Propofol Anesthesia and Sleep: A High-Density EEG Study

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Study Objectives: The electrophysiological correlates of anesthetic sedation remain poorly understood. We used high-density electroencephalography (hd-EEG) and source modeling to investigate the cortical processes underlying propofol anesthesia and compare them to sleep.
Design: 256-channel EEG recordings in humans during propofol anesthesia.
Setting: Hospital operating room.
Patients or Participants: 8 healthy subjects (4 males)
Interventions: N/A
Measurements and Results: Initially, propofol induced increases in EEG power from 12-25 Hz. Loss of consciousness (LOC) was accompanied by the appearance of EEG slow waves that resembled the slow waves of NREM sleep. We compared slow waves in propofol to slow waves recorded during natural sleep and found that both populations of waves share similar cortical origins and preferentially propagate along the mesial components of the default network. However, propofol slow waves were spatially blurred compared to sleep slow waves and failed to effectively entrain spindle activity. Propofol also caused an increase in gamma (25-40 Hz) power that persisted throughout LOC. Source modeling analysis showed that this increase in gamma power originated from the anterior and posterior cingulate cortices. During LOC, we found increased gamma functional connectivity between these regions compared to the wakefulness.
Conclusions: Propofol anesthesia is a sleep-like state and slow waves are associated with diminished consciousness even in the presence of high gamma activity.
Keywords: Slow oscillation, EEG, anesthesia, consciousness, gamma
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INTRODUCTION

Propofol is an intravenous anesthetic that is widely used in surgical settings to reversibly induce a state of diminished responsiveness behaviorally similar to NREM sleep.[1] These similarities have been expanded upon by work showing connections between anesthesia and sleep.[2,3] Positron emission tomography studies from both states show deactivation of the thalamus, the cingulate gyri, and the precuneus.[4,5] Intriguingly, propofol anesthesia applied after sleep deprivation lessens the intensity of subsequent recovery sleep in animal studies.[6,7] The aim of this study was to use high-density electroencephalography (hd-EEG) to investigate the electrophysiological correlates of propofol sedation and then compare them to natural sleep. We chose to use hd-EEG because it offers a unique combination of sub-millisecond temporal resolution and superior spatial resolution to traditional EEG.

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The EEG of both NREM sleep and propofol-induced anesthesia show increased power at low frequencies. During NREM sleep, this increase is due to large slow EEG waves generated by the near-synchronous oscillations of millions of cortical neurons between a hyperpolarized downstate and a depolarized upstate.[8,9] These slow waves are the largest electrophysiological events of sleep and may be responsible for some of the functional effects of sleep.[10-12] It is currently unknown to what extent slow waves during anesthesia are similar to sleep slow waves.[2,13,14] Here, we use hd-EEG and source modeling to detect, analyze, and compare slow waves during propofol anesthesia and spontaneous sleep.Although some molecular targets of propofol have been identified, the precise mechanisms by which anesthetics disrupt consciousness remain poorly understood. Sleep studies have suggested that consciousness may be disrupted when the EEG changes from low-voltage fast activity to large delta (0.5-4 Hz) waves.[15] Absence seizures, where consciousness is markedly reduced, are also characterized by spikes and waves in the delta range.[16] It has also been proposed that conscious awareness and perception is maintained, in part, by the synchronization of gamma (> 25 Hz) and/or theta (4-8 Hz) waves across large expanses of cortex.[17-19] However, the few previous EEG studies of gamma power and coherence during loss of consciousness (LOC) with anesthesia have produced conflicting results,[14,20] possibly due to the relatively small number of electrodes used.[21] Therefore, after characterizing propofol-induced slow waves and comparing them to sleep slow

waves, we use hd-EEG and source modeling to investigate the effects of propofol anesthesia on theta and gamma activity.

METHODS

Subjects and Recordings

This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege, and written informed consent was obtained from all participants. The subjects were recruited through advertisement in an internet forum and underwent a medical history and physical examination before participating in the study. Women were tested for pregnancy the day of the experiment (urine test) and were asked if they were using contraception. None of the subjects had a history of head trauma or surgery, mental illness, drug addiction, asthma, motion sickness, or previous problems during anesthesia. All volunteers received financial compensation for inconvenience and time lost during the experiment. Subjects fasted ≥ 6 h for solids and 2 h for liquids prior to sedation.

Fifteen-minute spontaneous 256-electrode hd-EEG recordings were acquired in 8 subjects (mean age 22 ± 2 y, 4 males) in 4 different states: normal wakefulness, sedation (slower response to command, Ramsay scale score 3), LOC with clinical unconsciousness (no response to command, Ramsay scale score 5), and recovery of consciousness.[22] The subject was asked to strongly squeeze the hand of the investigator. She/he was considered fully awake or having recovered consciousness if the response to verbal command ("squeeze my hand!") was clear and strong (Ramsay 2); in sedation if the response to verbal command was clear but slow (Ramsay 3); and in LOC if there was no response to verbal command (Ramsay 5-6). For each consciousness level assessment, Ramsay scale verbal commands were repeated twice. The most comfortable supine position was sought to avoid painful stimulation related to position.

Fifteen minutes of auditory evoked potentials were also acquired in each condition (results of the latter acquisition are not reported in the present study). The total acquisition duration was typically a half-hour per state. The total experimental procedure, including the positioning of the 256-electrode hd-EEG cap and the time for subjects' recovery, lasted about 5 hours. As it was not possible to insert this experimental procedure as part of a routine surgical procedure, the experiment was performed in healthy volunteers at the Cyclotron Research Centre, in a medical environment. All data acquisition and sedation procedures were continuously monitored by a certified anesthesiologist, who was responsible for the subjects' safety. Complete resuscitation equipment was always available.

During the study and the recovery period, electrocardiogram, blood pressure, pulse oximetry (SpO_2), end-tidal carbon dioxide partial pressure ($ETCO_2$), and breathing frequency were continuously monitored (In vivo Research, Inc., Magnitude, Model 3150M). Propofol was infused through an intravenous catheter placed into a vein of the right hand or forearm. Throughout the study, the subjects breathed spontaneously, and additional oxygen (5 liters/min) was given through a loosely fitting plastic face mask. Computer-controlled intravenous infusion of propofol (Alaris TIVA) was used to obtain constant effect-site concentrations. The propofol plasma and effect-site concentrations were estimated using a 3-compartment pharmacokinetic model.[23] After reaching the appropriate effect site concentration, a 5-min equilibration period was allowed to insure equilibration of propofol repartition between compartments. A simple constant rate infusion of propofol was used together with the computerized Marsh model to predict when to manually adjust infusion rate to maintain predicted steady-state propofol levels, although the main goal was to achieve the range of clinical states (Ramsay scores). Arterial blood samples were also taken immediately before and after scan in each clinical state for subsequent determination of the concentration of propofol and for blood gas analysis. Average arterial blood concentrations of propofol were 1.91 ± 0.52 mcg/mL for sedation and 3.87 ± 1.39 mcg/mL for LOC.

For comparison to the anesthesia data, we selected amplitude-matched spontaneous sleep slow waves from a population of slow waves collected from 6 male subjects (ages 24-35 years) at the University of Wisconsin and analyzed as part of a prior study.[24]

EEG Analysis

Artifact-free EEG epochs from each condition were selected for analysis. Electromyogram (EMG) and electroculograms (EOG) were selected from channels around the neck, jaw, and eyes. The raw signals were filtered from 0.5-40 Hz. For the power analysis, we used fast Fourier transforms (FFT) on 20-sec epochs (4-sec Hanning windows) to divide the signal into several frequency bands: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), spindle (12-15 Hz), beta (15-25 Hz), and gamma (25-40 Hz). We performed a similar analysis on the EOG and EMG signals. For the analysis of individual slow waves, we then referenced the signal to the linked mastoids, filtered the data between 0.5-6.0 Hz, and used an automated detection procedure to find slow wave events in the LOC data.[25] We selected single peak slow waves for further analysis and rejected waves that had amplitudes 3 standard deviations smaller than the mean amplitude in each channel. For each slow wave, we calculated the average scalp potential in a 100-millisecond window centered on the detection of the negative peak. For each channel within each wave, we calculated the negative-going slope by dividing the amplitude of the negative peak by the time from the negative-going zero crossing to the peak. For the positive-going slope, we divided the amplitude of the negative peak by the time from the negative peak to the positive-going zero crossing. For the spindle activity analysis, we filtered the data between 12-15 Hz and then segmented the data based on the slow wave detections. The root mean square (RMS) of the spindle power was calculated on the segmented data. Unless otherwise noted, all statistical tests at the sensor level or source level were run in MATLAB (The Mathworks) using statistical nonparametric mapping (SnPM) a permutation based method which accounts for multiple comparisons.[26] For the spindle RMS calculations, we compared the RMS at a midline electrode during the positive-going slope to RMS during the negative peak and after the wave with a Student *t*-test. For all comparisons in the paper, P values less than 0.05 were reported as significant.

Source Modeling

A standard set of electrodes was coregistered to the magnetic resonance image of an individual whose head closely approximates the Montreal Neurological Institute (MNI) head. The

forward model consisted of 4 nested spheres. The inverse matrix was calculated using a constrained, depth and orientation weighted, truncated singular value decomposition regularized (10^{-3}) L2 minimum norm.[27] The source space was a set of 2447 cortical voxels (7 mm^3) that were identified based on the MNI probabilistic brain atlas. The source space is restricted to the cortex because cortical pyramidal neurons are the most likely generators of the EEG.[28] For the power analysis, we source modeled about 5 min of artifact-free EEG (filtered from 0.5-40 Hz) from each subject in each condition. We then used the FFT to decompose the source signals into the same frequency bands as above. SnPM was used for comparison across behavioral states.[26] For the analysis of individual slow waves, we used filtered (0.5-6 Hz) EEG data and divided the source data by the average of several seconds of quiet waking data as a baseline. Source modeling was performed in GeoSource (Electrical Geodesics Incorporated), while all other calculations were performed in MATLAB (The Math Works).

Functional Connectivity

Phase synchrony was calculated using the spatial analytic phase difference (SAPD) method described in Pockett et al.[29] We chose this method because unlike magnitude-squared coherence, phase synchrony between signals in not related to the covariance of the amplitude of the signals and therefore provides direct evidence of synchrony.[30] We selected the 2 areas which showed statistically significant increases in gamma power for waking to LOC as regions of interest (ROIs) ($P < 0.05$, SnPM). We averaged the source vectors of 9 dipoles contained within and around each of the ROIs. Then, for each of the above frequency bands, we band-pass filtered the resulting vectors using a Chebyshev type II filter. We analyzed each frequency band independently. We extracted the instantaneous phase of the filtered vectors, unwrapped the phases, and subtracted the vectors. We then mapped the result back onto the interval $[0, \pi]$. SAPD values below 0.2 radians were counted as in-phase synchrony. Significant differences between conditions were calculated using SnPM.

Cortical Slow Wave Parameters

For each source modeled slow wave, we measured 3 parameters: probabilistic origin, propagation, and involvement.[24] Briefly, for each slow wave, we set a threshold equal to 25% of the maximum current during the wave. We then determined which voxels had a current maximum within that window with a magnitude greater than the threshold. These voxels were sorted according to peak time. The first 10% of voxels to have a peak are the origin. We used the timing of these peaks to create a spatial-temporal gradient. The flow of streamlines down this gradient from origin voxels was used to model the propagation of the slow wave. Finally, involvement was calculated as the average current at every voxel during the slow wave. Statistics were calculated using SnPM.[26]

RESULTS

Changes in EEG Power and Topography During Sedation and Loss of Consciousness

For each subject, we recorded several minutes of hd-EEG before the subject received propofol, after propofol infusion but before LOC (sedation), and after LOC (Figure 1A). Sedation was accompanied by an increase in spindle (12-15 Hz) and beta (15-25 Hz) power (Figure 1B). LOC was accompanied by an almost 20-fold increase in delta power. Smaller increases were also seen in alpha (8-12) and theta power (4-8 Hz). These changes were all reversed upon recovery of consciousness. These power increases were most apparent in a cluster of fronto-medial electrodes (Figure 1C, D).

We noticed that during sedation, gamma (25-40 Hz) power was more than double baseline levels and that this increase persisted even during LOC. While it has been shown that EEG power above 20 Hz can be modulated by muscle or eye movements, there are several reasons to suggest these factors are not driving our results.[31,32] First, we found a trend for EMG power to decrease following sedation ($P < 0.08$, paired *t*-test). While this does not rise to the level of statistical significance, it is in the opposite direction that we would expect to see if EMG activity was driving the gamma EEG signal. Furthermore, previous studies have reported that propofol anesthesia causes a decrease in facial EMG and depresses eye movements.[33-35] Secondly, we found no correlation between gamma power at channel Fz and gamma power in EMG or EOG signals and no change in EOG following LOC ($P > 0.7$, Student *t*-test). In addition, the topography of gamma power increase in sedation states (see Figure 1C) is unlike that of artifacts of ocular or muscular origin, which would be expected to be more lateral. Finally, unlike the gamma activity that has been associated with saccades, the gamma activity we observed during LOC did not consist of brief bursts, but was constantly elevated.[36]

Slow Wave Activity During Propofol Anesthesia Shares Many Features with Sleep Slow Waves

Upon visual inspection of the EEG recorded during LOC, we noticed several events that resembled the slow waves seen during natural sleep (Figure 2A). These events occurred during virtually all LOC epochs, typically about once every second, which is comparable to the occurrence of slow waves during NREM sleep.[8] The waves were only present during LOC (Ramsay score 5-6, 3.87 ± 1.39 mcg/mL propofol, see supplementary Figure S1). Each event could be seen in a large number of channels. The events were present in every subject with similar frequencies and spatial distributions (an average of 107.9 channels/wave per subject, ranging from 87.4 channels/wave to 124.8 channels/wave). We then used an automated detection procedure (see Methods and Reidner et al.[25]) to isolate a subset of these events. For our 8 subjects, we detected 295 waves. A comparison of the events recorded during propofol anesthesia to an amplitude-matched population of slow waves recorded during spontaneous NREM sleep in 6 other subjects confirmed the similarity (Figure 2B). We found that the propofol events have similar scalp voltage topography to spontaneous sleep slow waves (Figure 2C). Comparison of the topography of the negative-going and positive-going slopes showed that, like in spontaneous sleep, maximal slopes were found in a cluster of frontal central electrodes (Figure 2D, E). Aside from one channel that showed more negative slopes in propofol LOC than spontaneous sleep, there were no statistically significant differences in any of the slow wave parameters.

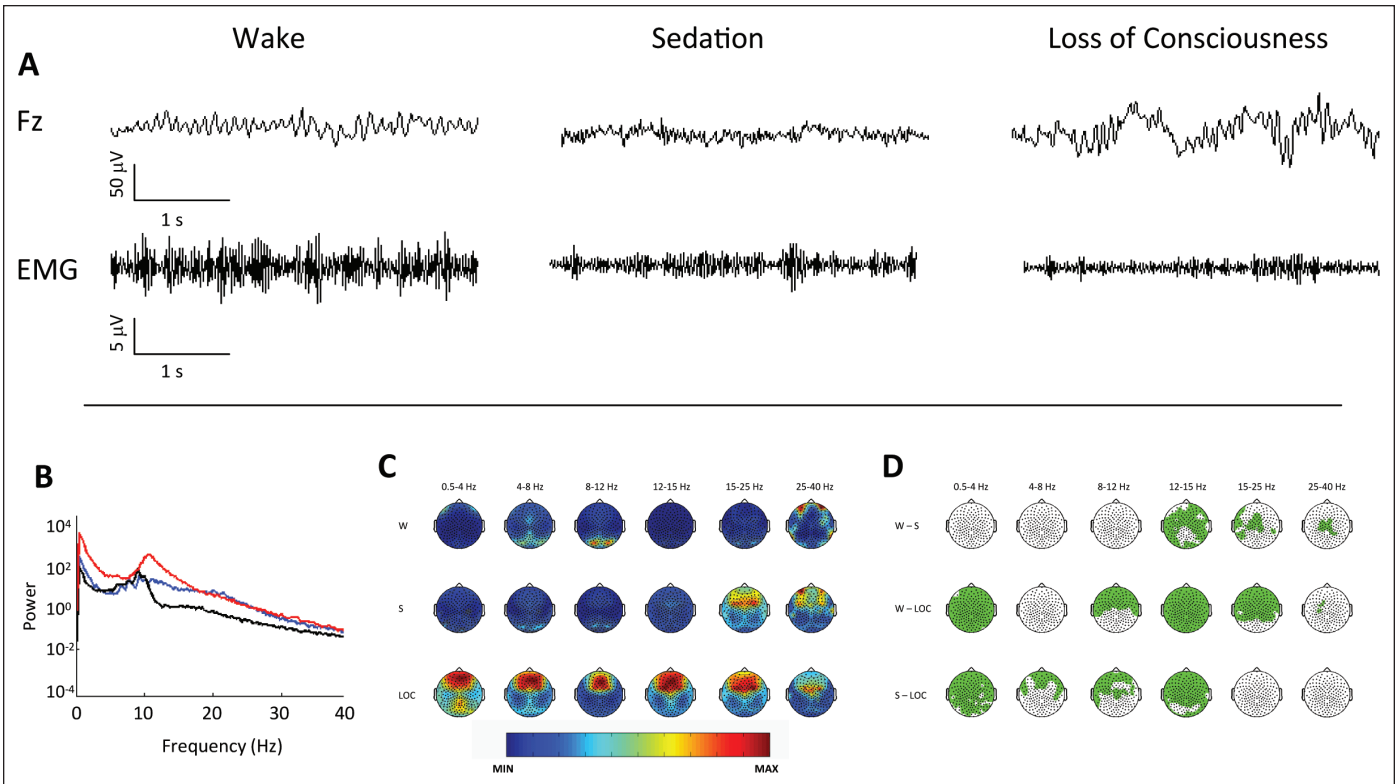

Figure 1—The descent into loss of consciousness (LOC) with propofol is accompanied by changes in the EEG signal. **(A)** The top row shows representative EEG traces from channel Fz during wakefulness, sedation, and LOC. The second row shows corresponding changes in the EMG. **(B)** A logarithmic plot of power spectra from channel Fz in waking (black), sedation (blue) and LOC (red). **(C)** Frequency band specific changes in EEG topography occur during the transition from waking to sedation to sleep. W, Waking; S, Sedation; L, LOC. The EEG following recovery from anesthesia is similar to the EEG preceding anesthesia. **(D)** Statistically significant clusters of electrodes (green, SnPM suprathreshold cluster test, $P < 0.05$) where power was different in sedation compared to waking (upper row), LOC compared to waking (middle row), and sedation compared to LOC (bottom row).

In a recent paper, we used hd-EEG and source modeling to analyze the cortical currents underlying individual sleep slow waves.[24] Here, we used these same techniques to examine individual propofol waves. Like sleep slow waves, each propofol slow wave is a unique, traveling cortical wave. Two representative propofol waves are shown in Figure 3. The wave on the left originates in the left insular cortex and then spreads anteriorly to bilateral frontal cortices. By the end of this wave, the insular currents have weakened. The other wave spreads anteriorly from a posterior cingulate origin that stays strongly activated throughout the duration of the wave.

For each propofol slow wave, we measured 3 parameters: origin, propagation, and involvement. The origin is a set of cortical voxels that is likely to contain the beginning of the slow wave (see Methods). As was previously reported for spontaneous sleep, propofol slow waves frequently originated in hotspots in insular and cingulate cortices (Figure 4A). We used the timing of the current peaks in each voxel to generate a gradient. Streamlines along the gradient from origin voxels describe the propagation of the wave through the cortex. We calculated how often propofol slow waves propagated through each voxel. We found high densities of propagation in several midline structures including the anterior cingulate, cingulate, and posterior cingulate gyri (Figure 4B). These same structures comprise the mesial highway previously reported in spontaneous sleep slow waves.[24] Both spontaneous slow waves and anesthesia slow waves preferentially propagate in a posterior direction along the highway. We defined involvement as the magnitude of the currents produced in each voxel during a wave (see Methods). Propofol slow waves are associated with large currents in many of the same areas as spontaneous sleep slow waves including the anterior cingulate, posterior cingulate, and the precuneus (Figure 4C).

Propofol Slow Waves Are Not Identical to Sleep Slow Waves

Although propofol slow waves are quite similar to slow wave observed during natural sleep, 2 differences are apparent. First, spontaneous sleep slow waves have been shown to group spindle (12-15 Hz) activity, with increases in spindle power occurring during the positive-going slope of the slow wave[37] (Figure 2C). Here, we measured the RMS of spindle activity in windows centered on the negative peak of each sleep and propofol slow wave. We found little grouping between the propofol slow waves and the RMS of spindle activity (Figure 2C). During spontaneous sleep, spindle RMS increased during the positive-going slope of the slow waves compared to before and after the positive-going slope ($P < 0.05$, Student *t*-test). This was not the case for propofol slow waves.

Second, evidence from both EEG and source level analysis suggests that propofol slow waves are spatially blurred compared to the spontaneous sleep slow waves. For the EEG parameters, the variance across electrodes was decreased in propofol versus spontaneous sleep for both positive- and negative-going slopes (unpaired *t*-test, $P < 0.05$) and also trended in that direction for the mean topography (unpaired *t*-test, $P < 0.08$, Figure 2D-F).

At the source level, propofol slow waves included significantly more cortical voxels than the amplitude-matched population of spontaneous sleep slow waves (unpaired *t*-test, $P < 0.05$, see Methods, Figure 4). Furthermore, the origin hotspots for propofol slow waves are more diffuse, and some parts of the occipital cortex that show few origins in spontaneous sleep contain several origins in LOC. Areas such as the posterior temporal and occipital cortices, which are mostly neglected by spontaneous sleep slow waves, show moderate levels of activation during propofol slow waves. Finally, there is a statistically significant asymmetry between the left and right frontal cortex in spontaneous sleep (Student *t*-test, $P < 0.05$), which is absent in propofol slow waves.[24]

Long-Range Cortical Gamma and Theta-Band Functional Connectivity Is Increased Following Administration of Propofol

Several authors have suggested that long-range functional connectivity, particularly in the gamma and theta bands, may be important for maintaining conscious awareness. Since functional connectivity measures at the level of EEG electrodes can be confounded by volume conduction, we first source modeled the data. Source modeling analysis revealed that gamma activity was significantly greater in LOC than in waking ($P < 0.05$, statistical nonparametric mapping [SnPM]) in 2 disjoint midline hotspots. These hotspots corresponded to the anterior and posterior cingulate cortices (Figure 5). We note that these hotspots are posterior to the saccade-related gamma hotspot described by Yuval-Greenberg, et al.[32] We used these areas to seed ROIs. For each behavioral state and frequency band, we measured the functional connectivity between these ROIs with a phase synchrony index called spatial analytic phase difference (SAPD, see Methods and Pockett et al.[29]). There were statistically significant increases in SAPD from waking to sedation in the theta and alpha bands and from waking to LOC in the theta, alpha, and gamma bands ($P < 0.05$, SnPM). We found no statistically significant changes in SAPD between sedation and LOC for any frequency band. While we cannot completely discount the possibility that some brain areas with unchanged gamma power may have decreased gamma synchrony, we also measured gamma SAPD between bilateral insular ROIs which roughly corresponded to the origin hotspots for slow waves. These areas showed no statistically significant change in gamma power across behavioral states. We also found no significant differences in gamma SAPD between waking and sedation ($P > 0.57$), sedation and LOC ($P > 0.21$), or waking and LOC ($P > 0.66$).

DISCUSSION

In this paper, we analyzed hd-EEG collected from subjects who were anesthetized with propofol. In agreement with previous reports, we found that fast

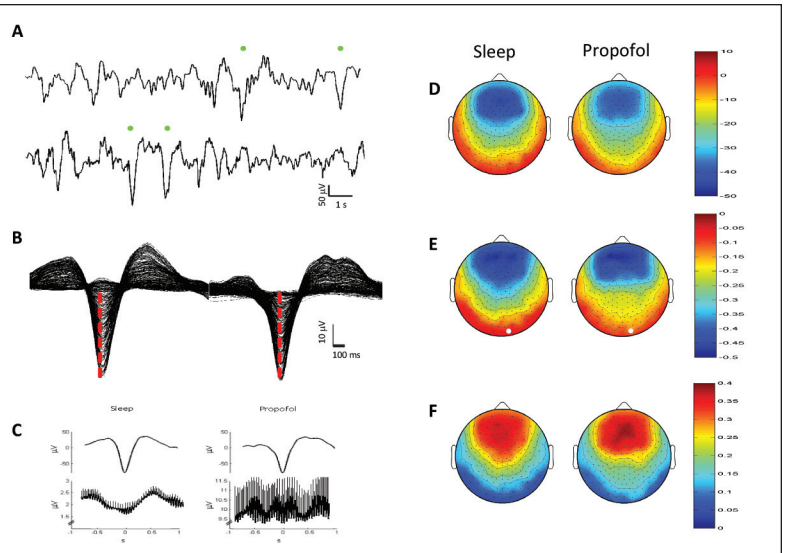

Figure 2—EEG slow waves occur during LOC with propofol anesthesia. **(A)** 15 seconds of data from channel Fz recorded during propofol sedation (upper) and spontaneous sleep (lower). The green dots indicate slow waves in the spontaneous sleep data and "slow wave-like events" in the propofol data. **(B)** Butterfly plots of mastoid-referenced hd-EEG traces for the average of 295 events detected during anesthesia (right panel) and 643 amplitude-matched slow waves (left panel). **(C)** The top row shows the average slow wave recorded from channel Fz (filtered at 0.5-6.0 Hz, see Methods) for spontaneous sleep and LOC with propofol. The bottom row shows the average RMS for spindle activity (12-15 Hz) with standard error bars across subjects during the slow waves. In spontaneous sleep but not propofol anesthesia, spindle RMS increased during the positive-going slope of the slow waves compared to the negative peak of the slow wave and after the slow wave ($P < 0.05$, Student's *t*-test). **(D)** The mean voltage topography during the propofol events and the spontaneous events. **(E)** The mean negative-going slopes calculated for each channel for the propofol events and the spontaneous events. The white dot indicates a channel that has a significantly larger negative slope in propofol compared to spontaneous sleep ($P < 0.05$, SnPM). **(F)** The mean positive-going slopes calculated for each channel for propofol and spontaneous events.

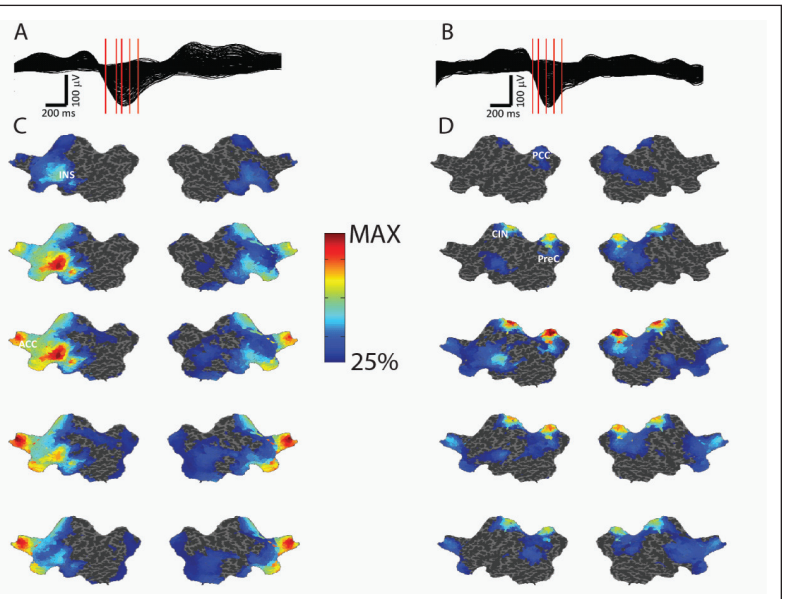

Figure 3—Slow waves induced by propofol anesthesia are unique events that spread across the cortex. **(A, B)** Butterfly plots of mastoid-referenced hd-EEG traces for 2 propofol slow waves. **(C)** Cortical flat maps showing relative current density at the time points indicated by the red lines in A. **(D)** Cortical flat maps showing relative current density at the time points indicated by red lines in B. INS, insula; AC, anterior cingulate cortex; PCC, posterior cingulate cortex; CIN, cingulate cortex; PreC, precuneus.

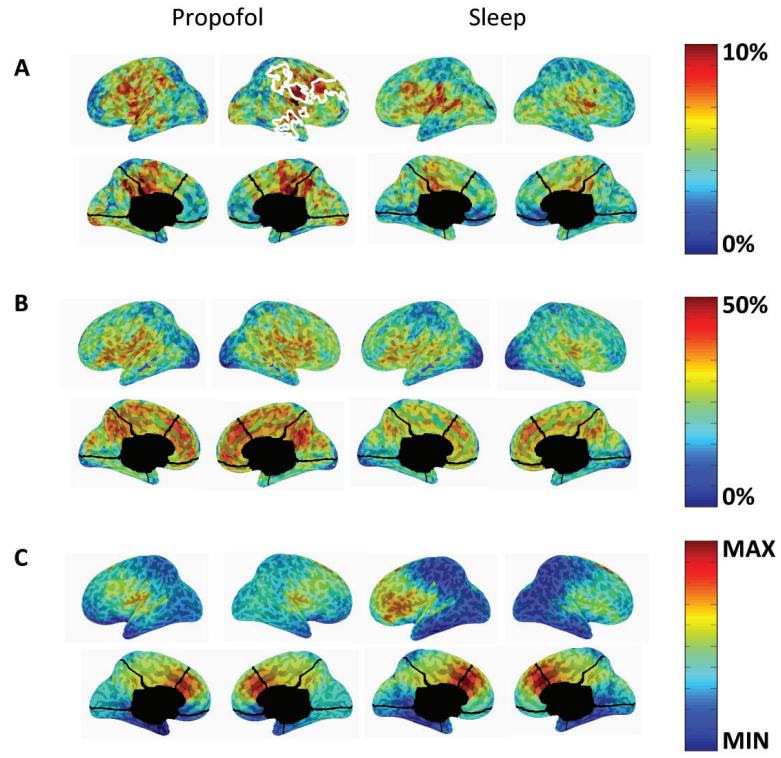

Figure 4—Slow waves during propofol anesthesia share similar patterns of origin, propagation, and involvement with spontaneous sleep slow waves but are more spatially blurred in the cortex. **(A)** Inflated cortical maps showing the average percentage of slow waves to originate in each voxel for propofol and spontaneous sleep. The areas outlined in white show significantly higher percentages of slow wave origins in propofol slow waves than in spontaneous sleep slow waves (SnPM suprathreshold cluster test, $P < 0.05$). **(B)** Inflated cortical maps showing the average percent of waves across subjects that propagate through each voxel. **(C)** Comparison of the mean involvement per voxel between propofol and spontaneous sleep slow waves.

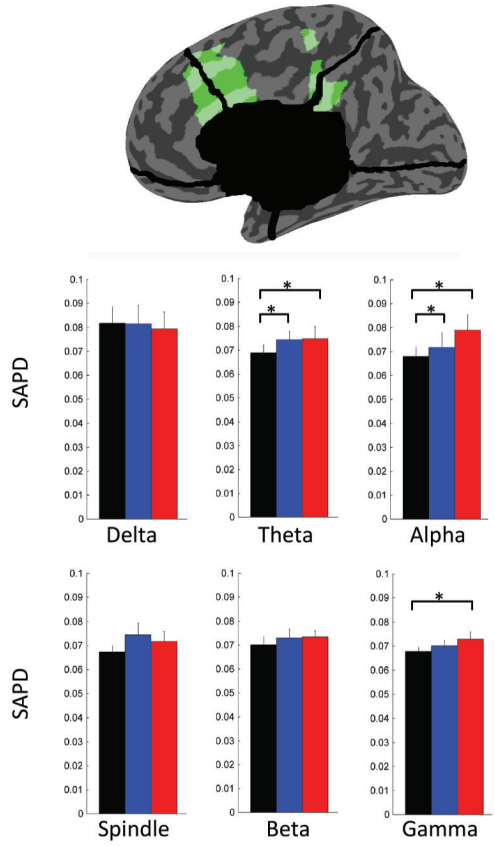

Figure 5—Long-range cortical functional connectivity varies across vigilance state. **(A)** Two ROIs showing increased gamma power in LOC compared to wakefulness ($P < 0.05$, SnPM). The frontal ROI is a portion of the anterior cingulate and the posterior ROI is a portion of the posterior cingulate. **(B)** Phase synchrony as measured by the SAPD metric between the ROIs at various frequencies. *$P < 0.05$, SnPM.

frequencies (12-25 Hz) increased in frontal electrodes during sedation. LOC was marked by a prominent increase in delta power in these same electrodes. The large slow waves induced by propofol anesthesia were similar in appearance, topography, negative-going slope, and positive-going slope to the slow waves seen during NREM sleep. Source modeling analysis revealed that propofol induced slow waves are unique, propagating cortical events that preferentially originate from diffuse hotspots centered on the lateral sulci and the cingulate gyrus. Propofol slow waves propagate preferentially via the same mesial highway as spontaneous sleep slow waves. While propofol slow waves recruit many of the same structures as spontaneous waves, they also appear to be more spatially blurred, and the distinctive asymmetries present in spontaneous sleep slow waves are not present in propofol slow waves. Furthermore, while spontaneous slow waves group spindle activity, propofol slow waves are unable to do so. In addition, propofol administration caused increases in gamma power and long-range gamma synchrony that persisted after LOC.

Anesthesia Is a Sleep-Like State

The well-known behavioral similarities between sleep and anesthesia have long suggested that there is some connection between these states.[38] Furthermore, propofol acts on many brain areas that have been implicated in the initiation and maintenance of natural sleep.[3] This connection has been bolstered by EEG studies that show both states are characterized by increased delta power in fronto-medial areas relative to waking.[39,40] In addition, several studies in rats have suggested that propofol anesthesia modulates and is modulated by the same processes that drive normal sleep homeostasis. These studies have established that sleep debt does not accrue during prolonged anesthesia, that anesthesia following sleep deprivation alleviates the need for subsequent recovery sleep, and that sleep deprivation potentiates the effectiveness of propofol anesthesia.[6,7,41] Here, we used hd-EEG and source modeling analysis, to further explore the relationship between slow waves in sleep and LOC with propofol. At the scalp level, we observed no clear differences between slow waves observed during sleep and those recorded during propofol LOC. We found that, like spontaneous sleep slow waves, propofol slow waves are unique events that travel across the cortex. Both propofol and sleep slow waves propagate across the cortex via the anatomical connectional backbone.[24,42] The default network, a set of cortical structures that are show correlated activity at rest and undergo decreases in activation during task performance, is highly recruited by sleep slow waves and propofol slow waves.[24,43]

In addition to these similarities, our research also highlights several differences between sleep and anesthesia. While both sleep and LOC are associated with increased frontal slow wave activity, anesthesia induces increases in faster frequencies that are not seen during normal sleep.[13,14,44] Propofol slow waves lack the left-right asymmetry of sleep slow waves and frequently involve posterior brain areas that are avoided by sleep slow waves. This may be due to the fact that propofol acts on γ-aminobutyric acid receptors present on neurons throughout the brain and is unlikely to precisely mimic the heterogeneous topography of neuromodulation in the sleeping brain.[45] During normal sleep, spindle activity is grouped by slow waves.[37] This relationship may play an important role in the consolidation of memories during sleep.[46] However, the connection between slow waves and spindle frequencies is greatly decreased in propofol slow waves. In addition, animal studies have shown that anesthetics that act on $GABA_A$ receptors decouple hippocampal and cortical oscillations.[47] Taken together, these results suggest that memory consolidation may be altered during prolonged propofol anesthesia compared to natural sleep.

A Marked Increase in Slow Waves Is Associated with LOC

When people are awakened from NREM sleep early in the night, they rarely report having dreamed.[15] EEG recorded during this period contains high-amplitude slow waves that are absent in waking. During NREM sleep and anesthesia, cortical and thalamic neurons oscillate between a hyperpolarized downstate with little spiking and a depolarized upstate when firing rates can exceed wakefulness.[8] Slow waves are the electrophysiological correlate of millions of neurons switching between up and down states.[9] Recently, investigators have used transcranial magnetic stimulation (TMS) and hd-EEG to measure effective connectivity (the ability of brain areas to influence each other).[48] They found that effective connectivity breaks down during NREM sleep compared to waking.[48] The decreased effective connectivity during sleep likely reflects an impaired ability of the brain to integrate information and could therefore contribute to the decrease in the level of consciousness.[49] The presence of widespread cortical bistability between up and down states culminating in large slow waves during early NREM sleep may be responsible for the decreases in effective connectivity.[48,50]

Anesthesia is a unique tool with which to examine the relationship between slow waves and effective connectivity. A recent report with a different anesthetic (midazolam) suggests that effective connectivity is decreased during anesthesia.[50] A similar phenomenon would be expected during propofol-induced LOC, in the presence of high-amplitude EEG slow waves. Further studies using TMS-EEG should confirm that the bistable dynamics established during propofol-induced LOC also induce a loss of effective connectivity.

It should be mentioned that several studies have reported that muscarinic agonists and antagonists can produce EEG slow waves in awake behaving animals.[51,52] However, many of these reports included very limited behavioral assessments. In addition, the authors were only able to achieve this "dissociation" between the EEG and behavior when the slow waves were relatively small and restricted to frontal electrodes.[51] When the slow waves grew to include posterior cortical areas, the animals transitioned to sleeping behavior.[51] Furthermore, studies in humans indicate that the EEG effects of these drugs cannot be dissociated from their sedative effects.[53,54] In our paper, we purposely selected large slow waves which incorporated most of our scalp electrodes

Gamma and Theta Activity Are Not Sufficient for Consciousness

Gamma power, gamma synchrony, and theta synchrony have all been proposed to contribute to conscious awareness.[17-19,55] Some reports suggest that gamma power may be decreased relative to waking during NREM sleep and anesthesia.[56,57] However, animal studies have found that gamma power is increased during anesthesia.[20] In addition, intracranial recording studies that have shown no differences in gamma coherence between REM and NREM sleep.[56] Furthermore, intrahemispheric EEG gamma coherence may even be higher in slow-wave sleep than in waking.[58] Here, we have shown that gamma and theta power are not decreased following LOC. In fact, there was an increase in gamma power that was localized to components of the default network. This suggests that gamma activity in this network is not sufficient to maintain consciousness when slow waves are present. We also found no change in gamma or theta functional connectivity after LOC. This is in contrast to previous reports that gamma functional connectivity is decreased during anesthetic sedation.[57] This disagreement may be related to the fact that these previous studies differ from our study in choice of anesthetic, depth of anesthesia (loss of consciousness versus surgical anesthesia), and animal model (rat versus human). In addition, in these previous reports decreases in gamma power and functional connectivity occurred at frequencies that were faster than the gamma we analyzed.[57] It may be that high-frequency gamma activity responds differently to propofol, although at these faster frequencies muscle and ocular-related EEG artifacts may complicate the interpretation of the results.[31,59] Therefore, we restricted our analysis to slower, relatively clean frequency bands where we were able to show clear increases in gamma power and functional connectivity that are most likely to be due to changes in brain activity. The fact that we find increased gamma power and increased gamma and theta synchrony during propofol-induced unconsciousness compared to wakefulness challenges the use of these parameters as neural correlates of consciousness. This is clinically relevant in that these parameters may be poor markers of the presence of awareness in noncommunicative brain-damaged patients.[60]

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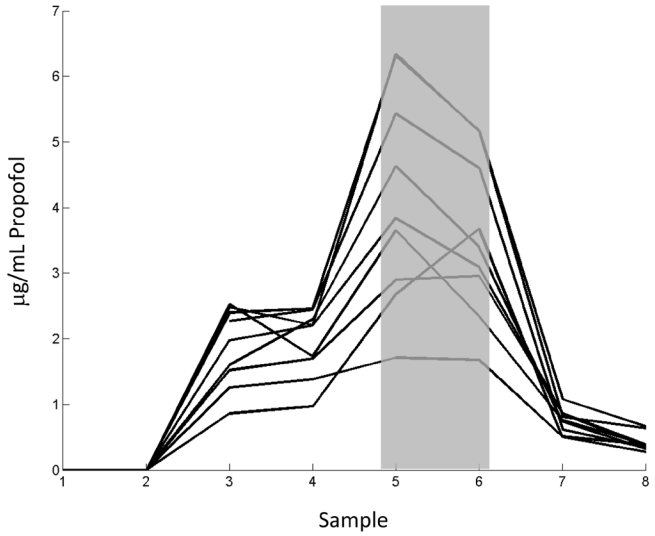

Figure S1—Arterial blood concentration of propofol changes over the course of the experiment. For each subject and each behavioral state, 2 samples of blood were taken and the concentration of propofol was measured. The black lines represent the data from each subject. The gray box indicates that Samples 5 and 6 were taken during loss of consciousness (LOC), Ramsay score 5–6. This was also the only behavioral state in which slow waves were observed (see Figure 2).