Report

Current Biology

Consciousness and Complexity during Unresponsiveness Induced by Propofol, Xenon, and Ketamine

Highlights

- The perturbational complexity index (PCI) in propofol and xenon anesthesia is low
- Both these anesthetics are associated with the lack of post-anesthesia reports
- Ketamine is associated with high PCI and by vivid post-anesthesia dream reports
- PCI may index the presence of disconnected consciousness during unresponsiveness

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In Brief

Sarasso, Boly, et al. show that the complexity of the cortical response to TMS is low during propofol and xenon anesthesia but high during ketamine. Crucially, no reports are obtained upon awakening from both propofol and xenon while after ketamine, all subjects report long, vivid dreams, possibly indicating a state of disconnected consciousness.

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Consciousness and Complexity during Unresponsiveness Induced by Propofol, Xenon, and Ketamine

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SUMMARY

A common endpoint of general anesthetics is behavioral unresponsiveness [1], which is commonly associated with loss of consciousness. However, subjects can become disconnected from the environment while still having conscious experiences, as demonstrated by sleep states associated with dreaming [2]. Among anesthetics, ketamine is remarkable [3] in that it induces profound unresponsiveness, but subjects often report "ketamine dreams" upon emergence from anesthesia [4–9]. Here, we aimed at assessing consciousness during anesthesia with propofol, xenon, and ketamine, independent of behavioral responsiveness. To do so, in 18 healthy volunteers, we measured the complexity of the cortical response to transcranial magnetic stimulation (TMS)—an approach that has proven helpful in assessing objectively the level of consciousness irrespective of sensory processing and motor responses [10]. In addition, upon emergence from anesthesia, we collected reports about conscious experiences during unresponsiveness. Both frontal and parietal TMS elicited a low-amplitude electroencephalographic (EEG) slow wave corresponding to a local pattern of cortical activation with low complexity during propofol anesthesia, a high-amplitude EEG slow wave corresponding to a global, stereotypical pattern of cortical activation with low complexity during xenon anesthesia, and a wakefulness-like, complex spatiotemporal activation pattern during ketamine anesthesia. Crucially, participants reported no conscious experience after emergence from propofol and xenon anesthesia, whereas after ketamine they reported long, vivid dreams unrelated to the external environment. These results are relevant because they suggest that brain complexity may be sensitive to the presence of disconnected consciousness in subjects who are considered unconscious based on behavioral responses.

RESULTS

TMS during Unresponsiveness Reveals Drug-Specific Cortical Reactivity Patterns

Transcranial magnetic stimulation (TMS)-evoked electroencephalographic (EEG) potentials (TEPs) recorded at the stimulation site in the various experimental conditions (responsive wakefulness, propofol-, xenon-, and ketamine-induced unresponsiveness) are depicted in Figure 1A for all the participants in the study. As in previous studies [11], TEPs recorded after stimulation of both Brodmann area (BA) 6 and BA 7 during responsive wakefulness (Ramsay score 2) before drug administration were low-amplitude, fast-frequency recurrent scalp waves (Figure 1A, gray traces). After drug administration and behavioral unresponsiveness (Ramsay score 6), we observed distinct, drug-specific TEP patterns that were consistent across participants. During propofol-induced unresponsiveness, we recorded low-amplitude, low-frequency positive-negative TEPs (Figure 1A, left). Xenon-induced unresponsiveness was associated with large-amplitude but stereotyped positive-negative TEPs (Figure 1A, middle). Finally, during ketamine-induced unresponsiveness, TEPs were characterized by fast-frequency components closely

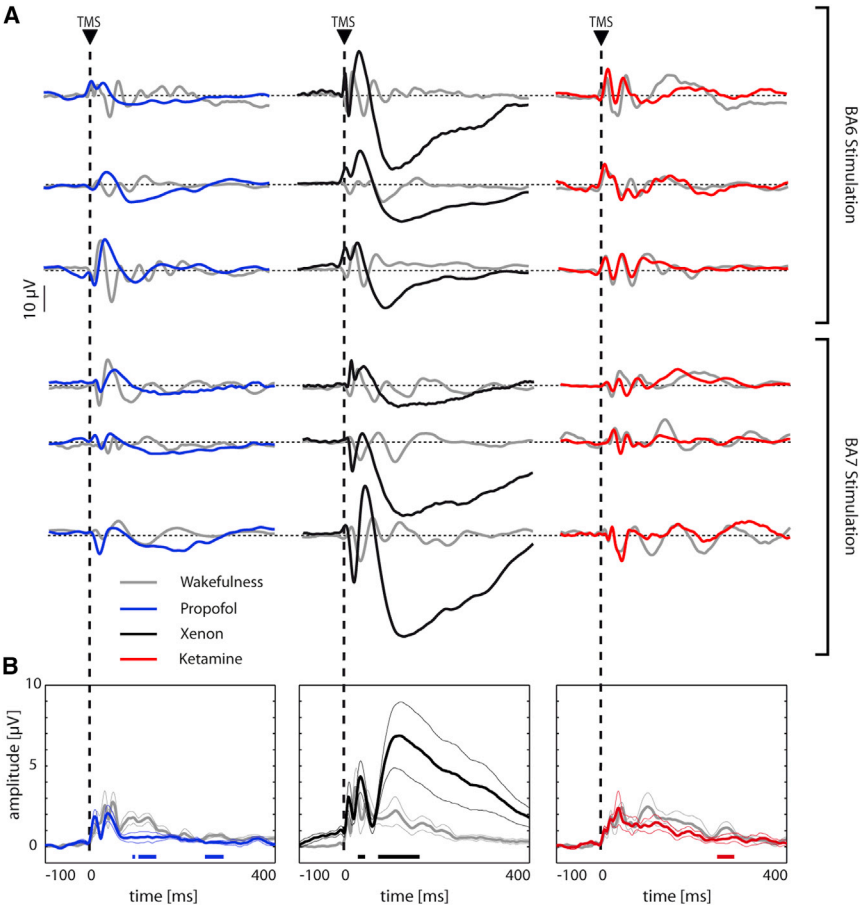

Figure 1. Different Patterns of Cortical Reactivity Induced by Propofol, Xenon, and Ketamine Anesthesia

(A) Averaged TMS-evoked potentials during wakefulness (gray traces), propofol (left, blue traces), xenon (middle, black traces), and ketamine (right, red traces) are shown for a representative EEG derivation located under the TMS coil for each of the 18 participants.

(B) Global cortical reactivity as measured by the global mean field power (GMFP) in the three experiments. Each trace (color coded as in A) represents the grand average (thick line) ± SEM (thin lines) GMFP normalized for each participant on the mean baseline value (100 ms pre-stimulus). For each experiment, statistical comparison between wakefulness and drug-induced unresponsiveness was performed by means of t tests on individual GMFP time series values. Color-coded, horizontal bars at the bottom of each panel represent significant time points (pairwise comparisons $p < 0.05$). Statistical comparisons of global cortical reactivity during the wakefulness condition across the three experiments are presented in Figure S1A. The effect of the three anesthetics on the spontaneous EEG activity patterns is presented Figure S2.

See also Figures S1 and S2.

resembling those evoked during wakefulness (Figure 1A, right). These results were confirmed when measuring the global mean field power (GMFP) for each TMS-EEG session across participants and sessions (Figure 1B). During wakefulness, the GMFP time course induced by TMS was highly reproducible across experiments (see Figure S1), in line with previous experiments [12]. During propofol-induced unresponsiveness, GMFP was reduced as compared to wakefulness soon after the first components ($p < 0.05$ at 91–94, 102–141, and 247–287 ms post-TMS). In contrast, xenon significantly increased GMFP both at early and late time points ($p < 0.05$ at 33–38 and 77–157 ms). Finally, ketamine GMFP was similar to wakefulness except for a reduction at late time points ($p < 0.05$ at 248–280 ms post-TMS).

We then characterized the spatiotemporal dynamics of TEPs by computing the corresponding cortical current density. Figure 2 shows the representative voltage and current maps during wakefulness as well as under propofol-, xenon-, and ketamine-induced unresponsiveness. As compared to wakefulness (Figure 2A), propofol-induced unresponsiveness was associated with local, short-lasting currents that did not propagate from the stimulated cortical site (white cross in Figure 2B). On the other hand, xenon resulted in a long-lasting, global response. This response was characterized by a large negative deflection associated with long-range, long-lasting currents that spread broadly to the surrounding cortex from a fixed local maximum (white cross in Figure 2C). In contrast, ketamine-induced unresponsiveness was characterized by a low-amplitude, complex wave associated with a spatially and temporally differentiated cortical activation pattern. In this case, the instantaneous maximum of cortical activation shifted over time among distant cortical areas (white cross in Figure 2D) giving rise to a widespread and complex response strongly resembling that obtained during wakefulness. We then quantified these results by generating a binary matrix from TMS-evoked significant cortical activations (Figure 3A), cumulated between 8 and 400 ms (Figure 3B). The resulting values were normalized within experiment for the wakefulness condition (see Figure S1). Results showed a larger spatiotemporal activation during xenon-induced unresponsiveness as compared to both propofol and ketamine condition (one-way ANOVA: $F_{(2,15)} = 8.47$, $p = 0.003$; pairwise comparison $p < 0.05$, Bonferroni corrected). In addition, the overall spatiotemporal activation during propofol-induced unresponsiveness was significantly reduced compared to wakefulness (mean ratio ± SEM: 0.31 ± 0.08; $n = 6$; Wilcoxon test, $Z = 2.2$, $p < 0.05$).

Finally, based on the same spatiotemporal matrices, we derived the perturbational complexity index (PCI) [13]. Figure 3C illustrates PCI values for the three experiments. A mixed-model ANOVA showed a clear "experiment" × "condition" interaction ($F_{(2,15)} = 18.08$, $p = 0.0001$). No difference was observed for wakefulness PCI values across experiments (Figure S1). Pairwise comparisons highlighted a decrease in complexity of the TMS/EEG response for both propofol-induced (mean: 0.24, range: 0.20 to 0.30) and xenon-induced (mean: 0.17, range: 0.08 to 0.24) unresponsiveness condition as compared to wakefulness

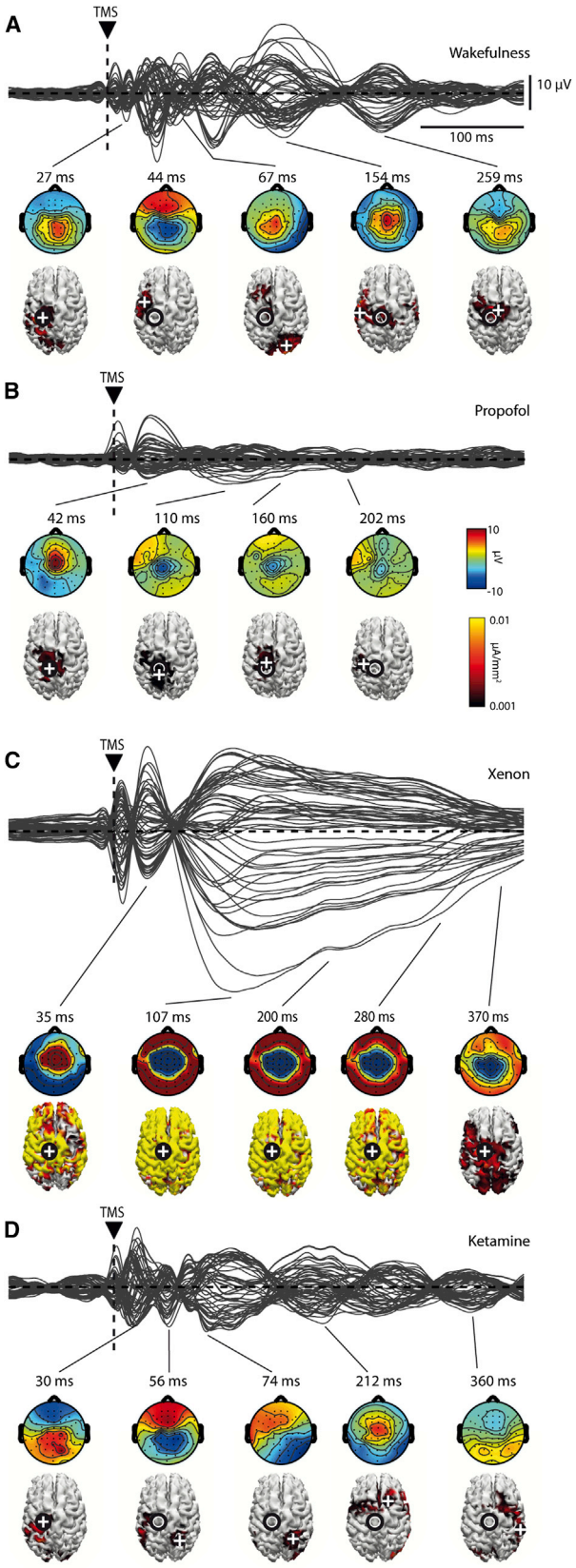

Figure 2. Different Spatiotemporal Dynamics Induced by Propofol, Xenon, and Ketamine

(A–D) Representative averaged TMS-evoked potentials at all electrodes, superimposed in butterfly plots together with voltage topographies and absolute cortical current density reconstructions estimated with L2 norm in periods of significant TMS-evoked activation during wakefulness (A), propofol (B), xenon (C), and ketamine (D). Black circle superimposed to the cortical surface represents TMS target; the current density distribution is thresholded to highlight the location of maximum current sources (white cross). The effect of the three anesthetics on the spontaneous EEG activity patterns is presented in Figure S2.

See also Figure S2.

(propofol experiment mean: 0.50, range: 0.42 to 0.59; xenon experiment mean: 0.47, range: 0.44 to 0.53; $p < 0.05$, Bonferroni corrected). On the other hand, ketamine-induced unresponsiveness was characterized by high PCI values (mean: 0.44, range: 0.35 to 0.55), comparable to those obtained during wakefulness (ketamine experiment mean: 0.48, range: 0.41 to 0.58; $p > 0.05$).

Drug-Induced Unresponsiveness Is Characterized by an Increase of Low-Frequency EEG Power

Changes in spontaneous EEG induced by the three anesthetics are reported in Figure S2. Overall, as compared to wakefulness, anesthetics induced a significant global increase in the amplitude of EEG traces accompanied by the occurrence of high-amplitude slow waves (Figure S2A). These were prominent, frequent, and rhythmic in the case of propofol and xenon (mean number of waves/min ± SEM propofol: 12.78 ± 2.88; xenon: 24.31 ± 3.82; data not shown) and sporadic as well as polymorphic in the case of ketamine (mean number of waves/min ± SEM: 2.77 ± 1.19; data not shown). Spectral analysis (Figure S2B) revealed increased slow wave activity (SWA; 0.5–4.5 Hz) for all three anesthetics ($p < 0.05$), but to a greater extent for propofol and xenon than for ketamine (one-way ANOVA: $F_{(2,15)} = 15.37$, $p = 0.001$; pairwise comparison $p < 0.05$, Bonferroni corrected). Theta (5–8 Hz) power was also increased by all three anesthetics ($p < 0.05$) to a similar extent (one-way ANOVA: $F_{(2,15)} = 0.18$, $p > 0.05$). Sigma (12–16 Hz) power increased ($p < 0.05$) only during propofol-induced unresponsiveness. Finally, power in the gamma frequency range (30–40 Hz) was decreased ($p < 0.05$) by xenon and increased ($p < 0.05$) by ketamine.

Retrospective Reports Are Present Only after Ketamine Anesthesia

Participants anesthetized with propofol or xenon did not report any conscious experiences when questioned upon emergence. One participant of the xenon experiment reported the impression of having felt something just before awakening but had no explicit recall. In contrast, all the participants of the ketamine experiment reported having experienced full-fledged dreams during the unresponsiveness phase, as previously reported [4–7, 9]. In all cases, the dream reports shared the following: (1) they contained many vivid experiences rich in visual and emotional components; (2) they had an explicit narrative structure; (3) they were extended in time; and (4) they were unrelated to the anesthesia environment. In addition to dreams, immediately upon emergence from ketamine unresponsiveness, four out of six participants reported hallucinations and perceptual

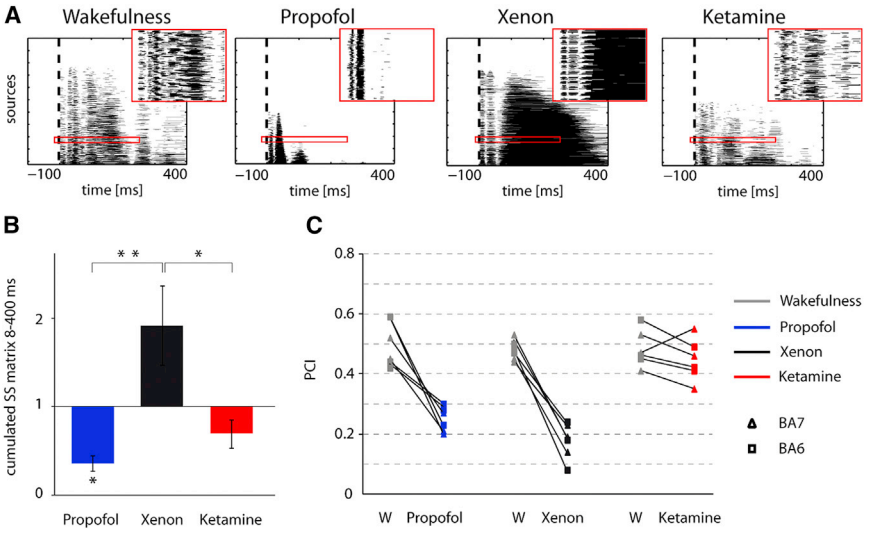

Figure 3. Overall Extent and Complexity of the Spatiotemporal Activations Induced by Propofol, Xenon, and Ketamine

(A) Representative examples of the binarized spatiotemporal matrices of significant sources (black marks: active source at a given time point; white otherwise) during wakefulness, propofol, xenon, and ketamine. In each matrix, sources are sorted from bottom to top according to their total amount of significant activation during the post-stimulus period. Vertical dashed line represents the time point in which TMS is delivered. The insets within the red frames show an expanded portion of the spatiotemporal matrix to highlight its structure at a finer grain.

(B) Average (±SEM) binarized significant post-TMS currents across cortical sources and time points (cumulated between 8 and 400 ms post-TMS) during propofol (blue), xenon (black), and ketamine (red). For each participant, values have been normalized for the values obtained in the wakefulness (W) condition. Statistical comparisons of global cortical reactivity during the wakefulness condition between the three experiments are presented in Figure S1B. *p < 0.05, **p < 0.005.

(C) Individual PCI values for the three experiments in the two conditions. Triangles indicate BA7 while squares indicate BA6 TMS cortical targets. Statistical comparisons of PCI values during the wakefulness condition across the three experiments are presented in Figure S1C.

See also Figure S1.

distortions of the surroundings, also as previously reported [7]. A representative excerpt from a ketamine dream report after emergence is included in the Supplemental Information.

DISCUSSION

In this study, we evaluated EEG responses to TMS during wakefulness and during behavioral unresponsiveness induced by propofol, xenon, and ketamine. We found that the complexity of EEG responses was high during wakefulness, low when subjects reported no conscious experiences upon emergence from anesthesia (propofol and xenon), and high when they reported intense dreams (ketamine).

During propofol, TMS triggered a low-amplitude, local positive-negative wave (Figure 1) that rapidly faded without propagating from the stimulated cortical site (Figure 2). Intracranial recordings during propofol-induced unresponsiveness suggest that the occurrence of asynchronous, local slow waves associated with periods of neuronal spiking suppression (down states) may substantially impair cortico-cortical communication [14]. The present study corroborates this view by showing that the neuronal effects of TMS remain confined to the stimulated site. The main effect of propofol is a strong enhancement of GABAergic inputs [15], which are likely involved in initiating down states in cortical neurons after an initial activation [16]. Large-scale computational models also suggest that increased inhibition is a potent mechanism for blocking cortico-cortical communication [17]. Hence, the local positive-negative wave elicited by TMS under propofol may reflect a local down state due to an increase in GABA inhibition that immediately gates cortico-cortical interactions. Consistent with this view, EEG responses to TMS delivered under anesthetic doses of midazolam, a benzodiazepine also potentiating GABA neurotransmission, are similar to those obtained with propofol, namely an initial cortical activation that remains local and fades rapidly [18]. Although the observed changes in cortical responsiveness during propofol may be contributed for by thalamic [19] and other subcortical [20] mechanisms, their role cannot be directly assessed in the current experiments.

During xenon anesthesia, instead, TMS triggered an initial positive component followed by a high-amplitude, stereotypical negative wave (Figure 1) that spread like an oil spot to the rest of the cortex (Figure 2). This pattern closely resembles the one evoked by high-intensity TMS during NREM sleep as well as spontaneously occurring sleep slow waves [21]. During NREM sleep, cortical neurons engage in large-scale bistable dynamics [22, 23] and oscillate synchronously between a depolarized up state and a hyperpolarized down state, which is reflected by a high-amplitude negative deflection in the scalp EEG. The key permissive factor that allows for the occurrence of global down states during sleep is the increased conductance of K+ channels due to the reduced firing of brainstem neuromodulatory systems [24]. Since xenon strongly potentiates the conductance of 2PK+ channels [15], in addition to antagonizing NMDA receptors, it may induce a state of diffuse cortical bistability through a similar mechanism. Hence, the large negative wave evoked by TMS during xenon anesthesia may reflect the occurrence of a widespread down state engaging large portions of the cortex, similar to evoked [25] and spontaneous [26, 27] sleep slow waves.

Finally, during ketamine-induced unresponsiveness, TMS evoked a series of fast, recurrent waves of activation (Figure 1) giving rise to a complex, long-range spatiotemporal dynamics closely resembling that evoked during wakefulness (Figure 2). While ketamine also antagonizes NMDA receptors, it does not potentiate GABA receptor activity like propofol, or K+ currents like xenon, which may explain why it may not be as effective in disrupting the complexity of cortico-cortical interactions. Furthermore, unlike propofol [28] and some inhalation anesthetics

[29], ketamine increases cortical acetylcholine concentrations [30]. A TMS/EEG response similar to that evoked by ketamine can also be recorded during REM sleep [31], a state of high cholinergic tone [32] during which subjects almost invariably experience dreams [33, 34]. Notably, during ketamine unresponsiveness, TMS evoked complex patterns of cortical interactions in a state that, at difference with REM, was characterized by the occurrence of high-amplitude slow waves in the spontaneous EEG (see Figure S2) and by unarousable unresponsiveness (Ramsay score 6).

The complexity of TMS-evoked activations was quantified by applying the PCI metric [13]. PCI computes the algorithmic compressibility of TMS-evoked deterministic activations and is high only when the initial perturbation is transmitted to a large set of integrated areas that react in a differentiated manner and low otherwise. Thus, PCI captures the joint presence of functional integration and functional differentiation in cortical circuits, which is considered a fundamental requirement for consciousness [35–37]. During both propofol and xenon, PCI values were comparable and invariably lower than in wakefulness across participants and stimulated sites. Notably, PCI was equally low despite the substantial difference in the extent of the activation evoked by TMS during propofol and xenon unresponsiveness (Figure 3C). Specifically, during propofol, PCI dropped because the matrix of activation engaged by TMS was spatially restricted (Figure 3A, second column), consistent with a loss of integration; during xenon, instead, PCI dropped because the pattern of spatiotemporal activation triggered by TMS was a widespread but stereotypical slow wave (Figure 3A, third column), consistent with a loss of differentiation. By contrast, the spatiotemporal activation during ketamine-induced unresponsiveness showed a complex pattern (Figure 3A, fourth column) leading to PCI values that were always higher than the ones obtained during propofol and xenon and comparable to those achieved during wakefulness (Figure 3C).

Complexity, Consciousness, and Responsiveness

Upon awakening from both propofol and xenon anesthesia, characterized by low PCI, all participants (n = 12) reported having had no conscious experience and/or no recall. On the other hand, when emerging from ketamine unresponsiveness, all participants (n = 6) reported conscious experience under the form of long, vivid dreams. The present report of ''ketamine dreams'' is consistent with many previous studies with pure ketamine anesthesia. In a large proportion of cases, subjects who had been unresponsive at surgical levels reported upon awakening, either spontaneously or upon questioning, that they had experienced dreams unrelated to the operating room [4, 6–9]. Assessing consciousness through retrospective reports requires a note of caution because subjects may forget their dreams or may confabulate upon awakening. However, the systematic collection of retrospective reports remains the only available procedure to behaviorally assess consciousness above and beyond responsiveness, allowing for the possibility of internally generated and stimulus-independent experiences to be recognized [38]; as such, dream reports upon awakening are commonly employed to study mentation during sleep [2, 34]. In the present study, it is unlikely that all subjects forgot their dreams upon awakening from propofol and xenon anesthesia because participants (1) were healthy volunteers with no memory deficits, (2) underwent the administration of a single anesthetic agent, and (3) were prompted for a report a few minutes after recovery of responsiveness (see [38]). On the other hand, it is unlikely that the recalls of subjects undergoing ketamine anesthesia were solely affected by confabulation or hallucinations upon emergence and recovery of responsiveness. These reports, which were collected a few minutes after recovery of responsiveness and confirmed 1 hr later, were highly structured and explicitly narrative, were rich in emotional components, and were extended in time like full-fledged dreams. Moreover, the four participants who reported hallucinations were retrospectively able to discern a long phase during which experience was completely unrelated to the external environment from a final phase (occurring upon recovery of responsiveness), characterized by perceptual distortions of the surroundings, including the experimental setting. In this context, the finding of a complex pattern of cortical interactions, typical of the awake conscious state, throughout the state of ketamine-induced unresponsiveness provides strong support to the view that consciousness and behavioral responsiveness may decouple in various conditions [1], including pharmacological interventions and brain injury [39, 40].

The finding of high brain complexity (PCI) observed during unresponsiveness induced by ketamine anesthesia is interesting in the context of previous studies employing sensory-evoked potentials and functional connectivity analyses. For example, the late positive P3b evoked by auditory stimuli is equally suppressed during both propofol [41] and ketamine [42, 43], even at sub-anesthetic concentrations, and can be absent in awake subjects who do not pay attention to the stimulus [44]. Similarly, front-to-back functional connections were found to be selectively reduced both during propofol- and ketamine-induced unresponsiveness (though coherence is preserved [45, 46]) at dosages comparable to the ones employed in the present study and in the presence of a similar background EEG. A parsimonious explanation is that while event-related potentials and fronto-parietal functional connectivity may reflect connectedness to the environment or executive functions, measuring the overall complexity of cortico-cortical effective interactions with TMS-EEG may capture the brain's capacity for experience as such, thus including ketamine dreams.

Conclusions

The present work aimed at differentiating states of equally deep unresponsiveness and profound disconnection from the external environment through direct cortical perturbations with TMS-EEG and retrospective reports. We find three distinct patterns of cortical reactivity to TMS underlying propofol-, xenon- and ketamine-induced unresponsiveness: a local, low-complexity response during propofol, a global, low-complexity response during xenon, and a complex spatio-temporal activation during ketamine. While the first two patterns are associated with loss of consciousness based on the lack of post-anesthesia reports, the complex pattern observed during ketamine precedes the report of vivid conscious experiences upon awakening. These findings are theoretically relevant, confirming the prediction that loss of consciousness during anesthesia is tied to a reduction of brain complexity, defined as the joint presence of

functional integration and functional differentiation in neural systems [47], and may have practical implications for those vegetative state patients who, just like ketamine-anesthetized subjects, often show an EEG characterized by polymorphic delta activity and may be open eyed, unresponsive, but conscious.

EXPERIMENTAL PROCEDURES

Here, we provide a brief summary of the experimental procedures. For full details, please refer to Supplemental Experimental Procedures. Eighteen healthy participants were randomly assigned to one of the three experiments (n = 6 for propofol, xenon, and ketamine, respectively). For each experiment, the EEG responses to TMS (150–200 pulses with a 2,000–2,300 ms randomly jittered period) performed over BA 6 (n = 3) and over BA 7 (n = 3) were recorded before drug administration, while the participants were fully responsive (Ramsay Scale score 2). TEPs were then recorded using the same stimulation parameters after subjects reached deep unresponsiveness (Ramsay Scale score 6, corresponding to no response external stimuli) following anesthesia administration. In addition, spontaneous EEG was also recorded during both wakefulness and unresponsiveness conditions. Finally, in order to assess the presence of conscious experience during anesthesia-induced behavioral unresponsiveness, retrospective reports were collected in all participants after awakening. We attained Ramsay Scale score 6 for all the subjects in the three experiments by employing anesthetic procedures based on previous works. Specifically, for propofol anesthesia see [45], for xenon see [48], while for ketamine we adopted induction procedures similar to [49] and anesthesia maintenance following several reports reviewed in [50]. TMS/EEG responses were quantified by calculating the GMFP [51] from the 60 channels averaged signals. Also, the primary electromagnetic sources of scalp EEG activity were calculated by performing source modeling, and the significant responses were estimated by applying a nonparametric bootstrap-based statistical procedure to TMS-evoked cortical currents as in [52]. The ensuing spatiotemporal matrices were then binarized and processed following the methods presented in [13] in order to derive PCI. Spontaneous EEG signals were analyzed computing power spectral density estimates with a 2-s Hamming window. Average power density across segments was computed for SWA, theta, alpha, sigma, beta, and gamma frequency bands. Data analysis was performed using the MATLAB (MathWorks) signal processing toolbox as well as custom scripts and EEGLAB (http://sccn.ucsd.edu/eeglab/) routines. Comparisons between conditions (wakefulness, unresponsiveness) within the same experiment were performed by means of the non-parametric Wilcoxon signed-rank test ($p < 0.05$). When testing differences across experiments, mixed-model ANOVAs were performed. To test contrasts, post hoc two-tailed t tests were used ($p < 0.05$, Bonferroni corrected).

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and two figures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.10.014.

AUTHOR CONTRIBUTIONS

M.B., J.-F.B., G.T., S.L., and M.M. designed the research. M.B., M.N., O.G., V.C.-V., S.C., M.R., P.B., S.R., and M.M. performed the research. S.S., M.N., S.C., and A.G.C. analyzed the data. S.S., M.B., G.T., and M.M. wrote the paper.

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