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Volatile anesthetics disrupt frontal-posterior recurrent information transfer at gamma frequencies in rat

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Abstract

We seek to understand neural correlates of anesthetic-induced unconsciousness. We hypothesize that cortical integration of sensory information may underlie conscious perception and may be disrupted by anesthetics. A critical role in frontal-posterior interactions has been proposed, and gamma (20–60 Hz) oscillations have also been assigned an essential role in consciousness. Here we investigated whether general anesthetics may interfere with the exchange of information encoded in gamma oscillations between frontal and posterior cortices. Bipolar electrodes for recording of event-related potentials (ERP) were chronically implanted in the primary visual cortex, parietal association and frontal association cortices of six rats. Sixty light flashes were presented every 5 s, and ERPs were recorded at increasing concentrations of halothane or isoflurane (0–2%). Information exchange was estimated by transfer entropy, a novel measure of directional information transfer. Transfer entropy was calculated from 1-s wavelet-transformed ERPs. We found that (1) feedforward transfer entropy (FF-TE) and feedback transfer entropy (FB-TE) were balanced in conscious-sedated state; (2) anesthetics at concentrations producing unconsciousness augmented both FF-TE and FB-TE at 30 Hz but reduced them at 50 Hz; (3) reduction at 50 Hz was more pronounced for FB-TE, especially between frontal and posterior regions; (4) at high concentrations, both FF-TE and FB-TE at all frequencies were at or below conscious-sedated baseline. Our findings suggest that inhalational anesthetics preferentially impair frontal-posterior FB information transfer at high gamma frequencies consistent with the postulated role of frontal-posterior interactions in consciousness.
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Despite decades of studies of anesthetic pharmacology and anesthetic-receptor molecular interaction, a mechanistic model of anesthetic ablation of consciousness has not emerged. This is arguably due in part, to our limited understanding of what phenomenal consciousness really is, our inability to objectively assess its presence or absence, and to our lack of general understanding of its neurophysiologic correlates.

Current thinking in neuroscience embraces the theory that consciousness is an emergent phenomenon of complex information processing in the brain. Bidirectional cortico-cortical and thalamo-cortical integration of sensory information may underlie conscious perception [1,19,34]. Feedforward (FF) connections among functional brain regions are believed to define the basic functionality of cortical areas, ranging from low-level to high-level areas and characterized by neuronal receptive fields and tuning properties. Feedback (FB) connections have been suggested to play an important role in higher order cognitive operations such as perceptual organization, visual awareness and attention [1,13].

An important role in the integration of sensory information has been attributed to brain oscillations in the gamma (20–60 Hz) frequency range [33]. Direct evidence exists that phase synchronization of gamma field potentials mediates visual binding [3] and conscious perception [26]. It has been proposed that general anesthetics may produce unconsciousness by disrupting the synchronization of gamma activity

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[7]. John et al. [8] showed that general anesthetics reduce gamma EEG coherence between frontal and posterior cortices in surgical patients. Since coherence does not distinguish between FF and FB interactions, this study could not specifically examine the anesthetic effect on directional information transfer. Nevertheless, indirect evidence exists that general anesthesia preserves FF but disrupts recurrent cortical interactions in monkeys [14,31]. To date, the anesthetic effects on cortical FF and FB information transfer at gamma frequencies have not been specifically investigated.

Our working hypothesis is that the disruption of recurrent cortico-cortical information transfer encoded in gamma oscillations correlates with the loss of consciousness (LOC) produced by general anesthesia. To test this hypothesis, we used the directional information-theoretic measure transfer entropy (TE) [28] to examine the effect of two common volatile anesthetics, halothane and isoflurane, on FF and FB information transfers at gamma frequencies between primary visual (V1), parietal association (PTA), and frontal association (FR) cortices in the rat. The importance of these regions in human [17,23,31] and animal [21] visual consciousness has been previously demonstrated. We chose to use two anesthetics to arrive at a unique neural correlate of the anesthetic-induced LOC that is invariant with respect to the administered anesthetic agent. Halothane and isoflurane are been known to have important differences in potency and region-specific effects [5,22]. The clinically effective concentrations of these agents are different for different end-points, such as analgesia, atonia, amnesia, and hypnosis. As we were interested in neural activities related to LOC, we compared the effects of these agents at equivalent concentrations that supress the righting reflex. The loss of righting reflex (LORR) has been extensively used as a standard behavioral index of unconsciousness in the rat [2,6,10].

The experimental procedures and protocols were reviewed and approved by the Institutional Animal Care and Use Committee (Medical College of Wisconsin, Milwaukee, WI). All procedures conformed to the *Guiding Principles in the Care and Use of Animals* (American Physiological Society, Bethesda, MD, USA) and were in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington, DC, 1996). Every effort was made to minimize the number of animals used and their suffering.

In six adult male Sprague–Dawley rats, four concentric, bipolar semi-micro electrodes (SNEX-100X, Rhodes Medical Instruments, Inc., Woodland Hills, CA, USA) were stereotaxically implanted in the right cerebral hemisphere for recording of intracortical field potentials. Using methods previously described [7], one electrode was placed in V1 (7 mm posterior, 2–3 mm lateral, 2–2.3 mm vertical), one in PTA (4–4.2 mm posterior, 2–3.5 mm lateral and 2, vertical) and two in FR. The precise locations within FR varied in each animal from prefrontal (5 mm anterior, 1–2 mm lateral, 3–3.3 mm vertical), frontal eye fields (1.5 mm anterior, 1 mm lateral, 1.8 mm vertical), and supplementary motor cortex (4.2 mm anterior, 2 mm lateral, 2.4 mm vertical). Following the implantation, the animal was kept in the reversed dark/light cycle room for 7–10 days.

Since the purpose of this study was to better understand conscious sensory perception, the experiments were designed to examine event-related activity rather than spontaneous EEG. Each rat was tested with both anesthetics one week apart. On the day of the experiment, the rat was placed in the cylindrical plastic restrainer inside a plexiglass anesthesia box, allowing limited movement of its head and limbs. The animal was breathing spontaneously, and its temperature was controlled at 37 °C.

Following 1 h of equilibration, 5 min of ERP was recorded to binocular flash stimulation (60 discrete flashes), achieved with a stroboscopic light source (EG & G Electro-Optics, Salem, MA, USA) housed in a soundproof box. Subsequently, the anesthetic concentration was raised from 0 to 2.0% halothane or isoflurane in increments of 0.1–0.2%, mixed with 30% oxygen and 70% nitrogen. The anesthetic concentration was monitored using a gas analyzer (POET II, Criticare Systems, Inc., Waukesha, WI, USA). Five minutes of ERP was recorded at each increased anesthetic concentration after a 20 min equilibration.

The signals were amplified at a gain of 10,000, analog bandpass-filtered at 1–250 Hz, notch-filtered at 60 Hz, and digitally sampled at 500 Hz (WINDAQ Data Acquisition Software, DATAQ Instruments, Akron, OH, USA).

One week after the ERP experiment, the rat was tested for the LORR as a function of anesthetic concentration. To induce righting, the anesthesia box was tilted by 30°, and the righting reflex was marked as present when the animal made a purposeful attempt to right itself. Spontaneous head or limb movements in the absence of righting were not taken as an indication of righting. The percent concentration at which the righting reflex was abolished was determined by averaging the concentrations at which the righting reflex was still present was and then lost. We defined this value as One Minimum Alveolar Concentration for the Loss of Righting (1 MAC_{LR}). For all subsequent analyses, the percent concentrations were expressed as a fraction of 1 MAC_{LR}. We assumed that 1 MAC_{LR} was not altered between the two experimental sessions.

Single-trial 1-s-long ERPs were extracted from V1, PTA, and FR field-potential records using a threshold peak-detection algorithm. Although the precise locations varied within the FR from animal to animal, the recording from one FR site only was used per animal. The statistical analysis showed no significant ($p \geq 0.05$) difference among ERPs from prefrontal, frontal eye fields, and supplementary motor cortices in each experiment. Single-trial ERPs were bandpass filtered to 20–60 Hz with a bi-directional Butterworth digital filter ($N = 2$). All consecutive analyses were performed on the single-trial gamma-filtered data.

The information transfer among the regions of interest was estimated by computed TE. TE is an extension of mutual information [29] and represents a non-parametric,

directional measure of information transfer among multiple time series [28]. As we were interested in the information transfer at specific frequencies, we estimated TE from the wavelet-transformed ERPs. This approach is different from Shreiber's [28], who proposed the estimation of TE from the unprocessed time series. Single-trial ERPs were wavelet-transformed using Morlet wavelets with central frequency of 20–60 Hz in increments of 1 Hz [32]. Temporal resolution and spectral bandwidth of wavelets ranged from 55.7 ms and ±2.8 Hz at 20 Hz to 18.5 ms and ±8.6 Hz at 60 Hz. Equation below is a mathematical representation of TE from region y to region x when estimated from two wavelet-transformed signals W_x (f_o, n) and W_y (f_o, n) at a central frequency f_o and time n.

$$\mathrm{TE}_{y(f_o)\to x(f_o)} = H(W_x(f_o, n+\tau)|W_x(f_o, n)) - H(W_x(f_o, n+\tau)|W_x(f_o, n), W_y(f_o, n)) \quad (1)$$

In this equation, TE is expressed in terms of conditional entropies $H(W_x(f_o, n+\tau)|W_x(f_o, n))$ and $H(W_x(f_o, n+\tau)|W_x(f_o, n), W_y(f_o, n))$ of $W_x(f_o, n)$ and W_y (f_o, n). This relationship implies that the information transfer from y to x exists only when the prediction of $W_x(f_o, n+\tau)$ from $W_x(f_o, n)$ is improved with the knowledge of $W_y(f_o, n)$.

To minimize frequency overlap introduced by wavelet decomposition, TE data at 30, 40, and 50 Hz were selected for statistical analysis. These components are central frequencies of three gamma bands: 30 ± 4 Hz, 40 ± 6 Hz, and 50 ± 7 Hz comprising most gamma frequencies of interest. To demonstrate anesthetic-agent invariant effect on TE, the data were pooled across two anesthetic groups. To minimize the variance in TE in similar anesthetized states, the data were averaged within the anesthetic ranges of 0–0.3, 0.8–1.25, and 1.8–2.40 $\mathrm{MAC_{LR}}$.

To test for a significant effect of anesthetic concentration on TE, MANOVA with planned comparisons was carried out with TE at 30, 40, and 50 Hz as response variables, anesthetic concentration and direction of information transfer (FF or FB) as fixed factors, and rat as a random variable. A paired *t*-test was carried out at selected anesthetic levels to test for a significant difference between feedforward transfer entropy (FF-TE) and feedback transfer entropy (FB-TE). In all tests, $p \leq 0.05$ was accepted for statistical significance.

The righting reflex of all rats was lost at 0.7–1.0% halothane (1 $\mathrm{MAC_{LR}} = 0.90 \pm 0.1\%$) or isoflurane (1 $\mathrm{MAC_{LR}} = 0.84 \pm 0.1\%$) concentration.

Fig. 1 shows an example of average gamma-filtered ERP from V1, PTA and FR in the waking state and at two selected halothane levels from all animals. The event-related gamma activity was present at all concentrations in all regions. Similar observations were made with isoflurane anesthesia.

The effects of anesthetics on FF-TE and FB-TE were qualitatively similar. Fig. 2 shows TE in the conscious-sedated state (0–0.3 $\mathrm{MAC_{LR}}$). The data shown represent group averages from all animals. Among all regions, FF-TE was not significantly different from FB-TE at any of the three frequencies, suggesting that FF and FB information transfers were balanced in the conscious-sedated state.

Fig. 3 shows the group-average effects of the anesthetics on FF-TE and FB-TE at three frequencies. The results are summarized as follows.

TE at 30 Hz: The anesthetics augmented both FF-TE (significant among all regions) and FB-TE (significant between PTA and FR) at intermediate levels (0.8–1.25 $\mathrm{MAC_{LR}}$), which included the concentration that produced LORR. At high concentrations (1.8–2.4 $\mathrm{MAC_{LR}}$), both FF-TE and FB-TE were reversed or depressed (significant depression between V1 and FR) relative to the conscious-sedated baseline.

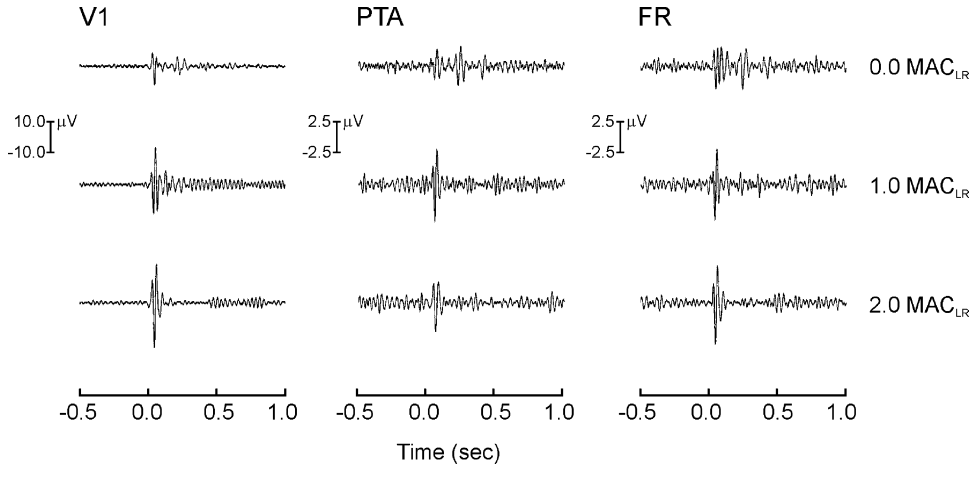

Fig. 1. Event-related potentials in primary visual (V1), parietal association (PTA), and frontal association (FR) cortices in the waking state and at two selected halothane $\mathrm{MAC_{LR}}$ levels in the same animal. One $\mathrm{MAC_{LR}}$ corresponds to the concentration at which righting reflex was abolished. Each trace shows 500 ms of prestimulus and 1000 ms of poststimulus activity filtered to gamma (20–60 Hz) frequencies and averaged across 60 trials. Note that the event-related gamma activity was present at all concentrations in all regions.

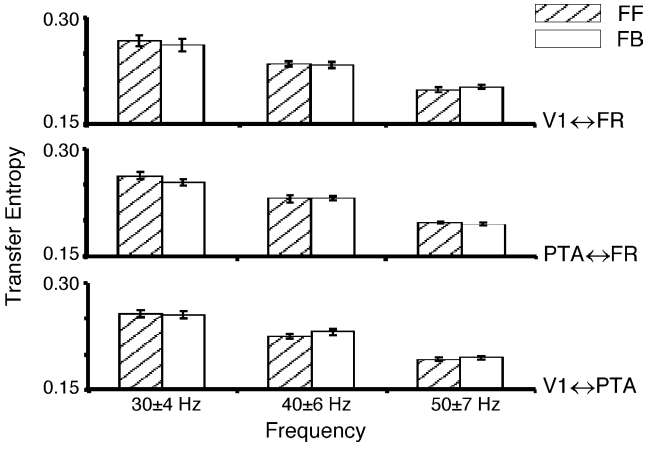

Fig. 2. Feedforward transfer entropy (FF-TE) and feedback transfer entropy (FB-TE) at 30, 40 and 50 Hz in the conscious-sedated state (0–0.3 MAC_{LR}) between primary visual (V1), parietal association (PTA), and frontal association (FR) cortices. Each bar represents a group average of transfer entropy data from all animals. Note that FF-TE was not different from FB-TE at any of the three frequencies suggesting that FF and FB information transfers were balanced in the conscious-sedated state.

TE at 40 Hz: The change in FF-TE and FB-TE at this frequency was intermediate between 30 and 50 Hz. The anesthetics at intermediate concentrations slightly augmented FF-TE (not significant) but depressed FB-TE (significant between V1 and PTA). At high concentrations, both FF-TE (all significant except between V1 and PTA) and FB-TE (significant among all regions) were depressed below the conscious-sedated baseline.

TE at 50 Hz: The anesthetics at intermediate concentrations depressed both FF-TE (significant between PTA and FR) and FB-TE (significant among all regions). The depression of FB-TE was always more pronounced than that of FF-TE; this difference was especially evident between V1 and FR. At high concentrations, both FF-TE and FB-TE were depressed below the conscious-sedated baseline (all significant except FF-TE between V1 and PTA).

Several studies in humans and animals have shown that cognitive functions including visual perception, attention and working memory depend upon the functional interactions of multiple cortical and subcortical regions [20,24,25,30]. Recently, Crick and Koch [1] proposed a hypothesis that visual consciousness itself may depend on a sparse network of neurons involved in the bidirectional, communication between frontal and posterior cortices. Experimental evidence from blindsight patients suggests that while unconscious visuomotor transformations are executed in a FF processing cycle, visual consciousness depends upon recurrent connections to V1 [12]. Likewise, it has been shown in primates that backward masking rendering visual stimuli unperceivable, evokes selective FF activation of visual sensory and higher areas but suppresses neurophysiological manifestations of recurrent interactions [15].

The principal cortical regions likely to comprise a neural network for conscious perception include frontal and parietal association regions [24]. In particular, medial and right dorsolateral areas of prefrontal cortex are part of the anterior attention system [23], responsible for top-down selection and enhancement of relevant sensory input [27]. The role of posterior parietal cortex in spatial attention has also been demonstrated [18]. Recently, Johnson and Burkhalter identified a similar polysynaptic FB circuit in the rat and found that it modulates striate cortical activity by top-down influences [9].

The question of whether anesthesia suspends consciousness by a disruption of cortical integrative processes has been raised before. Lamme et al. [14,31] showed in primates that FF processing of visual stimuli was preserved under general anesthesia but electrophysiological signatures of recurrent cortical interactions were suppressed. Neuroimaging studies of unconscious vegetative patients also demonstrated the critical importance of cortical interactions among premotor and parietal association [17] as well as primary sensory and other association cortices [16] in consciousness. Our results provide direct evidence for the preferential reduction of the frontal-posterior FB information transfer during general anesthesia at concentrations associated with LOC.

Our present results also suggest that the most sensitive change in frontal-posterior information transfer during anesthesia was in the 50 Hz gamma component of flash-induced field potentials. Long-range interactions at gamma frequencies have been implicated in visual binding and conscious perception [3,26,30]. John et al. [8] showed in humans that general anesthetics produced a reduction in high-gamma (35–50 Hz) coherence between frontal and posterior regions at LOC, which was sustained in surgical anesthesia. Likewise, we now show in the rat that anesthetics depress information transfer mostly at 50 Hz upon LOC as well as in surgically anesthetized states. In contrast to the anesthetic effects seen at 50 Hz, the change in 30 Hz information transfer was biphasic, i.e. it was enhanced at hypnotic concentrations and reversed in surgical anesthesia. Since for the neural correlate of LOC we look for an effect that persists at anesthetic levels past the point of LOC, we believe that the observed change in the information transfer at 50 Hz is a more likely neural correlate of the anesthetic-induced unconsciousness than at 30 or 40 Hz. Although 40 Hz is usually viewed as a prototypical gamma frequency in humans, the changes in the information transfer at 40 Hz in this study were intermediate between 30 and 50 Hz and therefore were less distinct. The reason for the divergence between our rat and previous human findings at 40 Hz is unclear, but may be due to the difference in species. Also, the TE method, although potentially of great utility, requires further validation. Fig. 4 summarizes our findings as generalized to both anesthetics, and illustrates the principal changes in FF and FB information transfers at 50 Hz in the conscious-sedated, LOC, and surgical states of anesthesia.

How anesthetic agents may selectively interfere with recurrent information transfer is presently unknown. It is possible that the anesthetics preferentially act upon neurons involved in either the transmission or reception of information

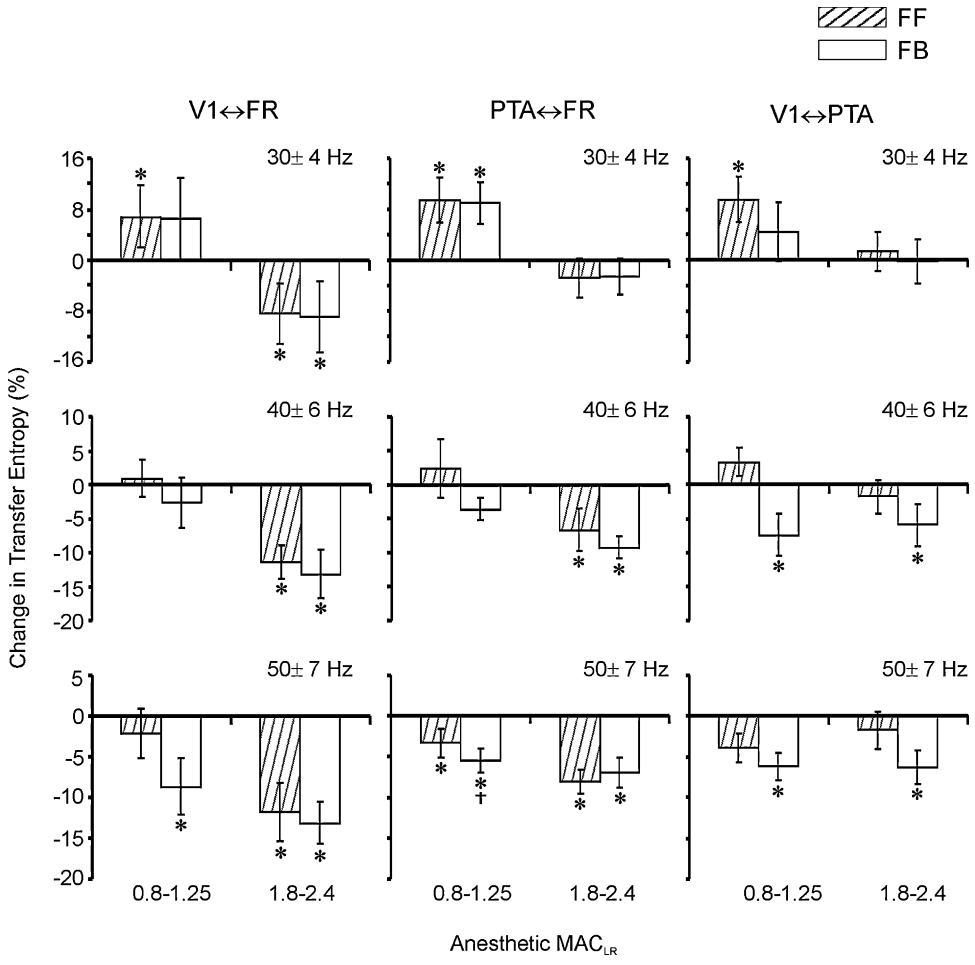

Fig. 3. Percent change in feedforward (FF-TE) and feedback (FB-TE) transfer entropy at 30, 40 and 50 Hz from the conscious-sedated state (0–0.3 MAC_{LR}) at intermediate anesthetic levels (0.8–1.25 MAC_{LR}) and in surgical anesthesia (1.8–2.4 MAC_{LR}) between primary visual (V1), parietal association (PTA), and frontal association (FR) cortices. One MAC_{LR} corresponds to the concentration at which righting reflex was abolished. Each bar represents a group average of transfer entropy data from all animals and pooled across both anesthetic groups. Asterisk (*) indicates significant difference from conscious-sedated baseline at ($p \leq 0.05$) level. Note differential changes in 30 Hz transfer entropy between intermediate and deep anesthetic levels, and more consistent depression at 40 and 50 Hz. The depression at 50 Hz is more pronounced for FB-TE at intermediate concentrations between primary visual (V1) and frontal association (FR) cortices.

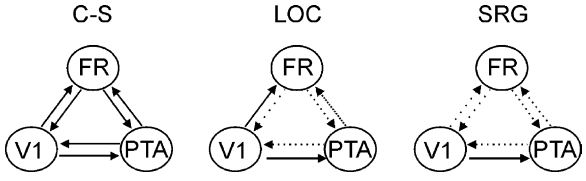

Fig. 4. Summary of anesthetic effects on feedforward (FF) (V1 → FR, PTA → FR, V1 → PTA) and feedback (FB) (V1 ← FR, PTA ← FR, V1 ← PTA) information transfers at 50 Hz as generalized to both, halothane and isoflurane. The schematic reflects principal changes in FF and FB information transfers at anesthetic-induced loss of consciousness (LOC) and in surgical anesthesia (SRG) from the conscious-sedated state (C-S). (1) Both FF and FB information transfers were balanced in C-S; (2) the anesthetics at LOC produced a stronger depression of the FB than FF information transfer, especially between frontal and posterior cortices; (3) in SRG, both FF and FB information transfers were depressed below the C-S baseline. These findings suggest that a preferential decrease in frontal-posterior FB information transfer at high-gamma frequencies is a possible neural correlate of the anesthetic-induced LOC.

traveling along the FB projection. The neurons that give rise to FB projections reside mainly in cortical layer V. These projections terminate on dendritic synapses located mainly in cortical layer I. All volatile anesthetics including halothane and isoflurane potentiate neurotransmission at GABA receptors [11]. Although FF and FB projections in the rat visual system are formed by the axons of pyramidal cells and most of them form synapses with pyramidal neurons, 10–20% of FF and FB inputs terminate at GABAergic non-pyramidal cells. In particular, the layer I of rat cerebral cortex contains only GABAergic inhibitory neurons. At least three distinct families of GABAergic neurons have been identified in the rat visual system and may explain the difference in the organization of FF and FB connections. A FB pathway-specific family of GABAergic neurons in rat's cortical layer I has recently been identified, and it is distinguished by the expression of calretinin ($GABA_{CR}$) [4]. Although volatile anesthetics are believed to act on all GABAergic neurons, one could

speculate that they exert preferentially stronger effects on $GABA_{CR}$ or other receptor types involved in the FB projection.

It has also been suggested [7] that a combination of synchronized cortico-cortical and thalamocortical interactions give rise to coherent cortical gamma activity. Hence, an alternative interpretation of our findings may involve the disturbance of coincidence detection between sensory specific and nonspecific inputs to cortical pyramidal cells, arising from FF and FB thalamocortical oscillations in the gamma frequency range [7]. Furthermore, anesthetic-induced phase or frequency shifts in thalamocortical gamma oscillations may also explain our observations.

In conclusion, our findings suggest that halothane and isoflurane preferentially impair frontal–posterior feedback information transfer encoded in high-gamma frequencies and thus are consistent with the hypothesis of Crick and Koch [1] for the role of frontal-posterior interactions in conscious perception.

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