Neural Correlates of Sevoflurane-induced Unconsciousness Identified by Simultaneous Functional Magnetic Resonance Imaging and Electroencephalography

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ABSTRACT

Background: The neural correlates of anesthetic-induced unconsciousness have yet to be fully elucidated. Sedative and anesthetic states induced by propofol have been studied extensively, consistently revealing a decrease of frontoparietal and thalamocortical connectivity. There is, however, less understanding of the effects of halogenated ethers on functional brain networks.

Methods: The authors recorded simultaneous resting-state functional magnetic resonance imaging and electroencephalography in 16 artificially ventilated volunteers during sevoflurane anesthesia at burst suppression and 3 and 2 vol% steady-state concentrations for 700 s each to assess functional connectivity changes compared to wakefulness. Electroencephalographic data were analyzed using symbolic transfer entropy (surrogate of information transfer) and permutation entropy (surrogate of cortical information processing). Functional magnetic resonance imaging data were analyzed by an independent component analysis and a region-of-interest–based analysis.

Results: Electroencephalographic analysis showed a significant reduction of anterior-to-posterior symbolic transfer entropy and global permutation entropy. At 2 vol% sevoflurane concentrations, frontal and thalamic networks identified by independent component analysis showed significantly reduced within-network connectivity. Primary sensory networks did not show a significant change. At burst suppression, all cortical networks showed significantly reduced functional connectivity. Region-of-interest–based thalamic connectivity at 2 vol% was significantly reduced to frontoparietal and posterior cingulate cortices but not to sensory areas.

Conclusions: Sevoflurane decreased frontal and thalamocortical connectivity. The changes in blood oxygenation level dependent connectivity were consistent with reduced anterior-to-posterior directed connectivity and reduced cortical information processing. These data advance the understanding of sevoflurane-induced unconsciousness and contribute to a neural basis of electroencephalographic measures that hold promise for intraoperative anesthesia monitoring. **(ANESTHESIOLOGY 2016; 125:861-72)**

GENERAL anesthetics have been in clinical use for almost 170 yr, but the mechanism by which they impair consciousness is incompletely understood. Rigorous studies of anesthetic-induced unconsciousness in humans have typically been conducted with the intravenous agent propofol. Studies using high-density electroencephalography in humans have identified anteriorization of coherent α oscillations,[1,2] characteristic phase–amplitude coupling changes,[2] and decreased frontoparietal connectivity[3] as electroencephalographic correlates of propofol-induced unconsciousness. Studies using functional magnetic resonance imaging (fMRI) have identified diminished corticocortical[4,5] and corticosubcortical[6] connectivity as neural correlates of propofol-induced unconsciousness; a preferential interference of functional connectivity between higher order thalamic nuclei and association cortex during propofol-induced

What We Already Know about This Topic

- The neurophysiologic correlates of anesthetic-induced unconsciousness include disruption of functional connectivity as assessed by electroencephalography and functional magnetic resonance imaging
- Resting-state functional magnetic resonance imaging and electroencephalography were analyzed in 16 artificially ventilated volunteers during sevoflurane anesthesia to detect functional connectivity

What This Article Tells Us That Is New

- Anesthetic concentrations of sevoflurane disrupted connectivity in higher-order frontal and thalamic networks, but not in primary sensory networks, and reduced cortical information processing, similar to the effects observed for propofol
- Intraoperative measurements of frontal electroencephalography might provide real-time intraoperative assessment of neurophysiologic correlates of anesthetic-induced unconsciousness

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 827. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). A.R. and D.G. contributed equally to this article, as did D.J. and R.I.

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unconsciousness has also been demonstrated.[7] Neural correlates of propofol-induced unconsciousness identified by simultaneous fMRI and electroencephalography have been explored more recently.[8,9] We have previously shown that functional disconnection between anterior and posterior brain structures as assessed by fMRI is associated with a reduction of frontal-to-parietal directed connectivity (DC) as measured by symbolic transfer entropy (STEn) and a reduction of frontal permutation entropy (PEn). These two electroencephalographic measures served as surrogates of the ability to process information in local (PEn) and widespread (STEn) cortical networks. In summary, consistent observations from different imaging modalities suggest that frontal and thalamocortical information processing might play a key role in the generation of consciousness and impairment of this processing might be an important neurophysiologic mechanism of the action of general anesthetics.

Despite significant progress in understanding the basis of propofol-induced unconsciousness, the neural mechanisms of halogenated ethers in humans are less well understood. Sevoflurane is arguably the best representative of this drug class to study in humans since it can be well tolerated during mask induction, thus enabling a single-agent technique. A recent study using high-density electroencephalography in healthy volunteers demonstrated that sevoflurane-induced unconsciousness was associated with a functional disconnection in the α bandwidth between anterior and posterior structures.[10] Consistent with this finding, a subsequent study of fMRI that meticulously controlled for head motion found functional disconnections in frontoparietal networks and a thalamocortical breakdown.[11] Positron emission tomographic studies demonstrated the important role of thalamus during anesthesia in humans in terms of specifically reduced thalamic metabolism.[12–14] Pharmacologic manipulation of the central medial thalamus could even reverse the effect of sevoflurane anesthesia in rodents.[15,16] Together, these results suggest a key role of the thalamus in unconsciousness induced by sevoflurane.

Thus far, there have been no reports of simultaneous fMRI and electroencephalography to bridge the gap between neural mechanisms and intraoperative monitoring strategies. Furthermore, investigations of sevoflurane have been limited by the number of participants and confounds such as head motion that possibly resulted from the lack of clinically relevant anesthetic concentrations.[11,17]

In this study of healthy volunteers, we took advantage of a simultaneous electroencephalography–fMRI protocol to test whether the modulation of network activity as assessed by fMRI is paralleled by corresponding changes in entropy-based surrogates of information transfer and information content in the electroencephalogram. We tested the hypothesis that, like propofol, sevoflurane would reduce frontal information processing (PEn) and disrupt frontoparietal connectivity, resulting in a decrease of frontal-to-parietal DC (as measured by STEn).

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Materials and Methods

Study Participants

The ethics committee of the medical school of the Technische Universität München (München, Germany) approved the current study, and the study protocol was in accordance with the Declaration of Helsinki. Volunteers were given detailed information about the protocol and risks, and written informed consent was obtained at least 48 h before the experimental session; volunteers were reimbursed for their participation. Twenty healthy adult men aged 20 to 36 (mean, 26 yr) were recruited by means of notices posted on campus and *via* personal contact. Before inclusion in the study, medical history was reviewed to assess any previous neurologic or psychiatric disorder, as well as other contraindications of the planned procedure (physical status other than American Society of Anesthesiologists physical status I, chronic intake of medication or drugs, hardness of hearing or deafness, absence of fluency in German, known or suspected disposition to malignant hyperthermia, acute hepatic porphyria, history of halothane hepatitis, obesity with a body mass index more than 30 kg/m^2, gastrointestinal disorders with a disposition for gastroesophageal regurgitation, known or suspected difficult airway, and presence of metal implants). A focused physical examination was performed, and a resting electrocardiogram was recorded. Experiments were conducted between June and December 2013.

Study Protocol

Sevoflurane concentrations were chosen so that burst suppression (BS) was reached in all participants (around 4.4 vol%) and that subjects tolerated artificial ventilation (reached at 2.0 vol%). We favored a fixed intermediate concentration of 3.0 vol% over individualized concentrations to make group comparisons feasible. At the beginning of the experiments, volunteers were in the supine position on a couch outside the fMRI scanner room, and a 63-channel electroencephalogram was recorded with eyes closed for 10 min. Afterward, the first combined electroencephalogram and fMRI measurement (700 s) was carried out using the magnetic resonance tomographic scanner. Participants were in a resting state with eyes closed. By means of visual online analysis of the electroencephalogram, it was verified that volunteers did not fall asleep during this baseline recording. After inserting an intravenous catheter in a vein on the dorsum of the hand, sevoflurane in oxygen was administered *via* a tight-fitting facemask using an fMRI-compatible anesthesia machine (Fabius Tiro, Dräger, Germany). Sevoflurane, as well as oxygen and carbon dioxide, was measured by using the cardiorespiratory monitor (Datex

AS/3, General Electric, USA); standard American Society of Anesthesiologists monitoring was performed. An end-tidal sevoflurane concentration (etSev) of 0.4 vol% was administered for 5 min and then increased in a stepwise fashion by 0.2 vol% every 3 min until the participant became unconscious, as judged by the loss of responsiveness (LOR) to the repeatedly spoken command "squeeze my hand" two consecutive times. Sevoflurane concentration was then increased to reach an end-tidal concentration of approximately 3 vol%.

When clinically indicated, ventilation was managed by the physician and a laryngeal mask suitable for fMRI (i-gel, Intersurgical, United Kingdom) was inserted. The fraction of inspired oxygen was then set at 0.8, and mechanical ventilation was adjusted to maintain end-tidal carbon dioxide at steady concentrations of 33 ± 1.71 mmHg during BS, 34 ± 1.12 mmHg during 3 vol%, and 33 ± 1.49 mmHg during 2 vol% (throughout this article, mean ± SD). Norepinephrine was given by continuous infusion (0.1 ± 0.01 μg kg^{-1} min^{-1}) to maintain the mean arterial blood pressure close to baseline values (baseline, 96 ± 9.36 mmHg; BS, 88 ± 7.55 mmHg; 3 vol%, 88 ± 8.4 mmHg; 2 vol%, 89 ± 9.37 mmHg; follow-up, 98 ± 9.41 mmHg). After insertion of the laryngeal mask airway, sevoflurane concentration was gradually increased until the electroencephalogram showed BS with suppression periods of at least 1,000 ms and about 50% suppression on parallel electroencephalography (reached at 4.34 ± 0.22 vol%), which is characteristic of deep anesthesia.[18] At that point, another 700 s of electroencephalogram and fMRI was recorded (fig. 1A). Twelve more minutes of data were acquired at steady etSev levels of 3 and 2 vol%, respectively, each after an equilibration time of 15 min.

In a final step, we reduced etSev to two times the concentration at LOR. Since under this condition, most of the subjects moved or did not tolerate the laryngeal mask any more, this stage was not included in the analysis. In order to monitor the subject's recovery from anesthesia, the scanner table was slid out of the scanner and sevoflurane administration was terminated. The volunteer was at that point manually ventilated until spontaneous ventilation returned and was regularly asked to squeeze the physician's hand; the recovery of responsiveness was noted as soon as the command was followed. The laryngeal mask was removed as soon as the patient opened his mouth on command. Fifteen minutes after the recovery of responsiveness, the Brice interview[19] was administered to assess for awareness during sevoflurane exposure; the interview was repeated on the phone the next day. After 45 min of recovery, another combined measurement of fMRI and electroencephalography was obtained in the resting state with eyes closed. When participants were alert, oriented, cooperative, and physiologically stable, they were taken home by a family member or a friend appointed in advance.

Electroencephalogram Data Acquisition

Simultaneous electroencephalographic fMRI recordings were performed using an fMRI-compatible, 64-electrode cap with equidistantly arranged ring-type sintered nonmagnetic Ag/AgCl electrodes (Easycap, Germany) and two 32-channel, nonmagnetic, battery-operated electroencephalographic amplifiers (BrainAmp MR, Brain Products, Germany). Electrode impedance was kept below 5 kΩ using an abrasive gel (Easycap). An interface unit (SyncBox, Brain Products) was additionally connected to the amplifiers to reduce timing-related errors in the fMRI artifact correction by synchronizing the clocks of the electroencephalographic amplifiers and the fMRI gradients. One of the 64 channels registered the electrocardiogram and was placed over the chest (left anterior axillary line). All signals were recorded at a 5-kHz sampling rate (BrainVision Recorder, Brain Products). The electroencephalographic signal preprocessing analyses were performed using BrainVision Analyzer 2 (Brain Products). fMRI gradient artifacts in the electroencephalogram were averaged using a sliding window and subtracted from the electroencephalographic signals.[20] The cardioballistic artifacts caused by cardiomechanical electrode induction were removed using a template detection method. The templates were based on the detected local maxima (R peaks) and subtracted from the electroencephalogram using sliding windows of 21 epochs.[20] Finally, zero-phase digital filtering with 0.5- to 30-Hz bandwidth at 200-Hz sampling frequency, basic artifact rejection (signals of 10-s length with amplitudes exceeding 250 μV), and average referencing were performed. Electroencephalographic analysis is based on nonoverlapping signals of 10-s length (N = 2,000 amplitude samples per signal).

Electroencephalographic PEn

PEn, a nonparametric time series measure, has been established to reliably separate wakefulness from unconsciousness.[21–23] PEn quantifies the regularity structure of the neighboring order of signal values in order to reflect the information content of the signal as a surrogate of local cortical information processing.[9,24] Distortions of the electroencephalogram recordings in high static and radiofrequency electromagnetic fields of the magnetic resonance tomographic scanner challenge the reliability of the signal analysis. A key advantage of the nonparametric PEn over parametric analysis methods is its robustness against artifacts, signal distortions, and poorly known characteristics of the underlying dynamics, which makes this approach comparatively permissive regarding the specific selection of embedding parameters (dimension, m; time lag, l).[21,25] To obtain a direct comparison to the previous analysis of simultaneous electroencephalogram and fMRI during propofol-induced LOR,[9] we used m = 5 and l = 5, which is in line with the signal length criterion m! less than N and allows a sufficient deployment of trajectories within the state space of the electroencephalographic β-band during wakefulness and sevoflurane anesthesia.[9]

Electroencephalographic STEn

We largely follow the 2013 article of our group and therefore refer to it for detailed formulas.[9] Briefly, STEn was introduced by Staniek and Lehnertz[26] in 2008 and has the advantages to analyze amplitude orders instead of amplitude values. In

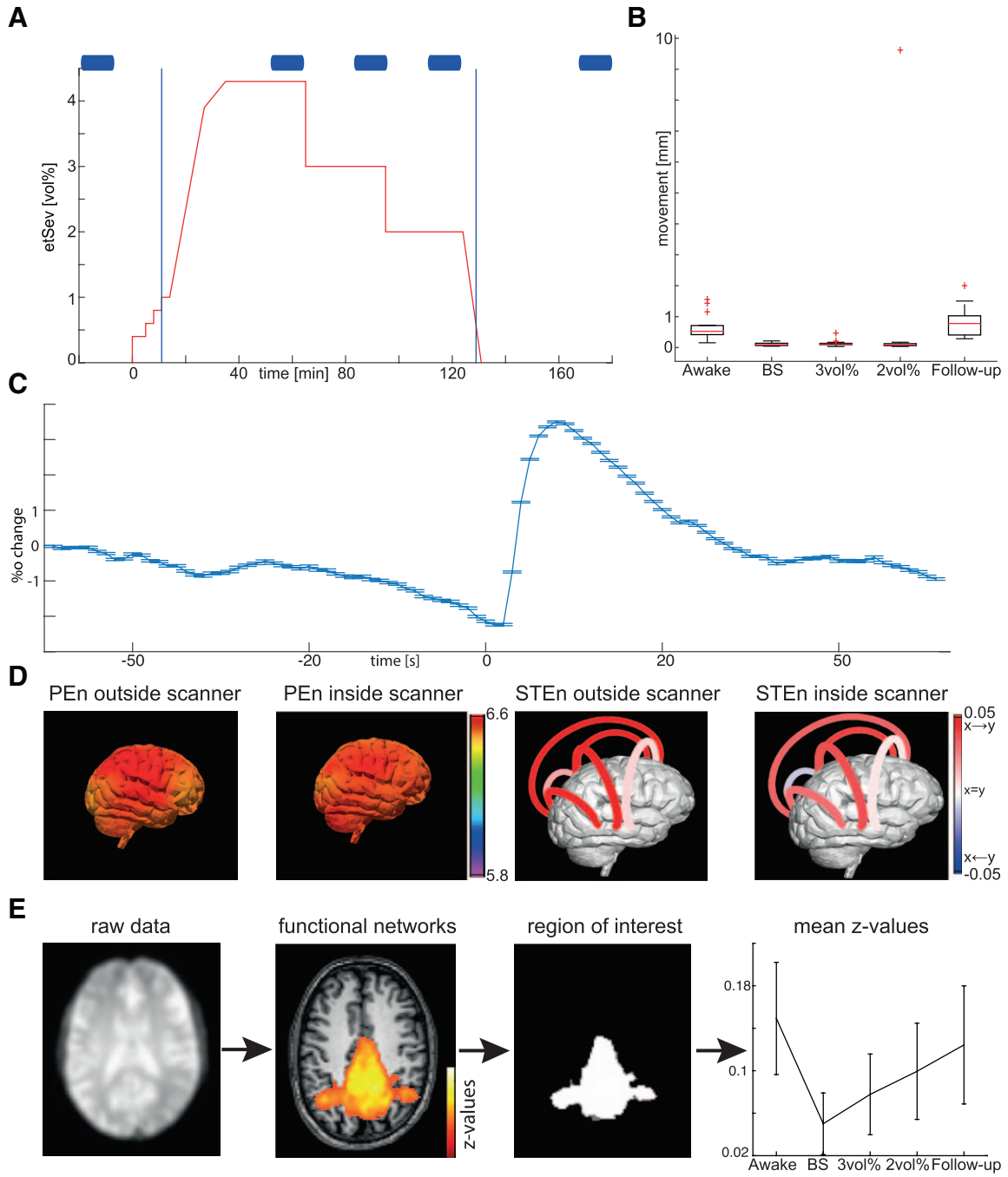

Fig. 1. (*A*) Scheme of the experiment: the *red trace* displays sevoflurane concentration in the course of the experiment. *Blue boxes* represent 700 s of parallel functional magnetic resonance imaging and electroencephalography, and *vertical blue lines* indicate the loss and recovery of responsiveness. (*B*) Box plots show the maximum translation of each single subject across all phases of the experiment. *Boxes* represent 25th, 50th, and 75th percentiles. *Whiskers* correspond to ± 2.7 × SD, and outliers are denoted as +. (*C*) Average blood oxygenation level dependent signal in a grey matter mask with respect to burst onset on parallel electroencephalogram (mean ± SE, 139 burst onsets in total). (*D*) Permutation entropy and symbolic transfer entropy inside and outside the scanner projected on the cortical surface (x → y, indicating frontal-to-parietal directed connectivity in frontoparietal electrode pairs). (*E*) Workflow of data analysis. Imaging data were realigned, normalized, and smoothed and then subdivided into 75 independent components (ICs) using an independent component analysis. Masks were generated through binarized maps, employing voxel-wise one-sample Student's *t* tests (uncorrected, $P < 0.001$; SPM8). Mean z values were calculated from the masks in each subject and given IC. BS = burst suppression; etSev = end-tidal sevoflurane concentration; PEn = permutation entropy; STEn = symbolic transfer entropy.

contrast to PEn, STEn represents a surrogate measure of cortical DC as indicated by directed information flow between two electroencephalographic signals X and Y. STEn is defined as the difference between unidirectional couplings $STEn_{X\to Y}$ and $STEn_{Y\to X}$ from signal X to Y or vice versa and is expected to attain positive values for directional coupling with X as the driver of Y and negative values for Y driving X. Assuming $STEn_{X\to Y}$ and $STEn_{Y\to X}$ greater than 0, an STEn value = 0 indicates balanced bidirectional information flow. STEn is less sensitive to the choice of specific embedding parameters than comparable parametric measures of directed mutual interaction.[26–30] As with PEn, we used m = 5, l = 5, and a transfer delay δ = 7 to 12 corresponding to 35 to 60 ms. Since STEn is computed in the time domain, a direct comparison to frequency-based signal analysis is not meaningful. Nevertheless, the applied settings result in a focus on information transfer in time scales within the electroencephalographic β-band, which is suspected to be relevant for long-range intercortical information exchange.[31,32] Computation of PEn and STEn was performed using Lab-VIEW 8.5 (National Instruments, USA), where the core algorithms of PEn and STEn were embedded in C programming language (Bell Laboratories, USA).

fMRI Acquisition and Preprocessing

Data acquisition was carried out on a 3-T whole-body magnetic resonance tomographic scanner (Achieva Quasar Dual 3.0T 16CH, The Netherlands) with an eight-channel, phased-array head coil. The data were collected using a gradient echo planar imaging sequence (echo time = 30 ms, repetition time = 1.838 ms, flip angle = 75°, field of view = 220 × 220 mm^2, matrix = 72 × 72, 32 slices, slice thickness = 3 mm, and 1-mm interslice gap; 700-s acquisition time, resulting in 350 volumes). Anatomy was acquired before the functional scan using a T1-weighted sequence and 1- × 1- × 1-mm voxel size.

Data were preprocessed using Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, University of London, London, United Kingdom) and Data Processing Assistant for Resting-State fMRI (DPARSF, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China).[33] Functional and T1-weighted images were first reoriented manually and realigned to the mean image of all functional images. Next, the first three time points were removed and slice timing was corrected. Functional images from all sessions and structural images were coregistered to the standard fMRI template implemented using SPM8 and resliced to 2- × 2- × 2-mm voxel size. Structural scans were not repeated for subsequent sessions. All images were resliced to 2- × 2- × 2-mm voxel size using third-degree spline interpolation and normalized to Montreal Neurological Institute (MNI) space. Functional images were smoothed using a 3- × 3- × 3-mm Gaussian kernel. Importantly, there were no relevant movement artifacts that required exclusion of data (fig. 1B, compare to Palanca *et al.*[11]). In fact, during sevoflurane anesthesia with laryngeal mask airway, participant movement was reduced compared with the waking state. One participant had a single movement artifact exceeding 11 mm, contaminating about three frames. Excluding the subject from the analysis resulted in no significant difference from the presented results. We therefore decided to include the participant in the final data analysis.

fMRI-Independent Component Analysis and Region-of-Interest–based Analysis

All data analysis steps not implemented using SPM8 or GIFT Toolbox (Medical Image Analysis Laboratory, University of New Mexico, USA) were implemented using Matlab 2014b (Mathworks, USA). To study the effect of different sevoflurane concentrations on brain networks, independent component (IC) analysis (ICA) was carried out. We used the INFOMAX algorithm of GIFT Toolbox with an ICASSO and 20 repetitions searching for 75 different ICs, including data from 16 subjects from all five stages of anesthesia (baseline awake, BS, 3 vol%, 2 vol%, and follow-up).[34] ICs were identified with ICs from the literature.[20] Masks of different ICs were created from T maps from all subjects, taking into account T more than 3.197 ($P < 0.001$, uncorrected) and binarized afterward.

For the region-of-interest (ROI)–based analysis, we chose regions from the coregistered Harvard-Oxford atlas. We then extracted a mean time course from each anatomic ROI and employed this time course as a regressor of interest in a general linear model in SPM together with the six movement parameters from the realignment procedure as nuisance regressors. Generated voxel-wise coefficients of the regressor of interest were transformed into T maps and plotted with SPM8 ($P < 0.001$, uncorrected, unless otherwise stated). Statistical testing was carried out using a one-way repeated measure ANOVA model for the five phases of our experiment (baseline awake, BS, 3 vol%, 2 vol%, and follow-up) as conditions. Significance levels are either reported on the voxel level (uncorrected) or on the cluster level with family-wise error correction (denoted as p_{FWE}).

In order to ensure intact blood oxygenation level dependent (BOLD) coherence during sevoflurane anesthesia,[12] we calculated the average cortical BOLD signal in a grey matter mask with respect to burst onset on the simultaneously recorded electroencephalogram. Through this analysis, we could demonstrate that the global grey matter BOLD signal leads to a plausible hemodynamic response function (fig. 1C).

Statistical Analysis

Electroencephalographic Measures. All statistical analyses were carried out using Matlab. *P* values less than 0.05 were deemed significant. Sample size was based on previous experiments using propofol. The effects of sevoflurane on the PEn in frontal, parietal, temporal, and occipital electroencephalograms (changes of information content) such as on the STEn-based information flow in frontoparietal, frontotemporal, frontooccipital, parietotemporal,

parietooccipital, and temporooccipital electroencephalograms (changes of DC) were of interest. Therefore, values of PEn and of STEn in the frontal (18 electrodes corresponding to Fp1 to FC6 according to the 10- to 20 schemes), central (11 electrodes, C5 to CP4), parietal (14 electrodes, P11 to PO8), temporal (12 electrodes, FT1 to TP12), and occipital (eight electrodes, O9 to I12) recordings on the electroencephalogram were averaged. The effect of anesthesia on both parameters over the whole time course was analyzed using a one-way repeated measure ANOVA. Sensitivity to discriminate between two different levels of anesthesia was analyzed using a two-sided Student's *t* test and Bonferroni-corrected for multiple testing. Both PEn and STEn measures led to the same results inside and outside of the MR scanner (waking state, fig. 1D).

fMRI Measures. Mean z values from the ICA analysis were extracted subject wise from all ICs and further analyzed visually using an error bar plot and, statistically, using two-sided Student's *t* test between states and Bonferroni-corrected (fig. 1E).

Similarly, all voxel-wise analyses of thalamocortical connectivity were carried out using one-side one-sample Student's *t* test implemented using SPM8 ($P < 0.001$, uncorrected). The same approach was used for group comparisons between different stages of anesthesia.

Results

Effects of Sevoflurane on Frontoparietal Interaction

Electroencephalographic Measures. All stages of sevoflurane anesthesia led to significant ($P < 0.05$, Bonferroni corrected) reduction of PEn values in all pooled electrodes, namely, frontal, central, right and left temporal, parietal, and occipital areas when compared to the waking state (fig. 2A). A one-way repeated measure ANOVA showed a significant modulation through sevoflurane concentrations in frontal electrodes (fig. 2B), parietal electrodes, right temporal, central, occipital, and left temporal electrodes (fig. 1A, Supplementary Digital Content, http://links.lww.com/ALN/B312, showing PEn values in temporal, parietal, and occipital regions). The PEn analysis also showed significant differences across states, while the differences across regions were not significant.

It is noteworthy that PEn shows higher values during BS when compared to 3 vol%. This effect results from higher values during suppression than during nonsuppression signals, which is a common issue for univariate electroencephalographic-based measures.[35,36]

In STEn analysis, sevoflurane-induced unconsciousness caused decreased connectivity in the frontal-to-posterior direction during the 2 and 3 vol% conditions ($P < 0.05$, Bonferroni corrected), whereas frontotemporal STEn was

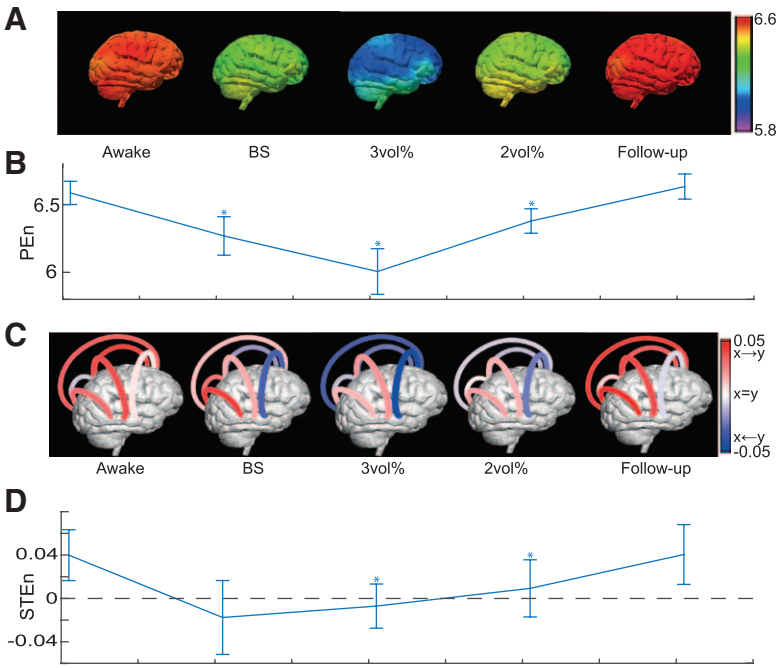

Fig. 2. Electroencephalogram reveals decreased frontal information content and breakdown of frontoparietal information flow during anesthesia. (*A*) Information processing as represented by permutation entropy (PEn) in different cortical regions rendered on a standard brain surface. (*B*) Plot of PEn (mean ± SD) in pooled frontal electrodes. * marks a significant decrease compared to the wakeful state. (*C*) Directed connectivity represented by symbolic transfer entropy between frontal, parietal, temporal, and occipital cortices. The color of loops encodes the direction of information flow (*e.g.*, with x → y, indicating information flow from rostral to caudal, *e.g.*, frontal-to-parietal directionality in frontoparietal connection). (*D*) Plot of frontoparietal information flow (symbolic transfer entropy, mean ± SD). * marks a significant decrease compared to the wakeful state. BS = burst suppression; STEn = symbolic transfer entropy.

not changed significantly during 2 vol% and decreased significantly during 3 vol% and BS (fig. 2C). An ANOVA analysis revealed a significant modulation through sevoflurane anesthesia between frontal and parietal electrodes (fig. 2D), parietal and temporal electrodes, frontal and occipital electrodes, parietal and occipital electrodes, and frontal and temporal electrodes. Temporal and occipital electrodes were not significantly modulated. Unlike PEn, frontoparietal STEn values were lower during BS when compared to 3 vol%, which were lower compared to 2 vol% (both not significant). It is noteworthy that only the frontoparietal STEn was reversed by sevoflurane anesthesia (fig. 1B, Supplementary Digital Content, http://links.lww.com/ALN/B312, showing STEn values between regions not shown in fig. 2D). Findings with PEn and STEn were congruent with previous findings during propofol-induced unconsciousness.[9]

fMRI Measures. In order to analyze how different concentrations of sevoflurane affect relevant cortical networks, we performed a group ICA (n = 16) employing the ICASSO algorithm (GIFT Toolbox V1.3) searching 75 different components in 20 repetitions. We found ICs that were stable across runs and that were consistent with ICs reported in the literature.[20] Visual inspection of T maps of different ICs suggested that they were differentially affected by sevoflurane concentration. To quantify this impression, we extracted mean z values of all 75 ICs and 5 levels of consciousness (baseline wake, BS, 3 vol% sevoflurane, 2 vol% sevoflurane, and follow-up) and performed group level statistics (table 1, Supplementary Digital Content, http://links.lww.com/ALN/B312, describing the most prominent ICs found with glass brain view, MNI coordinates, cluster sizes, and *P* values). Based on our preceding study of propofol, we had an *a priori* hypothesis about a breakdown of frontoparietal and default mode networks during loss of consciousness but expected sensory networks to be less affected or even unchanged. We grouped the ICs according to this hypothesis. The number of participants allowed segmentation of frontoparietal networks into anterior and posterior divisions.

Frontal networks revealed a significant decrease during 2 vol%, namely, in the left and right frontal parts of the frontoparietal networks (fig. 3A) and the anterior default mode network. To reflect the specificity of this observation, we also analyzed neighboring networks. The salience network, for example, did not show a significant decrease.

Parietal networks, containing the posterior division of the frontoparietal attention system and the posterior part of default mode network, exhibited changes that differed from their anterior counterparts (fig. 3B). The left and right dorsal frontoparietal networks showed a significant decrease only during BS. The posterior default mode network revealed a significant decrease only during BS and 3 vol% compared to the wakeful state but not at 2 vol%. Sensory networks, namely, the primary visual system showed a significant decrease during BS and 3 vol%, while the primary auditory system showed significant decreases only during BS (fig. 3C). In contrast, the thalamic network (fig. 3D) showed a significant decrease during all levels of anesthesia.

In order to further analyze these findings in an assumption-free way, we sorted all ICs with respect to their decrease during 2 vol% when compared to the waking state, assuming that networks with the most pronounced susceptibility to sevoflurane-induced loss of consciousness are the most functionally relevant. This approach also revealed that the most significant decrease could be seen in IC 31 (thalamic network), IC 48 (left anterior frontoparietal network), IC 53 (right anterior frontoparietal network), and IC 25 (dorsolateral prefrontal network). On the other hand, the most pronounced significant increase during 2 vol% could be seen in IC 33 (left auditory network), IC 3 (basal ganglia network), IC 8 (bilateral ventral hippocampus), and IC 23 (right auditory network). A complementary ANOVA analysis of all 75 networks yielded the same results. All findings presented here were consistent in bihemispheric networks.

Effects of Sevoflurane on Thalamocortical Connectivity

Based on the observations of impaired thalamocortical functional connectivity during sevoflurane anesthesia in previous studies[7,11] and our observation of a significant reduction of mean z values in the ICA analysis, we hypothesized a reduced connectivity between thalamus and frontal areas. Past animal experiments already suggested that projections of the central medial thalamus, with afferents from the brainstem, are involved in attention and arousal.[37–39] Pharmacologic manipulation of the central medial thalamus could even reverse the effect of sevoflurane anesthesia in rodents.[15,16]

To further elucidate the effect of sevoflurane on thalamocortical interaction, we analyzed the thalamic connectivity in a ROI-based approach using a general linear model in SPM8. Left and right thalamic ROIs, respectively, were taken from Harvard-Oxford atlas. Here, we could demonstrate that thalamocortical interaction was widespread during the waking state but diminished during all states of anesthesia (fig. 4, A to D).

During BS, the thalamus was functionally disconnected from cortical areas. The top five clusters that significantly correlated to thalamic BOLD fluctuations projected outside of the brain and were thus regarded as noise (table 2, Supplementary Digital Content, http://links.lww.com/ALN/B312, showing top five decreased clusters with *P* values, cluster size, MNI coordinate, and peak T value). It is also noteworthy that the thalamic BOLD activity was not synchronized with the occurrence of bursts on the electroencephalogram (fig. 4B).

During 3 vol% (fig. 4B), the decrease of connectivity compared to the wakeful state was widespread, including the thalamus itself, frontal areas, and the cerebellum. At 2 vol% sevoflurane, thalamic connectivity to mainly parietal, occipital, and temporal areas could be seen (fig. 4B, left). The comparison of the 2 vol% state *versus* both waking states (fig. 4C) revealed a significant decrease in thalamic connectivity in

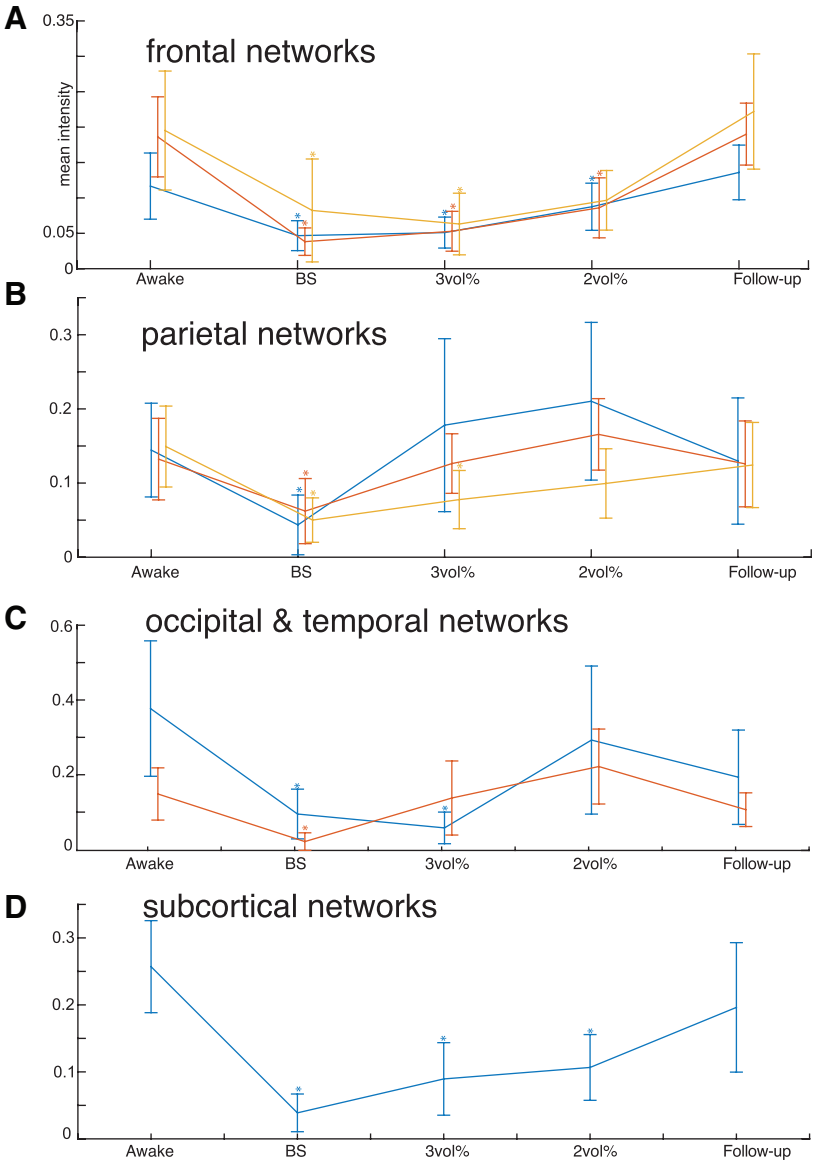

Fig. 3. Functionally relevant networks exhibit distinct sensitivity to sevoflurane. (Average z values from the given mask are shown as group mean ± SD; a significant change compared to the wakeful state is asterisked.) (*A*) Frontal networks. *Blue*: independent component (IC) 48/left anterior frontoparietal network, *red*: IC53/right anterior frontoparietal network, and *yellow*: IC63/anterior default mode network. (*B*) Parietal networks. *Blue*: IC42/left dorsal attention network, *red*: IC18/right dorsal attention network, and *yellow*: IC37/posterior default mode network. (*C*) Occipital and temporal networks. *Blue*: IC41/primary visual network and *red*: IC58/primary auditory network bilateral. (*D*) Subcortical networks: IC31/thalamic network. BS = burst suppression.

the thalamus itself, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, posterior cingulate cortex, and around the ipsi- and contralateral intraparietal sulcus. Medial prefrontal cortex did not show this significant reduction in thalamic connectivity either in the left- or in the right-sided thalamus analysis. Similarly, all other reported results were symmetrical. Also noteworthy is the fact that a significant decrease of connectivity of thalamus and primary sensory areas was not found.

These observations could be replicated by a voxel-wise one-way repeated-measure ANOVA analyzing the difference between both wakeful states at baseline and recovery and all stages of anesthesia. The main effects were seen in the posterior cingulate cortex, the thalamus, and the left dorsolateral prefrontal cortex. The same effects could be seen in the right-sided thalamus. This was consistent with findings from the ICA analysis, which showed preserved or increased activity in primary sensory networks.

Discussion

The current study demonstrates that sevoflurane differentially affects various functional networks of the brain. Sevoflurane at 2 and 3 vol% levels leads to a more profound decrease of fMRI-based measures of functional connectivity

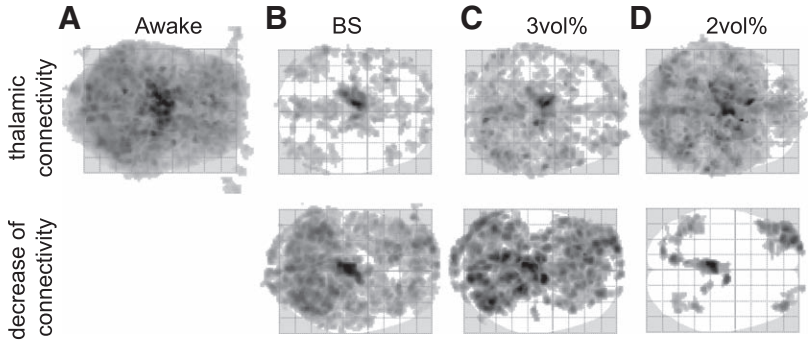

Fig. 4. Reduced thalamocortical connectivity during sevoflurane anesthesia. (*A*) Region-of-interest (ROI)–based analysis of the waking state with a seed ROI in the left thalamus of Harvard-Oxford Atlas, showing widespread functional connectivity. Note: the *top row* shows ROI-based connectivity, while the *bottom row* shows a decrease compared to the wakeful state using contrasts of the factorial design (all voxel-wise one-sample Student's *t* test, uncorrected, $P < 0.001$; voxel threshold: 100, Statistical Parametric Mapping). (*B*) Functional connectivity of the thalamus during burst suppression (BS) and difference to the wakeful state. (*C*) Functional connectivity of the thalamus during 3 vol% sevoflurane and difference to the wakeful state. (*D*) Functional connectivity of the same seed ROI during 2 vol% and difference to the wakeful state.

in frontal networks, especially ventral parts of the frontoparietal attention networks and, to a lesser extent, anterior parts of the default network. At the same time, thalamocortical functional connectivity was significantly decreased in all stages of anesthesia. By contrast, primary sensory networks demonstrated increased functional connectivity during 2 vol% sevoflurane, with activation levels similar to the waking state in 3 vol% sevoflurane. Electroencephalographic analyses revealed the consistent findings of a pronounced decrease in surrogates of information processing (PEn) in frontal cortex and reversal of DC (STEn) between frontoparietal electrode pairs.

Frontoparietal Networks and Consciousness

In the past decade, fMRI studies of anesthetic-induced unconsciousness have focused predominantly on propofol,[5,6,9,40–43] with very few including concomitant electroencephalographic recordings.[9] Almost all studies consistently found that propofol-induced unconsciousness was associated with a breakdown of medial or lateral frontoparietal network connectivity,[5,6,9,40,41,43] reflected also by a reduction of frontal-to-parietal information-theoretic measures in electroencephalography.[9,28,44] In particular, the default mode network and frontoparietal attention network have attracted attention, and impaired information exchange has been mainly attributed to these networks. Recent fMRI studies of sevoflurane anesthesia[11,40] and disorders of consciousness in brain-injured patients[5] have also reported diminished function of these networks. However, contradictory findings have been reported in the neuroimaging studies of sevoflurane.[45–47] Differential effects on anterior and posterior parts of both default mode and attention networks were not observed in the past.

The dorsolateral prefrontal cortex (IC 53/63/25) showed the greatest decrease in activation during 2 vol% of sevoflurane when compared to all other cortical networks identified *via* ICA, while the posterior parts of both networks did not show this behavior at all. This observation supports the assumption of a prominent role of the frontal cortex in consciousness in humans, either through perceptual or attentional mechanisms.

Previous studies have reported an impairment of frontoparietal information-theoretic and other directed functional connectivity measures derived from electroencephalographic recordings during propofol-induced loss of consciousness.[9,28,44] Furthermore, diminished frontal-to-parietal STEn during sevoflurane anesthesia has been described before with low-resolution electroencephalography.[28] Although the anesthetic protocol employed in the current study started with higher doses of sevoflurane, the findings are consistent with recent work demonstrating reduced frontal-to-parietal directed phase lag index (in the α bandwidth) during sevoflurane-induced unconsciousness at less than 1 vol% end-tidal concentration after slow uptitration.[48] Analysis of PEn as a surrogate for information content[24] further supports our fMRI data by revealing a pronounced reduction in frontal electrodes. In summary, both our electrophysiologic and neuroimaging results support the interpretation that frontal areas are differentially susceptible to sevoflurane, suggesting the interpretation that unconsciousness (of sensory information) might result from impaired top-down information access important for normal conscious perception.

The pronounced reduction of electroencephalography-based surrogates of information content in frontal cortex together with the concomitant changes of functional connectivity in frontal brain networks holds promise for the future development of a neuroscientifically informed strategy for real-time monitoring in the operating room.

Thalamocortical Connectivity during Sevoflurane-induced Unconsciousness

The role of the thalamus in anesthetic-induced unconsciousness has been extensively investigated,[9,12,13] and several imaging studies have demonstrated a reduction of thalamic

connectivity and metabolism associated during unconsciousness due to sedative hypnotics.[11,12,14] Pharmacologic modulation of thalamic activity has not only been associated with diminished consciousness but has also been shown to reverse anesthetic effects[15,16] and improve behavioral indices in patients with disorders of consciousness.[49] A common denominator of the thalamic role in consciousness is the attention to external stimuli and regulation of wakefulness. In the current study, we observed that sevoflurane anesthesia was associated with a reduction of bilateral thalamic connectivity with the posterior cingulate cortex and the bilateral frontoparietal attention system, while functional connectivity between the thalamus and sensory cortices was not altered significantly. This supports the interpretation that decreased consciousness cannot be explained by a decreased thalamocortical feed-forward processing of sensory information alone but is probably due to decreased interaction of higher order frontal networks with posterior sensory networks. In past studies, sevoflurane anesthesia led to an especially marked inhibition of thalamic metabolism.[12] Our experimental design cannot distinguish among the possibilities that (1) sevoflurane inhibits thalamic activation, which inhibits interaction with the frontal cortex, (2) sevoflurane inhibits frontal activation, which inhibits interaction with the thalamus, or (3) some combination thereof. The observation that the thalamus showed no synchronous activation with cortical burst activity offers some support for (1). However, the breadth of molecular targets of sevoflurane and their wide distribution in the brain[50–52] lend credibility to a combined set of effects; further work is clearly required.

Limitations

This study has numerous limitations. First, fMRI and electroencephalographic analyses of sevoflurane anesthesia started at higher concentrations (consistent with BS), followed by reduced concentrations (3 and 2 vol%). This introduces the possibility that observed neural changes were associated with sevoflurane drug effects unrelated to those required to induce loss of consciousness, rather than state-specific effects strictly associated with unconsciousness. It also introduces the possibility that findings at lower concentrations of sevoflurane merely reflect the inadequate recovery of a certain brain area (*e.g.*, frontal cortex) from higher doses of anesthetic. However, the functional breakdown of frontoparietal functional connectivity[10] and frontal-to-parietal DC[48] has also been identified with slow titration of sevoflurane to achieve unconsciousness at less than 0.5 minimum alveolar concentration, supporting our interpretation of the current findings. Furthermore, analyses at lower concentrations were conducted after steady-state equilibration. Second, the initially high doses have implications for the cerebral blood flow–metabolism coupling that forms the physiologic basis for functional neuroimaging. It is known that sevoflurane induces a dose-dependent increase of cerebral blood flow, despite its reduction in cerebral metabolism.[53] However, the differential effects of sevoflurane on functional brain networks of the same vascular territory—including preserved activity and connectivity of the posterior part of the default mode network—and the consistent findings with BOLD-independent electroencephalographic measures of information transfer suggest that this could not have been a major confound. Finally, all connectivity measures have limitations, especially when considering information transfer. We emphasize that the analyzed information-theoretic measures represent only a *surrogate* for true information exchange, which can occur on multiple scales in the brain not measurable with electroencephalography. Additionally, our data analysis gives an averaged picture of functional connectivity during various sevoflurane concentrations and is not capable of detecting dynamic changes of connectivity.[54]

Conclusions

In conclusion, this is the first study reporting concomitant fMRI and electroencephalographic data during clinically relevant concentrations of sevoflurane in healthy volunteers. We found that sevoflurane preferentially affected functional connectivity of higher order frontal brain regions both in fMRI and the electroencephalogram, as well as corresponding thalamocortical connectivity. These findings have significant implications for the understanding of the underlying mechanisms of unconsciousness induced by sevoflurane (and possibly other halogenated ethers), as well as intraoperative monitoring of general anesthesia using frontal electroencephalography.

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Competing Interests

Dr. Mashour has a pending patent (through the University of Michigan, Ann Arbor, Michigan) on measures of directional connectivity for brain monitoring (application no. 13/804706, filed on March 14, 2013, "System and Method to Assess Causal Signaling in the Brain during States of Consciousness"). Drs. Jordan and Kochs have the following pending patent applications (through the Technische Universität München, Munich, Germany) on the application of the symbolic transfer entropy for monitoring the state of consciousness (German DE 10 2011 115 116.1, European EP 12 718 076.8, US 14/114719, filed on May 5, 2011). The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Golkowski: golkowski@lrz.tum.de. Raw data available from Dr. Golkowski: golkowski@lrz.tum.de.

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