Differentiating Drug-related and State-related Effects of Dexmedetomidine and Propofol on the Electroencephalogram

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ABSTRACT

Background: Differentiating drug-related changes and state-related changes on the electroencephalogram during anesthetic-induced unconsciousness has remained a challenge. To distinguish these, we designed a rigorous experimental protocol with two drugs known to have distinct molecular mechanisms of action. We hypothesized that drug- and state-related changes can be separated.

Methods: Forty-seven healthy participants were randomized to receive dexmedetomidine (n = 23) or propofol (n = 24) as target-controlled infusions until loss of responsiveness. Then, an attempt was made to arouse the participant to regain responsiveness while keeping the drug infusion constant. Finally, the concentration was increased 1.5-fold to achieve presumable loss of consciousness. We conducted statistical comparisons between the drugs and different states of consciousness for spectral bandwidths, and observed how drug-induced electroencephalogram patterns reversed upon awakening. Cross-frequency coupling was also analyzed between slow-wave phase and alpha power.

Results: Eighteen (78%) and 10 (42%) subjects were arousable during the constant drug infusion in the dexmedetomidine and propofol groups, respectively (P = 0.011 between the drugs). Corresponding with deepening anesthetic level, slow-wave power increased, and a state-dependent alpha anteriorization was detected with both drugs, especially with propofol. The slow-wave and frontal alpha activities were momentarily disrupted as the subjects regained responsiveness at awakening. Negative phase-amplitude coupling before and during loss of responsiveness frontally and positive coupling during the highest drug concentration posteriorly were observed in the propofol but not in the dexmedetomidine group.

Conclusions: Electroencephalogram effects of dexmedetomidine and propofol are strongly drug- and state-dependent. Changes in slow-wave and alpha activity seemed to best detect different states of consciousness.

Visual Abstract: An online visual overview is available for this article at http://links.lww.com/ALN/B754. **(Anesthesiology 2018; 129:22-36)**

ANESTHETIC drugs induce distinct neurophysiologic effects reflected in electroencephalogram patterns, which have been well documented and recently summarized.[1] Online electroencephalogram processing is used in depth-of-anesthesia monitors, which aim to create a simple numerical value of anesthetic depth. Current monitors are not, however, applicable to all anesthetics,[2] and the indices express large individual variation at similar behavioral states.[3] Consequently, transitions between different states of consciousness are not reliably detected at individual level.

Unresponsiveness does not equal unconsciousness, as one may have conscious experiences without behavioral responsiveness.[4] In the field of anesthesiology, this can manifest—at the extreme—as intraoperative awareness with explicit recall. The incidence has been reported to be approximately 0.1 to 0.2%,[5–7] despite increasing use of depth-of-anesthesia monitors. Thus, the benefit of the monitors in decreasing the incidence has been questioned, and there is no strong evidence

What We Already Know about This Topic

- The effects of propofol and dexmedetomidine on the electroencephalogram have been well characterized. With increasing doses, increased frontal alpha and global slow-wave activity and suppression of beta activity are observed.
- Whether the changes in the electroencephalogram in response to anesthetic administration are due to a direct action of the anesthetics or due to a change in the state of consciousness itself is not clear.

What This Article Tells Us That Is New

- In humans rendered unresponsive with either propofol or dexmedetomidine, increased frontal alpha, increased slow-wave, and decreased beta activities were observed. Arousal in response to verbal or physical stimulation resulted in a reversion of the alpha and slow-wave activity, but not beta activity.
- The results suggest anesthetic effects on the electroencephalogram are a composite of the direct effect of the drugs on neuronal networks and the impact of the change in the state of consciousness itself.

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. The work presented in this article has been presented at the American Society of Anesthesiologists Annual Meeting in Chicago, Illinois, October 22, 2016, and at the Operatiiviset päivät in Helsinki, Finland, November 17, 2016.

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of their superiority to traditional methods in assessing the level of anesthesia during surgery.[8–11] It has, however, been suggested that raw electroencephalogram monitoring should be utilized to individualize dosing and improve therapy.[1]

The electroencephalogram effects of propofol include an increase in frontal alpha activity and an increase in slow-wave activity across the entire scalp.[12,13] Furthermore, differences in brain activity between light and deep anesthetic levels with propofol have been shown. For example, after the onset of unresponsiveness, the power of slow-wave activity has been demonstrated to further increase in association with increasing drug concentration and finally reach slow-wave activity saturation.[14] The point of slow-wave activity saturation—as opposed to initial unresponsiveness—has been suggested to be a correlate for profound perception loss, as assessed with simultaneous functional magnetic resonance imaging. Additionally, cross-frequency phase-amplitude coupling patterns between alpha and slow-delta bands appear to differentiate light and deep anesthetic levels with propofol.[13,15,16] During profound propofol-induced unconsciousness, alpha amplitudes are maximal at low-frequency peaks (peak-max), whereas during the transition, at low-frequency nadirs (trough-max).

Dexmedetomidine, an alpha$_2$-adrenoceptor agonist, is suggested to induce a sleep-like state, from which a person can be easily aroused with an external stimulus.[17,18] During dexmedetomidine exposure, the electroencephalogram shows an increase in occipital and frontal slow-wave activity, an increase in occipital theta activity, and an increase in frontal spindle oscillations. Also, a decrease in beta activity across the entire scalp has been demonstrated.[16,18,19] Phase-amplitude coupling results have not been reported for dexmedetomidine in humans.

Experimental anesthesia and electroencephalogram enable studying human consciousness to find possible markers for absence or presence of intact perception and behavioral responsiveness. However, there are two effects that must be differentiated in experimental settings: the direct—and probably concentration-dependent—drug effect, and the effect of changing level of consciousness itself. In several previous studies, the comparison between behavioral states has been made during multiple drug concentrations (*e.g.*, baseline, unresponsiveness, recovery), and the assumption that the observed spectral changes are independent correlates for consciousness may be premature. To discover electroencephalographic signatures for responsiveness or consciousness that are state-specific, it is necessary to design an experimental setting where these effects can be dissociated.

We investigated the effects of dexmedetomidine and propofol in a rigorously standardized protocol. We titrated the dosing carefully to similar behavioral endpoints, and performed comparative analyses of the two drugs and corresponding states of consciousness. Our aim was to distinguish state-related electroencephalogram patterns from drug or concentration dependent phenomena, by assessing changes induced by abrupt awakening during pseudo steady-state infusion. We hypothesized that with the applied study design, drug- and state-related changes can be separated.

Materials and Methods

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland (Turku, Finland), and the Finnish Medicines Agency (Fimea, Helsinki, Finland). The study was registered in ClinicalTrials.gov (NCT01889004) and carried out in a single site, *i.e.*, at the Intensive Care Unit of the Department of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Turku, Finland, between March 2014 and January 2015. The study was exploratory in nature and included a myriad of different measurements. The effects on event-related potentials and subjective reports will be reported separately.

Study Subjects

Forty-seven right-handed, healthy (American Society of Anesthesiologists physical status I), nonsmoking, 20- to 30-yr-old male subjects were recruited to participate in this open-label, randomized, parallel-group (n = 23 for dexmedetomidine and n = 24 for propofol) study. The randomization was carried out using permuted blocks to allocate subjects into two equally sized groups by the principal investigator (H.S.), who did not participate in the recruitment of the subjects or execution of the study. No statistical power calculation was conducted before the study, and the sample size was based on our previous experience with this design. Only male subjects were considered eligible because of radiation exposure related to a subsequent positron emission tomography study. Exclusion criteria included a history of psychiatric disorder, any somatic illness or drug allergy, cardiac arrhythmias, or substance abuse. Ongoing medications and hearing impairment were also considered as reasons for exclusion.

All participants underwent an interview and laboratory tests, including hearing test, drug screening, and an electrocardiogram recording. All subjects refrained from using alcohol or any medication for 48 h before study sessions, and

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they fasted overnight before anesthesia. A written informed consent was acquired from all participants according to the Declaration of Helsinki. The groups were comparable: the mean (SD) height was 179 (6) and 181 (8) cm, weight 77.7 (8.2) and 81.3 (16.6) kg, and age 23 (2) and 24 (3) yr in the dexmedetomidine and propofol groups, respectively.

Anesthetic Protocol

The state of consciousness was manipulated with step-wise increasing concentrations of either dexmedetomidine or propofol until loss of responsiveness, defined as participant's inability to press handles in the responsiveness test (see Responsiveness Testing below). Sedation represented the last sedated, but awake state. Both drugs were administered using target-controlled infusions, aiming at step-wise escalating pseudo steady-state plasma concentrations at 7-min intervals until loss of responsiveness was achieved. A Harvard 22 syringe pump (Harvard Apparatus, USA) and a portable computer running Stanpump software (by Steven L. Schafer, M.D., http://www.opentci.org/code/stanpump), was used for drug administration. Once loss of responsiveness was achieved, the pseudo steady-state target-controlled infusion was continued for approximately 25 min, allowing us to run an event-related potential paradigm during unresponsiveness. These results will be reported separately. After the stable 25-min period, an attempt was made to arouse the subject with verbal or mild physical stimulation without terminating or changing the drug infusion. First, the subject was addressed by name twice, with increasing volume. If the subject was not aroused, mild shoulder shaking was applied. These arousing stimuli were applied in an identical manner for all subjects. If no awakening was accomplished, the subject was considered nonarousable. If this awakening procedure was successful (return of responsiveness), the subjects were allowed to return to unresponsiveness (loss of responsiveness 2) for another 25-min period, and then again awakened (return of responsiveness 2) in order to achieve two cycles of two different states of consciousness during the constant infusion: loss of responsiveness, return of responsiveness, loss of responsiveness 2, and return of responsiveness 2. After return of responsiveness/return of responsiveness 2, or unsuccessful awakening, the drug concentration was increased by 50% to achieve what was presumed to be unconsciousness (loss of consciousness). The design of the study is illustrated in figure 1. Awake baseline, sedation, loss of responsiveness, return of responsiveness, and loss of consciousness refer to different states of consciousness, which were compared as outlined in the Statistical Analyses.

Dexmedetomidine (Dexdor 100 μg/ml, Orion Pharma, Finland) was administered using the pharmacokinetic parameters by Talke *et al.*[20] The infusion was started at a target plasma concentration of 1.0 ng/ml, followed first by a 0.5 ng/ml target concentration increase and 0.25 ng/ml increases thereafter (*i.e.*, 1.0–1.5–1.75–2.0–2.25–etc. ng/ml) until loss of responsiveness was achieved. Propofol (Propofol Lipuro 10 mg/ml, B. Braun, Germany) was administered with the same infusion system and scheme as dexmedetomidine, using the pharmacokinetic parameters by Marsh *et al.*[21] The infusion was started at a plasma target concentration of 1.0 μg/ml, followed first by a 0.5 μg/ml target concentration increase and 0.25 μg/ml increases thereafter (*i.e.*, 1.0–1.5–1.75–2.0–2.25–etc. μg/ml) until loss of responsiveness was achieved.

Subjects' pulse oximetry plethysmograms and electrocardiograms were monitored throughout the study. Noninvasive blood pressure was measured only in the beginning and at the end of the session to avoid possible cuff pain and ensuing arousal. End-tidal carbon dioxide was measured with a dual-operating nasal-cannula used also for oxygenation. A Datex-Ohmeda S/5 anesthesia monitor (Datex-Ohmeda Division, Instrumentarium Corp., General Electric Co., Helsinki, Finland) and a portable computer running the S5 Collect software (Collect version 4.0, GE Healthcare, Finland) were used to record and restore all vital parameters.

Responsiveness Testing

To test subjects' responsiveness, a standard responsiveness test (a prerecorded set of 10 sentences with a semantically congruent [n = 5] or incongruent [n = 5] last word) was presented through headphones at every drug concentration and whenever the state of consciousness was thought to have changed. The subjects were instructed to respond by left or right handle press according to the congruency of the sentence, and the hand corresponding congruous sentences (left or right) was balanced in both groups. Loss of responsiveness was defined as zero out of ten handle presses. The responsiveness test was considered superior to a simple request to press handles, as the ability to correctly respond to meaningful sentences reflects complex cognitive processing such as language comprehension and decision-making. This assured that the sedative concentrations still represented wakefulness with intact perception, preserved ability for semantic processing, and ability to respond. The responsiveness test was presented with Presentation 17.0 stimulus delivery and experimental control software system (Neurobehavioral Systems Inc, USA), and all the instructions and stimuli were delivered *via* headphones.

Electroencephalogram Data Acquisition

Electroencephalogram data were collected with NeurOne 1.3.1.26 software and Tesla no. MRI 2013011 and no. MRI 2013012 amplifiers (Mega Electronics Ltd, Finland). The electroencephalogram tracing was recorded using 64-channel EasyCap Active electrode cap (EasyCap GmbH, Germany) that had sintered silver/silver chloride active electrodes placed according to international 10-10 electrode placement system. Four additional electrodes were used to record horizontal and vertical eye movements and two for electrocardiogram recording. Electroencephalogram data were collected with a sampling rate of 1,000 Hz with amplifier low-pass filter having half-amplitude threshold of 360 Hz (transition band, 250 to 498 Hz) and high-pass filter of 0.16 Hz (6 dB/octave). Data were referenced to the fronto-central site,

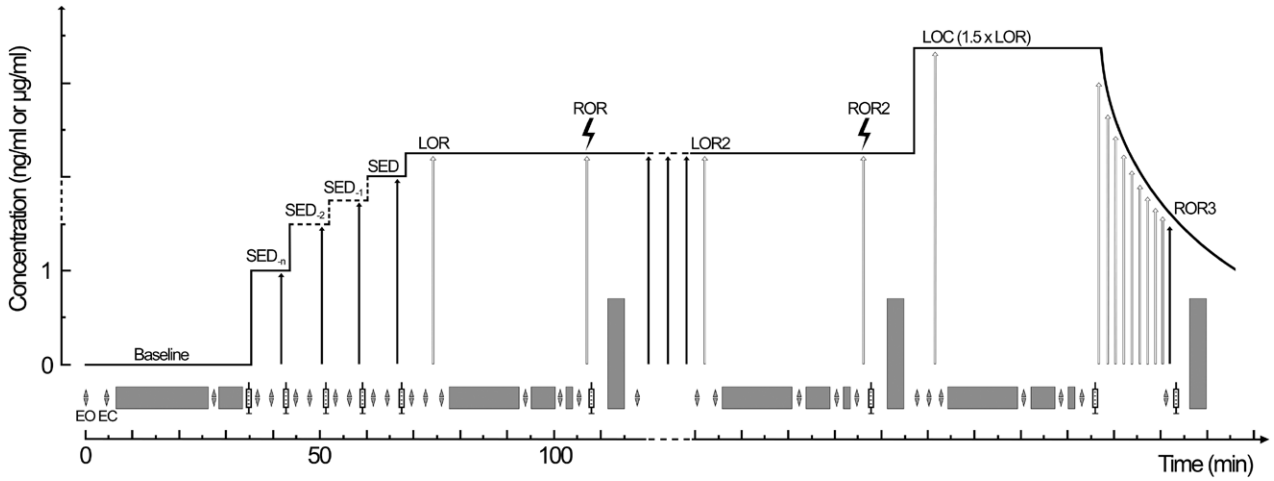

Fig. 1. Schematic presentation of the study design. The drug infusion was started at concentration of 1.0 ng/ml for dexmedetomidine or 1.0 µg/ml for propofol, followed first by a 0.5 concentration increase and 0.25 increases thereafter until loss of responses to auditory stimuli (responsiveness test), defined as loss of responsiveness (LOR). Responsiveness tests are indicated by *solid black* (signifying responsiveness) or *gray arrows* (signifying unresponsiveness). Sedative but responsive levels (SED-n-SED) are indicated in reverse numerical order, SED representing the last responsive state before LOR. After achieving LOR, auditory stimuli were presented (to study event related potentials), accounting for the relatively long LOR period(s). At the end of the stabile period, an attempt was made to arouse the subjects during the constant drug infusion to achieve return of responsiveness (ROR). After ROR, the subject was left unstimulated, to regain the unresponsive state (LOR2). The second cycle was conducted in an identical manner, with a second awakening at the end (ROR2). After ROR2 (or an unsuccessful awakening), the target concentration was increased to 1.5 × LOR concentration to reach presumable loss of consciousness (LOC). Again, auditory stimuli were presented. Finally, the drug infusion was terminated and a continuous responsiveness test was presented until a spontaneous response was detected (third return of responsiveness, ROR3). A continuous electroencephalogram recording was performed throughout the study session and the segments selected for spectral analyses have been visualized with *diamonds*. *Syringe symbols* indicate venous blood samples drawn for drug concentration analysis. *Horizontal gray bars* indicate auditory stimuli (event related potentials; to be reported separately) and *vertical bars* interviews of subjective experiences (to be reported separately). EC = eyes closed; EO = eyes open.

and the ground electrode was placed at the medial prefrontal site. The electroencephalogram signal was monitored online by a technician who specialized in clinical neurophysiology.

Electroencephalographic Analysis

Continuous electroencephalogram from stimulus- and response-free 2-min periods of the experiment was segmented from raw electroencephalogram (the timing of each segment is shown in figure 1) using EEGLAB toolbox for MATLAB (version 2015a; MathWorks, Inc., USA).[22] The segments were visually inspected, noisy channels were interpolated, and at most 10 s of electroencephalogram with artifacts (caused by, *e.g.*, head or eye movements) were removed. Each segment was shortened to 110 s, and the sampling frequency was reduced to 250 Hz. Fifty-nine channels on the scalp (fig. 2) were processed using custom-written functions in MATLAB.

Electroencephalogram signals were remontaged to Laplacian reference to mitigate the effect of volume conduction and improve spatial localization.[23,24] Spectrograms were computed using the multitaper method implemented in Chronux analysis software (http://chronux.org),[25] with window length of 4 s at a 2-s overlap, time-bandwidth product = 2, number of tapers = 3, and spectral resolution = 1 Hz. For statistical comparisons, the mean spectral distribution was obtained by taking the average across all the windows at each of the studied segments, and the electroencephalogram powers were calculated for delta (1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 14 Hz), beta (14 to 25 Hz), and gamma (25 to 45 Hz). Electroencephalogram power for slow-delta was calculated in temporal domain by applying a bandpass filter (passband edges: 0.1 to 1 Hz; –6 dB cutoff frequencies at 0.05 and 1.05 Hz) to the electroencephalogram signals, using the eegfiltnew function in the EEGLAB toolbox. The topographic maps of group-level spectral power for each studied segment and frequency band were constructed using the topoplot function in the EEGLAB toolbox.[22]

The phase-amplitude coupling analysis was performed as described in recent literature.[15] Briefly, each 110-s electroencephalogram segment was bandpass-filtered and Hilbert-transformed to obtain the slow-delta (0.1 to 1 Hz, eegfiltnew parameters same as above) phase and alpha (passband edges 8 to 14 Hz, –6 dB cutoff frequencies at 7 and 15 Hz) power component, which was then divided into windows of 60 s, with an overlap of 55 s. For each window, the modulogram was constructed by assigning each sample of alpha power to one of the equally spaced slow-delta phase bins (N = 18 bins), then averaging the power values in each bin, and applying entropy index to quantify this distribution,[26] which was deemed significant if it exceeded 95% of the surrogate values generated by shuffling the power series.[27,28] The coupling

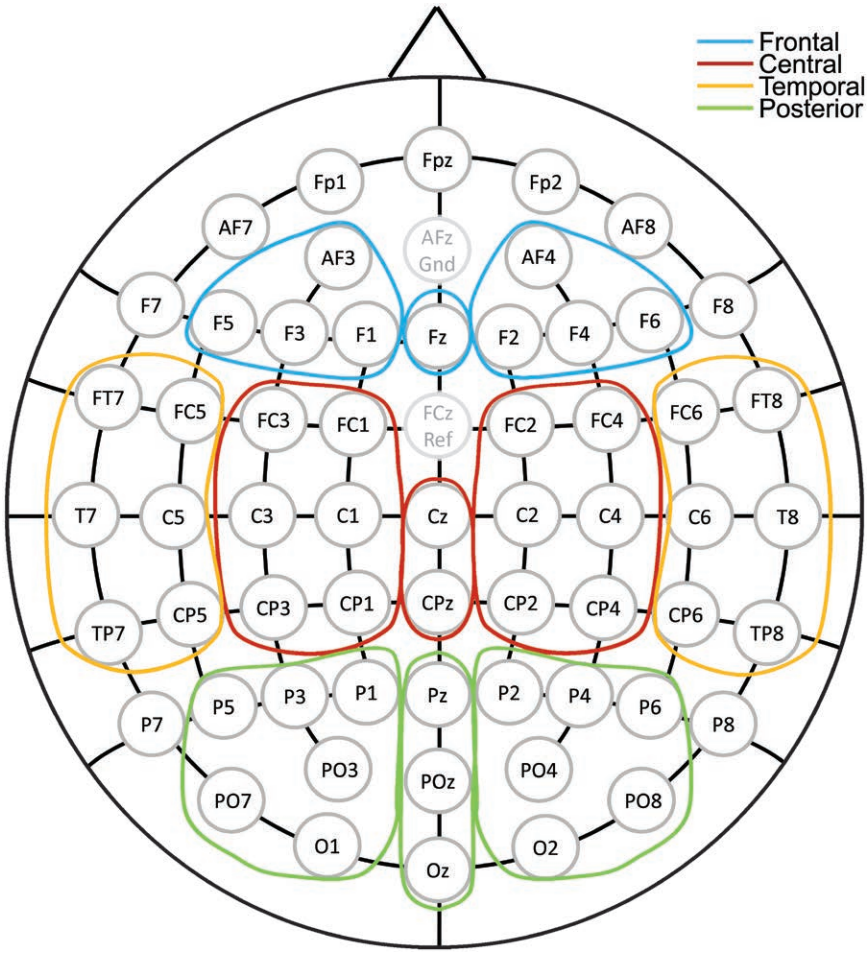

Fig. 2. Electrode positions and regions of interest that were used in the electroencephalogram collection and analyses.

type (trough-max or peak-max as defined by Mukamel *et al.*[15] and Purdon *et al.*[13]) was combined into the entropy index by assigning a negative or positive sign, respectively.[29] For statistical comparisons, the phase-amplitude coupling values across all windows were averaged and set to zero if insignificant (Bonferroni-corrected $P < 0.05$) at each of the studied segments. The topographic maps of group-level phase-amplitude coupling for each studied segment were constructed using the topoplot function in the EEGLAB toolbox.

Blood Samples and Drug Concentration Measurements

Both forearm veins were cannulated for drug administration and for blood sampling at baseline and at each drug target concentration. Ringer's acetate (B. Braun) was used to keep the intravenous lines open. Plasma concentrations of dexmedetomidine and propofol were determined using high-performance liquid chromatography with tandem mass spectrometry and fluorescence detection. The interassay coefficients of variation in the relevant concentration ranges were 1.2 to 2.9% and 0.7 to 2.3%, respectively.

Statistical Analyses

Because of the exploratory nature of the study, no predefined statistical plan was applied, and part of the groupings of the data was made *post hoc*. For the statistical comparison, mean spectral power values in four regions of interest were calculated (fig. 2). Only selected segments representing the states of interest were chosen for statistical analyses (fig. 3). Electroencephalogram power values at each frequency band were first analyzed using three-way repeated-measures ANOVA with two within-factors (state and region) and one between-factor (treatment; SAS/STAT, PROC MIXED; SAS Institute Inc., USA). Because not all subjects were arousable during the constant infusion, two separate overall analyses were performed. In the first analysis, the following states of consciousness were included: baseline (eyes closed), sedation, loss of responsiveness, and loss of consciousness; and in the second analysis, loss of responsiveness, loss of responsiveness immediately before awakening, and return of responsiveness (fig. 3). We hypothesized that when subjects were awakened during the constant anesthetic infusion, the spectral features would revert toward baseline values. Two loss of responsiveness segments were included because the loss of responsiveness state was relatively long (approximately 25 min), during which the features were found to be somewhat unstable. If significant region, state-by-region, and/or treatment-by-region interactions were found, the analyses were continued for each

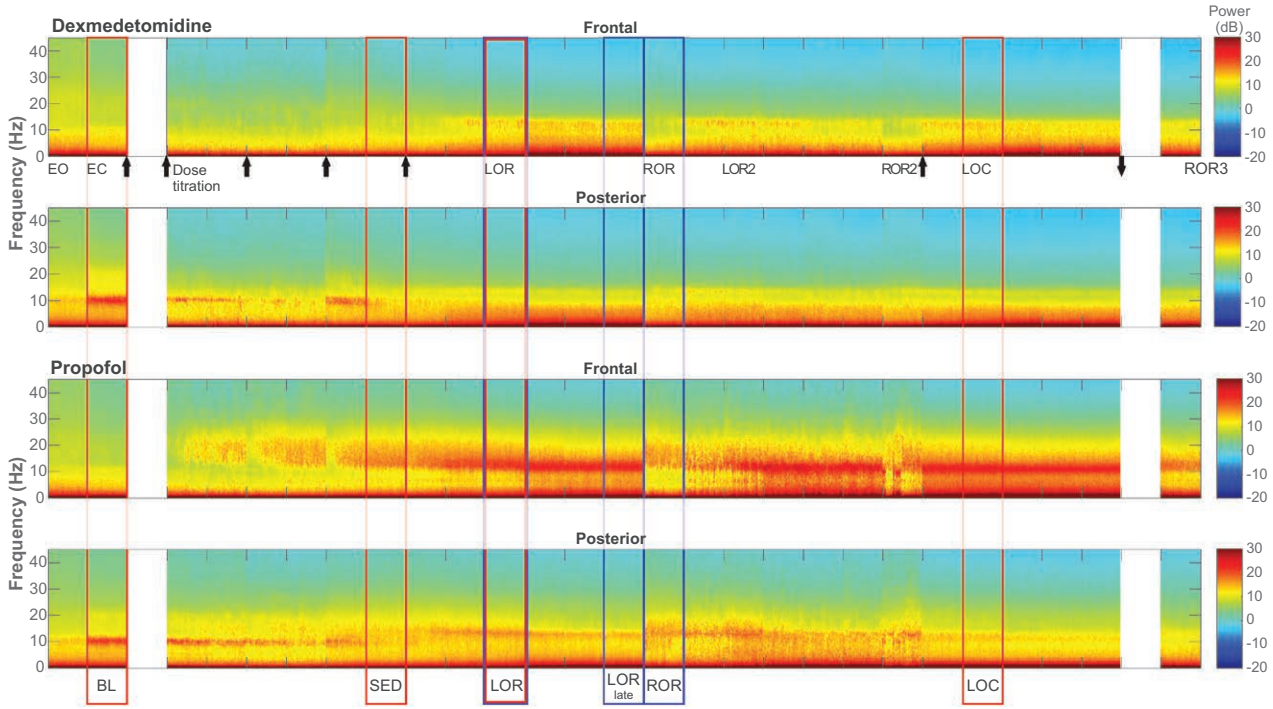

Fig. 3. Spectrograms of frontal and posterior regions (see fig. 2) throughout the session in the dexmedetomidine (*upper*) and propofol (*lower*) groups. Because not all subjects were arousable during the constant infusion, two separate overall statistical analyses were performed. Specific time points selected for these analyses are indicated by *colored frames*, *red* indicating the first and *blue* the second analysis (see text for details). BL = baseline; EC = eyes closed; EO = eyes open; LOC = loss of consciousness; LOR = loss of responsiveness; LOR2 = second loss of responsiveness; LOR_{late}= last loss of responsiveness segment immediately before awakening; ROR = return of responsiveness; ROR2 = second return of responsiveness; ROR3 = third return of responsiveness; SED = last responsive state before loss of responsiveness.

region separately using two-way repeated-measures ANOVAs with one within-factor (state) and one between-factor (treatment) followed by paired comparisons of different states and drugs using Bonferroni correction for multiple comparison. Unstructured covariance structure was used in the analyses. Data from the second cycle of different states (*i.e.*, loss of responsiveness 2 and return of responsiveness 2) were also not included in the statistical analyses because most of the arousable propofol subjects did not achieve loss of responsiveness 2. The alpha band power at sedation, loss of responsiveness, and loss of responsiveness immediately before awakening was compared between arousable and nonarousable subjects using two-way ANOVA. Because of positively skewed distributions, decadic (common) logarithm values of the absolute spectral powers were used in statistical analyses. Frontal and posterior phase-amplitude coupling at baseline, sedation, loss of responsiveness, and loss of consciousness were analyzed similarly to spectral variables, followed by paired comparisons using Bonferroni correction. Chi-square was used to compare arousability between groups. A two-tailed probability level of 5% ($P < 0.05$) was considered statistically significant. Results are given as means (SD) or model-estimated marginal means (standard error) if not otherwise stated. Statistical analyses were performed with SAS System for Windows, version 9.4 (SAS Institute Inc.).

Results

Behavioral Effects and Adverse Events

All 47 subjects reached loss of responsiveness and 45 reached loss of consciousness as defined in the study protocol. The target concentration for loss of responsiveness varied individually between 1.0 and 3.25 ng/ml for dexmedetomidine and 1.0 and 2.75 μg/ml for propofol. The mean (SD) measured concentration for loss of responsiveness was 2.06 (0.66) ng/ml for dexmedetomidine and 1.67 (0.62) μg/ml for propofol, and for loss of consciousness, 3.13 (0.94) ng/ml and 2.63 (0.79) μg/ml, respectively (table 1). The measured concentrations of dexmedetomidine at loss of responsiveness and loss of consciousness were somewhat higher than targeted.

At loss of responsiveness, 18 (78%) subjects in the dexmedetomidine group and 10 (42%) subjects in the propofol group were arousable (*i.e.*, return of responsiveness was achieved) during the constant drug infusion ($P = 0.011$ between the drugs). After awakening, propofol subjects tended to become restless and only four subjects reached loss of responsiveness 2 after arousal, despite continuing the drug infusion for all subjects. In contrast, all 18 arousable subjects in the dexmedetomidine group reached loss of responsiveness 2 after up to four 5-minute stabilization periods.

With two subjects in the propofol group, the drug infusion had to be terminated prematurely due to snoring and mild

Table 1. Drug Concentrations in Plasma during the Experiment

	SED		LOR		LOC		ROR3	
	Targeted	Measured	Targeted	Measured	Targeted	Measured	Estimated	Measured
Dexmedetomidine (ng/ml)	1.43 (0.58)	1.36 (0.86)	1.67 (0.54)	2.06 (0.66)	2.53 (0.82)	3.13 (0.94)	1.92 (0.85)	2.16 (0.91)
Propofol (μg/ml)	1.46 (0.44)	1.14 (0.53)	1.71 (0.41)	1.67 (0.62)	2.58 (0.63)	2.63 (0.79)	0.95 (0.23)	1.31 (0.51)

Mean (SD) targeted or estimated (with Stanpump software) and measured drug concentrations in plasma at the highest sedative concentration (SED), loss of responsiveness (LOR), loss of consciousness (LOC), and return of responsiveness after terminating the infusion (ROR3; see fig. 1 for details) in the dexmedetomidine (n = 23) and propofol (n = 24) groups. There were seven missing samples in the dexmedetomidine and six in the propofol group. The mean (SD) concentrations at second loss of responsiveness (see fig. 1 for details) were 1.95 (0.68) for dexmedetomidine (n = 16, 2 missing samples) and 1.54 (0.68) for propofol (n = 4).

apnea. Both subjects reached loss of responsiveness, but dose increase to achieve presumed loss of consciousness was not attempted because apnea worsened as the infusion continued. Two subjects in both groups required an additional increment to reach loss of consciousness. Otherwise the study was completed as planned and no clinically significant changes were observed in the vital parameters (data not shown).

Electroencephalogram Results

Spectra. There were statistically significant region, state-by-region, and/or treatment-by-region interactions in all spectral bands in both overall analyses ($P < 0.05$ for all). The analyses were therefore continued for each region separately. Spectral changes were strongly state- and drug-dependent, as revealed by significant differences between the states in all and between the treatments in many bands and cortical regions, and significant interactions between state and treatment (tables 2 and 3). These statistical analyses were then finalized by calculating paired comparisons of different states for both drugs separately (within-drug analyses) and between the drugs (between-drug analyses) using contrasts in two-way repeated-measures ANOVA models. In general, the interindividual variability of spectral powers at baseline and during the drug infusions was large (see Supplemental Digital Content, http://links.lww.com/ALN/B685). Figure 3 displays average spectrograms in the frontal and posterior regions during the whole session, and figure 4 shows average topographic scalp images for each band and the selected state. Spectral powers at baseline did not show any relation to target concentration needed for loss of responsiveness.

Comparison of Baseline and the Sedation, Loss of Responsiveness, and Loss of Consciousness States. Both drugs induced profound changes of the spectral powers in all regions and all frequency bands (state effect $P < 0.01$ for all, table 2, figs. 3 and 4). The drugs affected the band powers differently in all areas except the central, temporal, and posterior delta power and the temporal and posterior theta power (state-by-treatment interaction $P > 0.05$, table 2). In summary, propofol caused an increase in slow-delta, delta, and alpha power, particularly in the frontal regions, and an initial increase and then decrease in beta power. Dexmedetomidine caused a similar increase in slow-delta and delta power (maximal slow-wave activity already at loss of responsiveness immediately before awakening), and a lesser increase in frontal alpha power. Still, a clear alpha-anteriorization (shifting of alpha dominance from posterior to frontal regions) was observed also with dexmedetomidine. The increase, however, plateaued already at loss of responsiveness as opposed to propofol, which caused frontal alpha power to increase along escalating drug concentration. Dexmedetomidine induced a consistent decrease in beta power in all regions along deepening levels of anesthesia. Statistically significant decreases in the gamma band were observed across the entire scalp in both groups (dexmedetomidine greater than propofol, fig. 4, table 2). For detailed results, see table 2 and figures 3 and 4.

Comparison of Loss of Responsiveness, Loss of Responsiveness Immediately before Awakening, and Return of Responsiveness States. The spectral power changes tended to increase from loss of responsiveness to loss of responsiveness immediately before awakening in both groups. This was evident especially in the dexmedetomidine group, except for the alpha band, which plateaued at loss of responsiveness (figs. 3–5, table 3). At return of responsiveness, drug-induced spectral changes reverted toward awake baseline or sedation in most regions and bandwidths. Especially the global increases of slow-delta and delta bands and the frontal increase of alpha band powerfully reverted when subjects were awakened during the constant drug infusion (table 3). In contrast, the drug-induced changes of beta did not revert at return of responsiveness in either group. For detailed results, see table 3 and figures 3 and 4.

Prediction of Arousability. At baseline, sedation, and loss of responsiveness immediately before awakening, there were no statistically significant differences between arousable and nonarousable subjects, but at loss of responsiveness, frontal alpha power was greater in subjects who could not be awakened during the constant infusion ($P = 0.016$, two-way ANOVA, fig. 5). The arousability by treatment interaction was not significant, and the differences did not reach statistical significance for either drug in *post hoc* comparisons. There were no differences in the targeted concentrations between

Table 2. Spectral Powers at Baseline, Highest Sedative Concentration, Loss of Responsiveness, and Loss of Consciousness

	Baseline						SED						LOR						LOC						Two-way RM ANOVA (*P* Value)		
	Dexmedetomidine			Propofol			Dexmedetomidine			Propofol			Dexmedetomidine			Propofol			Dexmedetomidine			Propofol					
	Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE		State	Treatment	State × Treatment
Frontal																											
Slow delta	3.234	0.058		3.250	0.056		3.058	0.063		3.112	0.060		3.108	0.058	‖	3.159	0.056	|||||	3.321	0.059	§§,***	3.699	0.059	§§§	< 0.001	0.026	0.001
Delta	2.852	0.066		2.823	0.064		2.704	0.071	††	2.748	0.068	†	3.015	0.066		2.984	0.064	|||||	3.179	0.067	§§§,*	3.460	0.067	§§§	< 0.001	0.321	0.013
Theta	2.456	0.060		2.434	0.058		2.388	0.063	†	2.378	0.061	†	2.584	0.060		2.544	0.058	|||||	2.631	0.060	§§,**	2.942	0.060	§§§	< 0.001	0.373	< 0.001
Alpha	2.415	0.071		2.377	0.069	‡‡‡	2.321	0.076	††,***	2.726	0.073	†††	2.639	0.071	***	3.202	0.069	||||	2.642	0.072	§§,***	3.494	0.072	§§§	< 0.001	< 0.001	< 0.001
Beta	2.393	0.052		2.346	0.051	‡‡‡	2.236	0.057	***	2.946	0.054		2.178	0.052	||||,***	3.018	0.051		1.975	0.053	§§,***	2.916	0.053		< 0.001	< 0.001	< 0.001
Gamma	2.341	0.045	‡‡‡	2.332	0.044		1.977	0.049	***	2.389	0.047		1.836	0.045	‖,***	2.276	0.044		1.679	0.046	§§§,***	2.157	0.046	§§§	< 0.001	< 0.001	< 0.001
Central																											
Slow delta	3.086	0.066		2.992	0.065		2.982	0.072		2.825	0.068		3.098	0.066	‖	2.928	0.065	|||||	3.356	0.067	§§§	3.545	0.067	§§§	< 0.001	0.359	0.007
Delta	2.796	0.061		2.672	0.060		2.658	0.066	†††	2.581	0.063	†††	2.898	0.061	|||||	2.763	0.060	|||||	3.050	0.062	§§§	3.076	0.062	§§§	< 0.001	0.193	0.406
Theta	2.516	0.053		2.400	0.052	‡‡	2.410	0.057		2.214	0.055		2.526	0.053		2.359	0.052	||||	2.529	0.054		2.552	0.054	§§§	< 0.001	0.051	0.040
Alpha	2.677	0.061	‡‡	2.536	0.060		2.429	0.066		2.533	0.063	†††	2.516	0.061	***	2.854	0.060		2.428	0.062	***	2.989	0.062	§§§	< 0.001	< 0.001	< 0.001
Beta	2.441	0.053	‡	2.317	0.052	‡‡‡	2.269	0.057	***	2.685	0.054		2.169	0.053	|||||,***	2.719	0.052		1.939	0.054	§§§,***	2.583	0.053		< 0.001	< 0.001	< 0.001
Gamma	2.299	0.052	‡‡‡	2.196	0.051		2.006	0.054	†,*	2.214	0.052		1.850	0.052	|||||,***	2.136	0.051	‖	1.665	0.052	§§§,***	2.002	0.052	§§§	< 0.001	0.004	< 0.001
Temporal																											
Slow delta	3.354	0.058	‡‡	3.323	0.057	‡‡	3.104	0.063		3.054	0.060		3.152	0.058		3.036	0.057	|||||	3.348	0.059	§,***	3.722	0.059	§§§	< 0.001	0.402	< 0.001
Delta	2.963	0.056	‡‡‡	2.922	0.055	‡‡‡	2.683	0.060	††	2.699	0.058	††	2.868	0.056	|||||	2.817	0.055	|||||	2.957	0.057	§§§	3.115	0.057	§§§	< 0.001	0.723	0.078
Theta	2.502	0.049	‡‡‡	2.468	0.048	‡‡‡	2.354	0.051		2.286	0.049		2.423	0.049		2.362	0.048		2.399	0.049	§§	2.492	0.049	§§	< 0.001	0.757	0.062
Alpha	2.651	0.055	‡‡‡	2.574	0.054		2.349	0.059	*	2.584	0.057	††	2.362	0.055	***	2.801	0.054		2.243	0.056	***	2.843	0.056	§§§	0.010	< 0.001	< 0.001
Beta	2.498	0.047	‡‡‡	2.442	0.046	‡‡‡	2.195	0.050	†,***	2.668	0.048		2.040	0.047	|||||,***	2.689	0.046	|||||	1.833	0.048	§§§,***	2.485	0.047	§§	< 0.001	< 0.001	< 0.001
Gamma	2.502	0.048	‡‡‡	2.439	0.047	‡‡‡	2.079	0.051	†††	2.218	0.049	†	1.854	0.048	||||,**	2.067	0.047	‖	1.673	0.049	§§§,**	1.912	0.049	§§§	< 0.001	0.012	< 0.001
Posterior																											
Slow delta	3.055	0.062		3.060	0.060		3.014	0.067	††	2.916	0.064		3.289	0.062	*	3.070	0.060	|||||	3.487	0.063	§§§	3.700	0.063	§§§	< 0.001	0.679	0.001
Delta	2.852	0.055		2.832	0.054		2.745	0.059	†††	2.724	0.056	†††	3.107	0.055	||||	2.915	0.054	||||	3.189	0.056	§§§	3.119	0.055	§§§	< 0.001	0.189	0.148
Theta	2.680	0.058	‡‡	2.633	0.057	‡‡	2.600	0.061	†	2.436	0.059	†	2.736	0.058		2.524	0.057		2.696	0.059		2.470	0.058		0.007	0.014	0.106
Alpha	3.282	0.073	‡‡‡	3.189	0.072	‡‡‡	2.648	0.080		2.724	0.076		2.530	0.073	*	2.796	0.072		2.426	0.075		2.633	0.074		< 0.001	0.114	0.021
Beta	2.631	0.057	‡‡‡	2.577	0.056		2.239	0.060	***	2.634	0.058		2.104	0.057	‖,***	2.630	0.056	|||||	1.929	0.058	§§§,***	2.381	0.057	§§§	< 0.001	< 0.001	< 0.001
Gamma	2.320	0.049	‡‡‡	2.298	0.048	‡	1.994	0.051	††,*	2.179	0.049		1.863	0.049	|||||,**	2.111	0.048	|||||	1.699	0.049	§§§,**	1.925	0.049	§§§	< 0.001	0.010	<0.001

Estimated means and standard errors (SE) of absolute (10log) spectral powers of slow delta (0.1–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–14 Hz), beta (14–25 Hz), and gamma (25–45 Hz) bands in four cortical areas (see fig. 2) at baseline, highest sedative concentration (SED), loss of responsiveness (LOR), and loss of consciousness (LOC) during dexmedetomidine (n = 23) and propofol (n = 24) infusions. In the two-way repeated measures (RM) ANOVA analyses (three columns to the right), a significant state effect indicates differences between the states, a significant treatment effect indicates an overall difference in the level of spectral powers between the drugs, and a significant state by treatment interaction indicates that the drug effects are different. Paired Bonferroni-corrected *P*-values for within-group *post hoc* comparisons of the different states (†SED *vs*. LOR, ‡baseline *vs*. SED, §SED *vs*. LOC, and ‖LOR *vs*. LOC; baseline *vs*. LOR and baseline *vs*. LOC contrasts not shown for clarity) and between-group comparisons at baseline, and the SED, LOR, and LOC states (*dexmedetomidine *vs*. propofol). If the state-by-treatment interaction was not significant, treatment-adjusted *post hoc* comparisons of the different states are given. Within-group comparisons indicate dependency on state of consciousness and/or drug concentration and between-group comparisons differences between the drugs. The number of symbols refers to level of significance (*e.g.*, $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$ between the drugs). At baseline, there were no significant differences between the drugs in any of the spectral powers.

arousable and nonarousable subjects for either drug, but the mean (SD) measured concentration of propofol was significantly higher ($P = 0.036$) in nonarousable subjects, *i.e.*, 1.93 (0.50) μg/ml *versus* 1.36 (0.68) μg/ml.

Phase-amplitude Coupling. In the overall analyses, there were significant differences both in the frontal (state $P < 0.001$, treatment $P = 0.102$, state-by-treatment interaction $P < 0.001$) and posterior (state $P < 0.001$, treatment $P = 0.018$, state-by-treatment interaction $P = 0.013$) regions. In the *post hoc* comparisons, there were no differences between the states in the dexmedetomidine group, but two distinct phase-amplitude coupling patterns were seen in the propofol group (fig. 6). Group-level spatial distribution of propofol participants showed trough-max coupling (*i.e.*, alpha power was largest at the pi phase of the slow-delta activity) concentrated in the frontal area before and during loss of responsiveness (*blue* in fig. 6B), while peak-max coupling (*i.e.*, maximum alpha power at 0 phase) occurred in posterior and other regions at loss of consciousness (*red* in fig. 6B). At sedation and especially loss of responsiveness, trough-max coupling was detected over frontal channels, while peak-max coupling was present over the posterior region during loss of consciousness (fig. 6, E and F). The interindividual variability in the posterior region at loss of consciousness was large in the propofol group but differed significantly from all other states and from the dexmedetomidine group.

Discussion

We found the spectral effects of dexmedetomidine and propofol to be clearly drug- and state-dependent, but perhaps more importantly, the changes induced by the two drugs clearly reverted when the subjects were awakened during the constant pseudo steady-state drug infusion. There may be drug-specific patterns and even fingerprints in the electroencephalogram, but our study clearly demonstrates the fundamental importance of the interaction between the drug and the state of consciousness *per se* on the calculated spectral measures of electroencephalogram. Otherwise, our results largely corroborate the findings of previous studies,[13,15,16,18,19] most of which have, however, been noncomparative single-drug experiments. We increased the concentrations of the two drugs with distinct mechanisms of action carefully to similar behavioral endpoints, used random allocation of the treatments, and analyzed drug effects and differences at predefined states of consciousness with rigorous statistical methods.

Dexmedetomidine and propofol differ in their mechanisms of action, as they target distinct molecular sites. Propofol enhances the γ-aminobutyric acid–mediated synaptic currents through γ-aminobutyric acid receptor type A, whereas dexmedetomidine is an α_2-receptor agonist, and induces hyperpolarization of *locus coeruleus* neurons, reduction in the release of norepinephrine, and ultimately an increase in the inhibitory outputs in major arousal centers.[17,30] Dexmedetomidine induces a sedative response that superficially exhibits properties similar to natural sleep,[17] from which a person can be aroused with external stimuli without changes in drug dosing. Traditionally, propofol-induced unresponsiveness has not been considered similarly reversible, but we discovered that with careful dose titration to achieve loss of responsiveness, approximately half of the propofol subjects could be aroused despite continuous drug infusion. This finding may have implications for consciousness research as it enables the separation of direct, and probably concentration-dependent, drug effects on the brain from those on consciousness itself. Another experimental possibility for not changing the concentration of the anesthetic is to antagonize its effects with another pharmacologic agent. For example, physostigmine[31] has been shown to activate emergence from propofol anesthesia in human subjects. Possible direct or indirect effects of the other intervention cannot, however, be excluded with this approach.

At deeper anesthetic levels, increases in slow-wave activity and frontal alpha activity were observed with both treatments, although the magnitude and regional distribution of effects differed between the drugs. These features reverted toward baseline values at return of responsiveness, indicating association with the behavioral state, rather than plasma or effect site drug concentration *per se*. However, despite a consistent slow-wave activity increase toward deepening anesthetic levels, at low sedative levels, slow-delta and delta activity tended to decrease. A previous study has suggested that after losing behavioral responsiveness, slow-wave activity increases and finally saturates despite increasing drug concentrations.[14] We observed that slow-wave activity increased from loss of responsiveness to loss of responsiveness immediately before awakening in both treatment groups and from loss of responsiveness immediately before awakening to loss of consciousness in the propofol group. Our study design did not allow us to study this phenomenon further.

Interindividual variation of the alpha band power was large, but it differentiated loss of responsiveness from sedation and return of responsiveness with both treatments. Also, low alpha power at loss of responsiveness was associated with arousability during the infusions. The impact of this finding is not clear, but perhaps strengthens the view on individual susceptibility for general anesthetics. The targeted plasma concentrations did not differ between the arousable and nonarousable subjects, but significantly higher concentrations were found in the measured values for nonarousable subjects in the propofol group. The alpha band power at baseline did not, however, predict the concentration needed for loss of responsiveness. Interestingly, strong susceptibility for propofol has been found to associate with weak alpha band networks at awake baseline in a recent high-density electroencephalogram study in healthy subjects.[29] In contrast to past correlative studies of alpha anteriorization and delta power during general anesthesia, Gaskell *et al.*[32] identified volitional response to auditory command despite the presence of a strong frontal alpha-delta pattern in the electroencephalogram.

Table 3. Spectral Powers at Loss and Return of Responsiveness in Arousable Subjects

	LOR						LOR_{late}						ROR						Two-way RM ANOVA (*P* Value)		
	Dexmedetomidine			Propofol			Dexmedetomidine			Propofol			Dexmedetomidine			Propofol					
	Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE		Mean	SE		State	Treatment	State × Treatment
Frontal																					
Slow delta	3.090	0.066	†††	3.133	0.088	†††	3.357	0.066	‡‡‡	3.262	0.088	‡‡‡	3.004	0.066		3.116	0.088		< 0.001	0.830	0.133
Delta	2.953	0.075	†††	2.910	0.100	†††	3.230	0.075	‡‡‡	3.105	0.100	‡‡‡	2.745	0.075	§§	2.725	0.100	§§	< 0.001	0.565	0.595
Theta	2.550	0.081	††	2.441	0.109	††	2.659	0.081	‡‡‡	2.601	0.109	‡‡‡	2.357	0.081	§§§	2.340	0.109	§§§	< 0.001	0.639	0.436
Alpha	2.579	0.087		3.007	0.116		2.611	0.087	‡‡‡	3.205	0.116	‡‡‡	2.272	0.087	§§§	2.738	0.116	§§§	< 0.001	< 0.001	0.337
Beta	2.193	0.057	†††,***	2.855	0.076		2.041	0.057	***	2.750	0.076	‡‡‡	2.121	0.057	***	2.962	0.076		< 0.001	< 0.001	0.019
Gamma	1.856	0.044	†,***	2.254	0.059		1.754	0.044	***	2.150	0.059	‡‡‡	1.829	0.044	***	2.382	0.059		< 0.001	< 0.001	0.030
Central																					
Slow delta	3.078	0.069	†††	2.911	0.093		3.414	0.069	‡‡‡,*	3.120	0.093		2.931	0.069		2.912	0.093		< 0.001	0.108	0.045
Delta	2.831	0.068	†††	2.725	0.091	†††	3.138	0.068	‡‡‡	2.891	0.091	‡‡‡	2.618	0.068	§§	2.564	0.091	§§	< 0.001	0.176	0.132
Theta	2.510	0.067	†	2.304	0.090	†	2.564	0.067	‡‡‡	2.396	0.090	‡‡‡	2.321	0.067	§§§	2.215	0.090	§§§	< 0.001	0.145	0.186
Alpha	2.508	0.065		2.706	0.087		2.431	0.065	‡‡,**	2.834	0.087	‡‡‡	2.293	0.065	§§§,*	2.572	0.087		< 0.001	0.005	0.028
Beta	2.202	0.059	†††,***	2.610	0.079	††	2.027	0.059	‡,***	2.473	0.079	‡‡‡	2.106	0.059	§,***	2.706	0.079		< 0.001	< 0.001	0.001
Gamma	1.870	0.060	†††,*	2.131	0.081	††	1.768	0.060	*	2.020	0.081	‡‡‡	1.782	0.060	§§,***	2.171	0.081		< 0.001	0.003	0.003
Temporal																					
Slow delta	3.136	0.066	†††	3.016	0.088	†††	3.466	0.066	‡‡‡	3.276	0.088	‡‡‡	2.996	0.066		3.055	0.088		< 0.001	0.349	0.084
Delta	2.815	0.062	†††	2.799	0.083	†††	3.113	0.062	‡‡‡	2.979	0.083	‡‡‡	2.616	0.062	§§	2.682	0.083	§§	< 0.001	0.750	0.124
Theta	2.408	0.059	†	2.319	0.080	†	2.460	0.059	‡‡‡	2.419	0.080	‡‡‡	2.248	0.059	§§§	2.237	0.080	§§§	< 0.001	0.619	0.369
Alpha	2.353	0.060		2.716	0.080		2.261	0.060	‡	2.752	0.080	‡	2.193	0.060	§§	2.644	0.080	§§	0.002	< 0.001	0.135
Beta	2.069	0.050	†††,***	2.628	0.068	†††	1.927	0.050	‡,***	2.451	0.068	‡‡‡	2.024	0.050	***	2.781	0.068	§§	< 0.001	< 0.001	< 0.001
Gamma	1.878	0.053	†	2.119	0.071	†	1.785	0.053	‡‡‡	1.999	0.071	‡‡‡	1.904	0.053	§	2.290	0.071	§	<0.001	< 0.001	0.056
Posterior																					
Slow delta	3.258	0.066	†††	3.023	0.088	††	3.619	0.066	‡‡‡	3.362	0.088	‡‡	3.044	0.066	§	3.061	0.088		< 0.001	0.074	0.041
Delta	3.055	0.062	†††	2.912	0.083	†††	3.318	0.062	‡‡‡	3.101	0.083	‡‡‡	2.830	0.062	§§§	2.774	0.083	§§§	< 0.001	0.131	0.176
Theta	2.728	0.064		2.545	0.086		2.760	0.064	‡‡‡	2.588	0.086	‡‡‡	2.551	0.064	§§§	2.456	0.086	§§§	< 0.001	0.144	0.285
Alpha	2.551	0.062		2.785	0.083		2.426	0.062		2.732	0.083		2.464	0.062		2.794	0.083		0.181	0.002	0.576
Beta	2.143	0.056	†††,***	2.638	0.075	†††	1.983	0.056	‡‡,***	2.411	0.075	‡‡‡	2.099	0.056	***	2.737	0.075		< 0.001	< 0.001	0.005
Gamma	1.880	0.056	†	2.192	0.075	†	1.782	0.056	‡‡‡	2.058	0.075	‡‡‡	1.852	0.056	§	2.183	0.075	§	< 0.001	< 0.001	0.056

Estimated means and standard errors (SE) of absolute (10log) spectral powers of slow delta (0.1–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–14 Hz), beta (14–25 Hz), and gamma (25–45 Hz) bands in four cortical areas (see fig. 2) at loss (LOR) and return of responsiveness (ROR) during dexmedetomidine (n = 18) and propofol (n = 10) infusions in arousable subjects. LOR data were analyzed after reaching the state (LOR) and immediately before awakening the subject (LOR_{late}). In the two-way repeated-measures (RM) ANOVA analyses (three columns to the right), a significant state effect indicates differences between the states, a significant treatment effect indicates an overall difference in the level of spectral powers between the drugs, and a significant state-by-treatment interaction indicates that the drug effects are different. Paired Bonferroni-corrected *P*-values for within-group *post hoc* comparisons of the different states (†LOR *vs*. LOR_{late}, ‡LOR_{late} *vs*. ROR, and §LOR *vs*. ROR) and between-group comparisons at these states (*dexmedetomidine *vs*. propofol). If the state by treatment interaction was not significant, treatment-adjusted *post hoc* comparisons of the different states are given. Within-group comparisons indicate dependency on state of consciousness irrespective of drug concentration and between-group comparisons differences between the drugs. The number of symbols refers to level of significance (*e.g.*, *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ between the drugs). At baseline, there were no significant differences between the drugs in any of the spectral powers.

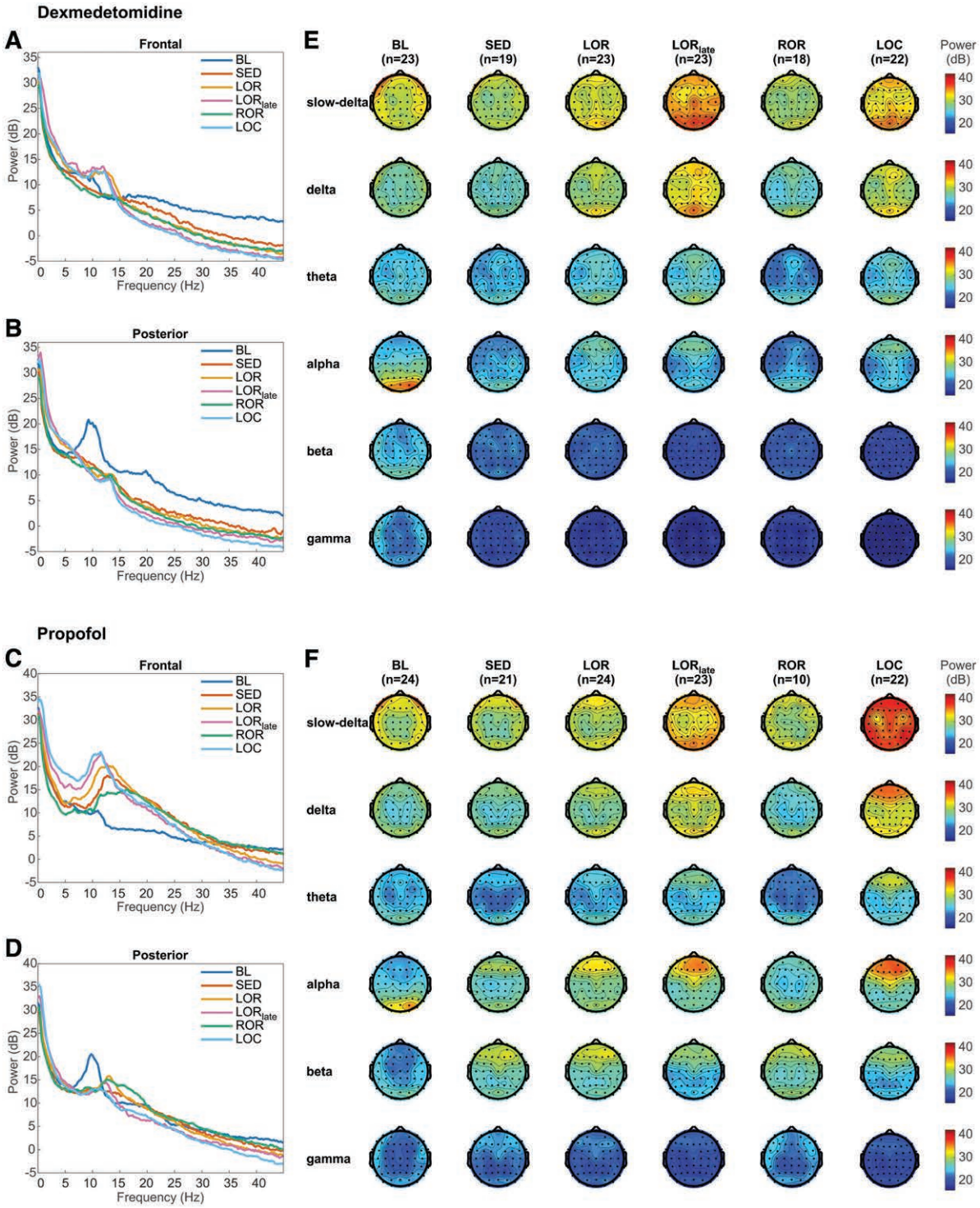

Fig. 4. (*A–D*) Group level power spectra in frontal and posterior regions at different behavioral endpoints with dexmedetomidine (*A and B*) and propofol (*C and D*). (*E and F*) Spatial distribution of average slow-delta (0.1–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–14 Hz), beta (14–25 Hz), and gamma (25–45 Hz) band powers at different behavioral endpoints during dexmedetomidine and propofol infusions. A clear alpha anteriorization was detected at loss of responsiveness (LOR) in both groups, despite greater absolute power values in the propofol group. With both treatments, the frontal alpha dominance separated last responsive state before LOR (SED) from LOR, and the pattern was disrupted momentarily when the subjects were awakened during the constant infusion (return of responsiveness [ROR]). An increase in slow-wave activity (slow-delta and delta) was observable in both groups with increasing concentrations. These features reverted upon ROR. A clear difference between the treatments was observed in the behavior of the beta bandwidth, as its power increased with propofol but decreased with dexmedetomidine toward a deepening anesthetic level. See text for more details. BL = baseline; LOC = loss of consciousness; LOR_{late}= last LOR segment immediately before awakening.

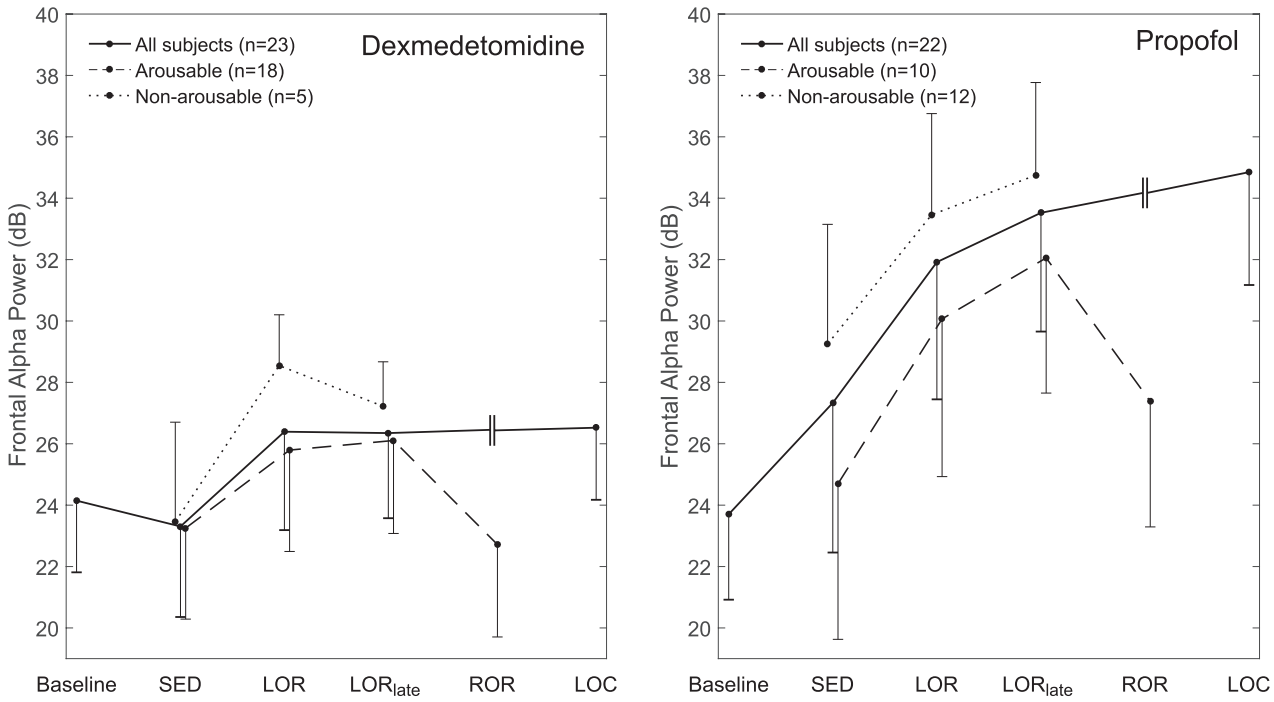

Fig. 5. Mean (SD) frontal alpha (8 to 14 Hz) power in all (*solid line*), arousable (*dashed line*), and nonarousable (*dotted line*) subjects at different behavioral endpoints in the dexmedetomidine (*left*) and propofol (*right*) groups. At loss of responsiveness (LOR), there was a statistically significant difference between arousable and nonarousable subjects in the overall analysis (P = 0.016), but the differences were not significant when the drugs were analyzed separately. LOC = loss of consciousness; LOR_{late} = last LOR segment immediately before awakening; ROR = return of responsiveness; SED = last responsive state before loss of responsiveness.

Throughout the study, a gross difference in the behavior of the beta band was detected between the groups. At sedative levels, propofol is known to elicit paradoxical excitation, encompassing an initial increase in beta power before decreasing in association with deepening sedative and ultimately anesthetic levels.[33] This is not detectable with dexmedetomidine, as beta power consistently decreases during continuous drug exposure.[19] Our results confirmed these findings during titration to loss of responsiveness, but at return of responsiveness, the magnitude and distribution of beta power remained identical to loss of responsiveness in both groups. Akeju *et al.*,[19] found increased beta oscillations at recovery from dexmedetomidine-induced unconsciousness. We suggest that this finding may not be a correlate for recovery of consciousness *per se*, but more likely a marker for dissipating drug effect after terminating the infusion. To summarize, beta oscillations seem to be poor indicators of loss or return of responsiveness or consciousness due to their diverse behavior after different anesthetic agents and equivocal patterns during recovery.

Phase-amplitude coupling between alpha and slow-delta bandwidths has been demonstrated for propofol with opposite patterns at light (trough-max) and profound (peak-max) anesthetic levels.[13,15] Despite lower propofol concentrations, these findings were corroborated in the current study. Dexmedetomidine has been shown not to induce phase-amplitude coupling in rat brain,[34] but no human studies have been reported to our knowledge. In our study, no consistent coupling phenomenon was evident with dexmedetomidine. This may be due to a smaller power increase of alpha oscillations in general and/or large interindividual variation of the spectral values. Ketamine[35] and sevoflurane[36] have also not revealed consistent cross-frequency coupling patterns in the frontal cortex; phase-amplitude coupling between alpha and slow oscillations therefore does not seem to be a drug-invariant indicator of anesthetic-induced unconsciousness.

This study has two major limitations. First, we observed that the loss of responsiveness state was not stable. To examine this issue, we compared two separate epochs of electroencephalogram from a period with a single plasma target concentration. We observed that over time—despite a theoretical constant plasma concentration—the anesthetic level deepened, indicated by an amplification of the spectral patterns related to drug administration and unresponsiveness. The pharmacokinetic model of dexmedetomidine[20] does not account for the decrease in cardiac output and ensuing hepatic blood flow with increasing doses,[37] which resulted in moderate overshooting of the targeted concentrations in the current study. This could, at least partly, explain the deepening anesthetic level with dexmedetomidine. With propofol, the average measured plasma concentrations were well in line with the targeted values, but a similar deepening of the electroencephalogram patterns was still observed. In future experimental studies, the duration of different conditions should be carefully considered

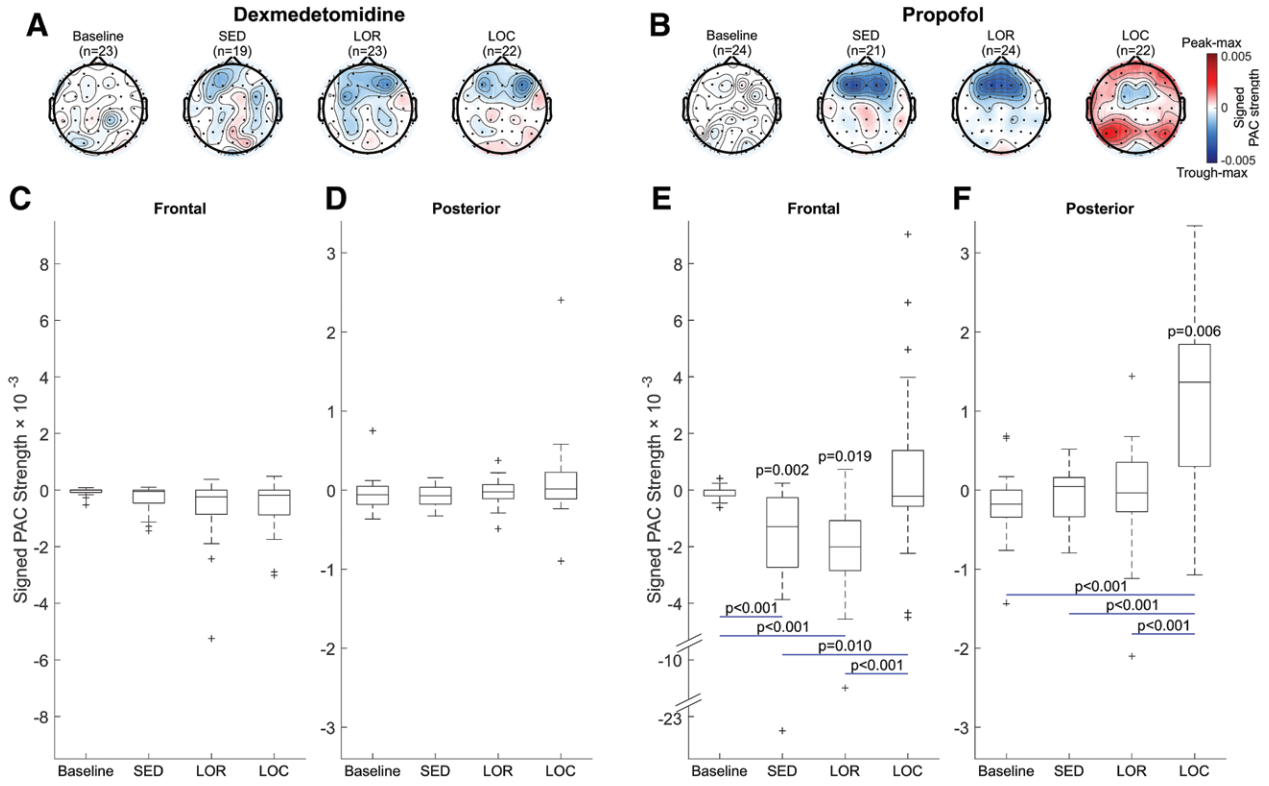

Fig. 6. (*A and B*) Spatial distribution of average phase amplitude coupling (PAC) strength at baseline, last responsive state before loss of responsiveness (SED), loss of responsiveness (LOR), and loss of consciousness (LOC) states in the dexmedetomidine and propofol groups. In the propofol group, trough-max (negative) coupling was seen in the frontal area at SED and LOR, and peak-max (positive) in the posterior and other regions at LOC. (*C–F*) *Box plots* of signed PAC strengths in the two groups. On each box, the *central mark* is the median, the *edges of the box* are the 25th and 75th percentiles, the *whiskers* extend to the most extreme values, and the outliers are plotted individually. During propofol exposure, there was trough-max coupling at SED and LOR, which reverted back to neutral at LOC in the frontal region (*C*), and peak-max coupling at LOC in the posterior region (*D*). *P*-values for statistically significant differences within the groups are given below the boxplots and between the groups above. No significant differences in the dexmedetomidine group (*E and F*).

and optimized to minimize changes due to nonstationarity of the behavioral states. In the current study, we applied relatively long pseudo–steady-state steps because of simultaneous collection of event related potential data (not yet reported).

Second, plasma drug concentration at loss of responsiveness may have, in some subjects, exceeded the minimum concentration needed for loss of responsiveness. Dose-response curves for anesthetic drugs are known to be extremely steep,[38] and supramaximal concentrations may have been administered in some of the cases despite rigorous dose-titration. This limitation can partially explain the observed association between frontal alpha power and arousability.

In conclusion, distinguishing direct drug effects from those on consciousness seems to be achievable, and the current study underscores the fundamental importance of their interaction. Electroencephalogram effects of dexmedetomidine and propofol were clearly different, but there were also common state-related patterns. Among different spectral estimates, changes in slow-wave and alpha, but not beta, activity seemed to best detect different states of consciousness, although the interindividual variability was large.

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Competing Interests

The authors declare no competing interests.

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From Benzene Rings to Political Ones: Metz and His Benzocaine, Anaesthesine

As a German-American born in New York, Herman August Metz (1867 to 1934) prospered as a manufacturer of pharmaceuticals and of dyestuffs. He produced a local anesthetic, benzocaine, the ethyl ester of para-aminobenzoic acid, which he trademarked as Anaesthesine (*left*). By embossing a benzene ring logo (*right*) on bottles of his numbing medicine, Metz hoped to frustrate competitors who might try to peddle a knock-off of his proprietary benzocaine. In the political ring, Metz frustrated Republicans by winning as a Democrat in the then largely Republican Tenth Congressional District of New York. As a Representative to the Sixty-third United States Congress (1913 to 1915), Metz favored neutrality toward Germany, a political position that fell out of favor with the start of World War I. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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