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Impaired Macroscopic Cerebrospinal Fluid Flow by Sevoflurane in Humans during and after Anesthesia

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The glymphatic system plays a role in the removal of potentially toxic metabolites from the brain
- Extrusion of waste products from the brain parenchyma to the extracerebral lymphatic system is facilitated by a continuous circulation of cerebral spinal fluid driven by local vasomotion, global respiration, and cardiac cycle oscillations
- A further driving factor is global synchronous neural activity that induces fluctuations in cerebral blood volume and, in turn, induces macroscopic fluctuations of cerebrospinal fluid flow across the basal cisternae and fourth ventricle of the brain
- Previous animal studies have provided conflicting data around how anesthesia affects the glymphatic system

What This Article Tells Us That Is New

- In this human study, sevoflurane anesthesia impaired macroscopic cerebrospinal fluid flow *via* a disruption of coherent global gray matter activity

ABSTRACT

Background: According to the model of the glymphatic system, the directed flow of cerebrospinal fluid (CSF) is a driver of waste clearance from the brain. In sleep, glymphatic transport is enhanced, but it is unclear how it is affected by anesthesia. Animal research indicates partially opposing effects of distinct anesthetics, but corresponding results in humans are lacking. Thus, this study aims to investigate the effect of sevoflurane anesthesia on CSF flow in humans, both during and after anesthesia.

Methods: Using data from a functional magnetic resonance imaging experiment in 16 healthy human subjects before, during, and 45 min after sevoflurane monoanesthesia of 2 volume percent (vol%), the authors related gray matter blood oxygenation level–dependent signals to CSF flow, indexed by functional magnetic resonance imaging signal fluctuations, across the basal cisternae. Specifically, CSF flow was measured by CSF functional magnetic resonance imaging signal amplitudes, global gray matter functional connectivity by the median of interregional gray matter functional magnetic resonance imaging Spearman rank correlations, and global gray matter–CSF basal cisternae coupling by Spearman rank correlations of functional magnetic resonance imaging signals.

Results: Anesthesia decreased cisternal CSF peak-to-trough amplitude (median difference, 1.00; 95% CI, 0.17 to 1.83; $P = .013$) and disrupted the global cortical blood oxygenation level–dependent and functional magnetic resonance imaging–based connectivity (median difference, 1.5; 95% CI, 0.67 to 2.33; $P < 0.001$) and global gray matter–CSF coupling (median difference, 1.19; 95% CI, 0.36 to 2.02; $P = 0.002$). Remarkably, the impairments of global connectivity (median difference, 0.94; 95% CI, 0.11 to 1.77; $P = 0.022$) and global gray matter–CSF coupling (median difference, 1.06; 95% CI, 0.23 to 1.89; $P = 0.008$) persisted after re-emergence from anesthesia.

Conclusions: Collectively, the authors' data show that sevoflurane impairs macroscopic CSF flow *via* a disruption of coherent global gray matter activity. This effect persists, at least for a short time, after regaining consciousness. Future studies need to elucidate whether this contributes to the emergence of postoperative neurocognitive symptoms, especially in older patients or those with dementia.

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A major question in anesthesia research is how anesthetics affect brain physiology. Here, we investigate the effect of sevoflurane on the recently discovered glymphatic

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system, which is thought to play a crucial role in the removal of potentially toxic metabolites from the brain. According to this model, the extrusion of waste products from the brain parenchyma to the extracerebral lymphatic system is facilitated by a continuous circulation of cerebral spinal fluid (CSF) flow along ventricles, subarachnoid, periarteriole/interstitial, and perivenous spaces.^{1–3} This process is driven by local vasomotion, global respiration, and cardiac cycle oscillations.^{1,3–9} A further driving factor is global synchronous neural activity that induces fluctuations in cerebral blood volume and, in turn, induces macroscopic fluctuations of CSF across the basal cisternae and fourth ventricle of the brain (Zimmermann J, Boudriot C, Eipert C, et al. Global neuronal activity drives cerebrospinal fluid motion mediated by brain blood volume changes in humans. Preprint. Posted online April 13, 2023. bioRxiv 2023:2023.04.13.536674).^{4,10} The glymphatic hypothesis implies that an alteration in these driving factors could lead to an abnormal accumulation of waste products, *e.g.*, β -amyloid peptides or tau, and is linked to neuropsychiatric

diseases such as Alzheimer and Parkinson diseases^{11–13} as well as healthy aging.¹⁴ Moreover, impaired glymphatic clearance has been proposed as an underlying mechanism for perioperative cognitive dysfunction, including delirium.^{15,16}

How anesthesia affects the glymphatic system is still unclear. Studies in rodents suggest that certain anesthetics affect the glymphatic system in different ways.^{3,17–21} For example, volatile anesthetics such as isoflurane reduce the diffusion of intrathecally administered magnetic resonance contrast agent in the brain parenchyma,^{17–19} while ketamine/xylazine or propofol enhanced it.^{19,22} However, how these results relate to humans is unclear.

The current study aims to investigate the effects of sevoflurane anesthesia on the glymphatic system in healthy human subjects. Because the perivascular compartment is not accessible to noninvasive functional neuroimaging methods, studies in humans typically focus on macroscopic CSF flow through the fourth ventricle^{4,10,23} and basal cisternae.^{12,13} This flow is driven by global gray matter blood oxygenation level-dependent signal amplitude fluctuations, which are thought to reflect the coherence of global gray matter activity. In simple terms, it has been suggested that the more coherent global gray matter neural activity is, the more coherent total cerebral blood volume increase, which in turn drives—due to the stable pressure in the fixed skull cavity—macroscopic CSF movement, for example in the fourth ventricle.^{4,23}

After animal findings about isoflurane effects,¹⁸ we hypothesized that the gaseous anesthetic sevoflurane impairs CSF flow in the basal cisternae, mediated by impaired global gray matter coherence that drives such flow. Furthermore, as impairments in cognition and neuronal activity outlast drug administration after general anesthesia,²⁴ we expected that this effect lasts beyond sevoflurane-induced anesthesia. We further hypothesized that a sevoflurane-dependent impairment of global gray matter functional connectivity and vascular activity in anesthesia^{25–29} may lead to impaired global gray matter coherence under sevoflurane anesthesia. To test these hypotheses, we reanalyzed an existing dataset of simultaneous electroencephalogram (EEG)–functional magnetic resonance imaging recordings in healthy human subjects before, during, and after sevoflurane anesthesia.

Materials and Methods

Participants

The current data set of 20 participants was derived from a previously recorded simultaneous EEG–functional magnetic resonance imaging study about sevoflurane effects on brain activity in adults at the Technical University of Munich (Munich, Germany) in 2016 by Ranft *et al.*²⁶ The study was performed in line with the Declaration of Helsinki and approved by the ethics committee of the medical school of the Technical University of Munich. Study participants were recruited by means of notices posted on campus and

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via personal contact. They obtained detailed information about the methods and potential risks and gave their written informed consent before the experiments. The original study examined only male participants to preclude sex-specific variability. The sample size was determined according to a previous study performed in our institution on propofol.³⁰ The original publication reports a detailed description of the participants and study protocol.²⁶

Experimental Protocol

Sevoflurane Protocol. In brief, 20 healthy adult males aged 20 to 36 yr (mean, 26 yr) were assessed by combined EEG–functional magnetic resonance imaging, carried out in one session but divided into five runs (*i.e.*, states), namely wakefulness preanesthesia, sevoflurane-induced anesthesia at a steady state with 4.22 volume percent (vol%; which elicited EEG burst suppression), 3vol%, and 2vol%, and wakefulness after postanesthesia (45 min after emergence from sevoflurane 2vol%). Anesthesia was initially administered *via* a tight-fitting facemask using magnetic resonance imaging-compatible anesthesia equipment (Fabius Tiro, Dräger, Germany) and increased until a stable burst suppression pattern was reached, with sevoflurane initially set at 0.4% for 5 min, followed by increments of 0.2% every 3 min. Mechanical ventilation *via* a laryngeal mask (i-gel, Intersurgical, United Kingdom) was inserted as soon as it was tolerated, and mechanical ventilation was performed to maintain normocapnia. The specific concentration required to reach burst suppression varied slightly across subjects, with an average effective concentration of 4.22% sevoflurane. Once burst suppression was achieved, each anesthesia level, *i.e.*, burst suppression, 3vol%, and 2vol% sevoflurane, was maintained for 12 min, with a 15-min equilibration period between each condition. A final session was recorded at twice the concentration of sevoflurane needed for loss of responsiveness; however, this session was later excluded from the analysis due to movement artifacts. After the completion of these conditions, sevoflurane administration was discontinued. Carbon dioxide, oxygen, and vital parameters were monitored with a cardiorespiratory monitor (Datex AS/3, General Electric, USA), and end-tidal carbon dioxide was kept constant throughout the study (mean $\pm$ SD 33.1 $\pm$ 1.77 mmHg during burst suppression, mean $\pm$ SD 33.6 $\pm$ 1.15 mmHg during 3 vol%, and mean $\pm$ SD 33.4 $\pm$ 1.54 mmHg during 2 vol%, respectively).

The current study focuses on states of wakefulness pre- and postanesthesia and states of anesthesia 2vol% but not higher to avoid any influence from burst suppression states.³¹ Of the 20 participants, we excluded all data from 4 subjects due to missing functional magnetic resonance imaging acquisition markers (*i.e.*, triggers; 1 case), inadequate imaging volume positioning (*i.e.*, incomplete brain coverage of basal cisternae; 2 cases), and poor magnetic resonance imaging data quality (*i.e.*, systematic band-like artifact across slices; 1 case). The remaining 16 subjects were included in all analyses.

Magnetic Resonance Imaging Data Acquisition. Magnetic resonance imaging data were acquired on a 3-T whole-body magnetic resonance imaging scanner (Achieva Quasar Dual 3.0T 16CH; Philips, Medical Systems International Inc., The Netherlands) with an eight-channel phased-array head coil. T1-weighted anatomical data were acquired with 1 $\times$ 1 $\times$ 1 mm³ voxel size. Functional magnetic resonance imaging data were recorded using a gradient echo planar imaging sequence (echo time, 30 ms; repetition time, 2 s; flip angle, 75°; field of view, 220 $\times$ 220 mm; matrix, 72 $\times$ 72; 32 slices; acquisition order interleaved odd first; slice thickness, 3 mm; 1 mm interslice gap; 350 dynamic scans).

Data Analysis: Preprocessing and Outcomes

Preprocessing. Magnetic resonance image preprocessing was done using FSL (www.fmrib.ox.ac.uk/fsl) and its programs such as FEAT (Functional Magnetic Resonance Imaging Expert Analysis Tool). The preprocessing pipeline follows recent publications (Zimmermann J, Boudriot C, Eipert C, et al. Global neuronal activity drives cerebrospinal fluid motion mediated by brain blood volume changes in humans. Preprint. Posted online April 13, 2023. bioRxiv 2023:2023.04.13.536674).⁴¹³ Concretely, it included removal of the first five volumes to ensure a steady state magnetization for all frames, slice time correction, realignment, and coregistration of functional images to T1-weighted data. As it is known that strong head movement (*i.e.*, framewise displacement greater than 2.5 mm) affects preprocessing results, we followed the approach of Fultz *et al.*⁴ and, for each subject, only included the longest epoch of the imaging session, in which no significant movement was detected (see Supplemental Digital Content table 1, <https://links.lww.com/ALN/D797>, for individual epoch lengths for different conditions). Independent component analysis-based automated removal of motion artefacts was used for disposal of motion-related artefacts.³² Tissue class segmentation of the T1-weighted image was performed for creating individual subject gray matter masks.

Global Gray Matter and CSF Functional Magnetic Resonance Imaging Signals.

Corresponding functional magnetic resonance imaging signals were extracted from subject-specific masks for gray matter and CSF, respectively, detrended, temporally filtered with a bandpass filter (0.01 to 0.1 Hz), and mean averaged per mask using custom programs in MATLAB 2023a (MathWorks, USA). Global gray matter mask was based on cortical gray matter voxels of each individual's segmentation gray matter probability map thresholded to 80%. To obtain the negative derivative (d/dt) of the global gray matter signal for linking global gray matter activity and basal cisternae CSF flow (see 'Global Gray Matter–CSF Coupling'), we followed the approach of Fultz *et al.*⁴: we calculated the first derivative of the extracted global gray matter blood oxygenation level-dependent signal, multiplied it by -1 , and set all negative values to zero.

CSF signals were derived from manually delineated masks following the approach of Han *et al.*,¹³ *i.e.*, by selecting voxels with the highest signal intensity from the bottom slice of the preprocessed functional magnetic resonance imaging data, but without an independent component analysis-based automated removal of motion artefacts motion correction step including CSF signal extraction. Anatomical accuracy of the masks was confirmed by comparison with the individual subjects' T1-weighted structural data.

Outcomes. CSF Peak-to-trough Amplitude

For each subject and each condition, the CSF-functional magnetic resonance imaging signals were normalized to have a mean value of 0. The peak-to-trough fluctuation amplitude—as a proxy for CSF-flow—was calculated by taking the difference in amplitude between the signal extremes, *i.e.*, maximum amplitude minus minimum amplitude.

Peak-to-trough Amplitude of Global Gray Matter Activity

For each subject and each condition, the global gray matter functional magnetic resonance imaging signals were normalized to have a mean of 0. The amplitude of the signal was calculated by taking the difference in amplitude between the signal extremes, *i.e.*, maximum amplitude minus minimum amplitude.

Global Gray Matter Coherence

For each subject and each condition, preprocessed voxel-wise functional magnetic resonance imaging data were additionally normalized to Montreal Neurological Institute space using SPM12 software (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). The Power *et al.*³³ whole-brain functional parcellation template was used and restricted to cortical regions by multiplying the template with a mask of cortical regions from the Harvard–Oxford anatomical template, from which mean cortical regional time courses were extracted. For each subject and each condition, the time course from each region was correlated with the time course of every other region using Spearman rank correlation, producing a global cortical functional connectivity matrix,³⁴ one per subject and condition. The median absolute correlation coefficient across all region pairs was taken as our metric of functional connectivity across all region pairs and used as a proxy of global gray matter coherence, giving us one correlation coefficient value per subject and condition.

Global Gray Matter–CSF Coupling

The coupling between $-d/dt$ global gray matter and CSF functional magnetic resonance imaging signal was calculated using a bivariate Spearman correlation. This resulted in one correlation value per subject per condition.

Statistical Analysis

We tested for significant differences in measures of CSF flow, global gray matter coherence, and global gray matter–CSF coupling, respectively, across conditions of pre-sevoflurane wakefulness, 2vol%, and post-sevoflurane wakefulness by the use of the Friedman test followed by *post hoc* testing using the Tukey–Kramer test *via* the “multcompare” function in MATLAB. For each of the three conditions, respectively, we tested for significant relationships between global gray matter–CSF coupling and global gray matter coherence (or global gray matter amplitude or CSF flow) using Spearman rank correlation tests.

Results

CSF Flow Is Reduced during Sevoflurane Anesthesia

The CSF signal amplitude in voxels of the bottom slice of the imaging volume (fig. 1A) is determined by the inflow effect with higher intensities for fluid entering the volume than stationary or exiting fluid.⁴ Moreover, for inflow, there is a correlation between signal intensity and flow velocity.^{10,35} Visual inspection of the CSF signal in preanesthesia wakefulness, anesthesia, and postanesthesia wakefulness in individual subjects (fig. 1B; see Supplemental Digital Content fig. 1, <https://links.lww.com/ALN/D797>, CSF signal amplitude during wakefulness and sevoflurane for an additional subject) indicated lower peak–trough amplitudes, corresponding to slower CSF inflow under anesthesia, which, remarkably, persists after emergence. Statistical analysis revealed markedly lower CSF amplitudes in anesthesia *versus* preanesthesia wakefulness (median difference, 1.00; 95% CI, 0.17 to 1.83; $P = .013$), and no significant difference for postanesthesia *versus* preanesthesia wakefulness (median difference, 0.31; 95% CI, -0.52 to 1.14 ; $P = 0.65$) and between anesthesia and postanesthesia wakefulness (median difference, -0.69 ; 95% CI, -1.52 to 0.14 ; $P = 0.13$; fig. 1C).

Global Gray Matter Coherence Is Reduced during and after Sevoflurane Anesthesia and Highly Correlated with Global Gray Matter Amplitude across All States

As CSF flow is driven by coherent global gray matter blood oxygenation level-dependent changes,^{4,13} we next asked whether sevoflurane reduced global gray matter coherence. To this end, we calculated, for each subject and condition, an index for the absolute cortical connectivity. We parcellated the cortical surface into 247 subregions (fig. 2A) and calculated the median of all connections among each other (fig. 2B). In line with previous reports of sevoflurane-induced uncoupling of brain networks,^{25,36} we found significant reductions in the median correlation of all gray matter regions during anesthesia (median difference anesthesia *vs.* preanesthesia wakefulness, 1.5; 95% CI, 0.67 to 2.33; $P < 0.001$). This effect persisted after the emergence from

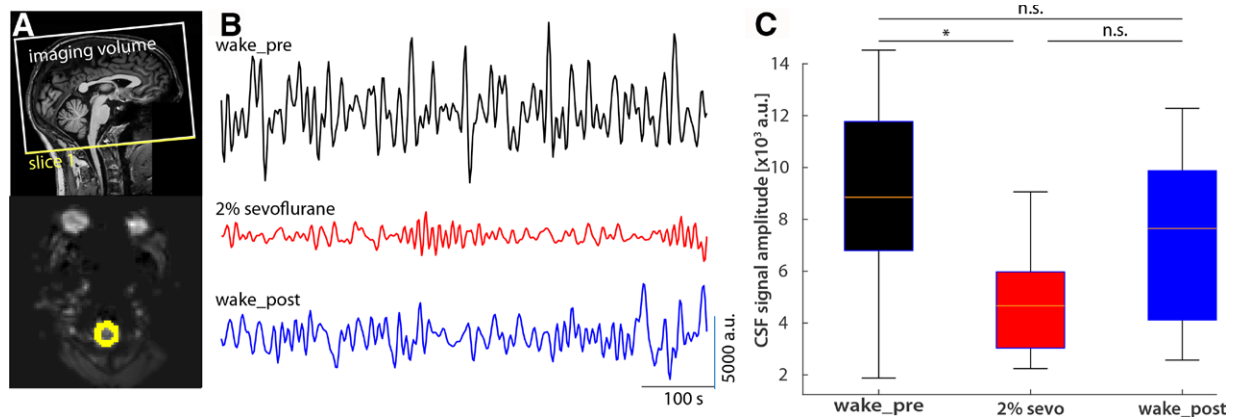


Fig. 1. Decreased cerebrospinal fluid (CSF) signal peak-to-trough amplitude as a marker of flow during anesthesia. (A) *Top*, Representative sagittal T1-weighted image of a subject and positioning of the imaging volume as well as the bottom slice (yellow). *Bottom*, Bottom slice of the imaging volume containing the CSF voxel mask (yellow). (B) Representative normalized CSF signal traces of a representative subject during preanesthesia wakefulness (wake_pre, top), anesthesia with 2% sevoflurane (sevo, middle), and postanesthesia wakefulness (wake_post, bottom). (C) Box plot of the peak-to-trough amplitude of the slice 1 CSF signal depicted in B for all $n = 16$ subjects during wake_pre (left), 2% sevoflurane (middle), and wake_post. Friedman test with *post hoc* comparison using Tukey honestly significant difference procedure. * $P < 0.05$; n.s., not significant.

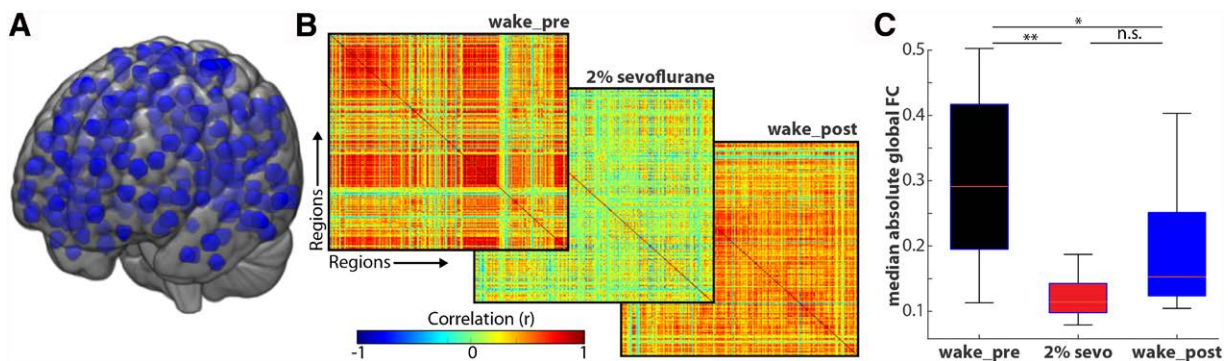


Fig. 2. Decreased absolute functional connectivity during anesthesia and after emergence. (A) Surface projection of the 247 subregions used for the correlation analysis. (B) Correlation matrix (Spearman correlation) of the subregions defined in A for one representative subject during the preanesthesia wakefulness (wake_pre), 2% sevoflurane, and wake_post stages. (C) Box plot of the median absolute global functional connectivity value (Spearman rank) for all $n = 16$ subjects during preanesthesia wakefulness (wake_pre, left), 2% sevoflurane (sevo, middle), and wake_post conditions. Friedman test with *post hoc* comparison via Tukey honestly significant difference procedure. ** $P < 0.01$; * $P < 0.05$; n.s., not significant.

anesthesia (median difference preanesthesia wakefulness vs. postanesthesia wakefulness, 0.94; 95% CI, 0.11 to 1.77; $P = 0.022$; median difference anesthesia vs. postanesthesia wakefulness, -0.56 ; 95% CI, -1.39 to 0.27 ; $P = 0.250$; fig. 2C).

As an additional measure for the coherence of the global gray matter blood oxygenation level-dependent signal, we calculated its peak-to-trough amplitude, a marker for vigilance in awake subjects³⁷ (see Supplemental Digital Content fig. 2, <https://links.lww.com/ALN/D797>, displaying the decreased global gray matter blood oxygenation level-dependent amplitude under sevoflurane). The

global gray matter blood oxygenation level-dependent signal amplitude was markedly decreased during anesthesia (median difference, 1.19; 95% CI, 0.36 to 2.02; $P = 0.002$). Again, this effect outlasted the delivery of sevoflurane (median difference preanesthesia wakefulness vs. postanesthesia wakefulness, 0.88; 95% CI, 0.05 to 1.70; $P = 0.036$; median difference anesthesia vs. postanesthesia wakefulness, -0.31 ; 95% CI, -1.14 to 0.52 ; $P = 0.651$; see Supplemental Digital Content fig. 2A, <https://links.lww.com/ALN/D797>: global gray matter blood oxygenation level-dependent amplitude changes across conditions). To

confirm the relation between global gray matter coherence and global gray matter amplitude, we performed a correlation analysis. Within all conditions, there was a significant correlation between global gray matter coherence and the global gray matter amplitude, indicating a state-independent tight link between the two measures (preanesthesia wakefulness: $r = 0.81$, $P < 0.001$; anesthesia: $r = 0.83$, $P < 0.001$; postanesthesia wakefulness: $r = 0.91$, $P < 0.001$; see Supplemental Digital Content fig. 2B, <https://links.lww.com/ALN/D797>: global gray matter blood oxygenation level-dependent amplitude changes across conditions).

Global Gray Matter–CSF Coupling Is Reduced during and after Sevoflurane Anesthesia

In light of the decreased CSF flow (fig. 1) and global gray matter coherence (fig. 2), we investigated whether the coupling between the CSF and the global gray matter functional magnetic resonance imaging signals—a measure typically used to determine glymphatic activity (for example¹³)—was also affected by anesthesia. We thus calculated the Spearman correlation between the two signals for the three conditions (fig. 3A) and found reduced correlation values for sevoflurane and postanesthesia wakefulness compared to preanesthesia wakefulness but no difference between anesthesia and postanesthetic wakefulness (median difference preanesthesia *vs.* anesthesia, 1.19; 95% CI, 0.36 to 2.02; $P = 0.002$; median difference preanesthesia *vs.* postanesthesia, 1.06; 95% CI, 0.23 to 1.89; $P = 0.008$; median difference anesthesia *vs.* postanesthesia, -0.13 ; 95% CI, -0.95 to 0.70 ; $P = 0.933$; fig. 3B). Next, we evaluated the temporal relationship of global gray matter blood oxygenation level-dependent and CSF signals. First, we calculated a cross-correlation of both signals. In line with previous reports,¹³ we detected a positive peak at -6 s (*i.e.*, shifting the CSF signal ahead of time) and a negative peak at approximately $+4$ s (fig. 3C; see also Supplemental Digital Content fig. 3, <https://links.lww.com/ALN/D797>, cross-correlations: global gray matter blood oxygenation level-dependent and CSF signal) under all three conditions. Anesthesia did not affect the temporal relationship between global gray matter blood oxygenation level-dependent and CSF flow (fig. 3C). However, the amplitude of the negative peak at approximately $+4$ s was strongly decreased by sevoflurane (fig. 3D; see also Supplemental Digital Content fig. 3, <https://links.lww.com/ALN/D797>, cross-correlations: global gray matter blood oxygenation level-dependent and CSF signal; mean $\pm$ SD blood oxygenation level-dependent amplitude preanesthesia wakefulness, 218.20 ± 100.23 a.u.; mean $\pm$ SD blood oxygenation level-dependent amplitude during anesthesia, 100.40 ± 30.49 a.u.; median difference, 1.19; 95% CI, 0.36 to 2.02; $P = 0.002$) and remained lower than the initial values after emergence (median difference preanesthesia *vs.* postanesthesia, 1.06; 95% CI, 0.23 to 1.89; $P = 0.008$; median difference anesthesia *vs.* postanesthesia, -0.13 ; 95% CI, -0.95 to 0.70 ; $P = 0.933$), indicating that sevoflurane anesthesia affected the strength of the correlation without shifting the two signals against each other.

Additionally, we calculated the cross-correlation between the negative derivative of the global gray matter blood oxygenation level-dependent (*i.e.*, $-dt/t$ global gray matter blood oxygenation level-dependent) and the CSF signal (fig. 3E; see also Supplemental Digital Content Figure 4, <https://links.lww.com/ALN/D797>, cross-correlations: $[-dt/t]$ global gray matter blood oxygenation level-dependent and CSF signal per condition). The highest correlation was at -2 s, as previously reported.¹³ Here, again, the shape of the cross-correlation was not altered by anesthesia, but the amplitude was lower during and after sevoflurane anesthesia (mean $\pm$ SD blood oxygenation level-dependent amplitude postanesthesia wakefulness, 129.81 ± 59.98 a.u.; fig. 3F).

Finally, we compared global gray matter–CSF coupling with both the global gray matter coherence driving it and the resulting CSF flow. Linear regression analysis revealed strong correlations of the global gray matter coherence with global gray matter–CSF coupling (fig. 4A; see also Supplemental Digital Content fig. 3, <https://links.lww.com/ALN/D797>, cross-correlations: global gray matter blood oxygenation level-dependent and CSF signal) for awake, preanesthesia conditions ($r = 0.76$; $P = 0.001$). This is in line with previous reports that these cortical markers of the arousal state³⁷ affect macroscopic CSF flow in awake subjects.³⁸ We did not find significant correlations between global gray matter coherence and global gray matter blood oxygenation level-dependent CSF coupling during anesthesia or awake postanesthesia conditions or postanesthesia wakefulness (fig. 4A, middle and right). Supporting this result, we observed a similar pattern for the correlation between the global gray matter amplitude and the global gray matter–CSF coupling, where we observed a strong correlation for preanesthesia wakefulness ($r = 0.78$; $P < .001$) but no correlation for the other conditions (anesthesia: $r = 0.08$, $P = 0.77$; postanesthesia: $r = 0.34$, $P = 0.2$; see Supplemental Digital Content fig. 5, <https://links.lww.com/ALN/D797>, correlations between global gray matter blood oxygenation level-dependent amplitude and global gray matter–CSF coupling per condition). Remarkably, regarding the relationship between CSF flow and global gray matter–CSF coupling, there was a significant correlation during pre-sevoflurane wakefulness ($r = 0.58$; $P = 0.021$), indicating faster inflow for higher coupling values (fig. 4B). Again, this correlation was not detectable under anesthesia ($r = -0.2$; $P = 0.460$) or during post-sevoflurane wakefulness ($r = 0.34$; $P = 0.190$).

Together, these results illustrate reduced CSF–global gray matter blood oxygenation level-dependent coupling during anesthesia and postanesthesia wakefulness and indicate that a major driver of this loss is impaired global gray matter coherence.

Discussion

Decreased CSF Flow by Sevoflurane Anesthesia

We observed that sevoflurane anesthesia impairs glymphatic activity, measured by CSF signal amplitude fluctuations and

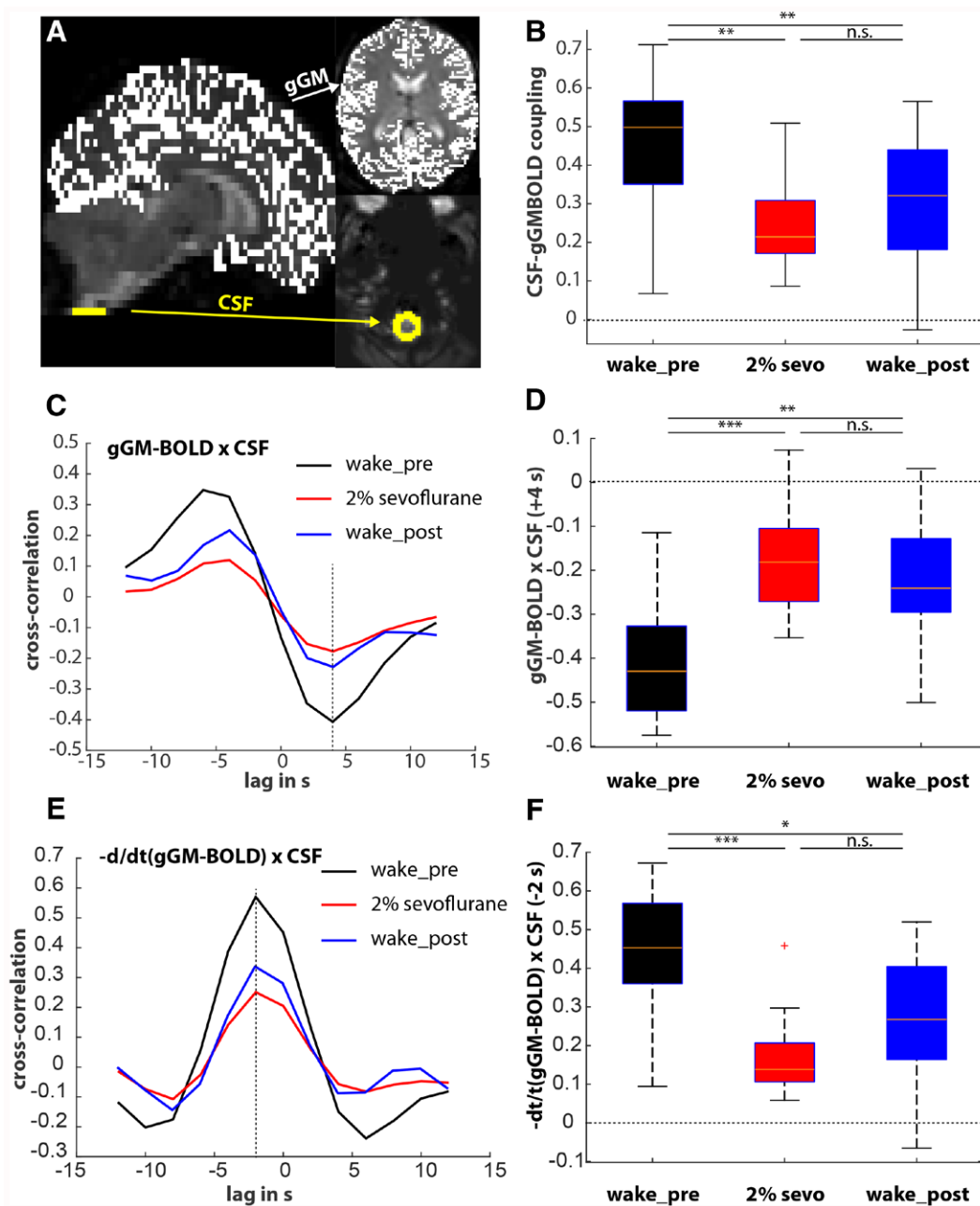


Fig. 3. Impaired global gray matter–cerebrospinal fluid (CSF) coupling during and after anesthesia. (A) *Left*, Sagittal blood oxygenation level–dependent (BOLD) image of a representative subject (*left*) with the global gray matter mask superimposed in *white* and the slice 1 CSF mask in *yellow*. *Right*, Axial slices from the same subject. (B) Box plot of the Spearman correlation coefficients between global gray matter (gGM)–BOLD and CSF for all $n = 16$ subjects during preanesthesia wakefulness (wake_pre) (*left*), 2% sevoflurane (*middle*), and wake_post conditions. Friedman test with *post hoc* comparison using Tukey honestly significant difference procedure. (C) Cross-correlation of the averaged gGM-BOLD and CSF signals under wake_pre (*black*), 2% sevoflurane (*red*), and wake_post (*blue*) conditions. (D) same as B for the amplitude of the lag at +4 s, the timepoint with the strongest anticorrelation. (E) Cross-correlation of the averaged $-d/dt$ of gGM-BOLD and CSF signals under wake_pre (*black*), 2% sevoflurane (*red*), and wake_post (*blue*) conditions. (F) Amplitude of the cross-correlation shown in E for the timepoint of –2 s, the timepoint with the highest correlation. *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$; n.s., not significant. CSF, cerebrospinal fluid.

global gray matter–CSF functional magnetic resonance imaging signal correlations, in humans. This conclusion is based on the following findings. First, we observed a reduction in the

peak-to-trough amplitude of the CSF signal in the basal cisternae during sevoflurane anesthesia. Since the signal intensity fluctuations of the CSF-containing voxels in the bottom slice

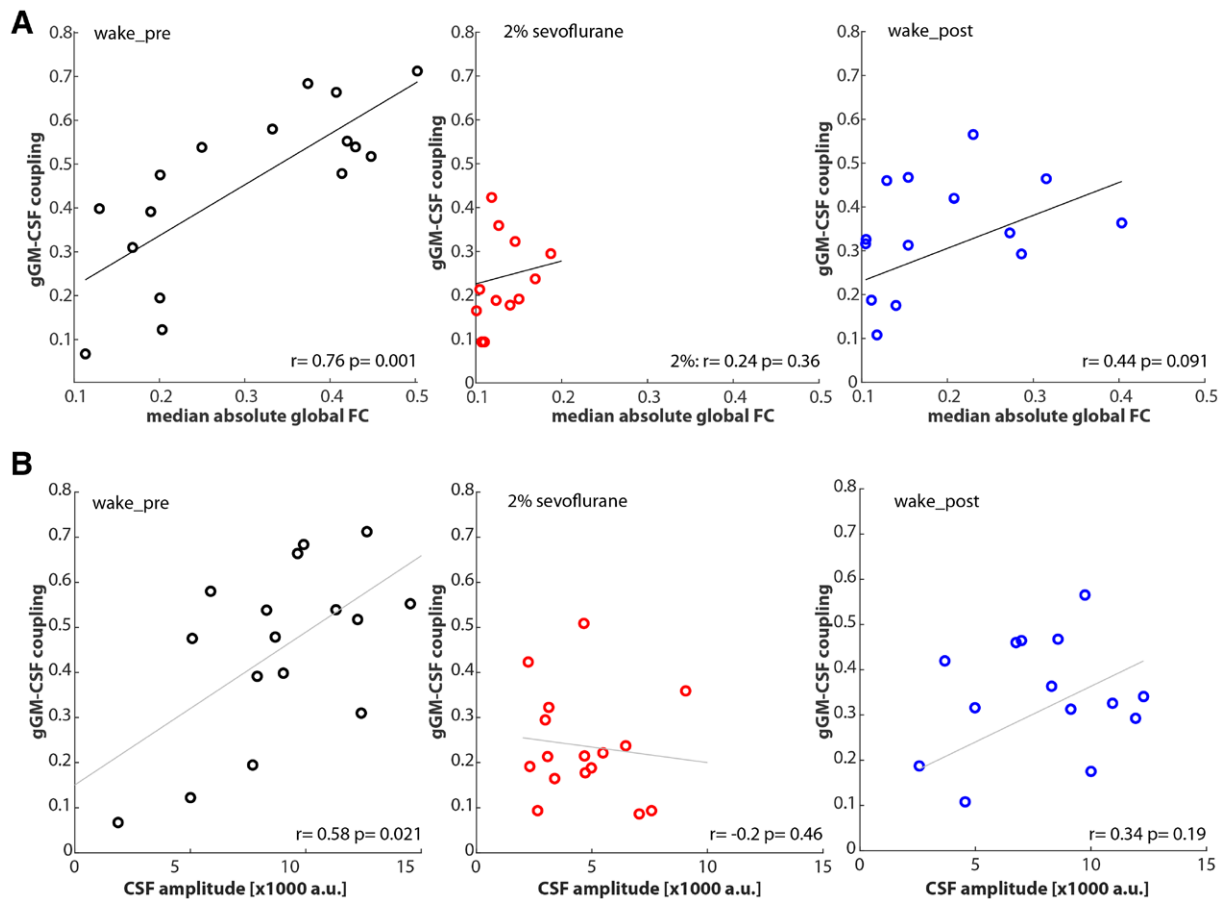


Fig. 4. The correlation of cortical connectivity or CSF flow with global gray matter (gGM)–CSF coupling is disrupted by sevoflurane. (A) Relationship between median absolute global functional connectivity (FC) and gGM–CSF coupling for preanesthesia wakefulness (wake_pre, black, left), during sevoflurane (red, middle), and after sevoflurane (wake_post, blue, right). Each circle corresponds to an individual subject. r and P values are derived from Spearman rank correlation testing. (B) Same as A for the relationship of CSF amplitude and gGM–CSF coupling.

of the imaging volume is dependent on the inflow effect⁴ and the signal amplitude is correlated to the velocity of incoming fluid,³⁵ we assume that higher peak amplitudes in the CSF signal at the bottom slice are associated with faster influx events, which penetrate further into the imaging volume.⁴ In consequence, although the peak-to-trough amplitude is a rather coarse qualitative measure, our data indicate that CSF flow is reduced by sevoflurane anesthesia.

Second, we found that sevoflurane anesthesia uncoupled global gray matter and CSF signals, *i.e.*, decreased their spearman correlation values. In previous observations, decreased global gray matter–CSF coupling was associated with impaired glymphatic system function in neuropsychiatric diseases such as Alzheimer^{13,39} and Parkinson¹² diseases. Conversely, global gray matter–CSF coupling increased in slow-wave sleep,⁴ which is associated with high glymphatic transport rates.^{5,40,41} This indicates that global gray matter–CSF coupling can be used as a proxy for the activity of

the glymphatic system in noninvasive human neuroimaging studies. A sevoflurane-dependent impairment of the glymphatic system also would be in line with rodent data reporting decreased distribution of intrathecally injected tracers during sevoflurane anesthesia.^{17,42}

In mechanistic terms, the observed sevoflurane-dependent impairment of the glymphatic system is likely linked to a reduction in neuronal activity and its coherence. Sevoflurane anesthesia reduces neuronal activity^{24,43,44} and has been shown to uncouple various cortical networks.^{25,27} This fits with our finding of reduced global neural coherence in global gray matter as well as peak-to-trough amplitude of the global gray matter–functional magnetic resonance imaging signal under sevoflurane anesthesia. Under awake preanesthesia conditions, both measures were correlated to the level of global gray matter–CSF coupling, with more coherent global gray matter activity or larger global gray matter fluctuation amplitudes predicting higher coupling values.

Previous studies reported increased glymphatic solute transport upon sleep or drowsiness.^{5,19,45,46} However, in physiologic sleep, the global gray matter amplitude and coherence are increased compared to the awake state,^{4,47} although sleep, like sevoflurane anesthesia, decreases overall neuronal activity levels.⁴⁸ The fact that sevoflurane anesthesia had opposite effects on CSF flow indicates that neuronal activity patterns, rather than levels, are important for driving CSF flow. In fact, this may also explain why other anesthetic agents like ketamine/xylazine, which also decrease neuronal activity levels but elicit different activity patterns,⁴⁹ increase glymphatic solute transport in animal models.^{19,20,45} Importantly, high levels of sevoflurane exceeding those used for surgical anesthesia induce strong global gray matter functional connectivity and coherent neuronal activity³¹ as well as large surges of CSF flux at burst suppression transitions. Although this suggests enhanced brain waste clearance, burst suppression activity patterns are not desired in clinical anesthesia as they increase the risk for postoperative delirium.⁵⁰

Implications for Postoperative Cognitive Deficits

Remarkably, global gray matter–CSF coupling as an indicator for glymphatic function was not only decreased during anesthesia but also 45 min after emergence, suggesting a postanesthesia delay in the restoration of the brain waste clearance system. This decoupling is—at least at trend—related to a prolonged decrease in global gray matter coherence after anesthesia, suggesting that prolonged sevoflurane effects on coherent neuronal activity might—at least partly—drive this effect. Another factor might be delayed sevoflurane effects on blood perfusion or volume, which could likewise influence blood oxygenation level–dependent functional magnetic resonance imaging coherence.^{25–29} Our finding suggests that the recently described postanesthesia “overhang” of neural activity changes^{24,49} may induce smaller global gray matter amplitude fluctuations that have a weaker driving effect upon CSF flow, leading to a reduced coupling between the two signals.

This “overhang” may become clinically relevant in older patients or patients with neurodegenerative disease already exhibiting a disbalance in excitatory–inhibitory neural activity.^{51,52} In these patients, the further disbalancing effects of perioperative factors such as the anesthesia protocol could lead to a more severe and/or persistent “overhang” in neural inhibition and brain waste clearance. This may contribute to postoperative cognitive disorders, for which these patient groups are particularly vulnerable.^{53,54} However, the absence of post-sevoflurane cognitive testing and the study sample of young healthy subjects means we could not analytically address this potential link. Furthermore, the lack of surgical trauma limits the implications of our findings for real-life postoperative complications. On the other hand, the design of the current study allows us to isolate and discern the effects of sevoflurane itself on CSF flow without

the additional effects of surgery and perioperative factors. Future studies could investigate CSF flow in older surgical patients admitted to the PACU (accompanied by preoperative baseline CSF flow and cognitive measures) and associate the change in CSF flow from baseline with cognitive decline over several days after surgery.

Limitations

In this study, we observed the effects of general sevoflurane anesthesia on functional magnetic resonance imaging–derived indicators of macroscopic CSF flow and neuronal activity/coherence. Note that general anesthesia also affects the cardiovascular and, by mechanical ventilation at fixed rates with positive intrapulmonary pressures, the respiratory system. While we cannot fully exclude that this affects the used functional magnetic resonance imaging measures, there does not seem to be a general influence of the mechanical ventilation in our study, as we found differences in our functional magnetic resonance imaging–derived biomarkers between the nonventilated preanesthesia condition and not only the ventilated anaesthetized condition but also the nonventilated postanesthesia condition.

In addition, the measures for CSF flow used in this study are indirect with respect to glymphatic clearance and may not fully relate to invasively measured distribution of fluorescent or paramagnetic tracers or the clearance of toxic substrates such as β -amyloid. However, global gray matter–CSF coupling may be not only an indicator for macroscopic CSF transport, a condition for glymphatic clearance, but also a predictor for cognitive decline and amyloid deposition¹³ as well as tau accumulation³⁹ in Alzheimer's disease. This indicates that impaired global gray matter–CSF coupling is indeed a plausible proxy for the function of parts of the brain's waste clearance system. However, it is important to note that the emerging model of the brain's waste clearance system is complex and that an impairment in one domain, such as the macroscopic CSF flux in this study, does not necessarily prove a disruption of the entire system.

Moreover, our study is limited by the inclusion of only male subjects as well as the low number of participants. Our findings suggest partial recovery of biomarker levels postanesthesia compared to intra-anesthesia conditions, and with a longer interval between anesthesia and postanesthesia scans, these levels may approach baseline. We acknowledge that relatively few patients are fully recovered at the 45-min mark in the postanesthesia care unit, and a longer delay until the postanesthesia scan could reveal additional normalization. This possibility should be recognized as a limitation, particularly in regard to interpreting prolonged effects on CSF flow and their potential relevance to postoperative cognitive dysfunction. Moreover, due to the experimental design, we cannot exclude that the earlier stages with higher anesthesia levels still had an impact on the 2% sevoflurane scan, as

well as the postanesthesia wakefulness condition, despite all efforts to allow for sufficient equilibration between conditions. However, these limitations do not affect our primary finding of significant differences between the preanesthesia wakefulness and anesthesia states, as well as between the preanesthesia wakefulness and postanesthesia wakefulness conditions.

Finally, the blood oxygenation level–dependent signal itself is driven by cerebral blood volume, flow, oxygen metabolism, and confounding factors such as motion, representing a complex signal driven by a number of parameters.⁵⁵ When extracting spatially large-scale synchronous blood oxygenation level–dependent activity such as the global cortical gray matter blood oxygenation level–dependent signal, questions are raised regarding its neurophysiologic origin.⁵⁶ Despite the work by Fultz *et al.*⁴ suggesting a neurophysiologic origin of the global cortical gray matter blood oxygenation level–dependent signal, it remains unknown to what extent other factors contribute to the signal and whether this varies across subjects.

In summary, future studies with a larger sample size, use of both sexes, longer periods between anesthesia and postanesthesia sampling, further nonimaging readouts of glymphatic function, and other anesthetics are needed to validate the generalizability of our findings.

Conclusions

We observed in human healthy subjects that sevoflurane affects functional magnetic resonance imaging–derived measures of CSF flow, global gray matter coherences, and global gray matter–CSF coupling. These findings might indicate impaired glymphatic system function during sevoflurane anesthesia, likely mediated by the impairment of neuronal coherence. These impairments outlast the duration of anesthesia at least for a short duration, thus encouraging further research into a contribution of sevoflurane-induced impairment of macroscopic CSF flow and postoperative neurocognitive disorders.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Supplemental Digital Content, <https://links.lww.com/ALN/D797>

Supplemental Digital Content Figure 1: CSF signal amplitude during wake and sevoflurane

Supplemental Digital Content Table 1: Number of time-frames included for each subject

Supplemental Digital Content Figure 2: Global gray matter blood oxygenation level–dependent amplitude is decreased by sevoflurane

Supplemental Digital Content Figure 3: Cross-correlations: Global gray matter blood oxygenation level–dependent and CSF signal

Supplemental Digital Content Figure 4: Cross-correlations: (–dt/t) Global gray matter blood oxygenation level–dependent and CSF signal

Supplemental Digital Content Figure 5: Correlations: Global gray matter amplitude and global gray matter–CSF coupling

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