

## ANESTHESIOLOGY

# Propofol Sedation Alters Perceptual and Cognitive Functions in Healthy Volunteers as Revealed by Functional Magnetic Resonance Imaging

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*ANESTHESIOLOGY* 2019; 131:254–65

Although we are skillful at inducing unconsciousness, we still lack clear understanding of the underlying neurophysiology.<sup>1</sup> Historically, general mechanisms of loss of consciousness have been elusive because anesthetic agents have diverse, nonoverlapping cellular actions.<sup>2</sup> Developing these theories has been further complicated by the fact that consciousness is a subjective experience and does not always correlate with loss of responsiveness (the common experimental endpoint).<sup>3</sup> Early work has emphasized thalamic control,<sup>4–6</sup> however, subsequent studies suggested that thalamic effects aren't causal<sup>7,8</sup> and are likely a secondary response to widespread cortical suppression.<sup>9,10</sup> Additionally, although ketamine can induce loss of consciousness, it paradoxically increases thalamic metabolism.<sup>11</sup> Phenomena like shifting  $\alpha$  rhythms<sup>12</sup> and phase-coupling<sup>13</sup> are promising as correlates of loss of consciousness, although these effects have only been demonstrated with  $\gamma$ -aminobutyric acid-mediated anesthetics and are not present using ketamine,<sup>2</sup> implying that they cannot be generalized to a unified mechanism of consciousness.

A promising correlate of loss of consciousness that is consistent across all known anesthetic agents,<sup>14,15</sup> sleep,<sup>16</sup> and coma<sup>17</sup> is the disruption of anterior-posterior connectivity from the frontal lobe to the temporal and parietal lobes.<sup>18</sup>

Partial results of this article were presented at the American Society of Anesthesiologists conference in San Diego, California, on October 25, 2015.

Submitted for publication May 1, 2018. Accepted for publication February 1, 2019. From the Departments of Anesthesiology (W.L.G., K.K.L., C.J.R., S.L., S.G.), Radiology (X.L.), and Neurology (J.R.B., S.-J.L.), Medical College of Wisconsin, Milwaukee, Wisconsin; and the Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan (A.G.H.).

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## ABSTRACT

**Background:** Elucidating networks underlying conscious perception is important to understanding the mechanisms of anesthesia and consciousness. Previous studies have observed changes associated with loss of consciousness primarily using resting paradigms. The authors focused on the effects of sedation on specific cognitive systems using task-based functional magnetic resonance imaging. The authors hypothesized deepening sedation would degrade semantic more than perceptual discrimination.

**Methods:** Discrimination of pure tones and familiar names were studied in 13 volunteers during wakefulness and propofol sedation targeted to light and deep sedation. Contrasts highlighted specific cognitive systems: auditory/motor (tones vs. fixation), phonology (unfamiliar names vs. tones), and semantics (familiar vs. unfamiliar names), and were performed across sedation conditions, followed by region of interest analysis on representative regions.

**Results:** During light sedation, the spatial extent of auditory/motor activation was similar, becoming restricted to the superior temporal gyrus during deep sedation. Region of interest analysis revealed significant activation in the superior temporal gyrus during light ( $t[17] = 9.71, P < 0.001$ ) and deep sedation ( $t[19] = 3.73, P = 0.001$ ). Spatial extent of the phonologic contrast decreased progressively with sedation, with significant activation in the inferior frontal gyrus maintained during light sedation ( $t[35] = 5.17, P < 0.001$ ), which didn't meet criteria for significance in deep sedation ( $t[38] = 2.57, P = 0.014$ ). The semantic contrast showed a similar pattern, with activation in the angular gyrus during light sedation ( $t[16] = 4.76, P = 0.002$ ), which disappeared in deep sedation ( $t[18] = 0.35, P = 0.731$ ).

**Conclusions:** Results illustrate broad impairment in cognitive cortex during sedation, with activation in primary sensory cortex beyond loss of consciousness. These results agree with clinical experience: a dose-dependent reduction of higher cognitive functions during light sedation, despite partial preservation of sensory processes through deep sedation.

(*ANESTHESIOLOGY* 2019; 131:254–65)

## EDITOR'S PERSPECTIVE

## What We Already Know about This Topic

- Loss of consciousness during anesthesia is associated with a loss of anterior-posterior connectivity
- However, during anesthesia local sensory cortex function may be preserved

## What This Article Tells Us That Is New

- During propofol sedation, activation on functional magnetic resonance imaging in higher cognitive areas, such as semantic and phonologic processing, is abolished with deep sedation and only partially suppressed with light sedation
- Activation related to lower sensory processing continues with deep and light sedation

In this model, posterior cortices communicate directly with sensory cortex, whereas anterior frontal regions communicate with sensory cortex indirectly, by communication with posterior regions. The interaction between these regions forms the integrated conscious percept. During anesthesia, top-down activity from frontal regions is reduced in animal and human studies,<sup>16,19</sup> although local sensory cortex function appears to be preserved.<sup>18,20</sup> This suggests that a key correlate of loss of consciousness may be disruption of communication to frontal circuits, leading to a loss of information integration across the brain.<sup>1,18</sup> According to this model, loss of consciousness should occur at a time when higher cortical function is suppressed and sensory cortical function is preserved.

Our goal was to expand previous studies to show progressive changes of cognitive and sensory systems during sedation, using a task-based paradigm. Most previous studies have used resting state paradigms,<sup>9</sup> with a few notable exceptions.<sup>21,22</sup> This paradigm has many advantages, particularly when participants are unable to participate in a task. However, it cannot specifically associate particular cognitive processes with particular brain regions. In contrast, task-dependent functional imaging can reveal specific associations of different levels of cognitive processing.<sup>23</sup> Previous studies using a task-based paradigm have found widespread reductions in activity around loss of consciousness, with persistent activity in the thalamus and primary sensory cortices.<sup>21,22</sup> We designed the current study using task contrasts chosen to highlight a hierarchy of cognitive systems: basic sensory, phonologic, and semantic processing. We assessed these cognitive systems across different depths of sedation. Specifically, we hypothesized that in light sedation, processing of simple sensory stimuli would be relatively preserved, but more complex semantic and phonologic processing would be degraded. At a deeper level of sedation, around the threshold of loss of consciousness, we hypothesized that global communication in the brain would be reduced, leading to reduced activity within cognitive systems, with preservation of activity in sensory cortices.

## Materials and Methods

### Participants

All participants were right-handed, fluent English speakers, and had no significant neurologic, cardiovascular, or pulmonary conditions. Participants were specifically excluded for any concern of sleep apnea on history. Of the 16 participants initially enrolled, one was excluded before scanning because of dental braces, one because of initially undisclosed methadone use, and one because of reported “throat tightness” at onset of the propofol infusion. Initial sample size was chosen based on previous experience with this task in our lab. The final sample included 13 participants (6 men) with an average age of 28 (range, 20 to 37 yr). During the deep sedation segment (detailed below), two participants were

excluded because of transient apnea events. No significant cardiovascular or respiratory events occurred in any participants. All research was performed under the supervision of the Institutional Review Board of the Medical College of Wisconsin (Milwaukee, Wisconsin). Written informed consent was obtained from all participants. No data presented here were previously published.

### Tasks

During scanning, participants performed two alternating tasks: Names and Tones. Individual trials were presented in a fast event-related design (with a 3- to 6-s variable inter-stimulus interval), to allow for deconvolution of mixed trials. To avoid excessive switching, tasks were clustered together in groups of seven regularly alternating blocks per run. Each block contained 10 foils and 5 targets, presented in a pseudo-randomized order (randomized with the above interstimulus interval restrictions). Participants responded on each trial with their right hand using one of two buttons on a magnetic resonance imaging compatible keypad, corresponding to a target or foil stimulus. A visual fixation stimulus was provided throughout, which participants were instructed to fixate.

Stimuli for the Names task consisted of spoken recordings of personally familiar (targets) and unfamiliar proper names (foils). Lists of unfamiliar names were created using automated scripts that pulled complete lists of names from online phonebook listings of the metropolitan area, and randomly sampled complete names from them. Lists of familiar names were collected from each participant several days before scanning, and a subset were recorded using the same voice and recording conditions as the unfamiliar names. Name stimuli were chosen because discriminating familiar from unfamiliar names requires a variety of cognitive processes, including perceptual analysis of the phonemes (consonants and vowels), holding the phonologic form briefly in working memory, and retrieving knowledge associated with the name. Familiar names are those for which retrieval of associated semantic and autobiographical knowledge is successful.<sup>24</sup>

Stimuli for the Tones task consisted of multiple sets of three to seven pure tones in succession (150 ms in duration, separated by 250 ms of silence). Each tone was created using one of two frequencies: either high (750 Hz) or low (500 Hz). Targets were defined as a set of tones containing exactly two high tones. Foils were all other combinations of high and low stimuli. Stimulus sets were created with all possible combinations of high and low stimuli, and targets and foils were sampled from these sets.

### Sedation Protocol

Participants were instructed to fast for 8 h before the study. Participants were placed in the magnetic resonance imaging scanner with compatible pulse oximeter, capnographer, electrocardiogram, and blood pressure cuff. Supplemental

oxygen was delivered throughout by nasal cannula. Intravenous catheters were placed in each antecubital vein for propofol infusion and blood sampling. An attending anesthesiologist was present at all times during sedation.

Participants were scanned in three steady-state blocks: before receiving propofol (Pre); at a light, responsive level (Low Propofol); and deep, unresponsive level of sedation (High Propofol). Each sedation block included two 7.5-min functional magnetic resonance imaging runs, separated by 1 min. Each block was initiated by sedating participants using a targeted infusion with predicted venous plasma concentrations of 1 and 2 mcg/ml (respectively) using the STANPUMP program.<sup>25</sup> Sedation level was then tested clinically using the Observer's Assessment of Alertness/Sedation scale before beginning each functional magnetic resonance imaging run, and dosing adjustments were made when appropriate. Light sedation was targeted to an Observer's Assessment of Alertness/Sedation score of 3 to 4 (lethargic to light sleep), while deep sedation was targeted to a score of 1 to 2 (asleep, arousable with mild stimulation). Based on the clinical decisions of the supervising anesthesiologist, deep sedation was not able to be achieved in all participants (fig. 1) To verify serum propofol level, venous blood samples were drawn from the non-infusion IV at the beginning of each sedation block, immediately before starting the functional magnetic resonance imaging run. Propofol concentration analysis was performed by NMS Labs (USA) using gas chromatography. Specimens were treated with 70% perchloric acid to disrupt propofol protein binding, and then extracted with isopropyl ether. Quantification was accomplished by capillary gas chromatography using flame ionization detection.

In order to increase the homogeneity of our sedation conditions, we further classified the data based on task responses into three sedation conditions: Pre, Light Sedation, and Deep Sedation. All trials before initiating propofol sedation were analyzed in the Pre condition. During the sedation blocks, to quantify responsiveness to external stimuli, we calculated the proportion of responses in a moving window of 20 trials. In the initial time period, while participants were responding to most trials, data were classified as Light Sedation. To avoid the confound of mixing response and no-response trials (which could lead to reduced activation simply because of averaging), only response trials were analyzed in this condition. When the moving average response rate (regardless of accuracy) dropped below 50% for 10 trials, the data were classified as in a transitional state. During this time the participants alternated between awake and unconscious states. Because these data were sparse and not stable, it was excluded from analysis. After participants' response rate dropped below 20% for 10 trials, they were classified as Deep Sedation. Again, to avoid averaging heterogeneous trials together, only nonresponses were analyzed in the Deep Sedation condition. Data were classified on a single-trial level, resulting in blocks of time that could include partial functional magnetic resonance imaging runs (e.g., if a participant stopped responding in the

middle of the run). The response rates and classifications of each individual participant is shown in figure 1.

## Functional Magnetic Resonance Imaging Scanning and Processing

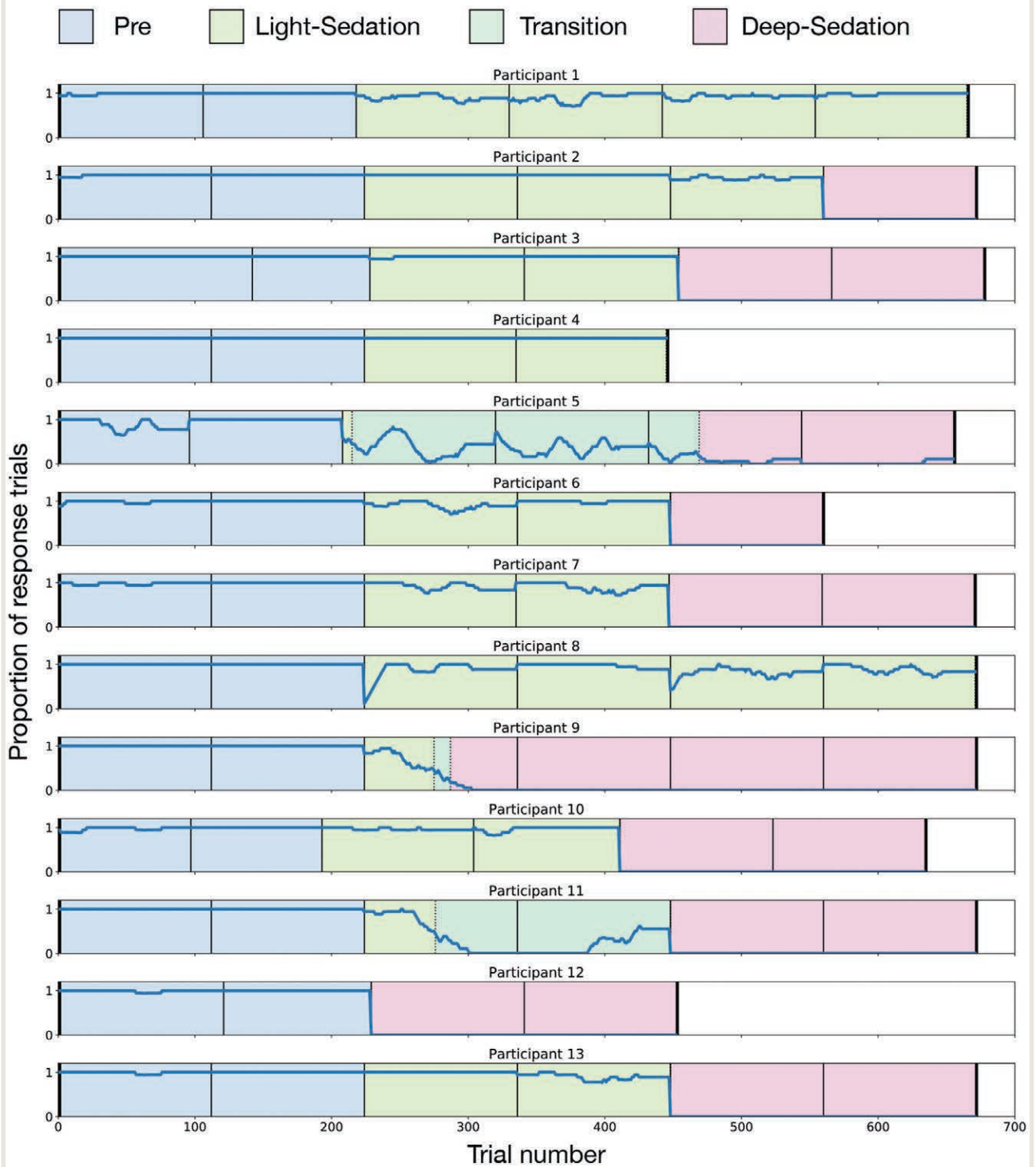
Scans were performed on a 3 Tesla General Electric Excite 750 scanner (GE Healthcare, USA) with a 32-channel head coil. High-resolution anatomical images were acquired using a spoiled gradient recalled acquisition in steady-state sequence. Functional images were obtained using an echo planar imaging sequence with repetition time of 2s, echo time of 25 ms, and 3.5-mm isotropic voxels using 41 axial slices.

Imaging data were processed using the Analysis of Functional NeuroImages software suite.<sup>26</sup> Echo planar images were slice time-corrected and rigid body-aligned, and time points with excessive motion were censored. A 2-mm Gaussian kernel spatial smoothing was applied to the raw data, and parameter estimation was performed using a deconvolution procedure. The deconvolution model was created using a gamma variate convolved with the stimulus time series in a fast event-related manner.

## Statistical Analyses

The deconvolution model in each subject consisted of the gamma variate convolved time series of each stimulus, for each sedation condition. Additionally, a tenth-order Legendre polynomial to account for low-frequency signal changes and motion parameters derived from the rigid body alignment were included as covariates. Trials that were not analyzed (*i.e.*, no-response trials during Light Sedation or response trials during Deep Sedation) were also coded as a separate covariate of noninterest. Data points were excluded from analysis using the Analysis of Functional NeuroImages tool 3dToutcount if more than 5% of voxels within the brain volume were classified as outliers (defined as having an  $\alpha < 0.001$  based on fitting a Gaussian distribution to the data).

To illustrate effects associated with processing at three distinct cognitive levels, the following hierarchical *a priori* task contrasts were designed. To identify basic auditory and motor response processing in the absence of deep semantic processing, all tone trials were compared to the inter-stimulus baseline (AudMotor contrast). Unfamiliar names were then contrasted with the tone stimuli (Phonologic contrast) to identify the additional processing necessary for perceiving speech stimuli with minimal semantic content. Finally, familiar names were contrasted with unfamiliar names (Semantic contrast) to specifically isolate processing of semantic knowledge. Each of these contrasts were performed on data from the three sedation conditions. Task contrast maps were calculated for each sedation condition by performing voxel-wise *t* tests using the Analysis of Functional NeuroImages program 3dttest++ on the corresponding stimulus coefficients for each of the preplanned task contrasts.



**Fig. 1.** Moving window (20 trials) of proportion of responses in each participant, along with sedation classifications assigned to the data. *Black lines* denote functional magnetic resonance imaging run breaks. *Blue shading*, Pre; *green shading*, Light Sedation; *teal shading*, transitional (not analyzed); *red shading*, Deep Sedation.

These task contrast maps were directly tested in a voxel-wise two-way fixed-effects repeated measures ANOVA of the difference in contrast coefficients, with sedation level

and task contrast as factors, using the R statistical package.<sup>27</sup> The effect of interest was the interaction between sedation level and task contrast, which reveals regions where

the effect of sedation was different across the task contrasts. These interaction effects were then further clarified using the average activity in significant clusters located within regions of interest, chosen *a priori* to be representative of the auditory, phonologic, and semantic systems. Activity in each of these three regions was contrasted using *post hoc t* tests, which included testing both names and tones in each sedation condition to baseline (18 tests total), along with the specific Phonologic (names *vs.* tones) and Semantic (familiar *vs.* unfamiliar names) in each sedation condition (an additional six tests). This resulted in 24 *post hoc* comparisons. Effects were considered significant with a two-tailed  $P < 0.05$ , Bonferroni corrected to  $P < 0.002$ . Because data points were assigned to sedation conditions based on the previously described behavioral criteria, the number of data points per condition was not equal.

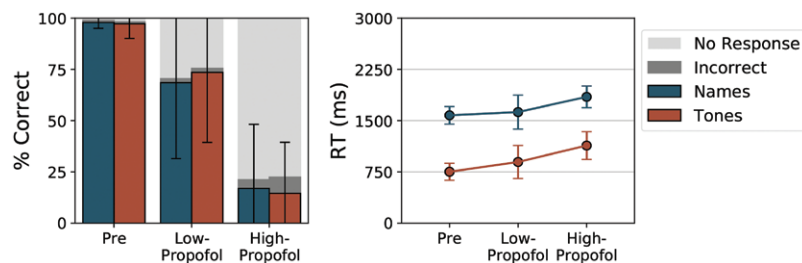
All functional maps were thresholded at an individual voxel  $P < 0.005$ , two-tailed, with a minimum cluster size of  $463\text{mm}^3$  (all displayed figures are thresholded using this level). This threshold was derived from Monte Carlo simulations using the Analysis of Functional NeuroImages program 3dClustSim with a mixed model (Gaussian plus monoexponential) spatial autocorrelation function derived from the measured smoothness of residual datasets. This model has recently been improved in response to criticism of previous functional magnetic resonance imaging clustering models.<sup>28,29</sup> All behavioral data were analyzed using the R statistical package.<sup>27</sup>

## Results

### Behavioral Results

Shown in figure 2 are the accuracy (*bars*) and reaction times (*lines*) of responses in each of the functional magnetic resonance imaging blocks. Missed responses were excluded from reaction time calculation. Before sedation, accuracy on both tasks was nearly perfect (names, 97.8%; tones, 97.2%), with an average reaction time of 1,578ms and 752ms for the names and tones, respectively. During the Low Propofol and High Propofol blocks, accuracy progressively declined ( $F[2,68] = 63.17; P < 0.001$ ) and reaction time lengthened ( $F[2,52] = 4.61; P = 0.014$ ). As seen when comparing the “Incorrect” (*dark gray*) and “No response” (*light gray*) bars, the majority of this performance drop was due to failing to respond, rather than incorrect responses, as during the High Propofol block, most participants were almost completely unresponsive to the task.

Measured serum propofol concentrations and Observer’s Assessment of Alertness/Sedation scores before each scanning run are shown in table 1. Relative to the serum concentration goals, the measured serum propofol concentrations were significantly lower in the Low Propofol ( $t[10] = 12.99; P < 0.001$ ) and High Propofol ( $t[8] = 4.11; P < 0.005$ ) blocks. In contrast, the Observer’s Assessment of Alertness/Sedation clinical sedation assessment scores were in line with our targets (as expected, since sedation was titrated to the Observer’s Assessment of Alertness/Sedation targets).



**Fig. 2.** Accuracy and reaction time to the perceptual and semantic tasks across levels of sedation. Accuracy decreased (due to increasing missed responses) while reaction times increased under deep levels of sedation.

**Table 1.** Measured Serum Propofol Levels and OAA/S Score before Each Scanning Block

		Low Propofol	High Propofol
Propofol	Goal	1.00	2.00
	Measured (mean±SD)	0.53 ± 0.12*	1.52 ± 0.35*
OAA/S	Goal	3–4	1–2
	Measured (mean±SD)	4 ± 1	2 ± 1

\* $P < 0.01$  on one-sample *t* test comparing measured to goal levels. OAA/S, Observer’s Assessment of Alertness/Sedation.

### Basic Perceptual Task Contrast

To illustrate progressive changes of the cognitive and perceptual systems, each of the previously specified task contrasts was performed in each sedation condition. Shown in figure 3 is the AudMotor contrast of tones *versus* baseline across the different sedation conditions. Before sedation, activation was observed during the Tones task in primary and secondary auditory and motor cortices, and somatosensory cortex. Motor and somatosensory activation was strongly left-lateralized, consistent with performance of the task response with the right hand. Increased activation during the fixation periods between trials (*blue color*) was observed in a widespread network linked with semantic and “default mode” processing,<sup>30</sup> including the angular gyrus, middle temporal gyrus, medial and dorsal prefrontal cortex, and posterior cingulate gyrus. This pattern of activation has been observed previously using this task and is hypothesized to reflect non-task related mental processing (“task-unrelated thoughts,” “mind wandering”) during short pauses in the task.<sup>31,32</sup>

During the Light Sedation condition, regions where activation increased during fixation (hypothesized to be associated with off-task processing) were markedly attenuated, whereas activity in auditory, motor, and somatosensory cortices exhibited a similar spatial extent. The marked decrease in interstimulus activation suggests that the off-task processes underlying this activation are highly sensitive to disruption by sedation.

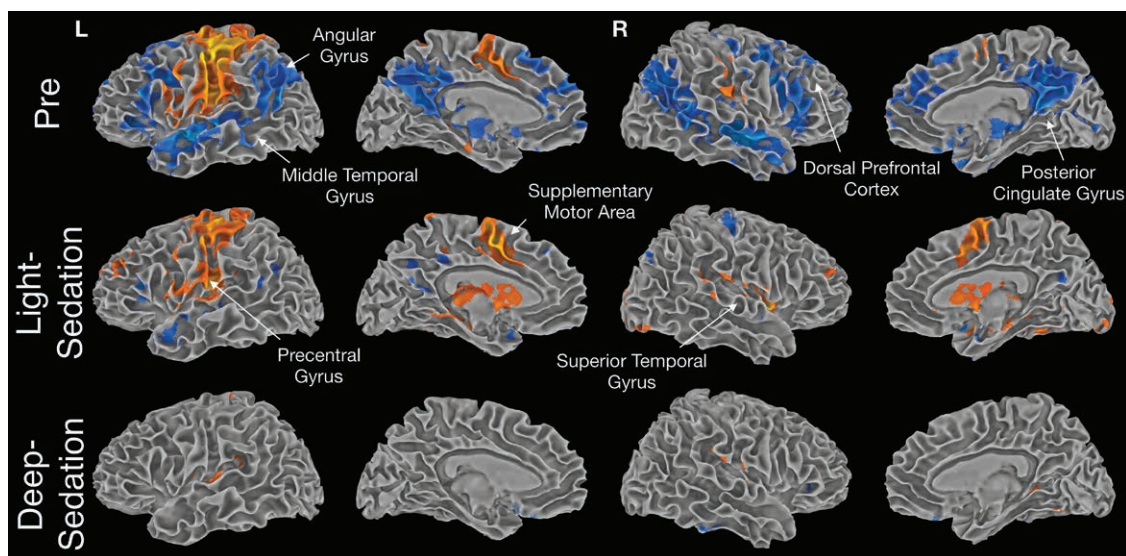
In the Deep Sedation condition, when participants were not responsive to external stimuli, motor activation disappeared, along with activation in temporal lobe auditory association areas. Notably, even under deep sedation

the tone stimuli continued to evoke activation in primary auditory cortex, in the superior temporal gyrus.

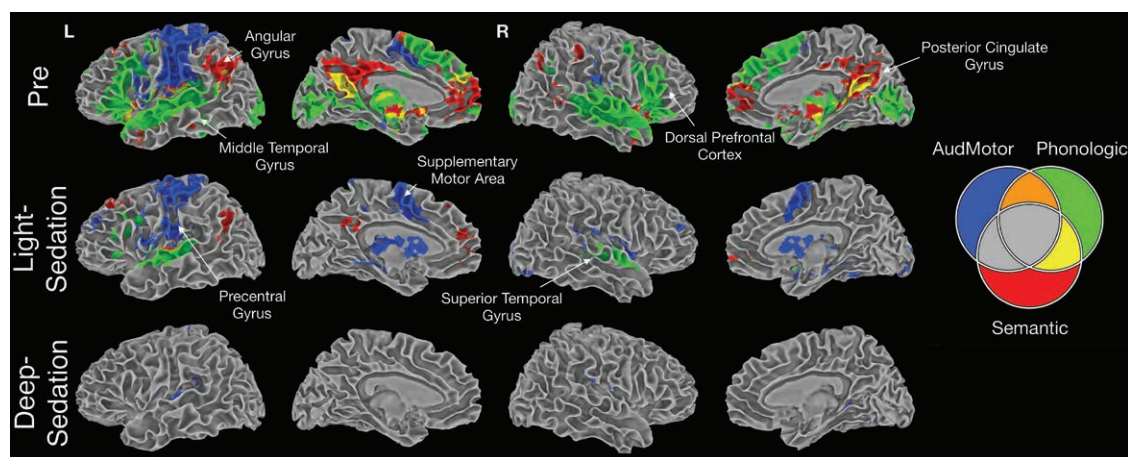
### Hierarchical Task Contrasts

Figure 4 illustrates a composite of the three hierarchical contrasts. AudMotor, shown in *blue* (the positive component of fig. 3), highlights lower-level auditory and sensorimotor processing. The Phonologic contrast in *green* highlights additional regions involved in processing unfamiliar names, including large regions of the superior temporal and inferior frontal lobes. A small area of overlap of these processes (highlighted in *orange*) can be seen in the superior temporal gyrus, consistent with previous findings that speech sounds activate the superior temporal gyrus more than tones.<sup>33</sup> The Semantic contrast (highlighted in *red*) shows the additional processing for familiar names, with areas in *yellow* showing the overlap between the Semantic and Phonologic contrasts. It is also interesting to note that the deactivations seen in the AudMotor contrast follow a similar pattern to the phonologic and semantic contrasts, supporting their role in off-task processing, as we have previously demonstrated.<sup>31</sup>

In the Light Sedation condition, almost all semantic activity disappeared, except for small foci in the left angular and bilateral posterior cingulate gyri. Most of the Phonologic contrast differences also disappeared in regions related to higher-order language processing, with activation maintained mainly in secondary auditory cortex and a small region of left posterior inferior frontal cortex. In contrast, as described in the Basic Perceptual Task Contrasts section, the extent of activation for the AudMotor contrast was not substantially affected. In the Deep Sedation condition, all



**Fig. 3.** Contrast of activation to tones *versus* baseline across levels of sedation. Activation to tones primarily (in *orange*) was centered around motor and sensory systems. Activation during baseline (in *blue*) highlights semantic processing in between task events.



**Fig. 4.** Combination of the three task contrasts, designated by color, to illustrate relative overlap. *Blue*, AudMotor; *green*, Phoneme; *red*, Semantic; *orange*, AudMotor + Phoneme; *yellow*, Phoneme + Semantic.

activity in the Phonologic and Semantic contrasts was completely abolished. As shown in figure 3, activity in the primary auditory and inferior parietal cortex was maintained in the AudMotor contrast.

### Voxel-wise Comparison of Sedation Conditions

The differences in these task contrasts across sedation levels was then tested using a two-way ANOVA. The main effect of sedation condition is shown in figure 5, illustrating regions where activity was reduced in all task contrasts across sedations conditions. Most the clusters shown here, including within the inferior frontal gyrus, temporal lobe, and posterior cingulate gyri, are driven by the interaction effects described in the next section. In contrast, clusters within the premotor area and supplementary motor area exhibited a global reduction across tasks with sedation, being abolished in the Deep Sedation condition. This was expected, as behavioral responses were also lost in this condition.

Regions with significant interactions across sedation by task contrast are shown in figure 6. To further elucidate these effects, the average activity within significant clusters in *a priori* chosen regions, representative of the three task contrasts, is shown in figure 7. Activation within the primary auditory cortex was significantly greater for Names *versus* Tones in the Pre condition ( $t[50] = 11.75; P < 0.001$ ). In the Light Sedation condition this effect remained significant ( $t[35] = 6.90; P < 0.001$ ) disappearing in Deep Sedation ( $t[38] = 0.93; P = 0.360$ ). Although (as demonstrated in fig. 3) activation significantly greater than fixation was still seen in both Tones stimuli during the Deep Sedation condition ( $t[19] = 3.676; P = 0.002$ ).

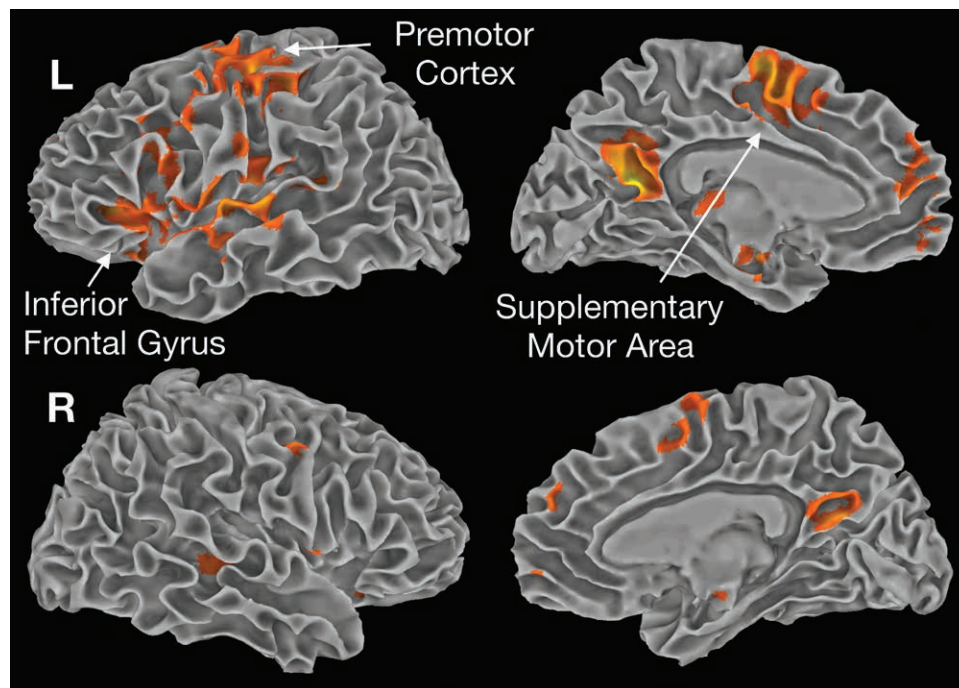
Phonologic regions, including the inferior frontal gyrus and posterior portions of the superior and middle temporal gyrus, displayed a similar pattern of activation across sedation.

Consistent with their posited role in phonology, significant activation was seen for Names over Tones in the Pre condition ( $t[50] = 11.36; P < 0.001$ ) and during Light Sedation ( $t[35] = 5.17; P < 0.001$ ), with no difference observed in Deep Sedation ( $t[38] = 2.57; P = 0.014$ ). As stated previously, in the Basic Perceptual Task Contrasts section before sedation, negative activation was observed in these regions during the Tones task ( $t[25] = 4.54; P < 0.001$ ). This difference disappeared in the Light Sedation ( $t[35] = 1.67; P = 0.113$ ) and Deep Sedation ( $t[18] = 0.84; P = 0.412$ ) conditions.

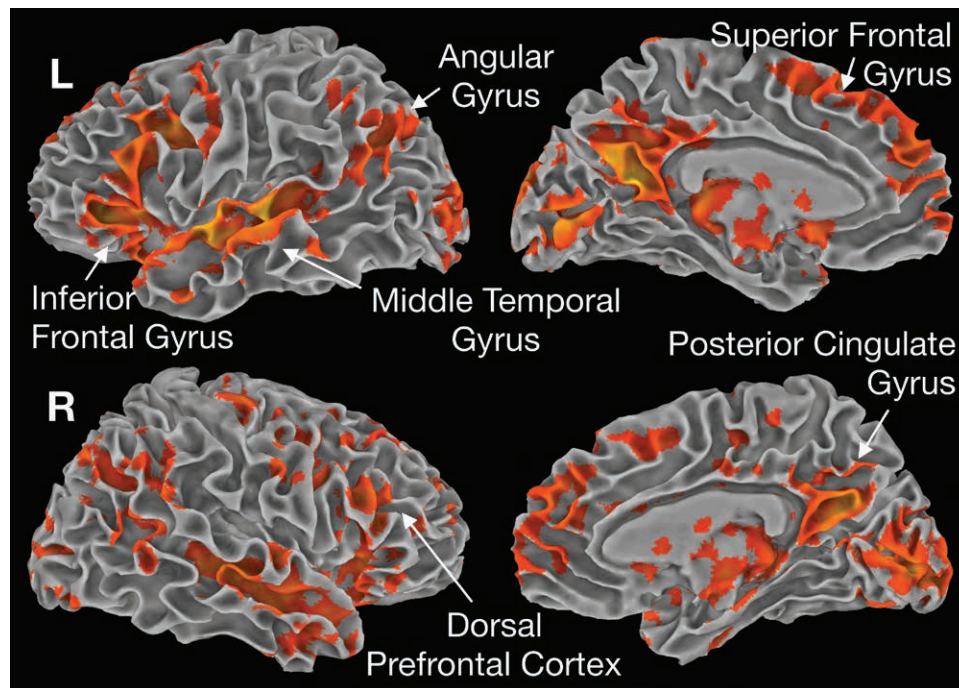
In semantic regions, including the angular gyrus and posterior cingulate, a significant increase in activation was seen during the Pre condition for familiar *versus* nonfamiliar names ( $t[24] = 6.36; P < 0.001$ ), which persisted during Light Sedation ( $t[16] = 4.76; P = 0.002$ ), and disappeared in Deep Sedation ( $t[18] = 0.35; P = 0.731$ ). As seen in phonologic regions, negative off-task activation was present in the Pre condition for tones ( $t[25] = 4.82; P < 0.001$ ), which disappeared in the Light Sedation ( $t[18] = 2.89; P = 0.010$ ), and Deep Sedation ( $t[38] = 1.10; P = 0.287$ ) conditions.

### Discussion

In this article we examined in detail the progressive disruption of function across multiple processing domains during increasing depths of sedation. As predicted, activation in higher cognitive areas (semantic and phonologic processing) is mostly abolished during deep sedation, whereas activation related to lower sensory processing continues. This is consistent with previous studies that suggest initial bottom-up processing is maintained under anesthetic conditions, while top-down processing is disrupted.<sup>18,20,34,35</sup> This was further demonstrated by Massimini *et al.*<sup>16</sup> using transcranial magnetic stimulation pulses during awake and anesthetized states. In the awake state, electroencephalography recorded activity after a transcranial

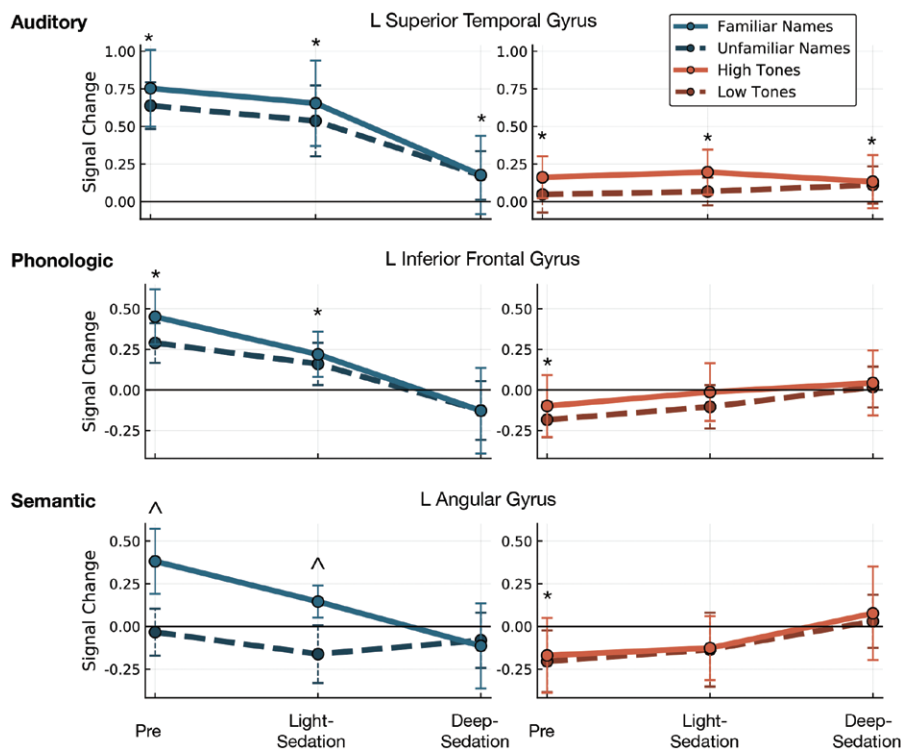


**Fig. 5.** Main effect of sedation level across all task contrasts. Regions in the motor (supplementary motor area, premotor cortex), auditory and phonologic (superior temporal gyrus, inferior frontal gyrus), and semantic (posterior cingulate, precuneus) all showed consistent reduction in activation across all task contrasts with increasing sedation. Colors represent F-values on a continuous scale from orange to yellow, with the maximum fixed at  $F = 15$ . L and R denote left and right hemisphere, respectively.



**Fig. 6.** Interaction effect of task contrast by sedation level. Sedation had different effects on task contrasts in most of the regions studied (detailed in the region of interest analysis in fig. 7). Colors represent F-values on a continuous scale from orange to yellow, with the maximum fixed at  $F = 15$ . L and R denote left and right hemisphere, respectively.





**Fig. 7.** Average activity within regions of interest derived from the voxel-wise interaction of task contrast by sedation level. Activity in auditory cortex diminished with sedation but remained active during deep sedation. Phonologic and semantic effects were reduced in light sedation and were not detected in deep sedation. \*Regions with activity significantly different than zero ( $P < 0.002$ ); ^regions with significant differences between foil and target stimuli ( $P < 0.002$ ). Error bars denote SEM. L denotes left hemisphere.

magneticstimulationpulseshowedasequenceofmultiplepotentials from different cortical sources. During deep anesthesia—although later downstream effects were not observed—the initial potential deflection coming from the primary sensory cortex was preserved.

Under light sedation, semantic and phonologic processes were both partially suppressed, with a large reduction in activation extent, although activity attributable to semantic processing was still detectable in the region of interest analysis. In the primary auditory cortex, the extent of activation was similar in light sedation, although the magnitude of activation was decreased. Consistent with our predictions, significant activity in primary perceptual cortex continued even during deep sedation conditions. Although we commonly observe that complex behavioral task performance is impaired during sedation, these data illustrate that in light sedation conditions some activity attributable to semantic processing remains. These behavioral effects may be due to disruption of long-range connectivity to these higher cortices (as mentioned in the Introduction), or due to a degradation in the information and processing fidelity within these regions.

Consistent with many previous observations,<sup>31,32</sup> our nonsemantic tones task elicited “deactivations” in many regions, attributed to the subtraction of positive activations

occurring during the short rest periods, associated with off-task processing when cognitive loads are low. Interestingly, in the light sedation condition, most of this activation was suppressed. The high sensitivity of this internal “mind wandering” activity to light sedation is consistent with evidence that it is a complex brain function dependent on a distributed network of high-level “hubs.”<sup>30,36</sup> According to one broadly accepted view, the main purpose of this brain activity is to support planning during intervals when there are no external stimuli that demand attention.<sup>31,36,37</sup> We speculate that the global dysfunction incurred by sedation leads to suspension of these nonessential planning processes, and prioritization of cognitive resources (attention, effort, and working memory, among others) to external task demands.

The general effects demonstrated here are also in line with the common clinical experience with patients during sedation. Gross observation reveals that light sedation is characterized by degradation of performance in higher cognitive functions, including the early loss of some episodic memory encoding. The loss of signal propagation under sedation observed here may underlie this state, in which patients are able to process simple stimuli, but integrative functions and complex knowledge retrieval are degraded. As anesthesia is deepened, patients reach a level where all

complex processing is abolished, and only stereotypical responses to stimuli are observed.

Although our data suggest that some brain regions (*e.g.*, primary auditory cortex) are active at loss of consciousness and reactive to external stimuli, it is important to recognize some caveats before applying this concept to clinical contexts. Although the auditory cortex was active even after loss of consciousness, this does not imply that during standard clinical procedures patients can “hear” their surroundings (*i.e.*, have conscious auditory perception after loss of responsiveness). As the objective measurement of consciousness used here is responsiveness, we cannot speak to whether conscious perception occurred independent of responsiveness. The reduction in phonologic and semantic processing does suggest that minimal complex processing occurred during deep sedation. Also, the level of sedation used was titrated specifically to loss of consciousness. Using a standard general anesthetic, with surgical levels of sedation, the cortex is likely substantially more depressed,<sup>38</sup> with expected further depression of both task reactivity and functional connectivity.

In summary, propofol sedation impaired cognitive task performance together with a decrease in frontotemporal–parietal functional activation involved in phonologic perception and semantic retrieval, while auditory–motor cortex activation to simple tone stimuli was more resistant to sedation. Lighter levels of sedation caused disruption of processing on multiple levels, although differential activity was observed even in higher cognitive regions. These results suggest that the performance of phonologic–semantic cognitive tasks is linked to the intact functioning of higher–order association regions, which are diminished during sedation. They agree with clinical experience in patients, implying the dose-dependent loss of higher cognitive functions despite partial preservation of low-level sensory analysis.

Several limitations should be considered when interpreting the findings presented here. As shown by the behavioral data, clinical responses to similar doses of propofol were more variable than expected. Although we attempted to standardize this using behavioral measurements, some variability likely remains. Similarly, although we targeted periods of steady-state propofol, the sedation level may have changed slowly during functional magnetic resonance imaging scans, contributing to additional variability. In addition, although we have demonstrated effects correlated with sedation, we cannot specifically attribute changes in brain activity to direct effects of propofol. Alternatively, sedation may disrupt task performance on a lower level, with the effects seen in higher cortices only subsequent indirect effects.

Future studies may be able to further detail the dynamics of cognitive function through sedation using more complex natural or multisensory stimuli or comparing the effect of pharmacologically diverse anesthetic agents. Observing brain activity at multiple levels of light sedation may also assist in separating effects of sedation on different cognitive systems.

## Acknowledgments

The STANPUMP program used for our propofol infusion is freely available from the OpenTCI initiative at <http://opentci.org/code/stanpump>.

## Research Support

Research reported in this article was supported by the National Institute of General Medical Sciences of the National Institutes of Health (Bethesda, Maryland; grant Nos. R01 GM103894 and T32 GM89586).

## Competing Interests

The authors declare no competing interests.

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After working as a farm laborer in Braintree, Vermont, George D. Blanchard (1834 to 1885) met and married Ellen Blood in Plainfield. Working 8 miles southwest in Barre, he labored in daguerreotyping and then precepted in dentistry. Two years after the 1862 birth of son Edwin, Dr. Blanchard moved his practice and family another 22 miles southwest to West Randolph, where he advertised eventually (*above*) that he had “used Gas and Ether for 25 years with perfect success.” Son Edwin earned his D.D.S. in 1885 just months before his father passed away. (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

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