Brain Imaging and Behavior (2019) 13:514–525
https://doi.org/10.1007/s11682-018-9886-0

ORIGINAL RESEARCH

Regional entropy of functional imaging signals varies differently in sensory and cognitive systems during propofol-modulated loss and return of behavioral responsiveness

Xiaolin Liu[1] · Kathryn K. Lauer[2] · B. Douglas Ward[3] · Christopher J. Roberts[2] · Suyan Liu[2] · Suneeta Gollapudy[2] · Robert Rohloff[4] · William Gross[2] · Zhan Xu[3] · Shanshan Chen[5] · Lubin Wang[5] · Zheng Yang[5] · Shi-Jiang Li[3] · Jeffrey R. Binder[4] · Anthony G. Hudetz[6]

Published online: 8 May 2018

Abstract

The level and richness of consciousness depend on information integration in the brain. Altered interregional functional interactions may indicate disrupted information integration during anesthetic-induced unconsciousness. How anesthetics modulate the amount of information in various brain regions has received less attention. Here, we propose a novel approach to quantify regional information content in the brain by the entropy of the principal components of regional blood oxygen-dependent imaging signals during graded propofol sedation. Fifteen healthy individuals underwent resting-state scans in wakeful baseline, light sedation (conscious), deep sedation (unconscious), and recovery (conscious). Light sedation characterized by lethargic behavioral responses was associated with global reduction of entropy in the brain. Deep sedation with completely suppressed overt responsiveness was associated with further reductions of entropy in sensory (primary and higher sensory plus orbital prefrontal cortices) but not high-order cognitive (dorsal and medial prefrontal, cingulate, parietotemporal cortices and hippocampal areas) systems. Upon recovery of responsiveness, entropy was restored in the sensory but not in high-order cognitive systems. These findings provide novel evidence for a reduction of information content of the brain as a potential systems-level mechanism of reduced consciousness during propofol anesthesia. The differential changes of entropy in the sensory and high-order cognitive systems associated with losing and regaining overt responsiveness are consistent with the notion of "disconnected consciousness", in which a complete sensory-motor disconnection from the environment occurs with preserved internal mentation.

Keywords Consciousness · Anesthesia · Entropy · Propofol sedation · Resting-state fMRI

Introduction

The richness of conscious experience is thought to depend on the brain's information capacity and the amount of integrated information (Tononi 2004; Tononi 2008; Oizumi et al. 2014). General anesthesia may suppress consciousness by reducing

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11682-018-9886-0) contains supplementary material, which is available to authorized users.

✉ Xiaolin Liu
xiliu@mcw.edu

✉ Anthony G. Hudetz
ahudetz@med.umich.edu

[1] Department of Radiology, Center for Imaging Research, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA

[2] Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI, USA

[3] Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI, USA

[4] Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

[5] Cognitive and Mental Health Research Center, Beijing Institute of Basic Medical Sciences, Beijing, China

[6] Department of Anesthesiology and Center for Consciousness Science, University of Michigan, 1301 East Catherine Street, Ann Arbor, MI 48109, USA

the brain's information capacity or disrupting its ability to integrate information (Alkire et al. 2008). To date, most investigations have focused on identifying anesthetic-induced changes of functional connectivity in large-scale brain networks as surrogate measures of disrupted information integration (Alkire 2008; Bonhomme et al. 2012; Hudetz 2012; Mashour 2014; Uhrig et al. 2014). In comparison, anesthetic modulation of information content in the brain has received considerably less attention. Particularly, an understanding of the region-specific effects of anesthetics on information content carried by signals of brain imaging modalities remains undetermined.

Intrinsic spontaneous brain activity measured by brain imaging exhibits incessantly changing spatiotemporal patterns (Britz et al. 2010; Chang and Glover 2010; Hutchison et al. 2013; Allen et al. 2014; Di and Biswal 2015) that may underlie the dynamic nature of the stream of consciousness (Mason et al. 2007). Presumably, if the repertoire of discriminable patterns exhibited at a given spatiotemporal scale were to shrink, for example, under the influence of anesthesia; information content and therefore, the amount of integrated information expressed by the intrinsic neural activities would be reduced. To date, direct evidence of anesthetic-modulated changes of the repertoire of brain states has been scarce, especially with functional imaging that could provide spatially detailed functional representation of the entire brain. A reduced repertoire of electroencephalographic responses to external perturbation with transcranial magnetic stimulation was observed during states of diminished consciousness in sleep, anesthesia, and patients with disorders of consciousness (Massimini et al. 2005; Ferrarelli et al. 2010; Casali et al. 2013; Casarotto et al. 2016). A handful of empirical studies (Barttfeld et al. 2015; Hudetz et al. 2015; Sarasso et al. 2015; Hudetz et al. 2016; Tagliazucchi et al. 2016), together with a few computer simulation studies (Steyn-Ross et al. 2001; Hudetz et al. 2014; Tagliazucchi et al. 2016), has suggested a reduction of the repertoire or the overall complexity of intrinsic brain states in anesthesia-induced loss of consciousness. Conversely, an increase of the variance or equally, the entropy of voxel-based functional imaging signals in the hippocampal region was observed in a psychedelic state induced by an injection of psilocybin, which presumably increases the criticality of brain activities (Carhart-Harris et al. 2014; Tagliazucchi et al. 2014). A few studies identified agent-dependent effects of anesthetics on the entropy of electroencephalogram (EEG) signals acquired on the brain surface (Sleigh and Donovan 1999; Bruhn et al. 2000; Vakkuri et al. 2004; Maksimow et al. 2006). However, the EEG provides limited spatial information for characterizing the effect of anesthetics on the entropy of deep cortical and subcortical brain regions. Moreover, different EEG-based entropy and complexity measures may produce conflicting results (Ferenets et al. 2006). In summary, a systematic examination of the region-specific effects of anesthesia on information content measured by functional brain imaging is lacking, especially in critical conditions associated with the change of the state of consciousness during anesthesia as indicated by the loss and return of overt responsiveness.

General anesthetics appear to suppress human consciousness and cognition in a graded manner. At a light sedative dose, anesthetics disrupt memory and lead to lethargic responses (Sanders et al. 2012), suggesting a reduction of information content and integration. At a higher dose, anesthetics lead to complete behavioral unresponsiveness, suggesting a loss of *external awareness*, i.e., awareness of the external environment, also known as a state of *disconnected consciousness* (Sanders et al. 2012). However, such a loss of *external awareness* does not necessarily indicate that *internal awareness*, i.e., the subjective experience of internally generated thoughts, images, and dreams, is erased (Sanders et al. 2012; Boly et al. 2013; Hudetz and Mashour 2016). Disconnected consciousness may be due to a disconnection of low-order sensory systems from high-order cognitive systems, with the latter continuing to maintain a residual level of information processing capacity for the generation of internal awareness, such as dreams (Leslie et al. 2009; Sanders et al. 2012). Insight into this possibility may be gained by investigating if the information content carried by brain imaging signals in sensory and high-order cognitive systems are differentially modulated by anesthetics during the critical stages of losing and regaining behavioral responses.

Accordingly, the goal of this study was to determine the region-specific changes of information content in the brain during graded, propofol-induced alterations of the state of consciousness as indexed by behavioral responsiveness. Intrinsic brain activity was measured using resting-state functional magnetic resonance imaging (rs-fMRI), which is a unique tool for mapping state-dependent intrinsic, spontaneous brain activities with high spatial precision (Biswal 2012). We scanned healthy volunteers in four states of consciousness: wakeful baseline (conscious), light sedation (conscious), deep sedation (loss of behavioral responsiveness), and the subsequent recovery state (the state immediately following the return of conscious responses after anesthesia). The region-specific information content carried by rs-fMRI signals was assessed by the entropy (H) of regional voxel blood oxygen level-dependent (BOLD) fMRI signals based on the definition of Shannon entropy for Gaussian processes. To make the calculations mathematically tractable, entropy was calculated from the principal components of regional voxel BOLD fMRI signals. By performing the analysis across neuroanatomically defined brain regions, a quantitative evaluation of the region-specific effects of propofol sedation on the information content of rs-fMRI signals could be obtained across the four states of consciousness.

With this approach, we tested two specific hypotheses. First, we hypothesized that, consistent with the theory of

information integration, propofol sedation would be associated with a general reduction of information content across the brain. Second, motivated by the theory for *disconnected consciousness* (Sanders et al. 2012; Boly et al. 2013), we hypothesized that information content in the sensory and high-order cognitive systems may be differentially modulated when behavioral responsiveness is lost and regained. Specifically, we theorized that the change of state of overt behavioral responsiveness would be related to entropy changes in the sensory systems, consistent with disconnection, rather than to those in high-order cognitive systems that support the potential generation of conscious mentation. As we show, our results indeed reveal region-specific entropy modulation by propofol, which supports our hypotheses. Thus, our findings suggest a systems-level mechanism for the presence of disconnected consciousness in deep propofol sedation.

Materials and methods

The experimental protocol was approved by the Institutional Review Board of the Medical College of Wisconsin (MCW). Data analyzed here were obtained previously as described in a former publication (Liu et al. 2017).

Study participants

Fifteen healthy volunteers aged 19–35 years (nine males and six females, mean age 26.7 years, standard deviation 4.8, body mass index <25) provided written informed consent to participate in this study. Participants consisted of native English speakers recruited from MCW communities with no history of neurological or psychiatric conditions.

Propofol administration

The anesthetic agent propofol was administered with a bolus dose followed by a target-controlled continuous infusion (STANPUMP) (Shafer 1996). We targeted a plasma concentration of 0.98 ± 0.18 μg ml^{-1} for light sedation and 1.88 ± 0.24 μg ml^{-1} for deep sedation. If necessary, the target plasma concentration was adjusted to achieve the desired state of sedation in each participant. The lower dose for light sedation was intended to induce a lethargic response to questions in participants (OAAS [observer's assessment of alertness/sedation] score: 4; (Chernik et al. 1990)). The higher dose for deep sedation was chosen to achieve the desired endpoint at which the participant showed no response when his/her name was called loudly at the scanner bedside and did not respond to mild prodding and shaking (OAAS score: 2–1). American Society of Anesthesiologists standard monitoring, including pulse oximetry, noninvasive blood pressure, electrocardiogram, and end tidal carbon dioxide, was followed for all subjects by a faculty anesthesiologist. Supplemental oxygen was administered (2 L/min) via nasal cannula.

Resting-state imaging acquisition

Structural and rs-fMRI data were acquired using a whole-body 3 T Signa GE scanner (GE Healthcare, Waukesha, WI, USA) with a standard 32-channel transmit-receive head coil. Functional imaging data were acquired during each of four 15-min scans in wakefulness, light sedation, deep sedation, and recovery, respectively, with repetition time (TR), 2 s; total volumes, 450; echo time, 25 ms; slice thickness, 3.5 mm; in-plane resolution, 3.5 × 3.5 mm; number of slices, 41; flip angle, 77°; field of view, 22.4 cm; matrix size, 64 × 64. High-resolution three-dimensional spoiled gradient-recalled echo axial images were acquired before functional scans with TE/TR/TI, 3.2/8.2/450 ms; slice thickness, 1 mm; 150 slices; flip angle, 12°; field of view, 24 cm; matrix size, 256 × 256.

Imaging data preprocessing

Imaging data preprocessing was conducted using a combination of Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/afni), Statistical Parametric Mapping (SPM, http://www.fil.ion.ucl.ac.uk/spm), FMRIB Software Library (FSL, (http://www.fmrib.ox.ac.uk), and Matlab software (MathWorks, Natick, MA, USA). Raw functional images first underwent retrospective correction for physiological motion effects using recorded cardiac and respiratory activities (*3dretroicor* in AFNI). The first five data points were discarded to reduce the initial transient effects in data acquisition. Subsequent data preprocessing included slicing timing correction (*3dTshift* in AFNI), despiking (*3dDespike* in AFNI), and motion correction (*mcflirt* in FSL, producing three translational and three rotational parameters for each volume image). No significant differences of head motion ranges were found among the four functional scan conditions. Physiological noise was estimated using the average voxel BOLD fMRI signals from regions of white matter (WM) and cerebrospinal fluid (CSF) determined in each individual's anatomical images. The BOLD fMRI signals from each run were then analyzed in a voxelwise manner using a general linear regression model (*3dDeconvolve* in AFNI) with eight regressors representing noise artifacts from the motion parameters, WM, and CSF, respectively. The residual voxelwise time courses from the regression analysis were considered as the resting-state BOLD fMRI signals with potential noise contaminations minimized. The denoised functional data were then transformed into the MNI (Montreal Neuroimaging Institute) space (MNI152; *flirt* in FSL) with resampling to a 3-mm cubic voxel size. In the MNI space, the functional data were further cleaned by regressing out potential artifacts originating from the subregions of the WM, CSF,

and major vein (e.g., the superior sagittal sinus) areas. The cleaned voxelwise BOLD fMRI signals were then standardized to z-scores (i.e., zero mean and unity standard deviation) and bandpass filtered to preserve only the amplitude of low-frequency fluctuations within 0.01–0.1 Hz for the subsequent analysis of regional information capacity.

Computation of PCA-based entropy of regional voxel BOLD fMRI signals

Regional information capacity was quantitatively assessed by the Shannon entropy (H) of voxel-based BOLD fMRI signals contained within individual neuroanatomical regions,

$$H = (1/2) * \log((2\pi e)^n * \det(COV)), \quad (1)$$

where n is the number of voxels (variables), COV is the covariance matrix of all voxel BOLD fMRI time series, and det(COV) denotes the determinant of the covariance matrix. Eq. 1 assumes that the distribution of the participating signal time series is Gaussian (Gokhale et al. 1989).

Entropy is a quantitative measure of uncertainty about the state of a dynamic system, with the uncertainty expressed by useful information and/or noise (Ben-Naim 2012). The entropy of a region-specific collection of voxel BOLD fMRI signals with minimized influence of noise indicates the extent to which regional neural activities acquire dynamic spatiotemporal configurations that recur and fade over time. When applied directly to regional voxel-based BOLD fMRI signals, the entropy formula (Eq. 1) suffers from a practical limitation due to the large number of voxels (variables in the signal space) and the strong linear dependency among individual voxel BOLD time series. This collinearity results in a near-zero determinant of the covariance matrix, making the calculation of entropy using Eq. 1 practically unfeasible. This limitation, however, can be overcome by calculating the entropy of the principal components (PCs) of regional voxel BOLD fMRI signals. Principal component analysis (PCA) is an effective way to reduce the dimension of multivariate BOLD fMRI signals into a set of linearly uncorrelated variables (PCs). The number of the first few significant PCs can be determined by specifying the total percentage of variance explained (PVE), achieving both a reduction of the dimensionality in the signal space and a further reduction of noise with the preprocessed BOLD fMRI signals.

The calculation of the PCA-based entropy of regional voxel BOLD fMRI signals was based on volumetric rs-fMRI data. The final results were overlaid on the brain surface (*fsaverage* in FreeSurfer) for a better visualization. First, a segmentation of 116 anatomical regions covering the whole brain was obtained using a standard brain atlas (Tzourio-Mazoyer et al. 2002) in the MNI space. For each participant, BOLD fMRI time series of all voxels included in each of the 116 anatomical regions were arranged into a data matrix, resulting in 116 matrices with column entries of each matrix representing individual voxels (variables) and row entries representing BOLD signals indexed by time (TR = 2 s). PCA was then conducted with each of the 116 matrices. The number of the first few significant PCs was then determined for each anatomical region by varying the PVE threshold across a range of values, i.e., 70%, 80%, 85%, and 90%, respectively. Next, the covariance matrix (COV) of the sets of PCs obtained at each PVE threshold was computed and the corresponding entropy was subsequently obtained using Eq. 1 for each anatomical region. In our analyses, we found that varying the PVE threshold across a range of values does not significantly alter the results and conclusions of our study. In this study, we chose to report the primary results obtained at the PVE threshold of 85%.

To examine the general trend of anesthetic-dependent regional changes in the number of PCs (the dimension of the signal space) and entropy (information content) at the chosen PVE threshold (i.e., 85%), the group mean differences of the two measures among the four conditions were calculated for each of the 116 anatomical regions, resulting in a total of six paired-state comparisons for each anatomical region. The six paired-state comparisons were arranged in the order of increasing dose to aid the visualization of anesthetic effects using a same colormap. To quantify changes in the number of PCs and entropy in the sensory and high-order cognitive systems of the brain, group paired *t*-tests of both measures were conducted for two sets of six well-known regions in each system. The set of sensory regions consisted of (1) sensorimotor cortex, (2) visual cortex, (3) superior temporal gyrus (STG; the auditory cortex), (4) fusiform gyrus (facial information encoding), (5) orbital prefrontal cortex (PFC; reward and olfactory information encoding), and (6) thalamus (relay of sensory information). The set of high-order cognitive regions contained (1) bilateral PFC and medial superior PFC (msPFC); (2) insula; (3) anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and precuneus; (4) supramarginal gyrus (SMG) and angular gyrus (AG); (5) hippocampus and parahippocampal gyrus; and (6) temporal poles. We report the results significant at $P < 0.05$.

Results

The statistical distribution of data of PCs

We performed a one-sample Kolmogorov-Smirnov test with the individual PC scores obtained in all 116 anatomical regions of all subjects to test the null hypothesis that data in individual PC scores come from a Gaussian distribution at its mean and standard deviation. The results indicated that 99.0%, 98.8%, 97.7%, and 99.0% of the PC scores of all subjects in wakeful baseline, light sedation, deep sedation, and recovery, respectively, were consistent with the null hypothesis at the 1%

significance level. Therefore, on average, more than 98.5% of the obtained PC scores could be considered coming from Gaussian distribution, supporting the calculation of entropy using Eq. 1 based on the PCs of regional voxel BOLD fMRI signals.

The number of PCs and entropy in the four states of consciousness

The resulting total number of PCs (i.e., the sum of the number of PCs across the 116 regions) in individual subjects varied in a state-dependent manner with the highest number found in wakeful baseline. The number of PCs was moderately reduced in light sedation, further reduced in deep sedation, and returned to the same level as in light sedation in recovery (Fig. 1a top). The same trend was present with the total amount of entropy (i.e., the sum of entropy across the 116 regions) in individual subjects across the four states of consciousness (Fig. 1a bottom). We found that the regional number of PCs and entropy obtained at the chosen PVE threshold (i.e., 85%) were linearly dependent on the number of voxels contained within individual anatomical regions (Fig. 1b and c). For both PCs and entropy, the amplitude of the linear regression line was greater in wakeful baseline than in deep sedation, with those of light sedation and recovery falling in between. Therefore, entropy also scales proportionally with the number of PCs obtained in individual anatomical regions (Fig. 1d). These results indicate that deepening the level of sedation was associated with a decrease in the total number of PCs and entropy identified in individual subjects, and that the decreasing trend was partially reversed in recovery. Varying the PVE threshold across a range of values (e.g., 70%, 80%, 85%, and 90%) did not alter the observed trends.

Regional group mean entropy in the four states of consciousness

To examine the region-specific entropy changes among the four states of consciousness, six pair-wise state comparisons of regional group mean entropies were performed. In light sedation compared with wakeful baseline, group mean entropy decreased in all brain areas (Fig. 2a). The entropy further decreased in deep sedation, especially in the major sensory cortices (Fig. 2b). Contrasting light and deep sedation revealed entropy decreases in most sensory information-processing areas including the auditory, visual, and somatosensory cortices; fusiform gyrus; and regions of the orbital PFC (Fig. 2c). In contrast, there was no change in group mean entropy in high-order cognitive regions including the bilateral PFC, ACC, PCC, insula, and others. In the recovery state, the decreases in entropy were reversed in the same set of sensory

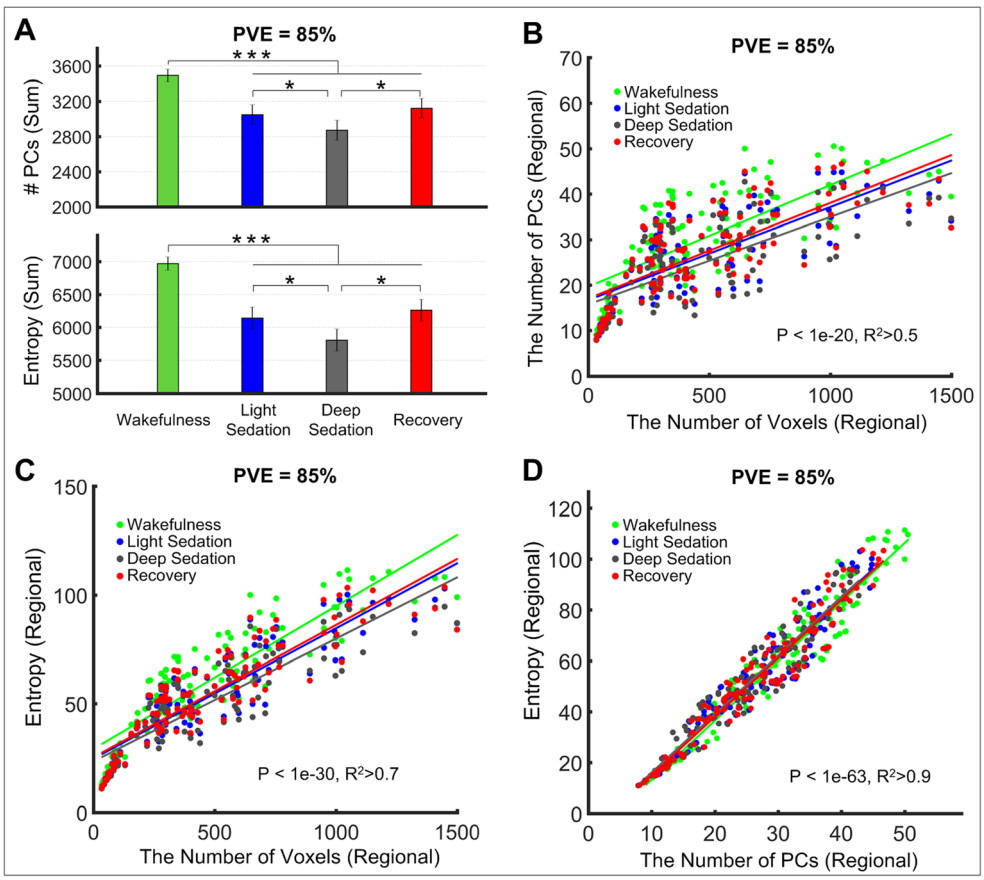

Fig. 1 The regional number of PCs and entropy in the four states of consciousness. a The sums of the number of PCs (top) and entropy (bottom) across all 116 anatomical regions obtained at the 85% PVE threshold in all 15 participants in the four states of consciousness. **b** The linear relationship between the regional number of voxels and PCs in all study participants in the four states of consciousness. **c** The linear relationship between the regional number of voxels and regional entropy in all study participants in the four states of consciousness. Note the similarity of distributions to (**b**). **d** The linear relationship between the regional number of PCs and regional entropy in the four states of consciousness. Entropy scales linearly with the number of PCs

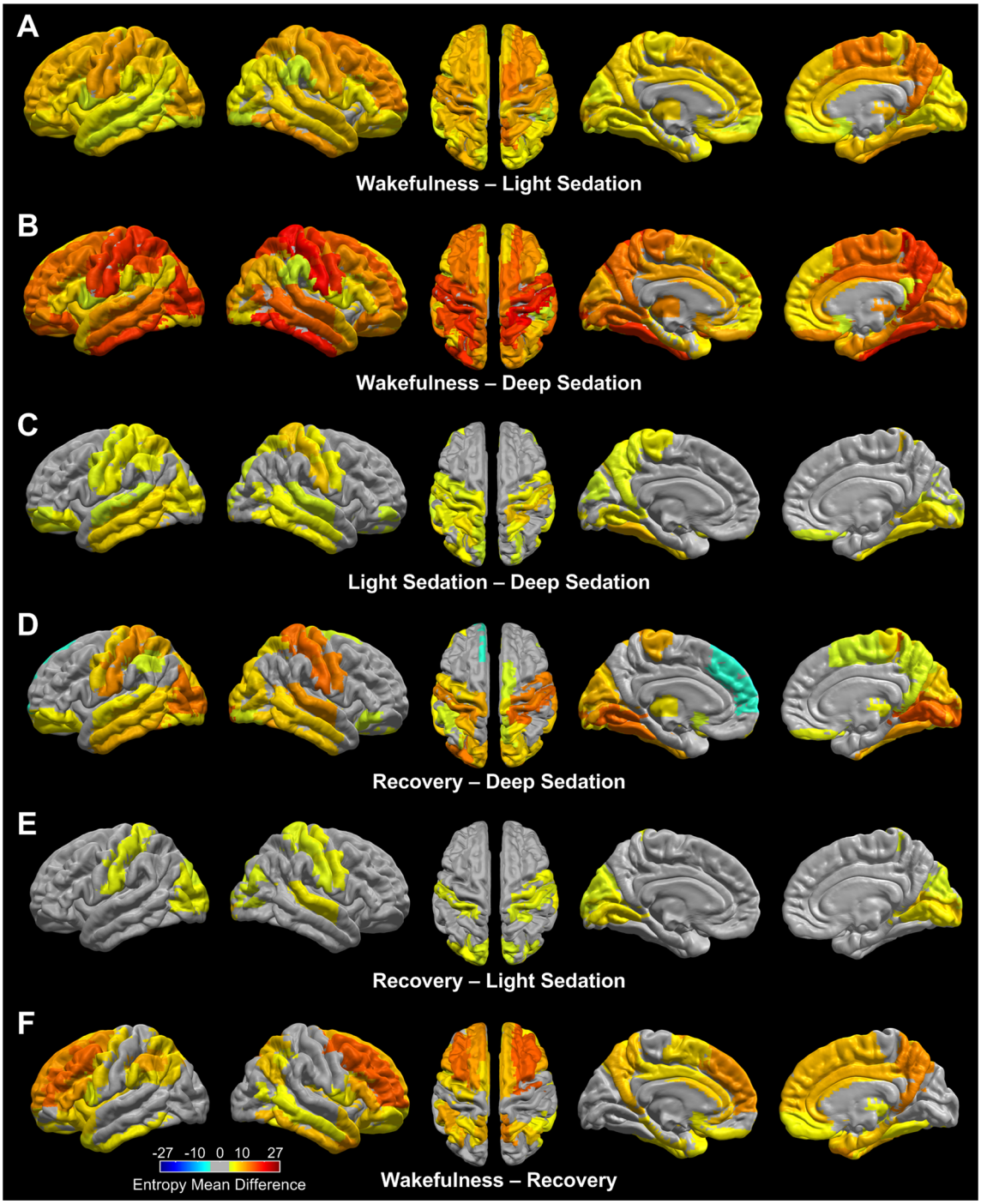

Fig. 2 Pairwise comparisons of group mean entropy among the states of consciousness. a–f Group mean differences in entropy among the four states of consciousness at the PVE threshold of 85%. Data from 90 anatomical regions are mapped onto the brain surface (*fsaverage* in Freesurfer). Regions with differences near zero are shown in gray to allow emphasis of changes in other regions. The results suggest that anesthetic suppression of consciousness is associated with a trend for global decrease of entropy across the entire brain (**a** – **b**). The critical transitions of losing and regaining overt responsiveness (used to index consciousness) are associated respectively, with a significant decrease and increase of entropy in the sensory systems but not in the high-order cognitive systems (**c**–**f**)

regions (Fig. 2d), with additional increases in the thalamus, right parietal lobule, and right cuneus and precuneus.

Contrasting recovery and light sedation (Fig. 2e) revealed a similar trend of increased group mean entropy in sensory cortices but to a lesser extent than in contrasting recovery and deep sedation (i.e., Fig. 2d). Contrasting wakeful baseline and recovery (Fig. 2f) showed that entropy was restored during recovery in most sensory systems but not in the high-order cognition regions including the bilateral PFC, insula, cingulate cortices, precuneus, AG, hippocampus, and temporal poles.

The corresponding changes of the regional number of PCs across the PVE thresholds were similar to those of the group mean entropies (Supplemental Fig. 1). Together, these results suggest that the loss and return of behavioral responsiveness from light to deep sedation and to recovery was predominantly associated with a decrease and increase in entropy and in the number of PCs in the sensory systems but not in the high-order cognitive systems.

State-dependent changes of entropy in the sensory and high-order cognitive systems

In further data analysis, state-dependent changes in the number of PCs and entropy were evaluated in six sets of sensory-information-processing-related regions including the sensorimotor cortex, visual cortex, STG, fusiform gyrus, orbital PFC, and thalamus (Fig. 3a–b). Compared with wakeful baseline and recovery, deep sedation was associated with a significant decrease in the number of PCs and entropy in all the sensory regions (20.8% ± 3.3% and 19.1% ± 2.6% reduction, respectively). In addition, a decreasing trend from wakeful baseline to light sedation and then to deep sedation was present in the six sets of sensory regions.

We also evaluated the state-dependent changes of the number of PCs and entropy in six sets of brain regions involved in high-order cognition, memory, and multimodal information integration. These regions included the bilateral PFC and medial PFC; insula; ACC, PCC, and precuneus; SMG and AG; hippocampus and parahippocampal gyrus; and temporal poles. Compared with wakefulness, the states of light sedation, deep sedation, and recovery showed significant decreases in the number of PCs and entropy in the six sets of regions (Fig. 3c–d). However, there were no significant differences in the number of PCs and entropy among light sedation, deep sedation, and recovery, suggesting that, after the initial decrease in light sedation, neither the number of PCs nor the entropy of the high-order cognitive systems correlated with the loss and return of overt behavioral responsiveness in deep sedation and recovery.

Discussion

Understanding how information processing in various brain systems is altered during anesthetic-induced loss and return of conscious responsiveness provides an important insight into the neurobiological mechanisms of consciousness and general

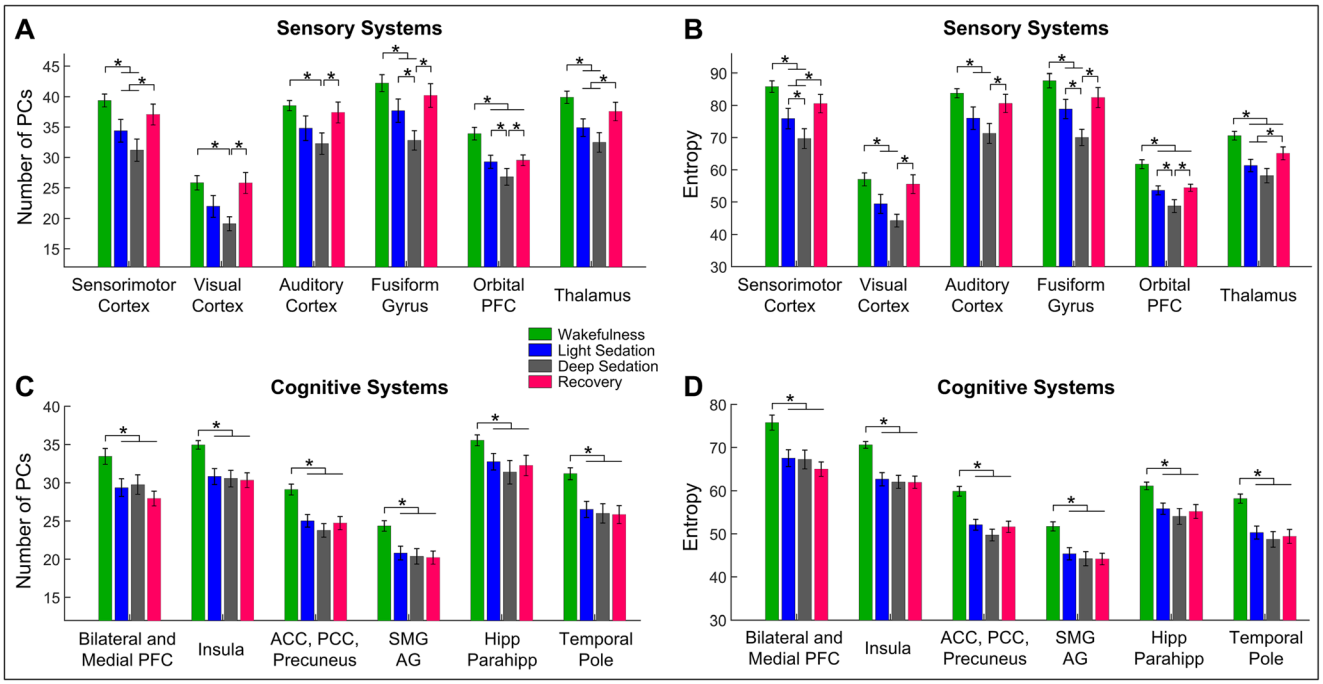

Fig. 3 State-dependent changes of the number of PCs and entropy in the sensory and high-order cognitive systems. a State-dependent changes in the number of PCs (group paired *t*-tests) in six sets of sensory information processing-related systems consisting of the sensorimotor cortex, visual cortex, auditory cortex, fusiform gyrus, orbital PFC, and thalamus. **b** State-dependent changes in entropy in the same six sets of sensory systems. **c** State-dependent changes in the number of PCs in six sets of high-order cognitive systems consisting of the bilateral PFC and msPFC; insula; ACC, PCC, and precuneus; SMG and AG; hippocampus (Hipp) and parahippocampal (Parahipp) gyrus; and temporal poles. **d** State-dependent changes in entropy in the same six sets of high-order cognitive systems. The number of PCs and entropy of the sensory systems vary consistently with the state of consciousness. In contrast, the number of PCs and entropy of the high-order cognitive systems decrease to their minimum in light sedation, remain at the same level in deep sedation, and do not reverse upon the recovery of consciousness. (*: $P <= 0.05$; error bars represent the standard error of measurement)

anesthesia. From an information theory perspective, the amount of information generated by a dynamic system is equivalent to the degree of uncertainty of its intrinsic states measured by the system's entropy, given that the influence of noise is minimized (Ben-Naim 2012). A high entropy of intrinsic brain activity indicates a high degree of uncertainty and, therefore, a rich repertoire of intrinsic metastable states that the brain can access over time (Haldeman and Beggs 2005; Shanahan 2010; Carhart-Harris et al. 2014; Tognoli and Kelso 2014). According to the Information Integration Theory (Tononi 2004; Oizumi et al. 2014), the richness of conscious experience is dependent on the diversity or "repertoire" of causal states available to the brain, and anesthesia may suppress consciousness by shrinking this repertoire or, equivalently, information capacity (Alkire et al. 2008). Using a novel PCA-based entropy analysis of regional voxel BOLD fMRI signals, our study provides direct evidence for the global reduction of information content in the brain during propofol-induced reduction of consciousness. Moreover, we show, for the first time, that the amount of information as carried by rs-fMRI signals in sensory and high-order cognitive systems is differentially modulated by propofol sedation during the critical stages of losing and regaining behavioral responsiveness.

It is worth emphasizing that entropy can be assessed at different spatial scales, from the level of single imaging voxels to large-scale networks. The appropriate scale of spatiotemporal organizational at which the repertoire of brain states should be defined and assessed is currently undetermined. Previously, the entropy of BOLD fMRI signals at the single voxel level as well as motifs of brain network connectivity were used to characterize alterations of the repertoire of brain states in altered states of consciousness (Carhart-Harris et al. 2014; Tagliazucchi et al. 2014; Huang et al. 2016). Entropy measures were also applied to brain networks identified by spatial independent component analysis in individuals receiving propofol sedation (Schrouff et al. 2011). In this study, we examined entropy at a spatial scale of neuroanatomical regions (Tzourio-Mazoyer et al. 2002). Because the input data for calculating entropy (Eq. 1) were the PCs of regional voxel BOLD fMRI signals, the derived entropy reflects the extent of richness of the instantaneous functional configurations of voxels in individual anatomical regions. This is a consequence of the definition that each PC is a linear combination of regional voxel signals. These functional configurations may be considered metastable functional states of the brain as constrained by neuroanatomical organization for two reasons. First, the macroscopic anatomical boundaries have a general, though imperfect, relation to functional boundaries. Second, according to the theory of nested network organization of the central nervous system, the basic functional units of the brain first emerge within individual anatomical structures (Agnati et al. 2004; Sporns et al. 2007). In future comparative studies, it will be important to clearly define the spatiotemporal scale as well as the neurophysiological meaning of entropy measures.

To assess regional information content measured by rs-fMRI, a direct calculation of entropy using voxel-based BOLD fMRI signals is not feasible because of the presence of collinearity among individual voxel signals within each anatomical region. To overcome this limitation, we applied a PCA-based approach to quantify entropy carried by regional BOLD fMRI signals. We showed that the time series of a predominant portion of the PC (>98.5%) conformed to the Gaussian distribution, supporting the use of Eq. 1 for entropy calculation. The predominantly Gaussian distribution of PCs is probably due to fact that each PC is a linear combination of many voxel BOLD fMRI signals within each anatomical region. According to the central limit theorem, the resulting time series of individual PCs converge to Gaussian distribution.

A few former studies more directly estimated the repertoire of brain states during anesthesia. Dynamic functional connectivity patterns derived from the short-time sliding-window analysis of rs-fMRI showed that wakefulness was associated with a rich repertoire of functional configurations that deviated from the anatomical structure more often than it did during anesthesia (Barttfeld et al. 2015; Tagliazucchi et al. 2016; Ma et al. 2017). A reduction in the temporal variability of regional homogeneity of BOLD fMRI signals suggested a reduced repertoire of large-scale brain states (Hudetz et al. 2015) and predicted reduced functional complexity (Hudetz et al. 2016). Computer simulations using a mean-field model (Steyn-Ross et al. 1999), a modified spin-glass model (Hudetz et al. 2014), and the Greenberg-Hastings model (Haimovici et al. 2013; Tagliazucchi et al. 2016) also predicted a reduction in the repertoire of brain states in anesthesia. Our findings add to the current body of literature, providing further evidence about the relationship between regional information from BOLD rs-fMRI and altered states of consciousness by propofol sedation.

A key finding of our study is the differential modulation of information content by propofol in the sensory and high-order cognitive systems. Specifically, the transition from light to deep sedation, the critical step in losing behavioral responsiveness, was marked by a significant additional decrease in entropy of the sensory systems but not of the high-order cognitive systems. Subsequently, the recovery of consciousness was accompanied by a reversal of the entropy decrease in the sensory systems alone. At first sight, we found this result surprising. Prior investigations reported that task-related BOLD response in the primary sensory cortices is reduced but preserved during anesthesia (Plourde et al. 2006; Davis et al. 2007; Bonhomme et al. 2011; Liu et al. 2012). In contrast, task-related responses in higher-order frontal-parietal regions, as well as their resting-state functional connectivity with the lower sensory regions, are suppressed during

anesthesia-induced unconsciousness (Bonhomme et al. 2011; Liu et al. 2012). Thus, prior observations suggest a primary role for the high-order association regions and networks in supporting consciousness. At variance, here we found that the entropy was reduced in the higher-order cognitive systems during light sedation only, whereas the change in entropy of the sensory systems was dose- or state-dependent. Clearly, the regional information content measured by entropy and task-related activation are not the same and probably reflect different functional properties of regional neural activities. While under sedation the sensory regions may still respond to stimulation, the information content processed by these structures may be distorted or diminished, due to a reduction of their representational diversity or complexity, and thus may not be properly interpreted and transmitted upstream. Meanwhile, higher-order cognitive systems engaged in processing internally generated information may continue to function autonomously, disconnected from the sensory systems, contributing to generate endogenous subjective experience. Thus, our findings do not invalidate the earlier activation- and connectivity-based findings in anesthesia. Rather, they support a different behavior of information-based properties in various brain systems modulated by anesthetics.

Our findings are also consistent with the recently proposed concept of "disconnected consciousness" (Sanders et al. 2012) that more precisely defines the state of complete behavioral unresponsiveness produced by general anesthesia. This state presumes a loss of "external awareness," i.e., the awareness of the entire environment and all exogenous sensory stimuli, but allows for "internal awareness," i.e., the possibility to have subjective experience of internally generated thoughts, images, or dreams (Sanders et al. 2012; Boly et al. 2013; Hudetz and Mashour 2016). In fact, dreaming is commonplace in anesthesia (Sanders et al. 2012), being reported by about a third of patients clinically anesthetized with propofol and desflurane (Eer et al. 2009; Leslie et al. 2009). The dose-dependent decrease of entropy of the sensory systems found in our study is a plausible indication of the brain being *en route* to disconnected consciousness. This is also supported by the reversal of entropy in the sensory systems upon the recovery of responsiveness. In contrast, the entropy of the high-order cognitive systems, which showed no difference between light and deep sedation, suggested the possibility for at least partially preserved information processing. It is plausible that the preservation of such information processing capability is the necessary condition for any form of internal mentation relying on information generated from within, e.g., from memory and imagination.

An acknowledged limitation of our study, as well as of many other similar studies, is that we do not have direct information about the study participants' internal mental state during deep sedation. We also did not take post-sedation dream reports from our participants. A posteriori assessment of internal consciousness during sedation is not trivial. Given the amnestic effects of anesthetics, not all internal conscious experience during a state of disconnected consciousness is reportable (Sanders et al. 2012). In addition, entropy was derived using rs-fMRI BOLD signals that are indirect, coarse-grained indicators of mass neuronal activity (Logothetis 2008). The signals also required denoising, which is an imperfect procedure. Our concerns on the denoising issue, however, were mitigated because of the reversal effects observed in recovery relative to changes observed from light to deep sedation, which could not be introduced by noise. In addition, the PCA performed in this study eliminated a portion of nuisance components that account for a small percentage of signal variance, thus contributing to further signal denoising. We also considered the possibility that changes in the physiological conditions of participants (blood pressure, breathing and heart beat rates, etc.) across different states of consciousness may have produced artificial changes in BOLD fMRI signals (e.g., the amplitude and variance) and in the entropy results. To minimize this effect, we performed a voxelwise z-score standardization of BOLD fMRI time series before low-pass filtering. Lastly, there is not always a clear-cut distinction between the sensory and high-order cognitive systems, especially with regard to certain neural structures. For example, while several thalamic nuclei serve sensory and motor functions, the intralaminar nuclei are related to multimodal information integration (Llinas et al. 1998; Liu et al. 2013; Mashour and Alkire 2013). In addition, structures like the fusiform gyrus and orbital prefrontal cortex are likely involved in high-level sensory information processing (e.g., facial information and reward encoding) compared with, for example, the primary visual cortex, but the high-order cognition and information integration may still require the participation of medial and lateral prefrontal cortices (Bokde et al. 2006; Farras-Permanyer et al. 2015; Zhang et al. 2016). Thus, the division of sensory and high-order cognitive systems in this study is only loosely defined to reflect the general trend of dose-dependent entropy changes in the respective systems. Future investigations may employ more advanced clustering approaches to reveal spatially detailed entropy changes.

In summary, our findings provide novel evidence for a general decrease of entropy or information content carried by rs-fMRI BOLD signals across brain regions during sedation by propofol. Importantly, the critical transition of losing and regaining behavioral responsiveness from light to deep sedation and to recovery are associated with differential changes in the entropy of the sensory and high-order cognitive systems such that the overtly expressed conscious state is correlated with entropy changes of the sensory but not of the

high-order cognitive systems. Together, these findings suggest a systems-level mechanism for disconnected consciousness during deep propofol sedation in terms of the regional entropy of hierarchically organized functional systems of the brain.

Acknowledgements Research reported in this publication was supported by grants from the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers R01-GM103894 and T32-GM89586. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank Ms. Lydia Washechek, BA, for editorial assistance.

Funding This study was funded by grants from the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers R01 GM103894 and T32 GM89586. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with ethical standards

Conflict of interest All authors have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Agnati, L. F., Santarossa, L., Genedani, S., Canela, E. I., Leo, G., Franco, R., Woofs, A., Lluis, C., et al. (2004). On the nested hierarchical organization of CNS: Basic characteristics of neuronal molecular organization. In P. Erdi (Ed.), *Cortical Dynamics LNCS 3146* (pp. 24–54). Berlin: Springer.

Alkire, M. T. (2008). Loss of effective connectivity during general anesthesia. *International Anesthesiology Clinics, 46*(3), 55–73.

Alkire, M. T., Hudetz, A. G., & Tononi, G. (2008). Consciousness and anesthesia. *Science, 322*(5903), 876–880.

Allen, E. A., Damaraju, E., Plis, S. M., Erhardt, E. B., Eichele, T., & Calhoun, V. D. (2014). Tracking whole-brain connectivity dynamics in the resting state. *Cerebral Cortex, 24*(3), 663–676.

Barttfeld, P., Uhrig, L., Sitt, J. D., Sigman, M., Jarraya, B., & Dehaene, S. (2015). Signature of consciousness in the dynamics of resting-state brain activity. *Proceedings of the National Academy of Sciences of the United States of America, 112*(3), 887–892.

Ben-Naim, A. (2012). *Entropy and the second law: interpretation and misss-interpretationsss*. New Jersey; London: World Scientific.

Biswal, B. B. (2012). Resting state fMRI: A personal history. *NeuroImage, 62*(2), 938–944.

Bokde, A. L., Lopez-Bayo, P., Meindl, T., Pechler, S., Born, C., Faltraco, F., Teipel, S. J., Moller, H. J., et al. (2006). Functional connectivity of the fusiform gyrus during a face-matching task in subjects with mild cognitive impairment. *Brain, 129*(Pt 5), 1113–1124.

Boly, M., Sanders, R. D., Mashour, G. A., & Laureys, S. (2013). Consciousness and responsiveness: Lessons from anaesthesia and the vegetative state. *Current Opinion in Anaesthesiology, 26*(4), 444–449.

Bonhomme, V., Boveroux, P., Hans, P., Brichant, J. F., Vanhaudenhuyse, A., Boly, M., & Laureys, S. (2011). Influence of anesthesia on cerebral blood flow, cerebral metabolic rate, and brain functional connectivity. *Current Opinion in Anaesthesiology, 24*(5), 474–479.

Bonhomme, V., Boveroux, P., Brichant, J. F., Laureys, S., & Boly, M. (2012). Neural correlates of consciousness during general anesthesia using functional magnetic resonance imaging (fMRI). *Archives Italiennes de Biologie, 150*(2–3), 155–163.

Britz, J., Van De Ville, D., & Michel, C. M. (2010). BOLD correlates of EEG topography reveal rapid resting-state network dynamics. *NeuroImage, 52*(4), 1162–1170.

Bruhn, J., Ropcke, H., & Hoeft, A. (2000). Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. *Anesthesiology, 92*(3), 715–726.

Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D. R., & Nutt, D. (2014). The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience, 8*, 20.

Casali, A. G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K. R., Casarotto, S., Bruno, M. A., et al. (2013). A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med, 5*(198), 198ra105.

Casarotto, S., Comanducci, A., Rosanova, M., Sarasso, S., Fecchio, M., Napolitani, M., Pigorini, A., A, G. C., et al. (2016). Stratification of unresponsive patients by an independently validated index of brain complexity. *Annals of Neurology, 80*(5), 718–729.

Chang, C., & Glover, G. H. (2010). Time-frequency dynamics of resting-state brain connectivity measured with fMRI. *NeuroImage, 50*(1), 81–98.

Chernik, D. A., Gillings, D., Laine, H., Hendler, J., Silver, J. M., Davidson, A. B., Schwam, E. M., & Siegel, J. L. (1990). Validity and reliability of the Observer's assessment of alertness/sedation scale: study with intravenous midazolam. *Journal of Clinical Psychopharmacology, 10*(4), 244–251.

Davis, M. H., Coleman, M. R., Absalom, A. R., Rodd, J. M., Johnsrude, I. S., Matta, B. F., Owen, A. M., & Menon, D. K. (2007). Dissociating speech perception and comprehension at reduced levels of awareness. *Proceedings of the National Academy of Sciences of the United States of America, 104*(41), 16032–16037.

Di, X., & Biswal, B. B. (2015). Dynamic brain functional connectivity modulated by resting-state networks. *Brain Structure & Function, 220*(1), 37–46.

Eer, A. S., Padmanabhan, U., & Leslie, K. (2009). Propofol dose and incidence of dreaming during sedation. *European Journal of Anaesthesiology, 26*(10), 833–836.

Farras-Permanyer, L., Guardia-Olmos, J., & Pero-Cebollero, M. (2015). Mild cognitive impairment and fMRI studies of brain functional connectivity: The state of the art. *Frontiers in Psychology, 6*, 1095.

Ferenets, R., Lipping, T., Anier, A., Jantti, V., Melto, S., & Hovilehto, S. (2006). Comparison of entropy and complexity measures for the assessment of depth of sedation. *IEEE Transactions on Biomedical Engineering, 53*(6), 1067–1077.

Ferrarelli, F., Massimini, M., Sarasso, S., Casali, A., Riedner, B. A., Angelini, G., Tononi, G., & Pearce, R. A. (2010). Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. *Proceedings of the National Academy of Sciences of the United States of America, 107*(6), 2681–2686.

Gokhale, D. V., Ahmed, N. A., Res, B. C., & Piscataway, N. J. (1989). Entropy expressions and their estimators for multivariate distributions. *IEEE Transactions on Information Theory, 5*(3), 688–692.

Haimovici, A., Tagliazucchi, E., Balenzuela, P., & Chialvo, D. R. (2013). Brain organization into resting state networks emerges at criticality on a model of the human connectome. *Physical Review Letters, 110*(17), 178101.

Haldeman, C., & Beggs, J. M. (2005). Critical branching captures activity in living neural networks and maximizes the number of metastable states. *Physical Review Letters, 94*(5), 058101.

Huang, Z., Zhang, J., Wu, J., Qin, P., Wu, X., Wang, Z., Dai, R., Li, Y., et al. (2016). Decoupled temporal variability and signal synchronization of spontaneous brain activity in loss of consciousness: An fMRI study in anesthesia. *Neuroimage, 124*(Pt A), 693–703.

Hudetz, A. G. (2012). General anesthesia and human brain connectivity. *Brain Connectivity, 2*(6), 291–302.

Hudetz, A. G., & Mashour, G. A. (2016). Disconnecting consciousness: Is there a common anesthetic end point? *Anesthesia and Analgesia, 123*(5), 1228–1240.

Hudetz, A. G., Humphries, C. J., & Binder, J. R. (2014). Spin-glass model predicts metastable brain states that diminish in anesthesia. *Frontiers in Systems Neuroscience, 8*, 234.

Hudetz, A. G., Liu, X., & Pillay, S. (2015). Dynamic repertoire of intrinsic brain states is reduced in propofol-induced unconsciousness. *Brain Connectivity, 5*(1), 10–22.

Hudetz, A. G., Liu, X., Pillay, S., Boly, M., & Tononi, G. (2016). Propofol anesthesia reduces Lempel-Ziv complexity of spontaneous brain activity in rats. *Neuroscience Letters, 628*, 132–135.

Hutchison, R. M., Womelsdorf, T., Allen, E. A., Bandettini, P. A., Calhoun, V. D., Corbetta, M., Della Penna, S., Duyn, J. H., Glover, G. H., Gonzalez-Castillo, J., Handwerker, D. A., Keilholz, S., Kiviniemi, V., Leopold, D. A., de Pasquale, F., Sporns, O., Walter, M., & Chang, C. (2013). Dynamic functional connectivity: Promise, issues, and interpretations. *NeuroImage, 80*, 360–378.

Leslie, K., Sleigh, J., Paech, M. J., Voss, L., Lim, C. W., & Sleigh, C. (2009). Dreaming and electroencephalographic changes during anesthesia maintained with propofol or desflurane. *Anesthesiology, 111*(3), 547–555.

Liu, X., Lauer, K. K., Ward, B. D., Rao, S. M., Li, S. J., & Hudetz, A. G. (2012). Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. *Human Brain Mapping, 33*(10), 2487–2498.

Liu, X., Lauer, K. K., Ward, B. D., Li, S. J., & Hudetz, A. G. (2013). Differential effects of deep sedation with propofol on the specific and nonspecific thalamocortical systems: A functional magnetic resonance imaging study. *Anesthesiology, 118*(1), 59–69.

Liu, X., Lauer, K. K., Douglas Ward, B., Roberts, C., Liu, S., Gollapudy, S., Rohloff, R., Gross, W., Chen, G., Xu, Z., Binder, J. R., Li, S. J., & Hudetz, A. G. (2017). Propofol attenuates low-frequency fluctuations of resting-state fMRI BOLD signal in the anterior frontal cortex upon loss of consciousness. *NeuroImage, 147*, 295–301.

Llinas, R., Ribary, U., Contreras, D., & Pedroarena, C. (1998). The neuronal basis for consciousness. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 353*(1377), 1841–1849.

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature, 453*(7197), 869–878.

Ma, Y., Hamilton, C., & Zhang, N. (2017). Dynamic connectivity patterns in conscious and unconscious brain. *Brain Connectivity, 7*(1), 1–12.

Maksimow, A., Sarkela, M., Langsjo, J. W., Salmi, E., Kaisti, K. K., Yli-Hankala, A., Hinkka-Yli-Salomaki, S., Scheinin, H., et al. (2006). Increase in high frequency EEG activity explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia. *Clinical Neurophysiology, 117*(8), 1660–1668.

Mashour, G. A. (2014). Top-down mechanisms of anesthetic-induced unconsciousness. *Frontiers in Systems Neuroscience, 8*, 115.

Mashour, G. A., & Alkire, M. T. (2013). Consciousness, anesthesia, and the thalamocortical system. *Anesthesiology, 118*(1), 13–15.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: The default network and stimulus-independent thought. *Science, 315*(5810), 393–395.

Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. *Science, 309*(5744), 2228–2232.

Oizumi, M., Albantakis, L., & Tononi, G. (2014). From the phenomenology to the mechanisms of consciousness: Integrated information theory 3.0. *PLoS Computational Biology, 10*(5), e1003588.

Plourde, G., Belin, P., Chartrand, D., Fiset, P., Backman, S. B., Xie, G., & Zatorre, R. J. (2006). Cortical processing of complex auditory stimuli during alterations of consciousness with the general anesthetic propofol. *Anesthesiology, 104*(3), 448–457.

Sanders, R. D., Tononi, G., Laureys, S., & Sleigh, J. W. (2012). Unresponsiveness not equal unconsciousness. *Anesthesiology, 116*(4), 946–959.

Sarasso, S., Boly, M., Napolitani, M., Gosseries, O., Charland-Verville, V., Casarotto, S., Rosanova, M., Casali, A. G., Brichant, J. F., Boveroux, P., Rex, S., Tononi, G., Laureys, S., & Massimini, M. (2015). Consciousness and complexity during unresponsiveness induced by Propofol, Xenon, and Ketamine. *Current Biology, 25*(23), 3099–3105.

Schrouff, J., Perlbarg, V., Boly, M., Marrelec, G., Boveroux, P., Vanhaudenhuyse, A., Bruno, M. A., Laureys, S., Phillips, C., Pélégrini-Issac, M., Maquet, P., & Benali, H. (2011). Brain functional integration decreases during propofol-induced loss of consciousness. *NeuroImage, 57*(1), 198–205.

Shafer, S. L. (1996). *STANPUMP User's Manual*. Stanford: Stanford University.

Shanahan, M. (2010). Metastable chimera states in community-structured oscillator networks. *Chaos, 20*(1), 013108.

Sleigh, J. W., & Donovan, J. (1999). Comparison of bispectral index, 95% spectral edge frequency and approximate entropy of the EEG, with changes in heart rate variability during induction of general anaesthesia. *British Journal of Anaesthesia, 82*(5), 666–671.

Sporns, O., Honey, C. J., & Kotter, R. (2007). Identification and classification of hubs in brain networks. *PLoS One, 2*(10), e1049.

Steyn-Ross, M. L., Steyn-Ross, D. A., Sleigh, J. W., & Liley, D. T. (1999). Theoretical electroencephalogram stationary spectrum for a white-noise-driven cortex: Evidence for a general anesthetic-induced phase transition. *Physical Review E: Statistical Physics, Plasmas, Fluids, and Related Interdisciplinary Topics, 60*(6 Pt B), 7299–7311.

Steyn-Ross, D. A., Steyn-Ross, M. L., Wilcocks, L. C., & Sleigh, J. W. (2001). Toward a theory of the general-anesthetic-induced phase transition of the cerebral cortex. II. Numerical simulations, spectral entropy, and correlation times. *Physical Review. E, Statistical, Nonlinear, and Soft Matter Physics, 64*(1 Pt 1), 011918.

Tagliazucchi, E., Carhart-Harris, R., Leech, R., Nutt, D., & Chialvo, D. R. (2014). Enhanced repertoire of brain dynamical states during the psychedelic experience. *Human Brain Mapping, 35*(11), 5442–5456.

Tagliazucchi, E., Chialvo, D. R., Siniatchkin, M., Amico, E., Brichant, J. F., Bonhomme, V., Noirhomme, Q., Laufs, H., & Laureys, S. (2016). Large-scale signatures of unconsciousness are consistent with a departure from critical dynamics. *Journal of the Royal Society, Interface, 13*(114), 20151027.

Tognoli, E., & Kelso, J. A. (2014). The metastable brain. *Neuron, 81*(1), 35–48.

Tononi, G. (2004). An information integration theory of consciousness. *BMC Neuroscience, 5*, 42.

Tononi, G. (2008). Consciousness as integrated information: A provisional manifesto. *Biological Bulletin, 215*(3), 216–242.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 273–289.

Uhrig, L., Dehaene, S., & Jarraya, B. (2014). Cerebral mechanisms of general anesthesia. *Annales Françaises d'Anesthèsie et de Rèanimation, 33*(2), 72–82.

Vakkuri, A., Yli-Hankala, A., Talja, P., Mustola, S., Tolvanen-Laakso, H., Sampson, T., & Viertio-Oja, H. (2004). Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. *Acta Anaesthesiologica Scandinavica, 48*(2), 145–153.

Zhang, W., Wang, J., Fan, L., Zhang, Y., Fox, P. T., Eickhoff, S. B., Yu, C., & Jiang, T. (2016). Functional organization of the fusiform gyrus revealed with connectivity profiles. *Human Brain Mapping, 37*(8), 3003–3016.