contains 95% of the posterior distribution around SWAS, where $Ce_{SWAS} = SWA(Ce) > SWAS - 1.65\sigma$ and $SWAS(\pm\sigma)$ is the estimate of location (and precision) of SWAS. Similarly, the power at SWAS is the absolute slow-wave activity power associated with C_{eSWAS} and 95% of the distribution around the slow-wave activity plateau. The steepness of the gradient of the sigmoid curve was calculated as $tan^{-1}[(s-r)/4u]$ in degrees.

Identifying SWAS in Individual Anesthetic Data Sets

For study 1, the end of the induction (and start of emergence) period was defined at the point where the maximum propofol concentration of 4 μg/ml was reached. For study 2, the end of induction was defined where the maximum effect site sevoflurane concentration (C_e) was reached, corresponding to the nadir of the spectral entropy. For the surgical data sets (*i.e.*, studies 3 and 4), anesthetic induction was determined on the basis of the rapid induction of propofol after a fentanyl (or remifentanil) bolus and infusions as is standard clinical practice. In these studies, the start of the emergence period was defined as 600 s before the end of surgery. Thus the SWAS parameters relate to the end of the maintenance period and include the flushing of the volatile anesthetic drug from the patient.

Subcategorization of Slow-wave Activity Dose-response Patterns

The responses were separated into two main categories as successful or unsuccessful fits. Successful fits were then further subclassified as to whether the slow-wave activity dose

response showed a "graded" (fig. 1, B and C, for induction and emergence, respectively), or an "abrupt" pattern (fig. 1E, on emergence). We also identified other situations where complex slow-wave activity dose response patterns occurred that potentially resulted in unsuccessful SWAS fits. If the slow-wave activity response pattern was graded but the model fitting was not able to identify a plateau, it was assumed that anesthetic dose administered during the electroencephalographic recording was not sufficient to achieve SWAS within that individual (fig. 1D, "no plateau"). If the slow-wave power was unchanged or increased but was associated with a sudden increase in high-frequency electromyography (seen as muscle activity and/or blinks; fig. 1F, *green data points*), the true baseline level of slow-wave activity was hidden by the noise and could not be estimated reliably. This often resulted in a flat line instead of the expected sigmoid regression and so were labeled as flat response and electromyography. Finally, burst suppression is manifest by prolonged periods of electrical near-silence at high anesthetic dose concentrations. This paradoxically decreases slow-wave activity at high anesthetic concentrations (fig. 1G). Our robust method of fitting the curve was resistant to this artefact.

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