Breakdown of within- and between-network Resting State Functional Magnetic Resonance Imaging Connectivity during Propofol-induced Loss of Consciousness


ABSTRACT

Background: Mechanisms of anesthesia-induced loss of consciousness remain poorly understood. Resting-state functional magnetic resonance imaging allows investigating whole-brain connectivity changes during pharmacological modulation of the level of consciousness.

Methods: Low-frequency spontaneous blood oxygen level-dependent fluctuations were measured in 19 healthy volunteers during wakefulness, mild sedation, deep sedation with clinical unconsciousness, and subsequent recovery of consciousness.

Results: Propofol-induced decrease in consciousness linearly correlates with decreased corticocortical and thalamocortical connectivity in frontoparietal networks (i.e., default- and executive-control networks). Furthermore, during propofol-induced unconsciousness, a negative correlation was identified between thalamic and cortical activity in these networks. Finally, negative correlations between default network and lateral frontoparietal cortices activity, present during wakefulness, decreased proportionally to propofol-induced loss of consciousness. In contrast, connectivity was globally preserved in low-level sensory cortices, (i.e., in auditory and visual networks across sedation stages). This was paired with preserved thalamocortical connectivity in these networks. Rather, waning of consciousness was associated with a loss of cross-modal interactions between visual and auditory networks.

Conclusions: Our results shed light on the functional significance of spontaneous brain activity fluctuations observed in functional magnetic resonance imaging. They suggest that propofol-induced unconsciousness could be...
Ing brain metabolism and cerebral activation in response to level, several studies have shown widespread decreases in rest-action of anesthetic agents in the spinal cord. At the brain, whereas descending signals modify the immobilizing contribution to the hypnotic actions of anesthetic agents in the brain, whereas descending signals modify the immobilizing action of anesthetic agents in the spinal cord. At the brain level, general anesthetic agents decrease transmission of noxious information ascending from the spinal cord to the brain, thereby likely decreasing supraspinal arousal. It is also likely that ascending signals from the spinal cord contribute to the hypnotic actions of anesthetic agents in the brain, whereas descending signals modify the immobilizing action of anesthetic agents in the spinal cord. At the brain level, several studies have shown widespread decreases in resting brain metabolism and cerebral activation in response to stimuli, especially in the cortex, thalamus, and midbrain. Brainstem sleep-promoting neurons have also been shown to be potentially involved in the mechanisms of anesthesia-induced unconsciousness.

Recent evidence suggests that cortical activity better correlates with propofol-induced sedative effects than subthalamic activity. At the cortical level, several positron emission tomography studies have shown correlations between anesthesia-induced unconsciousness and both cortical metabolism and thalamocortical connectivity. Previous electroencephalography studies also showed uncoupling of coherent anteroposterior and interhemispheric electrical activity during anesthesia-induced unconsciousness compared with wakefulness. Despite these recent advances, no consensus has been reached on the generic mechanisms by which anesthetic drugs induce loss of consciousness. In particular, systematic studies of whole-brain connectivity during anesthesia-induced unconsciousness are still sparse. It has been suggested that anesthesia is a sleep-like state and that common mechanisms could be involved in loss of consciousness in both cases. Indeed, sleep states and general anesthesia states share electroencephalographic and behavioral features. In both conditions, sensory input is attenuated and there is an inhibition of motor output and analgesia. Although sleep and anesthesia states are clearly distinct conditions, subcortical neuronal networks involved in the generation of sleep, such as the pontine cholinergic, brainstem noradrenergic, hypothalamic ventrolateral preoptic nucleus, and tuberomammillary nucleus, may also mediate some anesthetic effects. However, anesthesia and sleep are not identical in their mechanisms and neural correlates. For example, as opposed to natural sleep, anesthesia induces dramatic changes in airway muscle control, decreasing both ventilatory and upper airway dilator muscle activity. Hence, no consensus has yet been reached on the possible common final pathway by which sleep and anesthesia would induce loss of consciousness in humans or on the precise nature of neural correlates of conscious perception.

Propofol-induced sedation, like other states of unconsciousness, has been associated with regional hypometabolism in a widespread cortical network, encompassing bilateral frontal and parietal associative regions. In contrast, sensory and motor cortices metabolism was relatively preserved. There is now increasing evidence that the large frontoparietal network commonly impaired during altered states of consciousness can be divided into at least two parts with distinct functions. In particular, a distinction can be made between a network supposedly involved in the awareness of self (the default or default-mode network) and a more lateral and dorsal frontoparietal network involved in the awareness of environment (the executive-control network). The differential involvement of each of these frontoparietal subnetworks in the genesis of consciousness and the relative degree of impairment in their activity during altered states of consciousness remains to be determined. Furthermore, the role of sensory cortices and of frontoparietal networks in the genesis of consciousness remains controversial.

In recent years, increasing attention has been paid to spontaneous brain fluctuations in the low-frequency range as observed by functional magnetic resonance imaging (fMRI). Functional connectivity studies have shown that there exists a number of resting state networks, which are reproducible at the individual level. They include the default network, right- and left-lateralized executive control networks, and auditory and visual networks. However, the functional significance of these connectivity patterns remains unclear. It has been suggested that coherent spontaneous blood oxygen level-dependent (BOLD) fluctuations observed in the resting state reflect unconstrained but consciously-directed mental activity. These fluctuations were then found to persist in situations of reduced consciousness, such as in anesthetized monkeys, or in light sleep in humans. However, in these experiments, the extent of loss of
consciousness of the subjects was unclear. Indeed, precisely assessing the level of consciousness in sedated animals is challenging, and there is still a debate on the extent of loss of consciousness in light sleep.32

The aim of the present study was to investigate connectivity changes in resting-state networks correlating with loss of consciousness across several levels of propofol-induced sedation in healthy humans. We used a resting-state functional MRI connectivity technique allowing the investigation of functional connectivity in large-scale brain networks without requiring the subjects’ collaboration and thus ideally suited to investigate cerebral connectivity during altered states of consciousness.33 We hypothesized that propofol-induced loss of consciousness would be associated with a loss of connectivity in default-network and executive-control networks and with a relative preservation of connectivity in low-level sensory cortices. We also hypothesized that anesthesia could be associated with further disorganization of brain activity, reflected in decreased interactions between the different resting-state brain networks, as assessed by the measure of functional MRI connectivity.

Materials and Methods

Subjects

The study was approved by the Ethics Committee of the Medical School of the University of Liège (University Hospital, Liège, Belgium). The subjects provided written informed consent to participate in the study. Twenty healthy right-handed volunteers participated in the study (4 men and 16 women; age range, 18–31 yr; mean age ± SD, 22.4 ± 3.4 yr; body mass index range, 17.5–26.6; mean BMI ± SD, 21.5 ± 2.08). One subject’s data (female) had to be discarded because clinical unconsciousness could not be reached without excessive respiratory depression. The subjects were recruited through advertisement in an Internet forum and underwent a medical and physical examination before participating in the study. Women were tested for pregnancy the day of the experiment (urinary test) and were requested to use an appropriate contraceptive method. None of the subjects had a history of head trauma or surgery, mental illness, drug addiction, asthma, motion sickness, or previous problems during anesthesia. They had no contraindication for an MRI examination, such as vascular clips or metallic implants. All volunteers received financial compensation for inconvenience and time lost during the experiment.

Sedation Protocol

Subjects fasted for at least 6 h from solids and 2 h from liquids before sedation. During the study and the recovery period, electrocardiogram, blood pressure, pulse oxymetry (SpO2), and breathing frequency were continuously monitored (Magnitude 3150M; Invivo Research, Inc., Orlando, FL). Propofol was infused through an intravenous catheter placed into a vein of the right hand or forearm. An arterial catheter was placed into the left radial artery. Throughout the study, the subjects breathed spontaneously, and additional oxygen (5 l/min) was given through a loosely fitting plastic facemask.

Sedation was achieved using a computer-controlled intravenous infusion of propofol (Alaris® TIVA; Carefusion, San Diego, CA) to obtain constant effect-site concentrations. The propofol plasma and effect-site concentrations were estimated using the three-compartment pharmacokinetic model of Marsh et al.34 After reaching the appropriate effect-site concentration, a 5-min equilibration period was allowed to insure equilibration of propofol partitioning between compartments. Arterial blood samples were then taken immediately before and after the scan in each clinical state for subsequent determination of the concentration of propofol and for blood-gas analysis. For technical reasons, blood-gas concentrations were available for only 18 of 19 subjects. Details of the blood sample analyses are reported in Supplemental Digital Content 1, which contains additional information about propofol administration procedure and functional data analysis, http://links.lww.com/ALN/A627. The level of consciousness was evaluated clinically throughout the study with the scale used by Ramsay et al.35 The subject was asked to strongly squeeze the hand of the investigator. She/he was considered fully awake or to have recovered consciousness if the response to verbal command (“squeeze my hand!”) was clear and strong (Ramsay 2), in mild sedation if the response to verbal command was clear but slow (Ramsay 3), and in deep sedation if there was no response to verbal command (Ramsay 5–6). For each consciousness level assessment, Ramsay scale verbal commands were repeated twice. Before and after each scanning session, a reaction time task was also performed to provide additional information on the clinical state of the volunteers. Lying in the scanner, subjects were instructed to press a keypad as fast as possible each time they heard a beep through the headphones. At each test, a block of 20 beeps was presented to the subjects. Two certified anesthesiologists were present throughout the experiment, and complete resuscitation equipment was always available. Subjects wore earplugs and headphones. Table 1 summarizes mean and range of estimated effect-site concentration of propofol, measured concentrations of propofol, carbon dioxide arterial blood partial pressure (pCO2), and reaction time task performances of the subjects at each sedation level. Propofol estimated and measured plasma concentration, pCO2, and reaction time task performances at each sedation level are reported in table 1. One-way analysis of variance and post hoc Tukey Honestly Significant Difference tests were performed on these variables. An additional t test compared propofol plasma concentration during mild sedation scans acquired at induction of versus emergence from propofol-induced unconsciousness. Results of all these statistical analyses were considered significant at P < 0.05 corrected for multiple comparisons.
Table 1. Propofol Concentrations and Behavioral Performance in the Four Sedation States

<table>
<thead>
<tr>
<th></th>
<th>Wakefulness</th>
<th>Mild Sedation</th>
<th>Deep Sedation</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated effect-site (cerebral) propofol concentration, ( \mu g/ml )</td>
<td>0 ± 0</td>
<td>1.55 ± 0.51*</td>
<td>2.80 ± 0.85*</td>
<td>0.63 ± 0.21*</td>
</tr>
<tr>
<td>Measured propofol plasma concentrations, ( \mu g/ml )</td>
<td>0 ± 0</td>
<td>1.75 ± 0.67*</td>
<td>3.20 ± 0.99*</td>
<td>0.61 ± 0.22*</td>
</tr>
<tr>
<td>( PC_{o2} ) arterial blood gas sample, mmHg</td>
<td>38.2 ± 5.0</td>
<td>40.4 ± 5.0</td>
<td>48.6 ± 7.3*</td>
<td>39.0 ± 4.6</td>
</tr>
<tr>
<td>Reaction time task performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response, %</td>
<td>96 ± 1</td>
<td>74 ± 31*</td>
<td>0 ± 0*</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>Reaction times, ms</td>
<td>292 ± 39</td>
<td>654 ± 447*</td>
<td>—</td>
<td>309 ± 54</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD of individual values in each state.

* Values significantly different from wakefulness in Tukey Honestly Significant Difference tests (\( P < 0.05 \), corrected for multiple comparisons).

Functional Data Acquisition

Functional MRI acquisition consisted of resting-state functional MRI volumes repeated in four clinical states: normal wakefulness (Ramsay 2), mild sedation (Ramsay 3), deep sedation (Ramsay 5), and recovery of consciousness (Ramsay 2). The temporal order of mild- and deep-sedation conditions was randomized. The typical scan duration was half an hour in each condition. The number of scans per session was matched in each subject to obtain a similar number of scans in all four clinical states (mean ± SD, 251 ± 77 scans/session).

Functional images were acquired on a 3 Tesla Siemens Allegra scanner (Siemens AG, Munich, Germany; Echo Planar Imaging sequence using 32 slices; repetition time = 2460 ms, echo time = 40 ms, field of view = 220 mm, voxel size = 3.45 × 3.45 × 3 mm, and matrix size = 64 × 64 × 32). Simultaneous electroencephalographic recordings were also performed during the same-scanning session using a 68-electrode Brain Amp magnetic resonance compatible acquisition setup. A second scanning session was also performed during each clinical state, presenting simple auditory stimulations. These data are not reported in the present article. A high-resolution T1 image was also acquired in each volunteer at the end of the whole experiment for coregistration to the functional data. During data acquisition, subjects wore earplugs and headphones. The most comfortable supine position attainable was sought to avoid painful stimulation related to position.

Extraction of Individual Resting State Networks

Low-frequency BOLD correlations between brain regions were investigated using two different kinds of analysis: a region of interest (ROI)–driven analysis, searching for brain areas correlated to selected seed regions after removal of spurious physiologic noise, and a confirmatory analysis consisting of a convergent functional connectivity method, independent component analysis (ICA), using an automated template-matching procedure. Here we show results of ROI-driven analysis. ROI-driven data analysis procedure is summarized in figure 1. Figure 1A describes the relationships between local brain activity and BOLD signal, figure 1B describes the obtainment of single-subject resting-state network maps, and figure 1C describes the computation of group-level network maps. Results obtained with the ICA approach were similar to those obtained with the ROI-driven approach; ICA analysis methods and results are described in detail in Supplemental Digital Content 1, http://links.lww.com/ALN/A627; Supplemental Digital Content 2, which describes the procedure employed to perform single-subject and group-level ICA analyses, http://links.lww.com/ALN/A628; and Supplemental Digital Content 3, which displays the resting-state network templates used to select relevant components in the single-subject level analysis step, http://links.lww.com/ALN/A629.

Before ROI-driven analysis, functional and structural images were realigned, normalized, and smoothed (8-mm full width at half-maximum) using Statistical Parametric Mapping software version 5.

Low-frequency BOLD correlations were investigated after removal of spurious physiologic noise. For connectivity studies of default network, executive-control networks, and visual and auditory networks, we selected seed areas based on previous studies using ICA. BOLD time courses of interest for each network were computed as the principal component of the BOLD signal in 6-mm spherical ROIs centered on a priori coordinates reported in previous work investigating connectivity of default network (Montreal Neurologic Institute coordinates in millimeters: \( [x, y, z] = [6, -42, 32] \)), of executive-control network (\( [± 44, 36, 20] \)), and of primary auditory and visual cortices (\( [-40, -22, 8] \) and \( [-4, -84, 8] \), respectively).

Connectivity analyses investigated correlations with the signal extracted from one ROI per network, as commonly performed in previous studies. These seed-voxel connectivity analyses were all complemented by a parallel independent set of ICA analyses, whose results do not depend a priori ROI selection (see Supplemental Digital Content 1, http://links.lww.com/ALN/A627, and Supplemental Digital Content 4, which describes and compares the different procedures commonly used in the lit-
To analyze functional MRI connectivity data, literature to analyze functional MRI connectivity data, blood oxygen level-dependent (BOLD) signal correlates with regional neural activity. In response to a local neuronal activation, regional cerebral blood flow will increase more than what is needed to supply metabolic needs. The result is an increase in blood oxygen level and an increase in T²* MRI signal (corresponding to BOLD signal). Resting-state functional MRI studies assume that region-specific low frequency BOLD signal fluctuations correspond to fluctuations in underlying neural activity; the relationship between these two variables is given by the hemodynamic response function (HRF). Single-subject (first-level) analyses procedure: extraction of individual resting-state networks. In a first step, a principal analysis decomposition of a ROI time course is performed. The first eigenvariate of this time course is then used in a correlation analysis. In each subject, single-subject analyses identify regions positively and negatively correlated (or anticorrelated) to the seed ROI time course, after removal of spurious correlations due to physiologic nonneuronal signal. Regions positively correlated to a posterior cingulate ROI are found to be part of the default network. Regions positively correlated to middle frontal gyrus are typically part of the executive-control network. Executive-control network regions are usually anticorrelated to default-network regions. Second-level analyses: computation of group level–resting state networks. Individual connectivity maps obtained at the first level are entered in a second level random effects analysis, looking for consistent correlation patterns at the group level, taking into account intersubject variability. Group results are thresholded at false discovery rate (FDR) corrected p value less than 0.05 and rendered for display on the mean group structural MRI of the subjects. Color scale corresponds to group-level T values for each voxel.

deoxyHb = deoxyhemoglobin; oxyHb = oxyhemoglobin.

the movement parameters were further added as nuisance covariates in the design matrix. A separate design matrix was created for each ROI in each of the four sessions in every subject. Serial correlations were then estimated with a restricted maximum likelihood algorithm using an intrinsic autoregressive model during parameter estimation. The effects of interest were tested by linear contrasts, generating statistical parametric T maps in each subject. A contrast image was then computed in each session, identifying regions significantly correlated to the selected seed region after removal of sources of spurious variance.

Statistical Analysis

All statistical analyses were realized using Statistical Parametric Mapping software. For each network, individual summary statistics images were entered in a second-level analysis, corresponding to a random effects model in which subjects are considered random variables. These second-level analyses consisted of analyses of variance (repeated measures analysis of variance) with the four clinical conditions as factors: normal wakefulness, mild sedation, deep sedation, and recovery of consciousness. The error covariance was not assumed to be independent between regressors, and a correction for non-sphericity was applied. We used one-sided T contrasts, as implemented in Statistical Parametric Mapping software, to test for significant connectivity effects in all our analyses. After model estimation, a first T contrast searched for areas correlated with the selected seed region during normal wakefulness. A second analysis then searched for persistent correlations with the seed region during deep sedation. Finally, a linear one-tailed T contrast was computed for each network, searching for a linear relationship between functional connectivity and the level of consciousness of the subjects across the four conditions (i.e., normal wakefulness, mild sedation, deep sedation, and recovery of consciousness, contrast [1.5–0.5–1.5–0.5]). It should be noted that during the last condition (i.e., recovery of consciousness), subjects showed clinical recovery of consciousness (i.e., score 2 on Ramsay sedation scale) but showed residual plasma propofol levels and lower reaction times scores (table 1). Because the present study aimed to investigate progressive alteration of consciousness as a result of propofol administration, independently of the effects of time or of the effect of descent to unconsciousness versus emergence into wakefulness, we included the recovery stage as the most moderately altered conscious state induced by propofol administration in our dataset. Additional exponential ($y = \frac{1}{\tau} - 1/4 \sum_{i=1}^{4} - \frac{y_i}{\tau}$) and power-law ($y = 1/\tau - 1/4 \sum_{i=1}^{4} 1/\tau$) T contrasts were also computed to investigate whether nonlinear connectivity changes would represent a better model of our data. Finally, for each network, a complementary analysis was performed, using a two-sample t test to compare functional connectivity during mild sedation scans acquired during the induction of sedation (sessions temporally preceding propofol-induced unconsciousness, nine subjects) to those acquired at the recovery stage as the most moderately altered conscious state induced by propofol administration in our dataset.

Results

Propofol Plasma Concentrations and Physiologic Variables

Significant differences were observed between propofol plasma concentrations measured during waking, mild sedation, deep sedation, and recovery. pCO2 value was significantly different from wakefulness only during deep sedation (table 1). Detailed statistical results are reported in Supplemental Digital Content 5, http://links.lww.com/ALN/A631. Additional analyses revealed no significant difference between propofol plasma concentration measured during mild sedation scans acquired at the induction of versus the emergence from propofol-induced unconsciousness.

Frontoparietal Networks—Default Network and Executive-control Networks

During wakefulness, connectivity patterns in the default network and the executive-control networks were identified consistently across subjects. At the group level, the default network involved a significant contribution of brainstem, thalamus, posterior cingulate cortex (PCC)/precuneus, medial frontal cortex, superior frontal sulci, bilateral temporoparietal junctions, parahippocampal cortex, and temporal cortex (fig. 2A). Right and left executive control connectivity were identified as two right- and left-lateralized cortical patterns encompassing middle, inferior, and superior frontal cortices, dorsal anterior cingulate cortex/presupplementary motor area, temporo-occipital junction, and posterior parietal cortices (fig. 2, B and C). Thalamic involvement was identified in both right and left executive-control networks. Finally, significant anticorrelations (inverse correla-
tions) were identified between PCC and a set of lateral cortical areas encompassing inferior frontal/insular cortices, posterior parietal cortex, temporo-occipital junction, and premotor cortex (fig. 2D).

During deep sedation with clinical unconsciousness, we could identify partially preserved residual functional connectivity both in the executive-control networks and the default network (fig. 2). For the default network, we identified residual connectivity in PCC/precuneus, medial prefrontal cortex, superior frontal sulci, parahippocampal gyrus, and bilateral temporoparietal junctions (fig. 2E). For the right executive-control network, we could identify residual connectivity in middle frontal and posterior parietal cortices (fig. 2F). For the left executive-control network, residual connectivity was found in middle frontal, posterior parietal, and temporo-occipital cortices (fig. 2G). Significant anticorrelations with the default network could be identified during deep sedation (fig. 2H, Supplemental Digital Content 6, http://links.lww.com/ALN/A632), though their spatial extent was greatly diminished. Supplemental Digital Content 6 reports the peak areas of significance for connectivity in default and executive-control networks during wakefulness and deep sedation, http://links.lww.com/ALN/A632. Supplemental Digital Content 7 displays default and executive-control networks connectivity patterns obtained using ICA method during wakefulness and deep sedation, http://links.lww.com/ALN/A633.

A linear correlation was found between functional connectivity in key nodes of the three frontoparietal resting-state networks and the level of consciousness during propofol-induced sedation (fig. 3 and table 2). The linear contrast represented a better fit for the correlation between connectivity and consciousness than that provided by exponential and power-law contrasts. For the default network, a linear

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**Fig. 2.** Large-scale network connectivity is partially preserved during propofol-induced unconsciousness. (Left) Normal wakefulness resting-state networks connectivity in default network (A), right executive control network (B), left executive control network (C), and anticorrelations between default network and lateral frontoparietal cortices (D). (Right) Connectivity patterns in default network (E), right executive control network (F), left executive control network (G), and anticorrelations between default network and lateral frontoparietal cortices (H) during deep sedation with clinical unconsciousness. For display purposes, results are thresholded at false discovery rate corrected $P$ less than 0.05 and are shown on the mean structural T1 magnetic resonance scan of the subjects. Color scales correspond to T values of Statistical Parametric Mapping group maps. x and z indicate the Montreal National Institute coordinates of section planes.
relationship between connectivity and consciousness was found in a set of areas encompassing PCC/precuneus, medial prefrontal cortex, superior frontal sulci, parahippocampal cortex, and temporal cortex (fig. 3A). For the bilateral executive-control networks, this correlation was found in most cortical areas including inferior and superior frontal cortices, dorsal anterior cingulate/presupplementary motor area, and posterior parietal cortices (fig. 3, B and C). Finally, a linear relationship was observed between the level of consciousness and the strength of anticorrelations between default network and inferior frontoinsular cortices, posterior parietal cortex, temporo-occipital junction, and premotor cortex across sedation stages (fig. 3D, table 2). Figure 3 also reports parameter estimates for connectivity in default network (fig. 3E), right and left executive-control networks (fig. 3, F and G), and for the strength of anticorrelations between default network and lateral frontoparietal cortices (fig. 3H) across the four levels of consciousness. Supplemental Digital Content 8 reports additional parameters estimates of connectivity in default and executive control networks and provides a complementary illustration that the linear correlation between connectivity and consciousness was found across most cortical areas of these three networks, http://links.lww.com/ALN/A634. Table 2 reports peak areas of significance for a correlation between connectivity and consciousness in default and executive-control networks. Supplemental Digital Content 9, http://links.lww.com/ALN/A635, and Supplemental Digital Content 10, http://links.lww.com/ALN/A636, report similar results obtained using the ICA approach.

The relationship between default-network connectivity and consciousness remained present after taking into account possible confounding effects of pCO2 and propofol serum values on functional MRI BOLD measurements. Propofol-induced unconsciousness equally decreased long- and short-range connectivity in frontoparietal cortices. Indeed, in the default network, we could find some decreases of

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**Fig. 3.** Frontoparietal resting-state networks connectivity correlates with the level of consciousness across sedation stages. (Left) Areas of default network (A), right executive control network (B), left executive control network (C) where connectivity strength correlates with consciousness and lateral frontoparietal areas where the strength of anticorrelations with default network correlates with the level of consciousness (D). Results are thresholded for display at false discovery rate (FDR) corrected \( P \) less than 0.05 (yellow and light blue, FDR 0.05 scale) on an uncorrected (unc) \( P \) less than 0.01 background (red and dark blue, unc 0.01 scale) and are displayed on the mean structural T1 magnetic resonance scan of the subjects. x and z indicate the Montreal National Institute coordinates of section planes. (Right) Statistical Parametric Mapping parameters estimates (expressed as group means and 90% CI) for connectivity in default network (E), right executive control network (F), left executive control network (G), and anticorrelations between default network and lateral frontoparietal cortices (H) during wakefulness (W), mild sedation (MS), unconsciousness (U), and recovery of consciousness (R).
Visual and Auditory Networks

The ROI-driven approach could identify reproducible visual and auditory networks during normal wakefulness (fig. 4).

The visual network included a set of areas encompassing the thalamus, primary visual, lingual, fusiform, cuneal, middle, and inferior occipital cortices (fig. 4A). Auditory network encompassed the thalamus, Heschl gyrus, inferior parietal lobule, superior temporal cortices, PCC, inferior frontal, insular, and midcingulate cortices (fig. 4B).

During deep sedation, we identified a global preservation of functional connectivity within early visual (fig. 4C) and auditory (fig. 4D) cortices. We observed preserved connectivity within nodes of the visual network (i.e., in the thalamus, primary visual, lingual, fusiform, cuneal, middle, and inferior occipital cortices). In the auditory network, residual connectivity was found in the thalamus, Heschl’s gyrus, superior temporal cortices, PCC, inferior frontal, insular, and midcingulate cortices. In visual and auditory networks, there was no decrease of connectivity during loss of consciousness. Statistical Parametric Mapping parameter estimates in thalamus, primary sensory cortices, and association cortices in visual (fig. 4E) and auditory (fig. 4F) networks were similar or even bigger during unconsciousness compared with normal wakefulness. Supplemental Digital Content 11 reports peak areas of statistical significance for visual and auditory resting networks obtained using ICA method during wakefulness and deep-sedation stages, http://links.lww.com/ALN/A637. Supplemental Digital Content 12 displays visual and auditory networks connectivity patterns obtained using ICA method during wakefulness and deep-sedation stages, http://links.lww.com/ALN/A638.

In contrast to results obtained for default network and executive-control networks, no significant relationship could be identified between the level of consciousness and connectivity in visual and auditory cortices. In the same line, no relationship could be identified between thalamocortical connectivity in visual and auditory networks and consciousness across sedation states. Similar results were obtained with the ICA approach. A complementary confirmation of global preservation of network architecture across sedation stages was provided by the stability of individual visual and auditory ICA maps goodness-of-fit scores to templates, evaluating the spatial similarity to network templates during ICA component selection (see Supplemental Digital Content 13, http://links.lww.com/ALN/A639).

In contrast, for default and executive-control networks, a significant correlation could be found between the level of consciousness and the spatial similarity of individual ICA maps compared with template across different levels of sedation.

Table 2. Default Network and Executive-control Networks Peak Areas of Significance for Correlation between Connectivity and the Level of Consciousness

<table>
<thead>
<tr>
<th>Brain Area</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z</th>
<th>Corrected FDR</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Default network</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCC/precuneus</td>
<td>-60</td>
<td>24</td>
<td>3.64</td>
<td>0.025</td>
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<tr>
<td>MPFC/ACC</td>
<td>0</td>
<td>4</td>
<td>4.23</td>
<td>0.008</td>
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<tr>
<td>Superior frontal</td>
<td>32</td>
<td>44</td>
<td>4.67</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>sulcus</td>
<td>-24</td>
<td>20</td>
<td>4.19</td>
<td>0.008</td>
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<tr>
<td>Parahippocampal cortex</td>
<td>-16</td>
<td>-32</td>
<td>5.53</td>
<td>&lt;0.001</td>
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<tr>
<td>Temporal cortex</td>
<td>-4</td>
<td>-24</td>
<td>3.36</td>
<td>0.042</td>
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<tr>
<td>Brainstem</td>
<td>-12</td>
<td>-24</td>
<td>5.57</td>
<td>&lt;0.001</td>
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<tr>
<td>Cerebellum</td>
<td>4</td>
<td>-56</td>
<td>4.34</td>
<td>0.007</td>
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<tr>
<td>Thalamus</td>
<td>-4</td>
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<td>4.74</td>
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<td>Anticorrelations</td>
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P values are expressed after correction for false discovery rate (FDR) at the whole brain level.

ACC = anterior cingulate cortex; MPFC = medial prefrontal cortex; PCC = posterior cingulate; SMA = supplementary motor area; x, y, z = Montreal National Institute standard space coordinates.

short-range connectivity between two adjacent regions of the PCC and in executive-control networks, between the middle frontal gyrus and adjacent frontal cortices. It is noteworthy that the thalamic components of both the default network and bilateral executive-control networks were among the regions that showed the strongest correlation between connectivity and consciousness. Moreover, during propofol-induced unconsciousness, the thalamus as a whole was found to be paradoxically anticorrelated to default network and executive-control networks, although it was positively correlated to these networks during normal consciousness (fig. 3, E-G). Neither ROI nor ICA identified connectivity differences between mild-sedation sessions acquired during the induction of versus the emergence from unconsciousness.
Finally, we identified, during wakefulness, a significant temporal correlation between the activity of primary visual and primary auditory cortices. Indeed, during wakefulness, we could identify a contribution of primary auditory cortex to the visual-network map. This cross-modal interaction between auditory and visual networks was not found during deep sedation (see Supplemental Digital Content 11, http://links.lww.com/ALN/A637). Moreover, the strength of cross-modal functional connectivity between primary and auditory cortices showed a linear relationship with level of consciousness (fig. 5 and table 3). Figure 5A illustrates that connectivity between primary visual cortex (used as seed region of interest) and primary auditory cortex (shown in black) shows a linear correlation with the level of consciousness. Figure 5B displays effect sizes (statistical parameter estimates) for connectivity between auditory and visual cortices across sedation stages. Supplemental Digital Content 14, http://links.lww.com/ALN/A640, and Supplemental Digital Content 15, http://links.lww.com/ALN/A641, report similar results obtained using the ICA approach.

Discussion

Partially Preserved Functional Connectivity during Deep Sedation

During unconsciousness, some residual functional connectivity was identified in all resting-state networks. This result is in line with findings in anesthetized monkeys or in humans during conscious sedation, vegetative state, or light sleep. This partial preservation of functional connectivity in the absence of consciousness has been suggested to possibly reflect preserved anatomical connections dissociated from higher cognitive functions. However, quantitative analyses are still lacking to evaluate how much of conscious brain activity contributes to resting-state functional MRI fluctuations.

Theories of Anesthesia-induced Loss of Consciousness

The current study addresses the types of brain activity altered during propofol-induced variations of level of aware-
whether anesthesia-induced hypnosis results primarily from anesthetic agents and could contribute to the understanding of arousal behaviors, increased metabolism, and the persistence of sensory afferents in this information exchange and thus in the genesis of conscious perception. Our results would refine this global workspace view of consciousness.

We also identified, during wakefulness stages, anticorrelations with PCC in lateral frontoparietal regions involved in bilateral executive-control networks (as reported in 36,41,61). The strength of these anticorrelations decreased as the volunteers became more sedated (fig. 3). This finding reinforces the view that anticorrelations between higher-order frontoparietal cortices could be important for normal brain function and could allow the presence of structured cognitive processes during normal consciousness.

**Cross-modal Auditory-visual Interactions.** Propofol-induced unconsciousness was also associated with a loss of cross-modal interactions between early visual and auditory cortices. A cross-modal link between visual and auditory cortices has been recently demonstrated during wakefulness. During anesthesia, the loss of these cross-modal interactions could hypothetically be explained by a loss of top-down influence from frontoparietal networks on early sensory cortices (as suggested in 46). However, we are unable to discount the possibility of bottom-up modulation of low-level connections. The observed loss of cross-modal interactions dur-

<p>| Table 3. Visual Network Peak Area of Significance for Correlation between Connectivity and the Level of Consciousness |
|-------------------------------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
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<th>x</th>
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$P$ values are expressed after correction for false discovery rate (FDR) in a 10-mm radius spherical small volume centered on a priori coordinates identified in literature. Reprinted with permission from Eckert MA, Kamdar NV, Chang CE, Beckmann CF, Greicius MD, Menon V: A cross-modal system linking primary auditory and visual cortices: Evidence from intrinsic fMRI connectivity analysis. Hum Brain Mapp 2008; 29:848–57. x, y, z = Montreal National Institute standard space coordinates.

This provides a track toward understanding the mechanisms involved in the loss of consciousness induced by anesthetic agents and could contribute to the understanding of neural correlates of consciousness.

There is still a debate in the literature on the question whether anesthesia-induced hypnosis results primarily from action on the thalamus or on the cortex. At the cortical level, hypnotic anesthetic agents have traditionally been considered to decrease activity in a widespread bilateral frontoparietal network. However, this frontal cortex deactivation effect is variable from one anesthetic agent to another. For example, it is more marked with propofol than with thiopental. Other models refer to the notion of cognitive unbinding, in which the primary action of hypnotic anesthetic agents would be to functionally disconnect between the different parts of the cortex, which would probably impair the brain’s ability to integrate information. Such a view is supported by previous positron emission tomography connectivity analyses. A recent electroencephalography study similarly suggests the presence of some anterior-posterior functional uncoupling in the brain during anesthesia-induced loss of consciousness. As for the thalamus, some authors have proposed that thalamic activity could act as a consciousness switch, allowing cortical arousal. Other authors argue that thalamic function could rather serve as a relay for corticocortical transfer of information. In some cases, such as during ketamine-induced sedation, reduced awareness can occur despite preserved arousal behaviors, increased metabolism, and the persistence of an activated electroencephalographic activity. This is an argument against the proposal that the common effect of hypnotic anesthetic agents is a decrease in arousal.

**Functional Connectivity Patterns Correlating with Consciousness**

Corticocortical Connectivity in Fronto-parietal Networks—The Default Network and Executive-control Networks. Both ROI-driven analyses and ICA showed that the correlation between decreased connectivity and propofol-induced decrease in consciousness is a general rule in most areas of default network and executive-control networks (fig. 3; Supplemental Digital Content 7, http://links.lww.com/ALN/A633, and Supplemental Digital Content 8, http://links.lww.com/ALN/A634). Because the correlation between connectivity and consciousness also involved short-range connectivity, it is unlikely that a selective alteration of long-distance connectivity could explain our results. In contrast to default network and executive-control networks, no relationship between connectivity and consciousness could be identified in early visual and auditory cortices. Our results support a distinctive link between propofol-induced unconsciousness and connectivity in frontoparietal cortices. They are in line with a recent report showing a localized decrease in default network connectivity in PCC during midazolam-induced conscious sedation.

Some recent studies also showed decreased default network connectivity during sevoflurane-induced anesthesia. These results are coherent with previous positron emission tomography studies typically showing a selective frontoparietal metabolic impairment, compared with a relative preservation of specialized sensory cortices in altered states of consciousness. Our findings could fit the global workspace theory of consciousness. This theory states that awareness is generated by a central information exchange in the human brain, allowing some specialized processors, such as sensory systems in the brain, to distribute information to the system as a whole. Global workspace theory generally assumes a crucial role of higher-order associative cortices, such as frontoparietal cortices, and a less central role of sensory afferents in this information exchange and thus in the genesis of conscious perception. Our results would refine this global workspace view of conscious processes, showing that there exist at least two parts of the widespread frontoparietal network (the default networks and the executive-controls networks) that subserve different functions during wakefulness but are equally impaired during anesthesia-induced loss of consciousness.

We also identified, during wakefulness stages, anticorrelations with PCC in lateral frontoparietal regions involved in bilateral executive-control networks (as reported in 36,41,61). The strength of these anticorrelations decreased as the volunteers became more sedated (fig. 3). This finding reinforces the view that anticorrelations between higher-order frontoparietal cortices could be important for normal brain function and could allow the presence of structured cognitive processes during normal consciousness.
Propofol-induced unconsciousness reinforces the view that a breakdown of temporal coherence between different cerebral networks might have dramatic consequences on brain function.

**Potential Role of Thalamocortical Connectivity in Genesis of Consciousness.** The role of thalamocortical connectivity in anesthesia-induced loss of consciousness is widely discussed in neuroscience literature.9,14,62 We show that decreased thalamocortical connectivity in default network and bilateral executive-control networks correlates with propofol-induced decrease of consciousness. These results are in line with reports of impaired thalamocortical connectivity in default network in vegetative state.43,46 During unconsciousness, the thalamus became anticorrelated with default network and executive-control networks cortical networks activity (fig. 3). This effect is unlikely to be due to the regressing out of global brain signal employed in ROI-driven approach,63,64 because our complementary ICA analyses regressing out of global brain signal employed in ROI-driven approach.63,64 because our complementary ICA analyses showed similar findings (Supplemental Digital Content 9, http://links.lww.com/ALN/A635). The identified thalamocortical anticorrelations (the directionality of which cannot be reliably assessed) are suggestive of a potential inhibitory interaction between thalamus and cortex activity during propofol-induced unconsciousness. This finding could hypothetically be explained in light of a previous study on brain slices65 describing changes in intrathalamic modulatory activity under high doses of propofol, provoking a suppressive effect on thalamocortical activity. Our results are also in agreement with the concept of anesthetic agents mediating hypnogic effects by activating subcortical sleep-promoting neurons.7,66,67 However, the present study was not designed to investigate the precise mechanisms of modifications in thalamocortical interactions. To our knowledge, no thalamocortical anticorrelations have been reported so far in resting-state functional MRI studies during anesthesia-induced unconsciousness or during sleep. Decreased thalamocortical correlation, but no significant anticorrelation, has been reported in patients in coma and vegetative states.43 It is noteworthy that a recent report showed the presence of an anticorrelated pattern of thalamus and cortical activity in a model of limbic seizures in rats.68 In this study, subcortical stimulation induced increased thalamic blood flow and firing but reduced front-parietal blood flow, paired with the appearance of slow oscillations in the electroencephalographic activity. Likewise, several studies revealed negative functional MRI responses and increased δ power in the electroencephalographic recordings when applying external stimulation during non–rapid-eye-movement sleep.69,70 Additional research is needed to investigate the functional significance of the observed thalamocortical anticorrelations during propofol-induced loss of consciousness and to identify whether these anticorrelations are a drug-specific or anesthetic-state effect or a more general feature of brain function during altered states of consciousness.

In contrast to what was observed in default network and executive-control networks, a correlation between thalamocortical connectivity and consciousness was not observed in the visual and auditory networks. Our results suggest that the link between thalamocortical connectivity and consciousness can preferentially be found in higher-order frontoparietal networks. Among other possible mechanisms, our findings could be related to a study showing a selective GABAergic control of higher-order thalamic relays.71 A potential regional effect of anesthetics on thalamus was also shown in a work of Alkire et al.,72 in which a discrete thalamic infusion of a potassium channel blocker was shown to reverse the effect of inhalational anesthesia.

During propofol-induced loss of consciousness, a decrease in the thalamic involvement in resting-state networks was paired to a decrease in connectivity in most key nodes of these networks. To date, there is still a debate on whether the thalamus or the cortex plays the primary role of a consciousness switch mediating the effects of anesthetics.62 It has been suggested that the observed thalamic effects of anesthetics could be largely indirect as a consequence of reduced cortical activity.14,49 In the case of the thalamic switch hypothesis, propofol-induced thalamocortical anticorrelations could prevent global cortical arousal in response to external stimuli. The thalamocortical anticorrelation could provoke a paradoxical increase in cortical inhibition during stimulation (as found in73: decreased α and increased δ electroencephalogram power in response to surgical stimulation). In our study, the presence of a selective disruptive effect on thalamocortical connectivity in higher-order associative cortices, with preserved thalamocortical activity in sensory networks, does not support the hypothesis of propofol thalamic changes merely mediating a decrease in global cortical arousal. On the other hand, it is possible that anesthesia-induced loss of consciousness is due to a primary impairment of thalamic activity, leading to an indirect impairment of cortico-thalamocortical connectivity. In this context, it could be suggested that the pattern of reduced cerebral connectivity observed in our study matches the cortical projections of thalamic matrix cells (as previously observed in monkey), which were suggested to be involved in cortico-thalamocortical connectivity.74 In the hypothesis of the thalamus having primarily a relay function, thalamocortical anticorrelations could be a way to block the transmission of excitation from one part of the cortex to another and thus prevent cortical activation and arousal during sedation. Our data suggest that propofol-induced changes in cortical and thalamic connectivity are tightly related, but further work is required to investigate the precise contribution of changes in cortico-thalamocortical interactions during anesthesia-induced loss of consciousness.

**Methodological Considerations.** A general overview of common analysis methods used in functional MRI resting state connectivity studies is provided for the readers’ interest in Supplemental Digital Content 4, http://links.lww.com/ALN/A630. Results described in the main manuscript were obtained using a ROI-driven approach. In a second step, a confirmatory analysis was performed by means of a convergent functional connecti

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tivity analysis method, ICA. Complementing the ROI-driven correlation analysis, ICA offers the advantages of being able to isolate cortical connectivity maps from nonneural signals and of being unbiased by the selection of a seed ROI for correlation analysis. Therefore, ICA may allow the identification of network nodes missed by the conventional ROI-driven analysis. The fact that the ROI and ICA approaches show similar results provide additional arguments to refute the possibility of spurious correlations from the choice of seed voxels in our ROI analysis.

However, several possible technical issues raise the need to be cautious in asserting a direct link between the changes in connectivity observed in functional MRI resting-state studies and consciousness. First, asserting a correlation between the observed regional effects of propofol on functional MRI network connectivity and consciousness is beyond the scope of a single study and would first require that a number of other different anesthetics be studied with identical methods. This is similar to what happened with the positron emission tomography anesthetic studies. Because several groups are now working on the same topic, this field will be developed a little at a time as the different anesthetics are studied.

A sample size of about 20 subjects has been suggested to be optimal to obtain reliable statistics in functional MRI studies at the group level. The present work was performed on a sample of 19 healthy volunteers. This sample size is larger than that of most previous sedation functional MRI studies, typically including 7 to 14 subjects. Although the sample size is a general issue in functional MRI studies, the use of a random-effects approach at the group level, such as performed in the present study, allows generalizing results as being representative of the general population from which the volunteers are drawn.

One could also argue that the changes in connectivity observed in this study could be due in part to an increased dose of the anesthetic itself, independent of the level of consciousness. We therefore have added propofol serum values as a confounding factor in our analyses and showed no significant modifications in the reported relationships between functional MRI default network connectivity and the level of consciousness. On the other hand, because functional MRI studies measure regional changes in blood flow that are supposed to reflect changes in neural activity, it could be that hypnotic anesthetic agents affect cerebral blood flow independently of neuronal activity. Although we cannot totally rule out the possibility that our findings at least partially represent hemodynamic side effects of propofol, previous studies have shown that propofol does not modify the magnitude of cerebral blood flow response to neural activation at sedative concentrations and does not modify flow-metabolism coupling in humans. In our opinion, it is also unlikely that our findings can be explained by a propofol-induced global loss of signal-to-noise ratio or global alteration of cerebrovascular coupling, because visual and auditory networks showed preserved connectivity during unconsciousness.

Another possible methodological concern is that we chose to perform our sedation study in spontaneously breathing subjects (for ethical concerns) and therefore could not optimally monitor ventilation parameters. Previous studies have shown that although $pCO_2$ variations may effect the functional MRI BOLD signal, this does not seem to significantly modify the BOLD response to neural activity. In our view, the issue of regional effects of $pCO_2$ on BOLD is less relevant in the present study, because we were studying patterns of correlation, rather than specific regional effects per se. Given that $pCO_2$ effects were reported to be largely correlated to global brain signal changes, we here regressed out possible global signal effects from our functional MRI ROI time-course analyses. Finally, the identified linear relationship between default network connectivity and consciousness remained unchanged after explicitly modeling $pCO_2$ changes as a confounding factor in our analyses, reinforcing our view that the reported data cannot be interpreted to solely reflect the effect of propofol-induced $pCO_2$ blood changes on cerebral vascular reactivity.

In the present study, a linear contrast was used to search for a relationship between connectivity and level of consciousness during the different sedation stages. Nonlinear contrasts did not provide a better fit to our data. Moreover, displays of parameters estimates (fig. 3; Supplemental Digital Content 7, http://links.lww.com/ALN/A633, and Supplemental Digital Content 8, http://links.lww.com/ALN/A634) support a progressive, linear decrease of connectivity in frontoparietal networks after increasing propofol administration. However, it cannot be affirmed that changes in consciousness, like changes in connectivity, are a monotonically decreasing or increasing state, rather than a stepwise process, during propofol-induced sedation.

Previous studies suggested that brain activity (as reflected by electroencephalography or bispectral index) could be different during the induction versus the emergence of anesthesia-induced sedation. However, our functional MRI BOLD analyses revealed no significant connectivity differences between mild-sedation stages acquired during the induction versus the emergence of propofol-induced unconsciousness. Finally, the imaging technique used here might not be sensitive enough to detect changes in the activity of brainstem sleep promoting areas such as the ventrolateral preoptical nucleus. Indeed, these nuclei are too small to be reliably differentiated using our present functional image acquisition. Animal experiments that include selective lesions or pharmacological manipulations of these areas would be more adequate to address these questions.

Conclusion

Our findings suggest that propofol-induced unconsciousness is associated with widespread changes in functional connectivity in the human brain, with a preferential targeting in fronto-parietal networks, compared with the relative preservation of early sensory cortices. These findings suggest a cru-
cial role of higher-order frontoparietal associative networks activity in the genesis of conscious perception. Our results are also consistent with those from studies showing that the functional impairment of highly connected frontoparietal areas has greater repercussions on global brain function than that of less centrally connected sensorimotor areas.94,95

Taken as a whole, the present findings suggest that propofol-induced loss of consciousness could be related to a breakdown of the brain’s temporal architecture, which modifies both within- and between-network connectivity and thus prevents communication between low-level sensory and higher-order frontoparietal cortices, thought to be necessary for conscious perception. Further studies are needed to confirm these results in other pharmacologically-induced states of sedation to find a common final mechanism of anesthesia-induced alteration of consciousness14 and to link anesthesia, slow-wave sleep, epilepsy, or vegetative states.96

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