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Cortical Hypersynchrony Predicts Breakdown of Sensory Processing during Loss of Consciousness

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Summary

Intrinsic cortical dynamics modulates the processing of sensory information and therefore may be critical for conscious perception [1–3]. We tested this hypothesis by electroencephalographic recording of ongoing and stimulus-related brain activity during stepwise drug-induced loss of consciousness in healthy human volunteers. We found that progressive loss of consciousness was tightly linked to the emergence of a hypersynchronous cortical state in the alpha frequency range (8–14 Hz). This drug-induced ongoing alpha activity was widely distributed across the frontal cortex. Stimulus-related responses to median nerve stimulation consisted of early and midlatency response components in primary somatosensory cortex (S1) and a late component also involving temporal and parietal regions. During progressive sedation, the early response was maintained, whereas the midlatency and late responses were reduced and eventually vanished. The antagonistic relation between the late sensory response and ongoing alpha activity held for constant drug levels on the single-trial level. Specifically, the late response component was negatively correlated with the power and long-range coherence of ongoing frontal alpha activity. Our results suggest blocking of intracortical communication by hypersynchronous ongoing activity as a key mechanism for the loss of consciousness.

Results

For conscious perception, sensory signals have to be funneled through cortical networks across multiple stages of sensory pathways [1, 4–9]. This routing of sensory signals is not a passive process but depends on the intrinsic dynamics of cortical networks. These intrinsic dynamics are reflected by ongoing cortical activity, as measured, e.g., with electroencephalography (EEG) [3]. The influence of intrinsic cortical rhythms on the routing of sensory information may determine the emergence of consciousness. To investigate this hypothesis, we measured ongoing and stimulus-related brain activity in nine human participants by means of 126-channel EEG during stepwise loss of consciousness (LOC) under propofol (2,6-diisopropylphenol) anesthesia. We investigated how

these two types of cortical activity are modulated across several parametrically increased sedation levels (Figure 1A).

To define participants' level of consciousness, we quantified their state of vigilance using a standardized sedation scale based on behavioral criteria and widely used in clinical settings (MOAAS; modified Observer's Assessment of Alertness/Sedation; see Table S1 available online) [10]. In addition, we included one measurement block without medication (premedication). With increasing propofol concentration, all participants faded from full consciousness (MOAAS 5) into discrete stages of reversible loss of consciousness (MOAAS 3 to 1; no participant reached MOAAS 4) (Figure 1B). At the deepest level of sedation, participants became unresponsive even to painful stimuli (MOAAS 0). The behavioral characterization of the level of consciousness allowed us to directly correlate neuronal activity with the level of consciousness, rather than with drug dosage.

LOC Is Associated with Emergence of Highly Coherent Alpha Activity

The gradual increase of low-frequency activity across sedation levels could be readily recognized in individual EEG traces (Figure 2A). Sedation strongly modulated brain activity, in particular in the alpha frequency range (8–14 Hz; analysis of variance [ANOVA], $p < 0.05$, false discovery rate [FDR] corrected; uncorrected, $p = 10^{-15}$), with a massive increase during progressive loss of consciousness (MOAAS 3 to 1). Additionally, during low drug levels that did not decrease the participants' vigilance, and in accordance with previous reports [11, 12], we found an intermittent increase in beta power (18–22 Hz; paired one-sided t test, $p = 0.031$; Figure 2B; Figure S1). Compared to premedication, alpha power increased more than 20-fold at frontocentral electrodes during MOAAS 1 (Figure 2B). Source analysis revealed that the alpha power increase during progressive sedation was primarily confined to frontal brain areas (Figure 2D). This spatial pattern was distinct from the classical "resting" alpha-band activity that is primarily expressed in occipital areas (see Figure S1). The increase of alpha power in frontal brain sources was strongest during MOAAS 1 (Figure 2C). At MOAAS 0 (unresponsiveness), the frontal alpha power dropped again, which may indicate the beginning of burst suppression during deep anesthesia [13–15].

The raw EEG traces of distant electrodes suggested that the emerging alpha activity was abnormally phase coherent during sedation (Figure 2A). This was statistically confirmed by assessing frontal coherence in source space. We quantified the coherence of the frontal alpha rhythm by calculating the average coherence across pairs of frontal sources with more than 4 cm separation. The strongest coherence for drug-induced alpha activity appeared during MOAAS 1, showing a more than 1.4-fold increase in coherence as compared to premedication (Figure 2E; MOAAS 1 versus premedication, two-sided sign test, $p = 0.0039$).

Next, we investigated to what extent the frontal alpha activity was linked to the loss of consciousness. We calculated the correlation between sedation level and frontal alpha power as well as coherence during loss of consciousness

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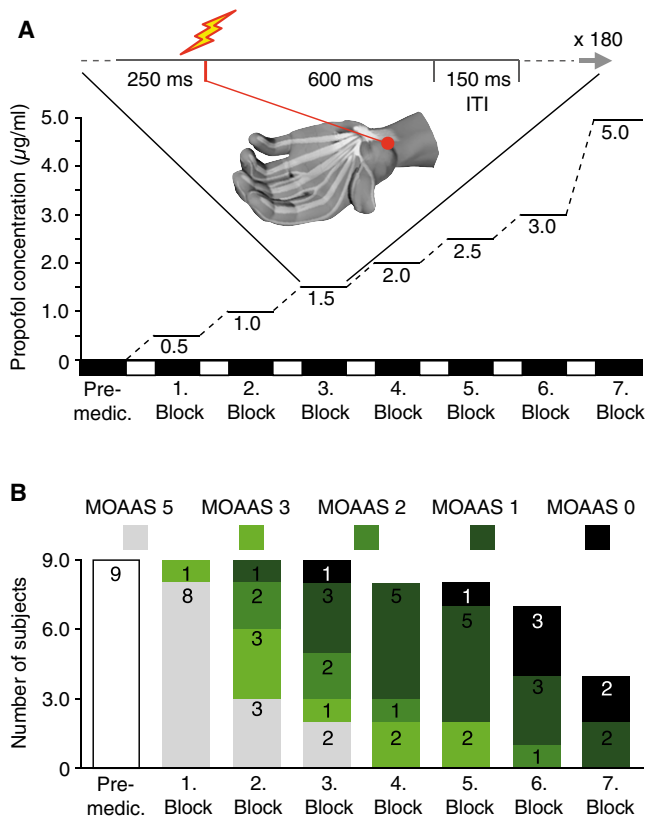


Figure 1. Experimental Design and Behavioral Results during Stepwise Increase of Propofol

(A) One block of data was recorded before drug application (premedication). Subsequently, seven experimental blocks were obtained by intravenous administration of increasing levels of propofol to each participant ($n = 9$). Using target-controlled infusion, we set the drug concentration for each block to a stationary level (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 5.0 $\mu\text{g/ml}$). During each block, participants received 180 electrical median nerve stimuli at their left wrist (trial length 600 ms, prestimulus baseline 250 ms, intertrial interval [ITI] 150 ms). Participants' eyes were closed during the entire session.

(B) Shifts in the participant's state of sedation induced by a given drug level were quantified by a standardized rating scale ranging from MOAAS 5 (fully conscious) to MOAAS 1 (only responsive after a painful physical stimulus), up to MOAAS 0 (unresponsive). Whenever a participant became totally unresponsive, the experiment was stopped before the end of all seven treatment blocks. No participant reached MOAAS 4.

(MOAAS 3 to 1). This analysis revealed that both local alpha power and long-range coherence were significantly correlated with loss of consciousness (alpha power correlation: Spearman's rank correlation coefficient; MOAAS 3 to 1; median rho, -0.92 ; two-sided sign test, $p = 0.0039$; alpha coherence correlation: Spearman's rank correlation coefficient; MOAAS 3 to 1; median rho, -0.82 ; two-sided sign test, $p = 0.0391$).

Interestingly, we found a markedly different modulation of alpha activity in occipital brain areas, that is, a decrease of alpha power during progressive sedation with the strongest decrease at MOAAS 0 (paired one-sided t test, $p = 0.0068$; see Figure S1). Thus, the drug-induced frontal alpha activity and the "classical" occipital alpha activity seem to be not only anatomically but also physiologically distinct.

Taken together, our analysis of ongoing cortical activity showed that, with progressive fading of consciousness, frontal brain areas expressed increasing levels of excessively

coherent alpha-band activity. Next, we characterized stimulus-related brain activity during anesthesia.

Suppression of Late Somatosensory Responses during LOC

During various states associated with an absence of consciousness such as anesthesia, deep sleep, and vegetative states, sensory information still enters the primary cortices [10, 16–19]. This raises the question as to why sensory awareness actually fades. To investigate this question, we applied electrical median nerve stimulation to the participants' left hand (Figure 1A). We assessed the cortical processing of the sensory input by analyzing the event-related response. We estimated the strength of the event-related response across time and frequency using a recursive algorithm that reduces the positive bias of conventional estimates due to non-phase-locked ongoing signals (see Supplemental Experimental Procedures).

During premedication, median nerve stimulation yielded three response components that were distinct in time and frequency: an early (component I), a midlatency (component II), and a late (component III) response component (Figure 3A). Source reconstruction showed that different brain regions gave rise to these different response components (Figure 3B). Whereas the early and midlatency components were mostly confined to primary somatosensory cortex (S1) contralateral to the stimulation site, the late component also involved more widespread brain areas, including contralateral temporal and parietal regions. Sedation differentially modulated each response component as indicated by a two-way ANOVA based on the factor sedation (six levels) and component (three levels; interaction: sedation \times component, $p = 4.7 \times 10^{-5}$; main effect sedation for all components, $p < 0.05$, FDR corrected; $p = 1.1 \times 10^{-3}$, $p = 2.06 \times 10^{-5}$, $p = 9.987 \times 10^{-5}$, uncorrected for components I–III, respectively). The different pattern of modulation across sedation levels for the three components is well illustrated by each component's topography (Figure 3B). The early component persisted throughout all sedation levels (Figure 3C; paired two-sided t tests versus prestimulus baseline, $p < 0.009$ for all MOAAS levels). In contrast, the midlatency and late components eventually vanished with progressive sedation (Figure 3C). The midlatency response component vanished at MOAAS 0 (paired two-sided t tests versus prestimulus baseline, MOAAS 5 to 1, $p < 0.05$; MOAAS 0, not significant [n.s.], $p = 0.63$). The late response component already was reduced at MOAAS 3 (paired two-sided t tests versus prestimulus baseline, MOAAS 5, $p = 0.00046$; MOAAS 3 to 0, n.s., $p > 0.07$). The late component decreased from MOAAS 5 to deeper levels of sedation (paired one-sided t test, MOAAS 5 versus average MOAAS 3 to 1, $p = 0.0370$), and the attenuation of the late component was correlated with the progressive loss of consciousness (Spearman's rank correlation coefficient; MOAAS 3 to 1; median rho, 0.58 ; two-sided sign test, $p = 0.0391$).

In summary, our results demonstrate that not only ongoing but also stimulus-related brain activity was parametrically correlated with the participants' level of sedation. In particular, we observed an increase of ongoing alpha power and a decrease of late sensory response components. This raises the question of whether both processes reflect independently driven drug-induced changes of neuronal activity or whether the strength of the ongoing alpha rhythm causes the suppression of the sensory responses. In the latter case, sensory-evoked and intrinsic neuronal activity should be

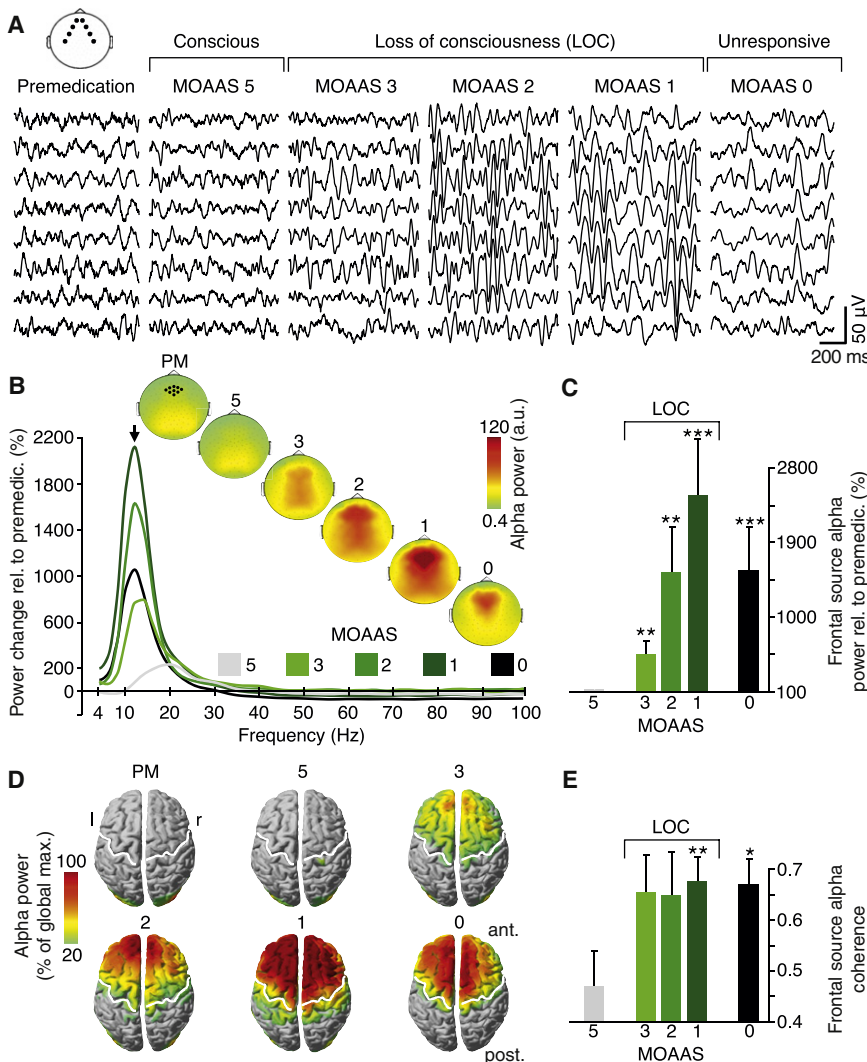


Figure 2. Spontaneous EEG Activity during Shifts in the State of Sedation Induced by Propofol Anesthesia

(A) Single participant's EEG traces exemplify the emergence of a low-frequency rhythm during loss of consciousness (LOC).

(B) As compared to premedication (PM), power at frontocentral electrodes (frontal region of interest selection highlighted by black dots in PM topography) increased in the low-frequency range during LOC, with a peak in the alpha activity at 12 Hz (arrow). Individual alpha peaks across subjects were consistent at either 10 or 12 Hz. The topographies of the drug-induced alpha power revealed a frontal maximum, spatially distinct from the classical alpha at occipital sites (as seen during PM and MOAAS 5).

(C) Change of alpha power in frontal brain areas across sedation levels. The alpha power increased with progressive LOC and dropped at MOAAS 0 (paired one-sided t tests, premedication versus MOAAS 5, 3, 2, 1, 0; *** $p < 0.001$, ** $p < 0.01$). Error bars represent standard errors. (D) Source reconstruction of alpha power across all sedation levels (all source solutions thresholded at 20% of the global maximum across all conditions).

(E) Change of alpha coherence within frontal brain areas. The alpha coherence showed the strongest coherence during MOAAS 1, while all conditions of lower sedation failed to reach significance (two-sided sign test, premedication versus MOAAS 5, 3, 2, 1, 0; ** $p < 0.01$, * $p < 0.025$). Error bars represent standard errors.

anticorrelated across single trials even at a constant drug level.

Single-Trial Correlation between Ongoing Alpha Activity and Stimulus-Related Processing

Indeed, we found evidence for a suppressive influence of ongoing alpha activity in frontal brain areas on the late sensory response. For all experimental blocks with strongly enhanced drug-induced alpha oscillations, we correlated the single-trial alpha power in frontal brain areas with single-trial estimates of the early, midlatency, and late somatosensory response components. We found a significant negative single-trial correlation between frontal alpha power and the amplitude of the late somatosensory evoked response (two-sided t tests, Bonferroni-Holm corrected; early response, n.s., $p = 0.0779$; midlatency response, n.s., $p = 0.3546$; late response, $p = 0.0317$). We tested whether this negative correlation also held for the alpha coherence between frontal regions. Indeed, we found a significant negative single-trial correlation between frontal alpha coherence and the late response component (two-sided t test, $p = 0.0230$). In summary, even for constant drug levels, frontal alpha power and coherence were anticorrelated with the late sensory response component.

parametric design revealed that this frontal alpha activity represents a continuous shift across several levels of loss of consciousness toward a synchronized mode rather than a switch between two distinct brain states. Second, our source analysis revealed that this modulation of frontal alpha activity involves both an increase of alpha power, presumably reflecting local synchronization, as well as enhanced phase coherence between frontal brain regions reflecting long-range synchronization. These findings may not be specific to propofol but may be generalizable to other anesthetic agents. In particular, isoflurane, sevoflurane, and thiopental have been shown to induce an increase of rhythmic activity around the alpha frequency range at frontal electrodes (so-called “anteriorization”) comparable to propofol anesthesia [11, 21, 22].

A recent modeling study provides a plausible network mechanism for the propofol-induced large-scale alpha-band synchronization [23]. This mechanism critically rests on propofol increasing the strength and decay time of GABAergic projections from cortical interneurons onto cortical pyramidal cells and from thalamic reticular neurons onto thalamic relay cells [18, 23–25]. This enhanced inhibition results in a thalamic inhibitory-excitatory rhythm that locks to the cortical drive in the alpha frequency range [23, 26]. Given the extensive

Discussion

Our results extend previous experimental studies that have demonstrated enhanced alpha activity at frontal electrodes during propofol concentrations that diminish or stop behavioral responses [11, 20–22]. First, our

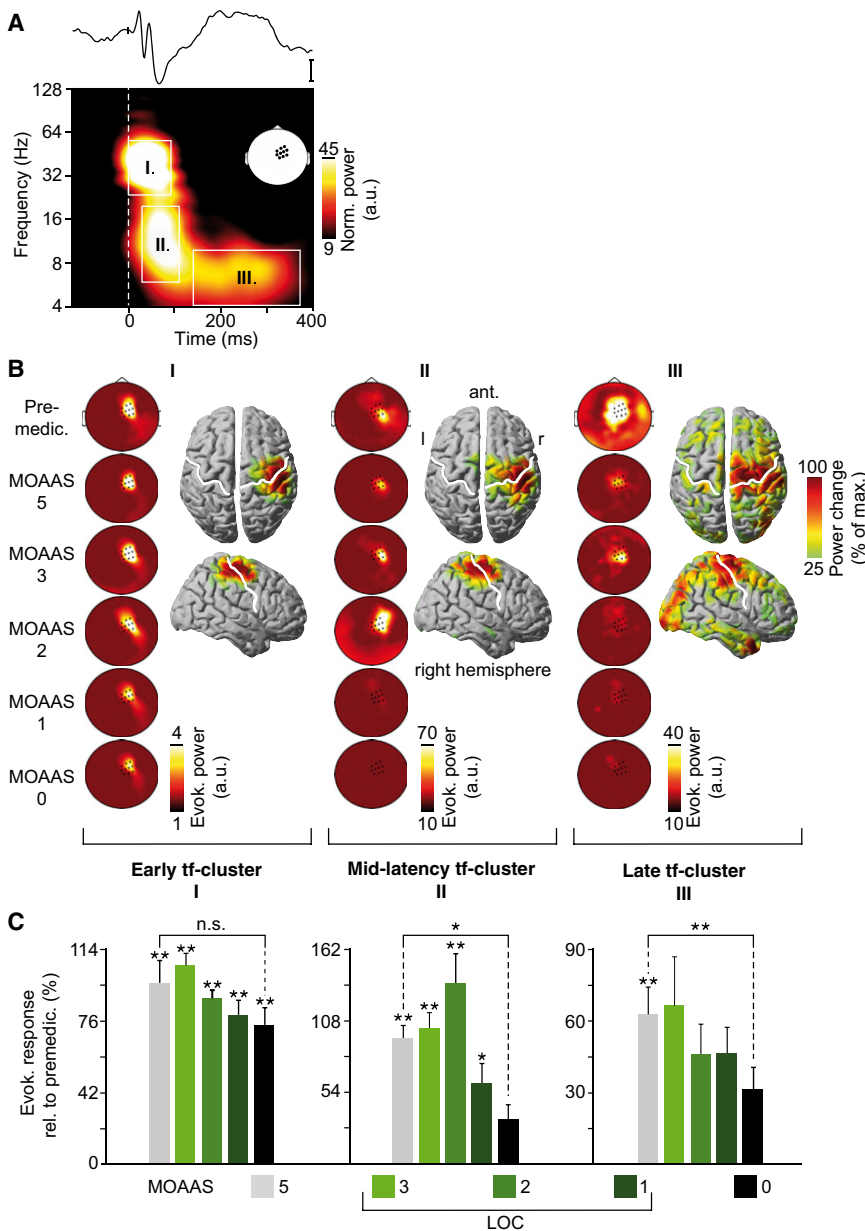


Figure 3. Somatosensory Evoked EEG Responses during Shifts in the State of Sedation Induced by Propofol Anesthesia

(A) Time-frequency representation of the average power of evoked responses during premedication (contralateral region of interest around electrode C4; to enhance readability, power is multiplied by squared frequency). Three somatosensory response components are evident (stimulus onset 0 ms): early (24–56 Hz, 0–90 ms), midlatency (6–20 Hz, 30–110 ms), and late (4–10 Hz, 140–370 ms). The corresponding time trace of the grand average evoked response is displayed above. Scale bar represents 1 μ V. (B) Topographic distributions and source reconstructions of each component (I, II, and III) are displayed column-wise. Source reconstruction during premedication revealed early and midlatency components largely confined to contralateral primary somatosensory cortex (S1). The late response also involved right temporal and parietal brain areas (all source solutions thresholded at 25% of maximum). The topographies display the modulation of each component with increasing sedation, showing a persistent early response across all sedation levels but a breakdown for both later components. (C) Normalized evoked response of each component for all sedation levels. The early response differed consistently from the prestimulus baseline (–250 to 0 ms) across all conditions, but both later responses vanished during increased sedation (** $p < 0.01$, * $p < 0.05$). The late component was reduced at lower MOAAS stages, its stepwise attenuation being correlated with progressive LOC. Error bars represent standard errors.

different thalamocortical circuits involving the lateral geniculate nucleus and the pulvinar [24, 27, 28]. The demonstrated dissociation between occipital and frontal alpha adds to the growing body of evidence suggesting different neural mechanisms underlying these rhythms.

Our data show that specifically late somatosensory responses in higher-order cortical areas are suppressed

while early responses, though modulated, persist during anesthesia. This accords well with other electrophysiological and imaging studies in humans and rodents [16, 29–33]. Thus, our results and others studies provide converging evidence that the routing of sensory information to higher processing stages is blocked during increased propofol sedation.

Importantly, our results suggest that the diminished routing of sensory signals may result from a shift of intrinsic cortical dynamics to a slow and hypersynchronous state. In particular, the single-trial anticorrelation between excessively synchronized ongoing activity and late sensory response components suggests that the drug-induced alpha activity may suppress the routing of sensory signals.

What could be a mechanism that links the drug-induced alpha activity and the breakdown of sensory transmission? As outlined above, the drug-induced alpha oscillations likely result from thalamocortical reverberations driven by a net increase of inhibition [23]. This alpha rhythm entrains large

connectivity between thalamic and pyramidal neurons and the divergence of thalamocortical projections, large populations of cortical neurons are recruited into a highly synchronized rhythmic activity [18, 25]. Such synchronized behavior across large cortical populations may result in patterns of strong coherence as measured in the present study. In summary, the demonstrated synchronized alpha activity likely reflects a propofol-induced shift in the dynamics of thalamocortical loops.

Notably, we found opposite modulations of frontal and occipital alpha activity during loss of consciousness. This dissociation may be rooted in different cortical projections and drug susceptibility of different thalamic nuclei. The frontal effects on alpha activity likely involve thalamic nuclei (e.g., mediodorsal) that are characterized by dense connectivity specifically with frontal cortices and that may be selectively affected by propofol anesthesia [23]. In contrast, the classical alpha rhythm in the occipital cortex is based upon

neuronal populations within frontal cortex and reduces their information processing capacity. Indeed, under propofol anesthesia, the complexity of frontal brain activity decreases when consciousness is lost [34] and metabolic demands are reduced in frontal cortex and the thalamus [35, 36]. The functional inhibition of frontal areas may either lead to a breakdown of recurrent interactions between sensory and frontal processing stages or reduce top-down signals necessary to gate sensory information beyond early processing stages [6, 37]. Both mechanisms may lead to a reduced transmission of sensory signals to higher sensory processing stages. Consistent with these scenarios, several EEG studies employing different measures of cortical interactions suggest a reduction in large-scale cortical information flow during anesthesia [7, 38–40].

Although our data show the strongest drug-induced modulations of ongoing activity in frontal regions, ongoing activity may also be modulated in higher-order somatosensory regions. Thus, another possible mechanism for impaired sensory processing is that propofol-induced alpha activity not only impairs frontal processing but also directly interferes with thalamocortical loops involving higher-order sensory areas (such as S2). Finally, our data suggest that the primary thalamic relay of sensory information remains comparatively unaffected by the propofol-induced alpha activity and is thus not the primary cause for the lack of sensory transmission to higher-order sensory regions.

Drug-induced alpha oscillations are likely not the only mechanism to impair sensory processing during propofol anesthesia. Intracellular recordings reveal enhanced slow membrane-potential fluctuations below the alpha range (<5 Hz) during anesthesia [41]. These slow fluctuations are characterized by a bimodal membrane-potential distribution termed “up” and “down” states that impairs normal cortical information processing [42]. In line with these invasive studies, several noninvasive studies have demonstrated enhanced power as well as coupling of the EEG at frequencies below 5 Hz during anesthesia [11, 13, 20, 22, 40]. It remains to be determined whether these slow fluctuations of the extracranial EEG indeed reflect the slow membrane fluctuation underlying up and down states at the cellular level.

The antagonism between low-frequency oscillations and sensory processing has been suggested to be relevant for cortical processing also during wakefulness [43, 44]. Specifically, prestimulus alpha activity may shape sensory processing during attention by inhibiting task-irrelevant neuronal populations [6, 45]. However, little is known about how cognitive tasks modulate the thalamocortical dynamics underlying alpha-band activity during wakefulness. Thus, it remains to be determined how alpha-band activity during anesthesia and the awake state are related on the mechanistic level and in terms of their functional consequences.

In summary, our results suggest that the emergence of conscious states may depend on the interaction of locally differentiated cortical processing that in turn depends on the current synchronous structure of intrinsic cortical dynamics. Specifically, consciousness may rely on the global availability of sensory information to multiple brain areas by transmission to higher-order processing stages [1, 4, 5, 8].

Experimental Procedures

Here we provide a brief summary of the experimental procedures; please see the [Supplemental Experimental Procedures](#) for full details. Nine male

participants received stepwise administration of a short-acting anesthetic drug, propofol (2,6-diisopropylphenol), via an intravenous catheter using a target-controlled infusion system (Graseby 3500, Graseby Medical). This study was approved by the local institutional review boards (Ethik-Kommission, Ärztekammer Hamburg, Germany). The experiment consisted of a habituation period, a premedication period, and up to seven treatment blocks of increasing drug concentrations (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 5.0 $\mu\text{g/ml}$). If a participant became totally unresponsive, the experiment was stopped. During each block, participants received electrical median nerve stimulation (180 square pulsed stimuli, 1 Hz stimulation rate, 100 μs pulse duration, intensity of 7 mA above motor threshold) at the wrist of the left hand. At the end of each block, the participant's vigilance was quantified by a standardized sedation scale, the MOAAS (see [Table S1](#)). The classification of participant's level of vigilance ranged from MOAAS 5 (fully conscious) to MOAAS 1 (only responsive after a painful physical stimulus), up to MOAAS 0 (unresponsive). We refer to intermediate levels of vigilance below MOAAS 5 and above MOAAS 0 as reversible loss of consciousness. We recorded the EEG from 126 electrodes during the entire experiment. The current study provides a reanalysis of a subset of data that were used in a previous study to investigate evoked responses in the time domain [10]. We applied Fourier transform to the Hanning windowed signals (window length 250 ms, step size 10 ms, window overlap 96%) to analyze the spectral characteristics of the EEG data. We estimated neural activity at the cortical source level by using the weighted minimum norm approach. We derived estimates of the event-related signal power from ten electrodes above the contralateral somatosensory cortex to quantify cortical processing of the medial nerve stimulation. Power of the conventional event-related signal (average across trials) is positively biased by the residual non-phase-locked signal components that do not average out for a finite number of trials. Because of the strong differences in ongoing activity across sedation levels, we implemented a method that reduces this positive bias of event-related signal power estimates (see [Supplemental Experimental Procedures](#) for details). Data were analyzed in MATLAB (MathWorks) using custom scripts and several open source toolboxes: BioSig (<http://www.biosig.sourceforge.net/>), EEGLAB (<http://www.sccn.ucsd.edu/eeglab/>), and Fieldtrip (<http://www.ru.nl/fcdonders/fieldtrip/>).

Supplemental Information

Supplemental Information includes three figures, one table, and Supplemental Experimental Procedures and can be found with this article online at [doi:10.1016/j.cub.2011.10.017](https://doi.org/10.1016/j.cub.2011.10.017).

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