ANESTHESIOLOGY

Source-level Cortical Power Changes for Xenon and Nitrous Oxide–induced Reductions in Consciousness in Healthy Male Volunteers

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Xenon and nitrous oxide are high-affinity *N*-methyl-D-aspartate receptor antagonists
- Stepwise comparison between the dose-dependent effects of xenon and nitrous oxide on cortical spectral power has not been previously reported
- Electroencephalography and magnetoencephalography imaging are complementary, and their combination leads to high resolution recording of neural activity

What This Article Tells Us That Is New

- Magnetoencephalography and electroencephalography recordings at increasing equivalent dose of xenon and nitrous oxide show distinct effects of these two drugs on neural activity
- While xenon increased low-frequency delta and theta activity, nitrous oxide induced alpha power depression
- These observations suggest that, despite their high affinity to the *N*-methyl-D-aspartate receptor, xenon and nitrous oxide are acting *via* distinct mechanisms to modulate neural activity

ABSTRACT

Background: Investigations of the electrophysiology of gaseous anesthetics xenon and nitrous oxide are limited revealing inconsistent frequency-dependent alterations in spectral power and functional connectivity. Here, the authors describe the effects of sedative, equivalent, stepwise levels of xenon and nitrous oxide administration on oscillatory source power using a crossover design to investigate shared and disparate mechanisms of gaseous xenon and nitrous oxide anesthesia.

Methods: Twenty-one healthy males underwent simultaneous magnetoencephalography and electroencephalography recordings. In separate sessions, sedative, equivalent subanesthetic doses of gaseous anesthetic agents nitrous oxide and xenon (0.25, 0.50, and 0.75 equivalent minimum alveolar concentration–awake [MAC_{awake}]) and 1.30 MAC_{awake} xenon (for loss of responsiveness) were administered. Source power in various frequency bands were computed and statistically assessed relative to a conscious/pre-gas baseline.

Results: Observed changes in spectral-band power ($P < 0.005$) were found to depend not only on the gas delivered, but also on the recording modality. While xenon was found to increase low-frequency band power only at loss of responsiveness in both source-reconstructed magnetoencephalographic (delta, 208.3%, 95% CI [135.7, 281.0%]; theta, 107.4%, 95% CI [63.5, 151.4%]) and electroencephalographic recordings (delta, 260.3%, 95% CI [225.7, 294.9%]; theta, 116.3%, 95% CI [72.6, 160.0%]), nitrous oxide only produced significant magnetoencephalographic high-frequency band increases (low gamma, 46.3%, 95% CI [34.6, 57.9%]; high gamma, 45.7%, 95% CI [34.5, 56.8%]). Nitrous oxide—not xenon—produced consistent topologic (frontal) magnetoencephalographic reductions in alpha power at 0.75 MAC_{awake} doses (44.4%; 95% CI [–50.1, –38.6%]), whereas electroencephalographically nitrous oxide produced maximal reductions in alpha power at submaximal levels (0.50 MAC_{awake}, –44.0%; 95% CI [–48.1,–40.0%]).

Conclusions: Electromagnetic source-level imaging revealed widespread power changes in xenon and nitrous oxide anesthesia, but failed to reveal clear universal features of action for these two gaseous anesthetics. Magnetoencephalographic and electroencephalographic power changes showed notable differences which will need to be taken into account to ensure the accurate monitoring of brain state during anaesthesia.

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Though effectively used in medical interventions on a daily basis, the molecular, neural and behavioral changes underlying anesthetic induced unconsciousness remain elusive. This is less true of general anesthetics like propofol that are primarily γ-aminobutyric acid (GABA) receptor agonists.[1] Ketamine, nitrous oxide, and xenon have a different pharmacologic profile, being predominately *N*-methyl-D-aspartate (NMDA) receptor antagonists with weak effects on the GABA receptor.[1,2] The distinction between the two classes of drugs extends to their

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electrophysiology. Electroencephalography (EEG) under propofol anesthesia is well characterized and reveals global changes in brain activity associated with the appearance of high-amplitude, low-frequency delta waves, frontal alpha oscillations and persistent reductions in higher frequencies, notably gamma activity.[3,4] In contrast, the electroencephalographic effects of NMDA antagonists are reported as quite variable. Ketamine and nitrous oxide are generally reported to increase high-frequency gamma power and to have little or no effect on low-frequency power.[5,6] However, conflicting evidence suggests that nitrous oxide sustains gamma and alpha activity and instead increases delta and theta power.[7,8] Such ambiguity extends to xenon anesthesia wherein topologically diverse increases and decreases in delta,[9] theta,[9,10] alpha,[10,11] and gamma[9,12] activity have been reported.

These anomalous effects of xenon and nitrous oxide may be attributed to a number of factors. First, investigations of gaseous nitrous oxide and xenon are limited to a small number of studies potentially due to the unclear clinical utility of xenon, as well as its reported association with postoperative nausea and vomiting,[13,14] and pronounced dissociative effects. In addition, dosage differences across studies ranging from subanesthetic to anesthetic levels and the common practice of the inclusion of concomitant agents,[7,9,11,12,15] encumber the ability to draw conclusive findings. Acquiring data is mostly limited to EEG recordings from depth of anesthesia monitors or other spatially low resolution systems,[6,15,16] which makes the investigation of network level changes and the concomitant mesoscopic processes difficult. While EEG is extremely useful, it suffers from the volume conduction problem and limited spatial resolution even in high density systems, all of which can be mitigated by implementing source level EEG and magnetoencephalography imaging.[17] When used in conjunction, the two techniques are highly complementary, simultaneously recording from both radial and tangential current sources within the brain and thus capable of registering a wider range of activity, particularly in the high-frequency range.[17] However, to date only a handful of studies have utilized such a method to study anesthetic effects, with most focused on task-related changes rather than changes in behavioral state.[18,19]

Given the documented uncertainties of the effects of the gaseous anesthetics xenon and nitrous oxide on brain activity, the further characterization of their actions using simultaneously recorded magnetoencephalography and EEG would be expected to enhance the study of anesthetic-induced unconsciousness, while offering novel insights into the associated neural correlates of consciousness. Therefore, our objective was to quantify similarities and differences between these two gaseous agents, contrasted to wakefulness by measuring the electromagnetic effects of subanesthetic administration of xenon and nitrous oxide in healthy volunteers using source level brain imaging and spectral analysis.

Materials and Methods

The study entitled "Effects of inhaled Xe and N_2O on brain activity recorded using EEG and MEG" was approved (approval No.: 260/12) by the Alfred Hospital and Swinburne University of Technology Ethics Committee (Melbourne, Australia) and met the requirements of the Australian National Statement on Ethical Conduct in Human Research (2007).

Study Population

Twenty-one volunteers were recruited from November 2015 to November 2017 using recruitment flyers posted throughout Swinburne University of Technology. Phone screening was conducted by a member of the research team to ensure eligibility for participation. All participants signed a written informed consent and were given monetary compensation for their time ($300 AUD).

Participants were regarded as eligible if they were right handed, adult males, between the ages of 20 and 40 (mean age, 24 yr), had a body mass index between 18 to 30 and were American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status I in accordance with the day stay general anesthesia procedure as designated in the Australia and New Zealand College of Anaesthetists (Melbourne, Australia) guidelines (Document PS15). Females were excluded due to the documented effects of menstruation on the EEG as well as having identified increases in the propensity to nausea and vomiting on xenon and nitrous oxide.[20,21] Contraindications to magnetic resonance imaging or magnetoencephalography (such as implanted metallic foreign bodies) were an additional exclusion criterion. Exclusion from the study resulted if candidates had neurologic disorders, psychiatric disorders, epilepsy, heart conditions, respiratory conditions, obstructive sleep apnea, asthma, motion sickness and claustrophobia. In addition, any recent intake of psychoactive or other prescribed medication as well as any recreational drug use resulted in non-inclusion. An inventory of previous surgeries was taken upon screening, importantly any unfavorable reactions to general anesthesia which would result in exclusion from the study. Finally, to ensure a good seal with an anesthetic face mask, participants with large beards were excluded unless they were willing to shave.

Anesthetic Protocol

A detailed description of the data acquisition protocol with accompanying video documentary has been published previously.[22] Here, the key components are summarized.

A two-way crossover experimental design was followed. Two separate testing sessions were performed for each subject separated by a maximum of 4 weeks, with xenon being administered in one session and nitrous oxide in a second session. Participants were blind to the type of gas being administered while the medical staff and researchers were

not due to the subtle differences in the procedure followed for their administration, safety and monitoring. At least one anesthesiologist was present in the control room to manage gas delivery and electronic monitoring. An anesthetic nurse or other suitably trained clinical observer sat with the subject in the magnetically shielded room, containing the magnetoencephalography and EEG equipment, to effectively monitor the participant's condition (in particular, the face mask seal and subject's airway patency).

In line with the day stay Australia and New Zealand College of Anaesthetists guidelines (document PS15), volunteers were asked to fast for at least 6 h and consume no liquids for at least 2 h before the start of the experiment. Participant eligibility was reaffirmed with an extensive medical history interview and vital sign measurements that included blood pressure, heart rate, body temperature, and peak expiratory flow followed by a brief measurement in the magnetoencephalography to ensure that there were no unanticipated sources of noise. A peripheral intravenous catheter was placed to enable antiemetic administration consisting of 4 mg dexamethasone and 4 mg ondansetron in order to reduce the reported incidence of emesis caused by anesthetic gas inhalation,[23] which is often observed with nitrous oxide at higher concentrations.[13] A face mask and breathing circuit was attached to the subject using a modified sleep apnea continuous positive airways pressure harness. Anesthesia gases were delivered using the Akzent Xe Color anesthesia machine (Stephan GmbH, Germany), located outside the magnetically shielded room with gas hoses passing through magnetically shielded room portals. End-tidal xenon concentrations were measured using katharometry and nitrous oxide concentrations were measured using infrared spectroscopy, both of which were implemented in the anesthesia machine. Before anesthetic administration, each participant inhaled 100% inspired oxygen for up to 30 min until their end-tidal oxygen concentration was greater than 90%, effectively denitrogenating the participant in order to ensure effective end-tidal anesthetic gas concentration monitoring.

In addition to magnetoencephalography and EEG recordings (see Data Acquisition), three bipolar biochannel recordings were made: electromyography to record the activity of the mylohyoid and digastric (anterior belly) muscles (to assess changes in muscle tone), electrooculography, and three-lead electrocardiography. Pulse oximetry and noninvasive blood pressure measurement were recorded on equipment outside the magnetically shielded room as per Australia and New Zealand College of Anaesthetists Guidelines (Document PS18). The ongoing level of responsiveness was behaviorally measured throughout the experiment using an auditory continuous performance task in which a binaural auditory tone of either 1 or 3 kHz frequency was presented of fixed stereo amplitude (approximately 76 dB). In order to minimize any habituation in the response to the stimulus, an interstimulus interval of 2 to 4 s drawn from a uniform distribution was used. Participants responded using two separate button boxes held in each hand. The left and right buttons on each box corresponded to a low- or high-frequency tone, respectively, and the left and right button boxes were respectively used for the participant to indicate the absence or presence of nausea. Three successive button presses indicating nausea or any signs of nausea, or airway difficulties, as identified by the anesthesiologist or clinical observer, were evaluated, and if severe, gas inhalation was terminated.

All participants underwent the following recordings with magnetoencephalogram and EEG data collection throughout each period. Three eyes-closed baseline conditions, all before gas administration: a 5-min resting period (baseline 1) followed by a 5-min period with the auditory continuous performance task being performed (baseline 2) and a final 5-min recording after antiemetic administration with the auditory continuous performance task being performed (baseline 3). Four stepwise increasing levels for xenon administration and three stepwise increasing levels for nitrous oxide administration: equivalent minimum alveolar concentration–awake (MAC_{awake}) levels of 0.25 (level 1), 0.5 (level 2), and 0.75 (level 3) times the MAC_{awake} concentration corresponding to concentrations at 8, 16, 24% and 16, 32, 47% concentrations for xenon/oxygen and nitrous oxide/oxygen, respectively. MAC_{awake} for xenon and nitrous oxide were assumed to be 32.6 $\pm$ 6.11% and 63.3 $\pm$ 7.12%, respectively.[12] At each level, a 10-min gas wash-in took place such that the target end-tidal gas concentration was reached, a 5-min steady-state period ensued followed by a final 10-min wash-out period with the administration of 100% oxygen, during which end-tidal gas concentration returned to 0. A fourth level was considered for xenon corresponding to 1.3 (level 4) times the MAC_{awake} concentration (42% xenon/oxygen), upon which 95% of participants were expected to lose responsiveness. In our experiment, 76% of volunteers reached the loss of responsiveness state (see the Results section for details on what happened to further excluded participants). A fourth level was not included for nitrous oxide administration as it is well known that high levels induce nausea and vomiting and are associated with greater risk of hypoxia at high concentrations. Once loss of responsiveness was achieved at xenon level 4, the xenon gas level was maintained for up to 10 min or until the medical staff considered airway patency compromised, after which, wash-out with 100% oxygen took place.

Participants were discharged once they were awake, alert, and responsive; without significant nausea or vomiting; able to ambulate with minimal assistance; and had a responsible adult to accompany them home. They were asked to complete a truncated version of the 5-Dimensional Altered States of Consciousness Rating Scale questionnaire and a short narrative of their overall experience during the experiment, as well as specific details about level dependent qualitative effects, both of which were performed 24 h after each recording session.[24,25] Cognitive and subjective report data collected are not discussed here.

Data Acquisition

Electrophysiologic Recordings. Data acquisition was simultaneously performed in a room shielded from magnetic or electric interferences (Euroshield Ltd., Finland). Brain magnetic field activity (magnetoencephalography) was recorded at a sampling rate of 1,000 Hz using a 306-channel Elekta Neuromag TRIUX magnetoencephalography system (Elekta Oy, Finland), consisting of 204 planar gradiometers and 102 magnetometers. Head position in relation to the recording system was recorded using five head-position indicator coils and was continuously monitored by measuring the magnetic fields produced by the coils in relation to the cardinal points on the head (nasion, and left and right preauricular points) which were determined before commencement of the experiment using an Isotrack 3D digitizer (Polhemus, USA). The internal active shielding system for three-dimensional noise cancellation was disabled to allow for subsequent source space analysis.

EEG data were acquired at a sampling rate of 512 Hz, using an magnetoencephalography compatible 64-channel waveguard cap (ANT Neuro, The Netherlands), an asalab battery-powered amplifier (ANT Neuro), a magnetically shielded cordless battery box and asalab acquisition software (ANT Neuro). All electrical contact impedances were kept below 5 kΩ.

Structural T1-Magnetic Resonance Imaging. A single structural T1-weighted magnetic resonance imaging scan was performed using a 3.0 TIM Trio MRI system (Siemens AB, Germany) with markers (vitamin E capsules) used to highlight the digitized fiducial points for the nasal apex and left and right preauricular points for subsequent source space reconstruction. T1-weighted images were acquired on a sagittal plane with a magnetization prepared rapid gradient echo pulse sequence with an inversion recovery (176 slices: slice thickness, 1.0 mm; voxel resolution, 1.0 mm^3; pulse repetition time, 1,900 ms; echo time, 2.52 ms; inversion time, 900 ms; bandwidth, 170 Hz/Px; flip angle, 9°; field of view; 350 mm × 263 mm × 350 mm; orientation, sagittal; acquisition time, approximately 5 min).

Data Analysis

Preprocessing. Data analysis was performed in Fieldtrip version 20170801 and custom MATLAB (MathWorks, USA) scripts and toolboxes.[26] Magnetoencephalography data from 21 subjects and electroencephalogram (EEG) data from 19 subjects (one dataset missing due to an administrative error and a second excluded due to issues with forward model construction, potentially due to a corrupt EEG digitization file) were visually inspected to exclude any malfunctioning channels from further analysis. Magnetoencephalography data was filtered using the temporal signal-space separation algorithm of MaxFilter software version 2.2 (Elekta Neuromag Oy, Finland) and the signal from magnetometers and planar gradiometers combined in Fieldtrip using provided algorithms.[27] The two datasets were time adjusted for any temporal differences in acquisition using a synchronization trigger. Given the EEG and magnetoencephalography machines did not share the exact same electronic clock, meaning that synchronization of the two data types had a small margin of error, the EEG and magnetoencephalography data were analyzed separately. The relevant periods of interest were selected for EEG and magnetoencephalography data which included the three 5-min baselines, three 5-min anesthetic steady-state periods, and the entire loss of responsiveness period for xenon. All data was bandpass filtered at 1 to 100 Hz and any line noise at 50, 100, and 150 Hz was removed using notch filters. EEG data were re-referenced using the common average reference method. All periods of interest were visually inspected and any artefactual segments resulting from eye movements or blinks, jaw clenches or movements, head movements, breathing, and other muscle artefacts were excluded from further analysis. Six classical bandpass-filtered versions of the datasets were created for subsequent source analysis: delta (1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 13 Hz), beta (13 to 30 Hz), low gamma (30 to 49 Hz), and high gamma (51 to 99 Hz).

Source Localization. Coregistration of each subject's magnetic resonance imaging to their scalp surface was performed using fiducial realignment, and boundary element method volume conduction models were computed using a single shell for the magnetoencephalography and best fit dipole orientation for the EEG.[28,29] Both were spatially normalized to a template magnetic resonance imaging using the Segment toolbox in SPM8 to serve as a volume conduction model in subsequent source level analyses.[30] An atlas-based version of the linearly constrained minimum variance spatial filtering beamformer was used to project sensor level changes onto sources.[31,32] Global covariance matrices for each band (after artefact removal) were derived, which were utilized to compute a set of beamformer weights for all brain voxels at 6-mm isotropic voxel resolution. Following inverse transformation, the 5,061 voxels were assigned 1 of 90 automated anatomical labeling atlas labels (78 cortical, 12 subcortical) in the subjects' normalized coregistered magnetic resonance imaging (based on proximity in Euclidean distance to centroids for each region) in order to reveal regional anesthetic-induced changes in oscillatory power.[33] The resulting beamformer weights were normalized to compensate for the inherent depth bias of the method used.[32] Finally, the original time-series were segmented into contiguous 3-s epochs (approximately in accordance with epochs used in other studies),[34] and the final epoch covariance matrices were used along with normalized weights to compute the power at each voxel across all frequencies within a band.[31]

Statistical Analysis

Statistical analysis was performed using custom MATLAB (MathWorks) scripts and toolboxes. Any statistical analyses

performed as part of this study were defined before data assessment. To ensure equal numbers of epochs across subjects, gases and gas levels, epochs from larger datasets were selected at random, resulting in a total of 17 3-s epochs (*i.e.*, 51 s or 51,000 samples) for magnetoencephalography data and a total of 9 3-s epochs (*i.e.*, 27 s or 13,824 samples) for EEG data being used for nonparametric group statistical analysis within each frequency band. The discrepancy in final epoch numbers was due to the independent artefact removal performed on the magnetoencephalography and EEG recordings, the latter being more sensitive to eye blinks and jaw movements. In addition, the variation in filtering techniques could influence the presence of artefactual segments with max-filtering (as previously described) applied to the magnetoencephalogram being a powerful and highly effective additional filter not applicable for EEG data.[27]

In order to correct for the multiple comparisons inherent to this study, permutation testing was performed followed by maximum statistics across voxels with significance level $P = 0.05$ to correct for the voxel multiple comparisons problem and Bonferroni correction to compensate for multiple comparisons between each condition and the eyes-closed postantiemetic baseline.[35] These methods were chosen over more conservative approaches as they are commonly employed in source level magnetoencephalography and EEG analysis.[34,36] Permutation testing allows for the influence of the testing condition on statistical testing to be eliminated while maximum statistics across voxels minimizes the occurrence of false significances by evaluating the two-tailed significance across all voxels based on the two voxels with the maximum and minimum change across participants.[35] Bonferroni correction finally enables the accurate contrast across the multitude of xenon and nitrous oxide administered doses relative to the conscious postantiemetic baseline. These corrections also enable for any outliers to be discounted if they do not cross the multiple comparisons' significance barrier.

Within Gas Comparison. For each individual, Student *t*-statistic images of the source power at every voxel were calculated for the two preantiemetic baselines and all gas levels *versus* the postantiemetic baseline to allow for comparative imaging. In order to reject the null hypothesis stating that a given condition in either the xenon or nitrous oxide case is not significantly different to the postantiemetic baseline, a null distribution was constructed using 5,000 permutations of the *t*-statistic sign, with a one-sample *t* test being finally used to compute the effect at each voxel across individuals.[35] Maximum statistics across 5,061 voxels with a significance level of $P = 0.05$ were utilized to correct for the voxel multiple comparisons problem and Bonferroni correction was further utilized to compensate for multiple comparisons between each condition and the eyes-closed postantiemetic baseline.[37] This resulted in a threshold of $P = 0.004$ for the xenon conditions and $P = 0.005$ for the nitrous oxide conditions ($P = 0.025$ to allow for two-tailed comparison of increases and decreases in power; $P =$ [0.025 divided by 6] and $P =$ [0.025 divided by 5] to correct for the six xenon and five nitrous oxide condition comparisons, respectively).

Across Gas Comparison. To compare the effects of the two anesthetic agents, Student *t*-statistic images were computed for each of the three baselines and three equivalent MAC_{awake} conditions of nitrous oxide against xenon on each individual's source power. In order to reject the null hypothesis that there is no significant difference in a given condition between xenon or nitrous oxide, a null distribution was constructed using 5,000 permutations of the *t*-statistic sign and a one sample *t* test was finally used to compute the effect at each voxel across individuals.[35] Maximum statistics across 5,061 voxels with a significance level of $P = 0.05$ were utilized to correct for the voxel multiple comparisons problem, and Bonferroni correction was used to compensate for the multiple comparisons of considering each condition (three baselines and three levels).[37] This resulted in a threshold of $P = 0.004$ for both xenon and nitrous oxide conditions ($P = 0.025$ to allow for two-tailed comparison of increases and decreases in power; $P =$ [0.025 divided by 6] and $P =$ [0.025 divided by 6] to correct for the six xenon and nitrous oxide condition comparisons, respectively). Figure 1 offers an overall view of the experimental design and briefly summarizes both data acquisition and data analysis for this study.

Results

Anesthetic Protocol Outcomes

All 21 participants included in the analysis successfully completed the 0.25, 0.50, and 0.75 MAC_{awake} nitrous oxide subanesthetic levels and completed the 0.25, and 0.50 MAC_{awake} xenon subanesthetic levels. One participant was excluded from further xenon analysis as they were unable to continue beyond 0.50 MAC_{awake} xenon; therefore, 20 participants accomplished 0.75 MAC_{awake} xenon anesthesia. Of the remaining 20, 16 participants achieved loss of responsiveness at the final 1.30 MAC_{awake} xenon concentration, while the remaining 4 failed to meet this criterion at the highest level due to gas leakage or excessive nausea. The period of loss of responsiveness varied across the 16 individuals between 60 and 480 s (mean, 213 s). All remaining periods of interest for baselines and gas levels were 300 s. All magnetoencephalography datasets were utilized while two EEG datasets were excluded from the analysis. (See table S1A in Supplemental Digital Content 1, http://links.lww.com/ALN/C240, for additional details).

Sensor level power analysis was contrary to the scope of this article in that it would not have taken advantage of the

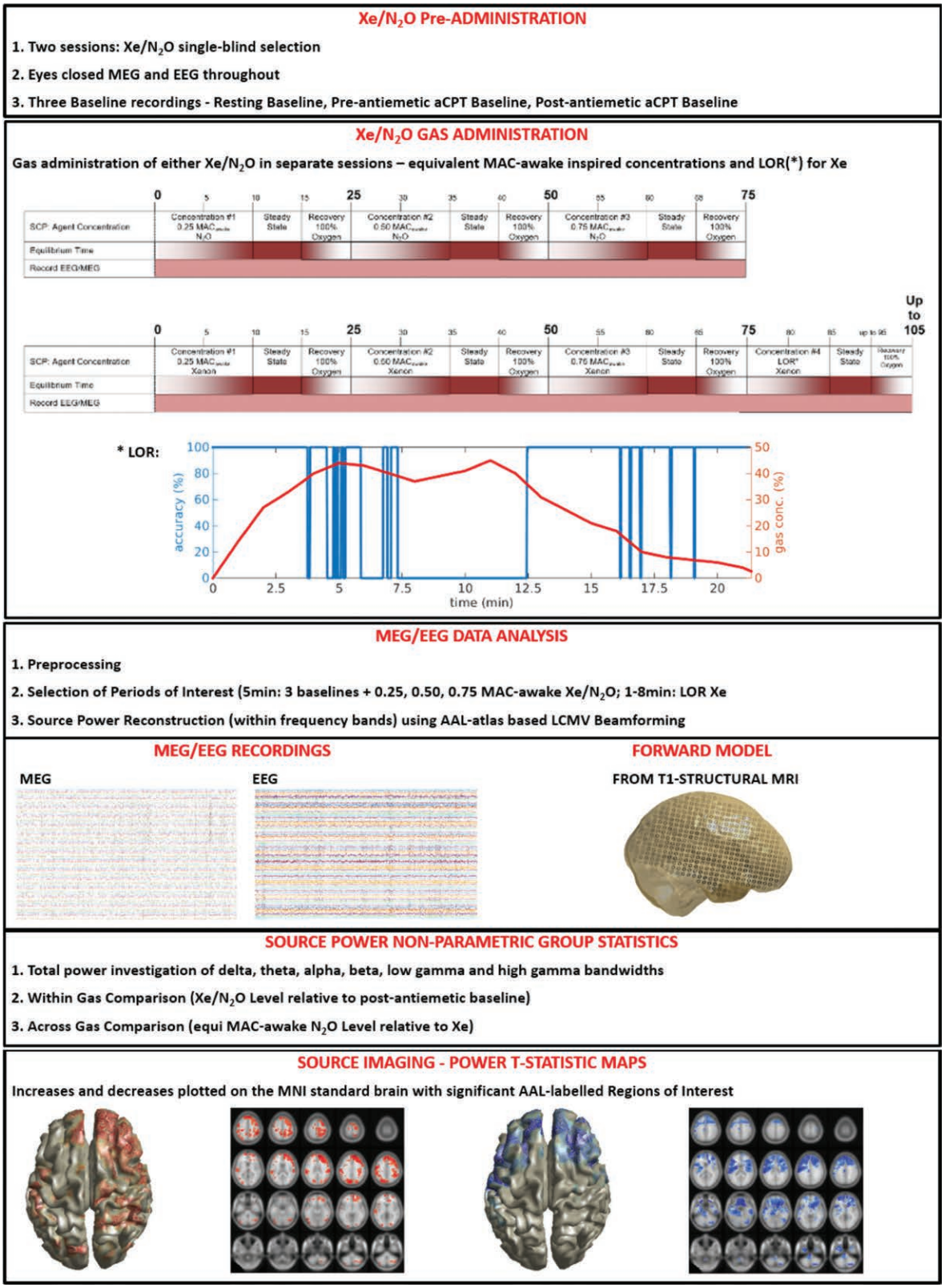

Fig. 1. Study Synopsis. Illustration of the data acquisition, magnetoencephalography (MEG) and electroencephalography (EEG) data analysis and statistical analysis. Delta, 1 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz; beta, 13 to 30 Hz; low gamma, 30 to 49 Hz; high gamma, 51 to 99 Hz. aCPT, auditory continuous performance task; LOR, loss of responsiveness.

spatial resolution inherent in simultaneous magnetoencephalography and high-density EEG. Nonetheless, the authors performed sensor level data analyses in both the within and across gas comparisons as they might be of relevance to a readership who is unfamiliar or skeptical with the source space methods employed here. The results and relevant figures can be found in Supplemental Digital Content 2 fig. S2A and table S2A for the within gas comparison (http://links.lww.com/ALN/C241) and Supplemental Digital Content 3 fig. S3A and table S3A for the across gas comparison (http://links.lww.com/ALN/C242).

Preliminary Spatially Averaged Source Level Total Power Analysis

Average total power (±1 SD) and relative percentage changes ([(gas power–baseline power) / baseline power] × 100) across all subjects and across all voxels were compared to post antiemetic baseline (baseline 3). This was performed within each gas type, within each inspired gas concentration and within each of the six frequency ranges investigated (fig. 2, *error bars*). Table S1B in Supplemental Digital Content 1 (http://links.lww.com/ALN/C240) gives the corresponding numerical values ±1 SD for all differences briefly summarized here. Magnetoencephalography clearly demonstrated increases in low-frequency delta (1 to 4 Hz), theta (4 to 8 Hz), and beta (13 to 30 Hz) power at the highest levels of xenon anesthesia. Reductions in alpha-band (8 to 13 Hz) power and increases in high-frequency gamma power (30 to 99 Hz) were observed at the highest inspired doses of both xenon and nitrous oxide. Electroencephalographically-calculated source power changes showed increases for both gases at highest dosage of xenon and nitrous oxide. Decreased electroencephalographic alpha-band power was also observed, but was more prominent at the intermediate 0.50 MAC_{awake} level compared to higher 0.75 MAC_{awake}. High-frequency gamma-band (30 to 99 Hz) activity, as for magnetoencephalographically calculated power, showed increases in the highest xenon- and nitrous oxide–inspired concentrations. These results reveal that the effects of anesthesia on electromagnetically recorded brain activity depend on both the agent

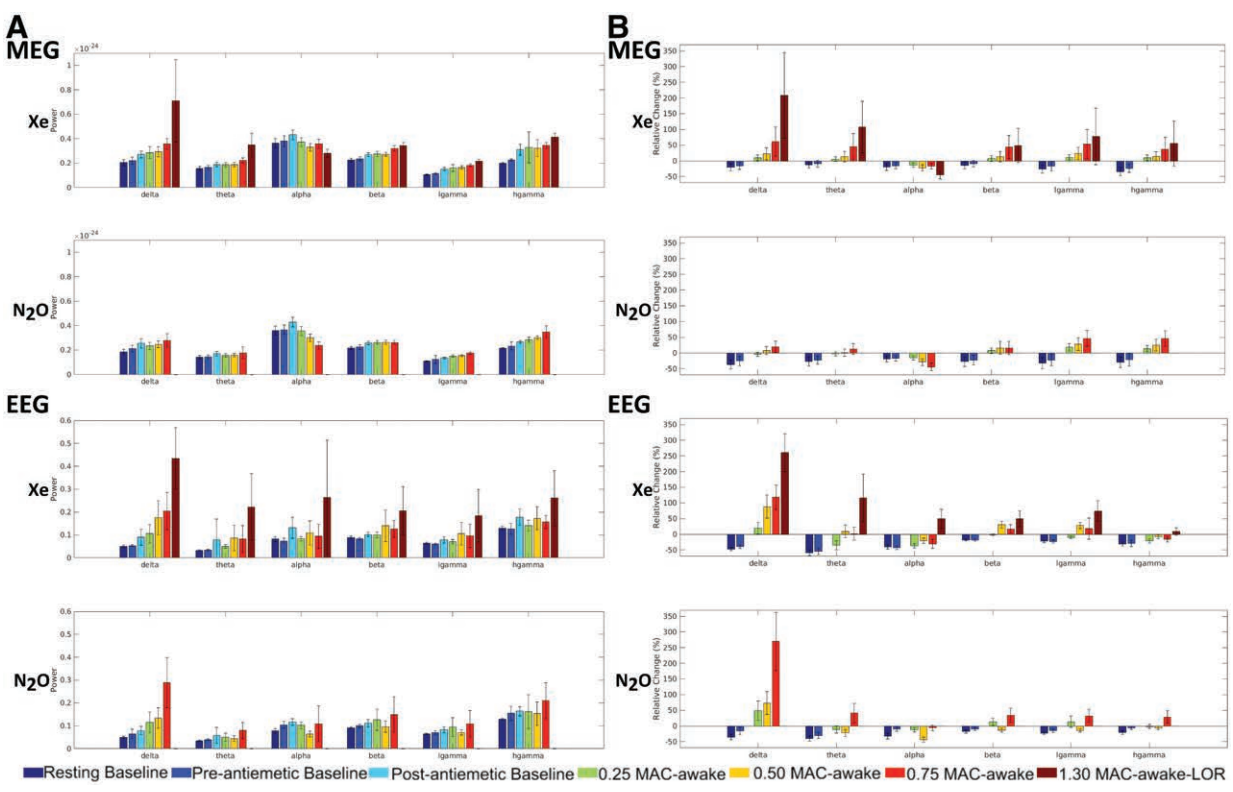

Fig. 2. Total power alterations under xenon and nitrous oxide anesthesia relative to postantiemetic baseline in various frequency bands. Baseline and gas power (*A*) at each concentration is averaged across all samples for all subjects (MEG, n = 21; EEG, n = 19) and considering all voxels of the magnetoencephalogram (MEG) and electroencephalogram (EEG). Units of power for MEG (*A*) are T^2 and for EEG (*B*) are μV^2. The figure demonstrates changes in all frequency bands that are different for the two modalities, and in some cases, correlate to increasing gas concentration. Error bars illustrate ±1 SD. Relative change (*B*) ([(Gas or Baseline Power – Postantiemetic Baseline Power) / Postantiemetic Baseline power] × 100) is calculated and all changes are shown with each sub-figure in bold percentage values. Delta, 1 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz; beta, 13 to 30 Hz; low gamma, 30 to 49 Hz; high gamma, 51 to 99 Hz.

administered and the recording modality used. Therefore, we chose to independently compare the agent and modality in subsequent analysis and corresponding results.

Relative changes in total power were computed with respect to the conscious postantiemetic baseline (baseline 3) for each gas level and each of the 21 subjects and 5,061 voxels. The average relative change was then calculated for each gas level along voxels and along subjects. Two-sided CIs for $\alpha = 0.05$ were also calculated for these changes.

Upon evaluation of magnetoencephalographic power, increases relative to baseline were seen in the delta- (relative change, 208.3%; 95% CI [135.7, 281.0%] at loss of responsiveness) and theta-bands (relative change, 107.4%; 95% CI [63.5, 151.4%] at loss of responsiveness) for xenon. No changes were seen in the delta and theta power for nitrous oxide. In addition, a minor increase in the beta-band was observed at the highest xenon concentration (relative change, 49.0%; 95% CI [20.2, 77.9%]. Both gases decreased alpha power compared to baseline (relative change, −44.6%; 95% CI [−51.5, −37.7%] at loss of responsiveness for xenon; relative change, −16.8%, 95% CI [−21.3, −12.3%] at 0.75 MAC_{awake} for xenon; relative change, −44.4%; 95% CI [−50.1, −38.6%] at 0.75 MAC_{awake} for nitrous oxide) and increased gamma activity, particularly in the high-frequency range (51 to 99Hz) (relative change [low gamma], 77.5%; 95% CI [29.6, 125.4 %] at loss of responsiveness for xenon; relative change [low gamma], 46.3%; 95% CI [34.6, 57.9%] at 0.75 MAC_{awake} for nitrous oxide; relative change [high gamma], 55.0%; 95% CI [16.8, 93.2%] at loss of responsiveness for xenon; relative change [high gamma], 45.7%; 95% CI [34.5, 56.8%] at 0.75 MAC_{awake} for nitrous oxide).

EEG results showed similar trends to those of magnetoencephalography in lower-frequency activity however, it has to be noted that total power across subjects displayed larger variability throughout (table S1B, Supplemental Digital Content 1, http://links.lww.com/ALN/C240), particularly in the highest 1.30 MAC_{awake} xenon concentration and in the lower delta- and theta-bands. Nonetheless, delta-band increases were observed for all stepwise increasing concentrations of both gases relative to baseline (relative change, 260.3%; 95% CI [225.7, 294.9%] at loss of responsiveness for xenon; relative change, 269.7%; 95% CI [223.4, 315.9%] at 0.75 MAC_{awake} for nitrous oxide. Theta-band power significantly increased only at loss of responsiveness (1.30 MAC_{awake} xenon) for xenon (relative change, 116.3%, 95% CI [72.6, 160.0%]). As observed for the magnetoencephalogram, reductions in alpha-band power were observed for electroencephalographic sources after nitrous oxide administration, reductions that were larger for 0.50 MAC_{awake} compared to the higher 0.75 MAC_{awake} concentrations (relative change, −5.7%; 95% CI [−10.2, −1.2%] at 0.75 MAC_{awake} for nitrous oxide *vs.* −44.0%, 95% CI [−48.1,−40.0%] at 0.50 MAC_{awake} for nitrous oxide). Of note, alpha power was increased at loss of responsiveness due to xenon administration (relative change, 49.3%; 95% CI [31.4, 67.1%] at loss of responsiveness for xenon *vs.* relative change, −44.0%, 95% CI [−48.1,-40.0%] at 0.50 MAC_{awake} for nitrous oxide), in contrast to the relative reductions seen in source calculated magnetoencephalography alpha-band power. This deviation between measurement types and any dissimilarities observed for higher-frequency activity likely reflect the high degree of variation in the data.

"Within Gas" Statistical Analysis

Average power changes were evaluated at each gas level relative to the postantiemetic baseline (baseline 3). Since our focus was on reliable statistically significant changes, we controlled significance by combined corrections for multiple comparisons across space using maximum statistics and across conditions using Bonferroni correction. It should be noted that significant maximum statistics corrected (without subsequent Bonferroni correction) *t*-statistic maps of the power changes relative to baseline across subjects displayed potential trends in the data with increasing gas concentration (see fig. S2B in Supplemental Digital Content 2 for magnetoencephalography and EEG recordings, http://links.lww.com/ALN/C241). While magnetoencephalography source power changes spanned the whole frequency spectrum being investigated, EEG alterations were prominent only in lower frequencies.

Magnetoencephalography Results. Figure 3 shows statistically significant topologic power changes (xenon, $P = 0.004$; nitrous oxide, $P = 0.005$) in magnetoencephalographic activity and table 1 displays a selection of corresponding regions of interest (see table S2B in Supplemental Digital Content 2 for complete list of statistically significant regions of interest, http://links.lww.com/ALN/C241). Overall, xenon effects were restricted to delta- and theta-band frequencies with no changes observed on high-frequency power. Conversely, nitrous oxide did not significantly alter low-frequency delta and theta activity, but rather increased high-frequency low and high gamma activity. Effects on the alpha-band were specific to nitrous oxide administration which induced reductions in alpha power, most prominently in frontal regions. Neither gas resulted in a statistically significant alteration (xenon, $P = 0.004$; nitrous oxide, $P = 0.005$) in beta power.

Participants that lost responsiveness at xenon 1.3 MAC_{awake} anesthesia displayed a marked rise in delta-band power, primarily involving frontal regions. Theta-band power also demonstrated a statistically significant increase ($P = 0.004$) during xenon loss of responsiveness, but displayed a different source-level topology, with widespread changes observed somewhat lateralized to the right hemisphere. Less pronounced effects were observed for xenon 0.75 MAC_{awake} and were primarily centered on parietal and subcortical regions (Supplemental Digital Content 2, http://links.lww.com/ALN/C241). Conversely, all inspired concentrations of nitrous oxide produced no substantial

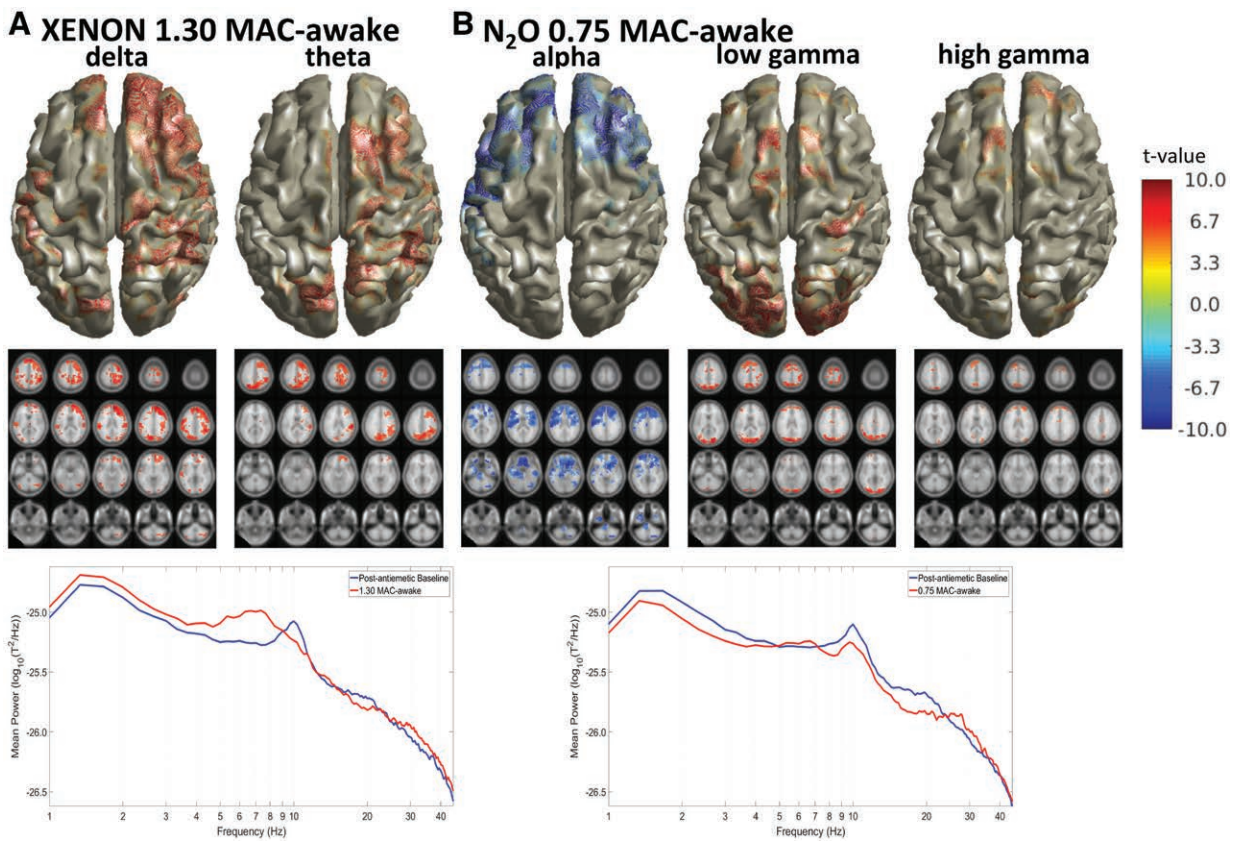

Fig. 3. Group level magnetoencephalography source power for highest administered xenon and nitrous oxide concentrations. Xenon (Xe) effects (*A*) at loss of responsiveness (1.30 MAC_{awake}) are increases in low-frequency delta (widespread change) and theta activity (right brain lateralized). 0.75 MAC_{awake} nitrous oxide (N_2O) (*B*) results in a primarily frontal alpha reduction and a rise in high-frequency gamma activity centered around frontal and occipital regions. Maximum statistics and Bonferroni corrected *t*-maps ([*top row*] Xe, $P = 0.004$; N_2O, $P = 0.005$) of magnetoencephalographic sources across participants (n = 21). Brain slices (*middle row*) display region specific alterations plotted on the template Montreal Neurological Institute and Hospital (MNI) brain. Magnetoencephalography source spectral power ([*bottom row*] 1 to 45 Hz) is shown in the logarithmic scale for the postantiemetic baseline and the highest administered doses of the two gases averaged across all magnetoencephalographic sources and all subjects. Delta, 1 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz; low gamma, 30 to 49 Hz; high gamma, 51 to 99 Hz. MAC_{awake}, minimum alveolar concentration–awake.

effects on low-frequency activity. Alpha-band power was not affected by xenon, but was statistically significantly decreased ($P = 0.005$) by nitrous oxide administration and were predominately frontal in location. Increasing nitrous oxide concentrations seemed directly correlated to the degree of significance and the topologic extent of reductions in alpha power (see Supplemental Digital Content 2 for stepwise changes, http://links.lww.com/ALN/C241), with the most pronounced effect being observed at 0.75 MAC_{awake} nitrous oxide as shown in figure 3.

Changes in higher-frequency band power (13 to 99 Hz) showed statistically significant alterations for nitrous oxide ($P = 0.005$), but not by xenon ($P = 0.004$), administration and were limited to the highest 0.75 MAC_{awake} nitrous oxide concentration given. Nitrous oxide substantially increased both low gamma- and high gamma-band power with the effects primarily observed in occipital voxels. Finally, both xenon and nitrous oxide gases induced significant beta-band power changes only a small number of seemingly random voxels (Supplemental Digital Content 2, http://links.lww.com/ALN/C241), suggesting that neither gas had a statistically significant effect (xenon, $P = 0.004$; nitrous oxide, $P = 0.005$) in this frequency.

EEG Results. Statistically significant power changes in electroencephalographic source power are outlined in figure 4 with a condensed list of corresponding regions of interest shown in table 2 (refer to Supplemental Digital Content 2 for complete list of statistically significant regions of interest, http://links.lww.com/ALN/C241). Xenon inhalation significantly increased delta- and theta-band frequency power whereas it did not induce statistically

Table 1. Magnetoencephalographic Sources Most Significantly Altered by Xenon and Nitrous Oxide Administration

Frequency Band	MAC_{awake} Level	Region of Interest	Voxel Coordinate	*t* value	*P* Value
Delta	1.30 Xe	Parietal_Inf_R	54, −42, 48	9.61	0.0001
	1.30 Xe	Frontal_Sup_Medial_L	0, 54, 24	9.25	0.0002
	1.30 Xe	Frontal_Sup_Medial_R	12, 48, 24	9.13	0.0002
	1.30 Xe	Precuneus_L	0, −48, 54	9.13	0.0002
	1.30 Xe	Frontal_Sup_R	18, 54, 30	9.11	0.0002
Theta	1.30 Xe	Parietal_Sup_L	−30, −66, 48	8.52	0.0003
	1.30 Xe	Precuneus_L	−6, −78, 54	8.40	0.0004
	1.30 Xe	Frontal_Sup_R	24, 24, 60	8.20	0.0004
	1.30 Xe	Parietal_Sup_R	18, −60, 54	8.15	0.0004
	1.30 Xe	Precuneus_R	12, −66, 42	8.09	0.0004
Alpha	0.75 N_2O	Frontal_Sup_Medial_L	0, 66, 0	−9.92	0.0001
	0.75 N_2O	Frontal_Mid_L	−42, 54, 6	−9.70	0.0002
	0.75 N_2O	Frontal_Inf_Tri_L	−48, 36, 18	−9.60	0.0002
	0.75 N_2O	Frontal_Sup_Orb_R	12, 18, −18	−9.38	0.0002
	0.75 N_2O	Frontal_Inf_Orb_R	30, 30, −24	−8.83	0.0002
Low gamma	0.75 N_2O	Occipital_Sup_L	−12, −90, 30	9.58	0.0001
	0.75 N_2O	Occipital_Mid_R	30, −90, 18	9.21	0.0002
	0.75 N_2O	Occipital_Sup_R	24, −84, 12	8.84	0.0002
	0.75 N_2O	Occipital_Inf_L	−24, −96, −6	8.50	0.0002
	0.75 N_2O	Occipital_Mid_L	−30, −84, 36	8.42	0.0002
High gamma	0.75 N_2O	Frontal_Mid_R	24, 54, 30	7.18	0.0001
	0.75 N_2O	Frontal_Sup_Medial_L	−6, 30, 60	6.94	0.0002
	0.75 N_2O	Precuneus_R	6, −78, 48	6.92	0.0002
	0.75 N_2O	Frontal_Sup_R	24, 54, 36	6.83	0.0002
	0.75 N_2O	Cingulum_Mid_L	0, 0, 42	6.81	0.0002

A selection of five representative regions of interest was picked from the 20 highest *t* value and *P*-value ($P < 0.005$ for N_2O; $P < 0.004$ for Xe) regions for each frequency band. Region of interest analysis reveals most pronounced increases for delta in frontal regions and a widespread theta rise relative to baseline during xenon loss of responsiveness (1.30 MAC_{awake}). The highest N_2O-inspired concentration (0.75 MAC_{awake}) resulted in primarily frontal alpha reductions and effects on low gamma were primarily observed in occipital voxels while high gamma was localized to a small number of frontal and occipital regions. Voxel coordinates are in Automated Anatomical Labeling atlas coordinate system along with associated labels.[46] Delta, 1 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz; low gamma, 30 to 49 Hz; high gamma, 51 to 99 Hz.

Inf, inferior; L, left; $MAC_{awake,}$ minimum alveolar concentration–awake; Mid, middle; N_2O, nitrous oxide; R, right; Sup, superior; Xe, xenon.

significant changes ($P = 0.004$) in higher frequencies. In contrast, nitrous oxide administration did not alter low-frequency delta and theta power. Instead, nitrous oxide alone reduced frontal alpha power in a dose-dependent manner (see "Across Gas" Statistical Analysis section details). Neither anesthetic resulted in statistically significant alterations (xenon, $P = 0.004$; nitrous oxide, $P = 0.005$) in high-frequency beta or gamma electroencephalographic source power.

The statistically significant increases ($P = 0.004$) observed in the magnetoencephalography delta- and theta-band power were also seen in the EEG data, though they were widespread and evident only at the highest 1.3 MAC_{awake} xenon concentration and not for low concentrations of xenon or nitrous oxide. In addition, the localization of alterations was substantially different between the two recording modalities, particularly in the delta-band, where more widespread EEG changes were evident. As for magnetoencephalographic data, alpha-band electroencephalographic power was significantly depressed by nitrous oxide, but not xenon, and it was predominately frontal in topology. Of note: for electroencephalographic power, the highest degree of reduction in terms of the number of statistically significant voxels ($P = 0.005$) and corresponding *t*-values was observed at nitrous oxide 0.50 MAC_{awake}, while only a small number of frontal and parietal voxels displayed decreased power at nitrous oxide 0.75 MAC_{awake} (Supplemental Digital Content 2, http://links.lww.com/ALN/C241).

No statistically significant differences (xenon, $P = 0.004$; nitrous oxide, $P = 0.005$) from baseline were observed in higher-frequency electroencephalographic power for all beta and low and high gamma ranges.

"Across Gas" Statistical Analysis

To look for specific differences between xenon and nitrous oxide effects, the three equivalent MAC_{awake} concentrations of xenon and nitrous oxide administered were compared within each equivalent MAC_{awake} level. A figure illustrating group-level frequency specific *t*-statistic maps across the anesthetic agents for both magnetoencephalography and EEG power can be found in Supplemental Digital Content 3 (http://links.lww.com/ALN/C242).

Unlike the "within gas" comparison against the postantiemetic baseline and despite the presence of an effect of gas on the calculated *t*-maps, most observations did not survive multiple comparisons correction using maximum statistics and Bonferroni correction. The results that demonstrated

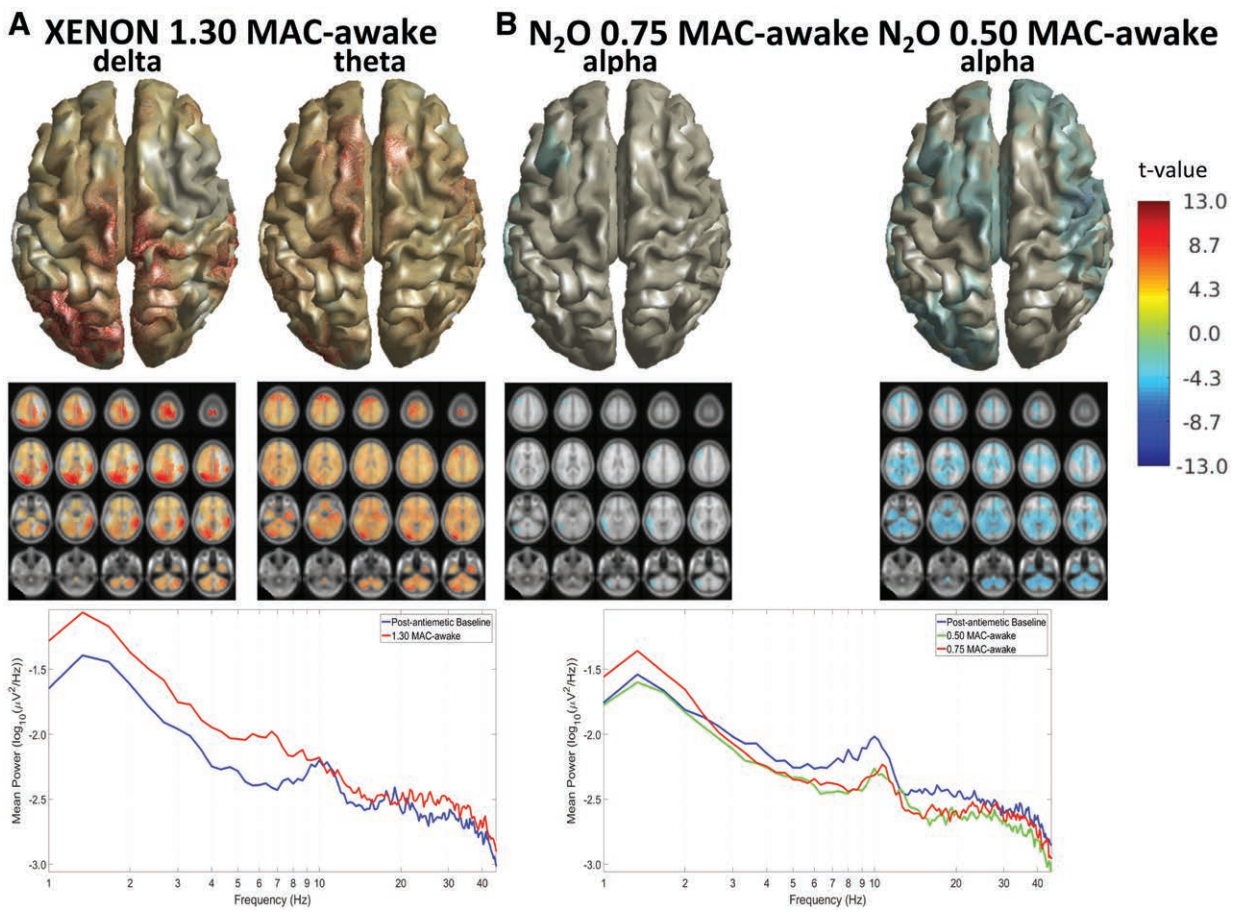

Fig. 4. Group level electroencephalography source power with most statistically significant effects under xenon and nitrous oxide anesthesia. Loss of responsiveness at 1.30 MAC_{awake} xenon (Xe) administration (*A*) yields pronounced widespread increases in low-frequency delta and theta activity. Nitrous oxide (N_2O) effect (*B*) is a reduction in alpha activity that is global and more pronounced for 0.50 MAC_{awake} N_2O. 0.75 MAC_{awake} N_2O effects were subtle and centered on frontal and temporal regions. There were no statistically significant high-frequency power changes. Maximum statistics and Bonferroni corrected *t*-maps ([*top row*] Xe, $P = 0.004$; N_2O, $P = 0.005$) of electroencephalographic sources across participants (n = 19). Brain slices (*middle row*) display region specific alterations plotted on the template Montreal Neurological Institute and Hospital (MNI) brain. Electroencephalography source spectral power ([*bottom row*] 1 to 45 Hz) is shown in the logarithmic scale for the postantiemetic baseline and the highest administered doses of the two gases averaged across all electroencephalographic sources and all subjects. Delta, 1 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz. MAC_{awake}, minimum alveolar concentration–awake.

statistically significant changes ($P = 0.004$) are shown in figure 5 and only relate to alpha-band differences between the two gases. First, magnetoencephalographic alpha-band source power was significantly lower for 0.75 equivalent MAC_{awake} nitrous oxide against xenon administration in four frontal regions (see table 3 for details). In addition, EEG source power in the alpha-band range was significantly smaller at equivalent 0.50 MAC_{awake} nitrous oxide against xenon over a number of automated anatomical labeling regions, but was primarily frontal (see table 3 for details and Supplemental Digital Content 3, http://links.lww.com/ALN/C242, for full list). Additionally, four frontal regions displayed statistically significant reductions ($P = 0.004$) in theta power for the nitrous oxide 0.50 MAC_{awake} dosage relative to xenon. Minor differences at this equivalent MAC_{awake} concentration were observed in delta power and in beta power in a small number of regions (table S3B, Supplemental Digital Content 3 http://links.lww.com/ALN/C242).

Discussion

The primary aim of this study was to examine the electroencephalographic and magnetoencephalographic effects in response to the administration of xenon and nitrous oxide in healthy volunteers, and to quantify to what extent they differed, given that they nominally share similar molecular targets of action. Subanesthetic doses of nitrous oxide

Table 2. Electroencephalographic Sources Most Significantly Altered by Xenon and Nitrous Oxide Administration

Frequency Band	MAC_{awake} Level	Region of Interest	Voxel Coordinate	*t* value	*P* Value
Delta	1.30 Xe	Occipital_Sup_L	–12, –96, 12	13.13	1.00E-04
	1.30 Xe	Temporal_Sup_R	66, –24, 0	11.52	0.0002
	1.30 Xe	Parietal_Inf_L	–36, –72, 42	11.00	0.0002
	1.30 Xe	Parietal_Sup_L	–24, –72, 42	9.69	0.0002
	1.30 Xe	Precuneus_L	–12, –72, 36	9.57	0.0002
Theta	1.30 Xe	Occipital_Mid_L	–30, –96, 0	12.50	1.00E-04
	1.30 Xe	Frontal_Mid_L	–24, 24, 54	8.81	0.0002
	1.30 Xe	Frontal_Sup_R	18, 24, 54	8.62	0.0002
	1.30 Xe	Frontal_Sup_Medial_L	0, 30, 54	8.56	0.0002
	1.30 Xe	Frontal_Sup_Medial_R	6, 30, 54	8.31	0.0002
Alpha	0.75 N_2O	Frontal_Mid_L	–48, 18, 42	–5.16	0.0011
	0.75 N_2O	Temporal_Mid_L	–66, –30, –6	–5.13	0.0012
	0.75 N_2O	Temporal_Inf_L	–60, –54, –12	–5.01	0.0014
	0.75 N_2O	Frontal_Sup_L	–12, 66, 18	–4.94	0.0016
	0.75 N_2O	Frontal_Sup_Medial_L	0, 42, 54	–4.63	0.0022
	0.50 N_2O	Occipital_Inf_L	–24, –96, –6	–7.22	1.00E-04
	0.50 N_2O	Occipital_Mid_L	–24, –96, 0	–7.12	0.0002
	0.50 N_2O	Frontal_Sup_R	24, 66, 12	–6.27	0.0004
	0.50 N_2O	Temporal_Inf_L	–42, 6, –42	–6.15	0.0004
	0.50 N_2O	Temporal_Pole_Mid_L	–30, 6, –42	–5.87	0.0008

Five representative regions of interest were selected from the 20 highest *t* value and *P* value ($P < 0.005$ for N_2O; $P < 0.004$ for Xe) regions. Region of interest analysis reveals widespread increases for delta in frontal regions and a widespread theta rise relative to baseline during xenon loss of responsiveness (1.30 MAC_{awake}). The highest N_2O inspired concentration (0.75 MAC_{awake}) resulted in primarily frontal alpha reductions while intermediate N_2O dosage (0.50 MAC_{awake}) displayed widespread decreases across participants. Voxel coordinates are in Automated Anatomical Labeling atlas coordinate system along with associated labels.[46] Delta, 1 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz. Inf, inferior; L, left; MAC_{awake}, minimum alveolar concentration–awake; Mid, middle; N_2O, nitrous oxide; R, right; Sup, superior; Xe, xenon.

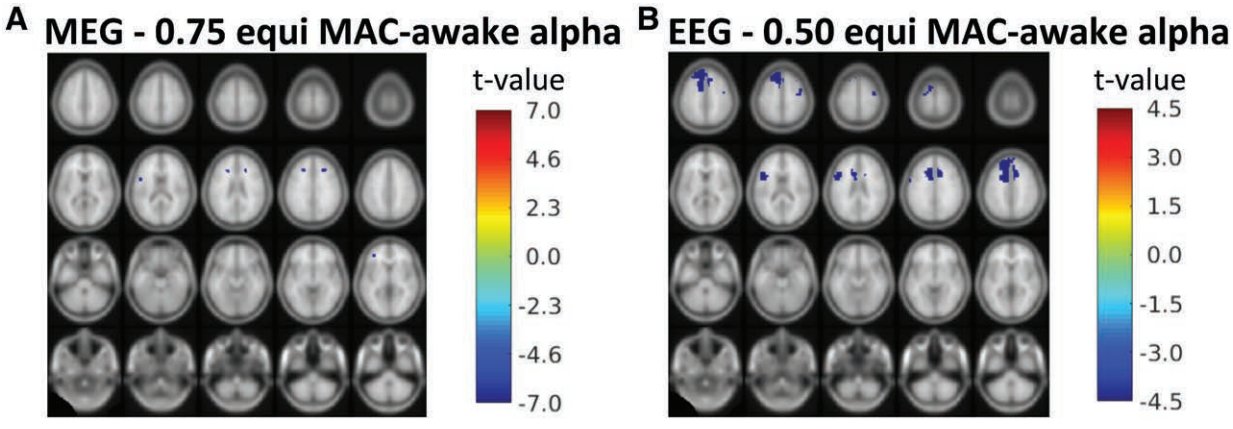

Fig. 5. Alpha magnetoencephalographic and electroencephalographic source power is substantially less for nitrous oxide compared to xenon administration. Maximum statistics and Bonferroni corrected *t*-maps across volunteers (MEG, n = 21; EEG, n = 19) are plotted on the template Montreal Neurological Institute and Hospital (MNI) brain. Alpha bandwidth magnetoencephalography (MEG-A) source power was considerably lower for nitrous oxide (N_2O) when compared to xenon (Xe) anesthesia (0.75 equivalent MAC_{awake}). Alpha bandwidth electroencephalographic source power (EEG-B) was substantially less for 0.50 MAC_{awake} N_2O against Xe administration and was specific to numerous regions. Representative regions of interest shown here reveal that differences between the two gases were predominately frontal. (Automated Anatomical Labeling [AAL] Atlas Labels: Frontal_Mid_R, Frontal_Sup_Medial_L, Frontal_Mid_L, Frontal_Sup_L and corresponding Voxel Coordinates). The difference in scale between A and B should be noted. Alpha, 8 to 13 Hz. MAC_{awake}, minimum alveolar concentration–awake.

yielded no statistically significant effects on low-frequency delta and theta activity. In contrast, xenon significantly increased total power in both bands. These findings were reflected in both the magnetoencephalography and EEG data. Alpha power depression was observed only under nitrous oxide administration and was predominately of frontal origin. Higher-frequency activity increases were observed in the magnetoencephalographic, but not the

Table 3. Magnetoencephalographic and Electroencephalographic Sources Most Significantly Altered in Equivalent Gas Concentrations of Xenon and Nitrous Oxide

Measurement	Frequency Band	MAC_{awake} Level	Region of Interest	Voxel Coordinate	*t* value	*P* Value
MEG	Alpha	0.75	Frontal_Mid_R	24, 30, 30	−6.97	0.0017
		0.75	Frontal_Inf_Oper_L	−48, 6, 18	−6.86	0.0020
		0.75	Frontal_Inf_Tri_L	−36, 42, 0	−6.64	0.0032
		0.75	Frontal_Mid_L	−24, 30, 30	−6.42	0.0038
EEG	Alpha	0.50	Frontal_Mid_R	42, −6, 54	−6.22	0.0013
		0.50	Frontal_Sup_Medial_L	−6, 42, 54	−6.15	0.0016
		0.50	Frontal_Mid_L	−24, 30, 54	−6.14	0.0016
		0.50	Frontal_Sup_L	−18, 42, 48	−5.98	0.0026
		0.50	Frontal_Inf_Oper_L	−48, 12, 18	−5.8	0.0026
		0.75	Frontal_Mid_L	−42, 48, 18	−3.71	0.0141
		0.75	Frontal_Inf_Tri_L	−54, 24, 12	−3.45	0.0230
	Theta	0.50	Frontal_Inf_Tri_L	−48, 36, 24	−4.66	0.0111
		0.50	Frontal_Inf_Tri_R	54, 30, 24	−4.37	0.0156
		0.50	Frontal_Mid_L	−48, 30, 30	−4.36	0.0156
		0.50	Frontal_Mid_R	36, 24, 54	−4.11	0.0208

Representative regions of interest were selected from the 20 highest *t* value and *P* value ($P < 0.004$) regions. Magnetoencephalographic alpha-band power was significantly lower for 0.75 equivalent MAC awake N_2O against Xe administration in four frontal regions). Electroencephalography source power in the alpha-band range was significantly smaller at 0.50 equivalent MAC_{awake} N_2O against Xe, as well as 0.75 equivalent MAC_{awake} and was also primarily frontal. Frontal regions displayed significant reductions in theta power for the 0.50 MAC_{awake} N_2O dosage relative to Xe. Voxel coordinates are in Automated Anatomical Labeling atlas coordinate system along with associated labels.[46] Delta, 1 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz. EEG, electroencephalography; Inf, inferior; L, left; $MAC_{awake,}$ minimum alveolar concentration–awake; MEG, magnetoencephalography; Mid, middle; N_2O, nitrous oxide; Oper, operculum; R, right; Sup, superior; Xe, xenon.

electroencephalographic, signals for nitrous oxide, with occipital low gamma and widespread high gamma rises in power. Xenon showed no significant gamma-band alterations, and neither gas gave rise to beta-band activity changes when compared to baseline. Finally, contrasting the effects of nitrous oxide relative to xenon did not reflect the differences observed when the agents were evaluated independently against the postantiemetic baseline. Consistent with the analysis with respect to baseline, nitrous oxide showed reduced alpha-band magnetoencephalographic source power compared to xenon for the highest inhaled concentration of nitrous oxide and, somewhat surprisingly significantly pronounced effects for the intermediate dosage administered in electroencephalographic source power. In summary, electroencephalographic and magnetoencephalographic recordings reveal an array of differences and similarities among the two agents, that incorporate effects that have been observed for both ketamine and a range of γ-aminobutyric acid–mediated anesthetic agents that include the volatile gases and propofol.[3,4] On this basis, we find no clear evidence that xenon and nitrous oxide gaseous anesthesia are acting *via* similar mechanisms, at least when evaluated in terms of dose- and modality-dependent variations in spectral power.

An important result is the increase in delta power under subanesthetic xenon anesthesia, which has been documented in other electrophysiologic investigations of xenon.[9,11] Increases in delta-band power are commonly observed in unconsciousness under propofol anesthesia and often demonstrate patterns of increase that correlate with dosage and inversely correlate with participant responsiveness.[3,38] The rise in delta may be relevant to xenon's potentiation effect on depolarization-dependent potassium channels and subsequent hyperpolarization of cortical neurons, which—as has been described for propofol—might result in cortical bistability.[2,39] A recent study comparing xenon, propofol, and ketamine subanesthetic dosage using electroencephalographic recordings under transcranial magnetic stimulation attributed the stimulation-evoked global negative wave observed under xenon anesthesia to this cortical hyperpolarized state, while propofol-induced local positive−negative waves were thought to be the result of GABA-induced local hyperpolarization.[40] However, despite these differences in evoked response, propofol and xenon appeared functionally equivalent in that they both gave rise to reduced measures in complexity when compared to the awake state.[40] Conversely, ketamine administration, which, like nitrous oxide, has no influence on these molecular targets, resulted in multiple activation waves and a high measure of complexity, comparable to wakefulness, suggestive of no effect on corticocortical interactions.[40] In summary, the potentiating effect on potassium currents and resulting generation of delta oscillatory activity with xenon, but not nitrous oxide,[2,41] might offer an explanation as to why we report delta-band changes for xenon alone.

The observed theta power increases under xenon anesthesia is in line with the EEG literature.[9,11] The absence of nitrous oxide–induced theta-band changes has been previously reported;[42] however, it remains unlike most reports pointing to theta power increases under nitrous oxide and ketamine.[6–8,19,38] The statistically significant reduction in electroencephalographic alpha power upon subanesthetic

nitrous oxide administration has been observed and replicated using ketamine anesthetic dosage.[38,42] Importantly, due to the close resemblance to our paradigm, a theta rise was replicated using magnetoencephalography and subanesthetic ketamine doses.[19] However, we do not report the same result for EEG and magnetoencephalography power. This may be explained by the necessary common average re-referencing scheme performed only on EEG data and used as the standard re-referencing scheme for EEG source imaging.[17,43] It could alternatively relate to dosage, with previous work reporting no alterations in alpha at lower concentrations (40% nitrous oxide/oxygen[7]; 47% in our study), but significant reductions at higher concentrations (60% nitrous oxide/oxygen[42]; not administered in our study due to safety concerns). Xenon did not significantly alter alpha power, an observation reported by other authors.[9] It should be noted that the observed power changes, can be complemented by functional connectivity measures which may yield more powerful functional specificity.[38] The distinctive effects of the two agents on the theta- and alpha-band we outlined by contrasting their anesthetic action on each individual may ultimately relate to large-scale (low-frequency dependent) network alterations along the anterior to posterior axis, but further investigations are required to corroborate such a speculation.

Higher-frequency increases in the gamma range, as seen here, are common under nitrous oxide–induced reductions in consciousness.[5] The widespread high gamma power rise reported resembles global gamma power increases in magnetoencephalographic recordings under ketamine infusion.[19] Furthermore, we report no statistically significant changes in beta power, as has been previously shown for lower nitrous oxide–administered doses and for γ-aminobutyric acid–mediated anesthetics.[7,8,39] Xenon inhalation did not exhibit statistically significant effects on high-frequency gamma and beta activity, and previous findings remain unclear on this relationship.[9,12] Nonetheless, the different high-frequency profiles observed for the two agents may be suggestive of nitrous oxide–mediated noise, influencing the firing of pyramidal neurons and hence, disrupting consciousness.[44]

Important points also emerge relating to the protocol followed. Noteworthy is the fact that high-frequency nitrous oxide observations were not replicated for xenon, of particular interest in magnetoencephalography datasets. Electromagnetic gamma activity is often contaminated with muscle artefacts which commonly oscillate in a similar range of frequencies,[45] a critical concern in subanesthetic gaseous anesthesia, where psychomotor agitation is pronounced, particularly reflected in increased jaw movements.[18] Changes in gamma were not evident in both gas conditions for the same volunteers, and since rigorous measures were taken to eliminate head and body movement, we can assume that the anesthetic-induced gamma-band variations are not the result of artefact. In addition, statistically significant high-frequency power changes for magnetoencephalography, but not EEG, data were observed. This may be explained by the wider frequency range of acquisition of magnetoencephalography when compared to EEG, which extends to gamma activity.[46] On a similar point, overall differences observed across the two modalities may be attributed to the higher spatial and source localization accuracy of magnetoencephalographic recordings.[17,47,48] We therefore speculate that magnetoencephalography (and simultaneous magnetoencephalography/EEG) source imaging may offer an excellent alternative to the more commonly employed EEG, upon investigation of the fine-tuned and region-specific neural networks involved in reductions of consciousness under anesthesia and beyond.

Various strengths of this study are worth mentioning. The crossover design applied here enabled the true and direct comparison of the two administered agents and induced reductions in consciousness. In addition, the various equivalent MAC_{awake} concentrations of xenon and nitrous oxide were administered with the same gas wash-in, maintenance, and wash-out steps, potentially reducing any effects that lower concentrations may have had. In addition, the administration outcomes could only be credited to each gaseous anesthetic as no other psychoactive medication was administered; a common confounding factor in anesthesia research. The use of magnetoencephalography and high density EEG have yielded unprecedently high-resolution recordings, thus allowing for source level imaging techniques to be applied, in order to reveal the region specific origins of any observed signals.

There are also multiple important weaknesses worth mentioning. Males alone were utilized in this study which may raise concern for the validity of the results in both sexes. Nonetheless, females were excluded due to the documented effects of menstruation and/or age extremes on the resting magnetoencephalography/EEG signal and increased propensity to nausea and vomiting.[20,21] Second, the direct comparison of the magnetoencephalography and EEG results is difficult due to a number of differences in the datasets and analysis pipeline. Participant numbers and sampling rates were significantly less for electroencephalographic data, and sample sizes have shown a contribution to the quality of source localization.[49] Necessary re-referencing was performed on EEGs, while magnetoencephalographic recordings alone were filtered using temporal signal source space separation. Also, forward model calculation differs for the two modalities since electrical, but not magnetic, signals are influenced by the skull.[17] With this volume conduction issue in mind, we chose not to illustrate sensor-level data. No connectivity analyses were performed to investigate network changes under anesthesia. A final drawback was the use of highly conservative statistics that resulted in loss of potentially interesting information.

In conclusion, this study investigated the effects of increasing equivalent doses of xenon and nitrous oxide on magnetoencephalographic and electroencephalographic source power in healthy volunteers. Magnetoencephalography and EEG

recordings revealed increased low-frequency delta and theta power at the highest xenon concentration and reduced alpha power under subanesthetic nitrous oxide administration. Finally, a rise in high-frequency gamma activity was demonstrated in the magnetoencephalography data. Higher specificity and range of magnetoencephalography results point to important benefits of exploiting this underused technique to provide temporally- and spatially-specific functional imaging.

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Competing Interests

Dr. Cormack received a one-time payment from Swinburne University (Melbourne, Australia) for provision of anesthetic services essential to the study. The other authors declare no competing interests.

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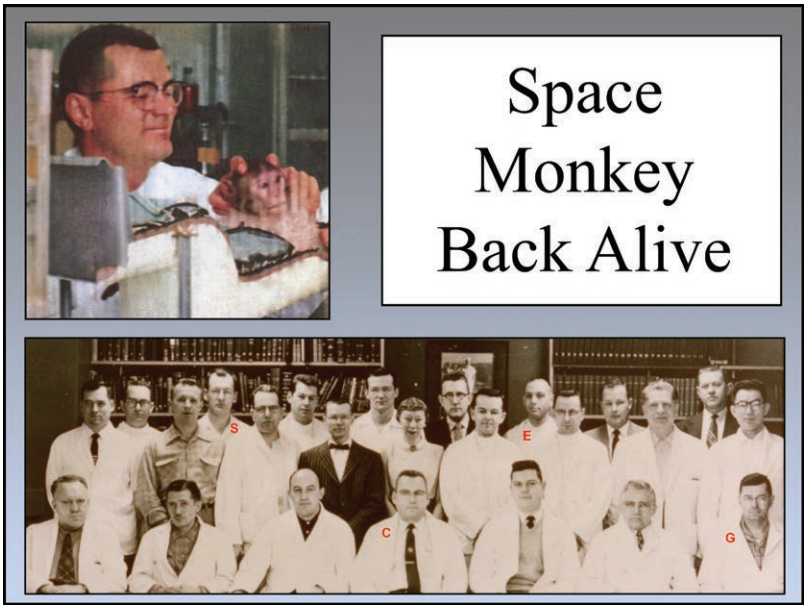

In October of 1957, cold war tensions rose between the United States and the Soviet Union after the latter launched the first artificial satellite, Sputnik. A year later, newly formed NASA was recruiting a young anesthesiologist to design a new instrument for Project Mercury and the first manned space flight. Cloid D. Green, M.D. (1921 to 2001, *upper left*) was tasked with building a biopack, or life support system, for primates in the test space missions that ultimately informed the equipment for the Apollo mission. Dr. Green was well positioned to create this new instrument based on his strong research background at the University of Iowa and his recent study of pilots flying at high altitude. While at the University of Iowa, Green (G) had been part of an all-star group (*bottom*) of anesthesiologists, which had included Drs. Stuart Cullen (C) and rising stars, such as Drs. John Severinghaus (S) and Edmond "Ted" Eger (E). By 1959, Dr. Green and NASA were celebrating the successful launch and retrieval of the Little Joe Capsule and the survival (headlined, *upper right*) of a rhesus monkey named Sam. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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