ISAP 33rd Annual Meeting

2024 Syllabus

October 18th, 2024

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PHILADELPHIA, PA

33rd Annual Meeting

Mission Statement

The International Society for Anaesthetic Pharmacology (ISAP) is a nonprofit organization with an international membership, which is dedicated to teaching and research about clinical pharmacology in anesthesia, with particular reference to anesthetic drugs.

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Objectives

After Attending This Program You Should Be Able To:

1. Appreciate the immediate opportunities for the advancement of clinical pharmacology as well as potential threats.
2. Effectively recognize the use and utility of new and upcoming pharmacologic receptors including VX-548, a selective NaV1.8 channel blocker.
3. Understand the potential importance of pharmacogenomics in the delivery of effective perioperative care.
4. Consider the pros, cons, and nuances of the use of opioid-free analgesia in clinical practice.
5. Evaluate the best practices for analgesia for knee pain for the general populations and armed forces.
6. Comprehend the pharmacologic basis of chemotherapy-associated peripheral neuropathy.
7. Reflect on the contributions of outstanding clinical pharmacologists to perioperative care.

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Mohamed Naguib Lecture:

Carrying on what Dr. Naguib Started: Chemotherapy Induced Peripheral Neuropathy

Daniel Rotroff, PhD, MSPH, Director, Center for Quantitative Metabolic Research, Cleveland Clinic, Cleveland, OH, USA

GENEROUS SUPPORT PROVIDED BY SENZIME CORPORATION

ISAP has established the Mohamed Naguib Lecture to honor his many accomplishments, which will be presented at every ISAP Annual Meeting. The Inaugural Lecture was given at the 2021 ISAP Annual Meeting. ISAP has established a fund to endow the Mohamed Naguib Lecture and donations may be made at isaponline.org.

In the world of clinical pharmacology, Dr. Naguib was a renaissance man. As a man of many talents, his influential work has provided direction in many spheres of investigation and discovery. He made significant contributions to the scientific foundation and clinical applications of neuromuscular monitoring. He formed and led a coalition of thought leaders to prepare and disseminate expert consensus guidelines on neuromuscular monitoring. He had substantial interest in the mechanisms of and treatment for neuropathic pain. He led a laboratory that created molecules to treat neuropathic pain. At the time of his passing, he was a principal investigator on a NIH funded multi-center observational study focused on the discovery and validation of a biomarker signature for chemotherapy induced peripheral neuropathic pain. He was the co-founder of a company that is developing a novel therapy for neuropathic pain and Alzheimer's disease based on his research on the mechanisms of neuroinflammation. For each of these activities, he created a wake of opportunities for many that continue to have a vibrant and productive future. He was a prolific writer. He was the principal author or co-author of 130 peer-reviewed journal articles, 25 book chapters (including the premier Miller's Textbook of Anesthesia) and 150 abstracts.

By way of professional service, for years, he served on the editorial board of numerous anesthesia journals and was influential not only in his reviews but in preparing thought provoking editorials and commentary. He also served for many years in various leadership positions, including President of ISAP.

33rd Annual Meeting Schedule

0815–1700 Eastern Time Zone, USA

0815 – 0830 **ISAP Welcome/Announcements**
Joseph Foss, MD

0830 – 1000 **Session 1 – New Horizons in Clinical Pharmacology**
MODERATOR: *Amanda Kleiman, MD*

- **0830 – 0900** **Taking Over the Reins at A&A: Challenges and Opportunities for Clinical Pharmacology**
  Jaideep J. Pandit, MA, BM, DPhil, FRCA, FFPMRCA, DM, MBA, Professor of Anaesthesia, University of Oxford & Editor-in-Chief, Anesthesia & Analgesia; Oxford, England, United Kingdom
- **0900 – 0930** **Recent Advances in pEEG Monitoring**
  Patrick L. Purdon, Ph.D, Professor of Anesthesiology, Perioperative and Pain Medicine, Professor of Bioengineering (by Courtesy), Member, Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, USA
- **0930 – 1000** **Pilot Findings of Pharmacogenomics in Perioperative Care: Initial Results from the First Phase of the ImPreSS Trial**
  Peter H. O'Donnell, MD, Associate Professor of Medicine, Chair, Committee on Clinical Pharmacology and Pharmacogenomics, The University of Chicago, Chicago, IL, USA

1000 – 1015 **Break**

1015 – 1200 **Session 2 – Personalizing Anesthetic Delivery**
MODERATOR: *Ken Johnson, MD*

- **1015 – 1045** **The Pros and Cons of Opioid Free Anesthesia**
  Girish P. Joshi, MBBS, MD, FFARCSI, FASA, SAMBA-F, Professor, Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
- **1045 – 1115** **The Opioid Paradox**
  Evan Kharasch, MD, PhD, Professor, Department of Anesthesiology, Duke University, Durham, NC, USA
- **1115 – 1145** **The SKOAP Study: A Large National Study of Treatments for Knee Pain Involving Veterans, Active Military, and the General Public**
  Carina Jackman, MD: Site PI SKOAP Study, University of Utah School of Medicine; Quality Improvement Officer, Division of Pain, Associate Professor, Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, UT, USA
- **1145 – 1200** **Selective Nav1.8 Inhibitors for the Treatment of Pain**
  Sandra Lechner, PhD, Vice President - Pain Research, Vertex Pharmaceuticals, Inc. (non-CME session)

1200 – 1245 **Luncheon – ISAP Business Meeting**

1245 – 1330 **Mohamed Naguib Lecture**
Introduction: Dr. Foss & Dr. Johnson
Carrying on What Dr. Naguib Started: Chemotherapy Induced Peripheral Neuropathy
Presenter: Daniel Rotroff, PhD, MSPH, Director, Center for Quantitative Metabolic Research, Cleveland Clinic, Cleveland, OH, USA

1330 – 1445 **Moderated Poster Session 75 minutes**

1445 – 1500 **Break**

1500 – 1545 **Keynote Speaker & Lifetime Achievement Awardee**
Introduction: Joe Foss, MD, ISAP President
Keynote: Following a Pharmacological Path from Molecules to Clinical Fruition: *An Anesthesiologist's Journey*
Mervyn Maze, MB, CHB, Professor in the Department of Anesthesia and Perioperative Care, Intensive Care at the University of California, San Francisco, CA, USA

1545 – 1700 **Gathering**

16:30 – 1830 **ISAP Board Meeting**

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Amanda M Kleiman, MD
Associate Professor of Anesthesiology
University of Virginia, Department of Anesthesiology, Charlottesville, VA, USA

Speakers & Moderators

Jaideep J. Pandit, MA, BM, DPhil, FRCA, FFPMRCA, DM, MBA
Professor of Anaesthesia, University of Oxford & Editor-in-Chief, Anesthesia & Analgesia; Oxford, England, United Kingdom

Patrick L. Purdon, Ph.D
Professor of Anesthesiology, Perioperative and Pain Medicine Professor of Bioengineering (by Courtesy); Member, Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, USA

Peter H. O'Donnell, MD
Associate Professor of Medicine, Chair, Committee on Clinical Pharmacology and Pharmacogenomics, The University of Chicago, Chicago, IL, USA

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Carina Jackman, MD
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Director, Center for Quantitative Metabolic Research, Cleveland Clinic, Cleveland, OH, USA

Mervyn Maze, MB, CHB
Professor in the Department of Anesthesia and Perioperative Care, Intensive Care at the University of California, San Francisco, CA, USA

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MOHAMED NAGUIB LECTURE

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Modulation of human brain areas for memory and pain by propofol, dexmedetomidine, and fentanyl: A randomized controlled 7 T functional MRI study in healthy young adults

Presenting Author: Keith M. Vogt
Co-authors: Marcus A. Simmons, Courtney N. Kozdron, James W. Ibinson
Department of Anesthesiology, University of Pittsburgh School of Medicine; Pittsburgh, PA, USA

Introduction: Anesthetic and analgesic drugs have distinct clinical profiles and are well-accepted to impair memory and relieve pain to varying degrees. However, anesthetic effects on the human brain systems for memory encoding and pain processing are less well demonstrated. We developed a novel paradigm with periodic painful stimulation during an auditory memory encoding task which reflects the clinical conditions under which anesthetic and analgesic agents are commonly used. This framework was used to study the effects of three different anesthetic agents using high-field functional MRI (fMRI).

Methods: This was an IRB-approved, pre-registered clinical trial (NCT04062123) of healthy adults age 40 and under. There were two separate scan sessions, both with crystalloid infusion. In one session, a constant effect-site concentration (ESC) was targeted using stanpumpR (https://stanpumpr.io/). Subjects were blinded and randomized to propofol (n= 22; ESC=1.0 mcg/ml), dexmedetomidine (n=25; ESC=0.15 ng/ml), or fentanyl (n=25, ESC=0.9 ng/ml). A nerve stimulator connected to the left index finger was set to 7/10 intensity rating. Subjects listened to a series of 80 words and while creating a mental picture involving the word, adding more detail as the word repeated over 6 s. Thirty of the words were accompanied by a 2 s painful shock, and pain ratings and sedation scores were recorded throughout. Blood oxygen-weighted images (1 s temporal resolution, 2 mm isotropic spatial resolution) were obtained at 7 T using custom hardware. Testing 1 day afterwards included 80 not previously-heard words, and assessed recognition using the normalized signal detection metric, d-prime (d'), for which 0 indicates chance performance. FMRI analysis was performed with FSL 6 (https://fsl.fmrib.ox.ac.uk/), and group results were thresholded for $Z > 2$ and cluster significance adjusted to $p < 0.05$.

Results: Due to inter-subject variability, pain ratings were not significantly different under any drug. Memory performance (Fig. 1) was reduced under propofol. The fMRI signature of successful memory (Fig. 2, top row) included activity in (predominantly right-sided) hippocampus (Hpc) and parahippocampal (PHC) areas. The Hpc/PHC memory areas were modulated by: propofol (right brain, decrease), dexmedetomidine (right brain, increase) and fentanyl (left brain, increase). Amygdala (bilateral) activity decreased with propofol, for the memory task. Shock-related activity (bottom half of Fig. 2) was decreased with fentanyl, in the right primary somatosensory cortex, and insula (predominantly left brain, inferior). Propofol decreased shock-related activity in the anterior cingulate, insula (bilateral), and amygdala (bilateral).

Conclusions: Propofol, dexmedetomidine, and fentanyl distinctly modulated brain areas for memory and pain processing, despite achieving similar levels of sedation. This suggests that anesthetic effects on specific aspects of cognition are mediated through different brain circuits when agents with different pharmacology are administered. Specific findings that do not match clinical intuition are: decreased activity in affective pain processing areas under propofol and modulation in memory areas under fentanyl. Further neuroimaging studies under broader anesthetic conditions will help to further elucidate the systems-level neural correlates of action for these agents.

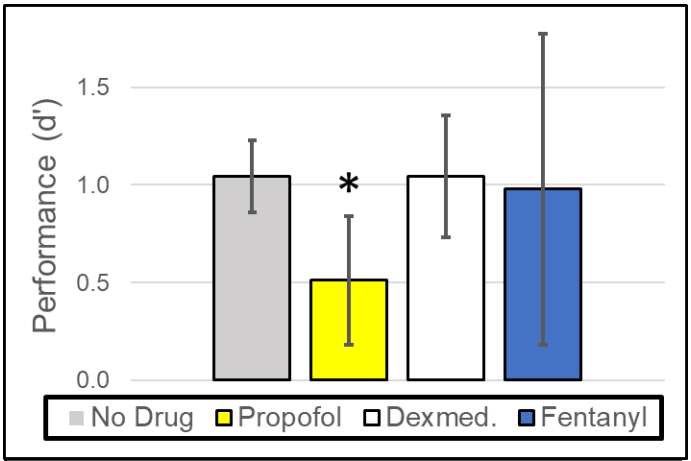

Fig. 1. Memory performance by drug, mean +/- 95% confidence interval. Dexmed.= dexmedetomidine.

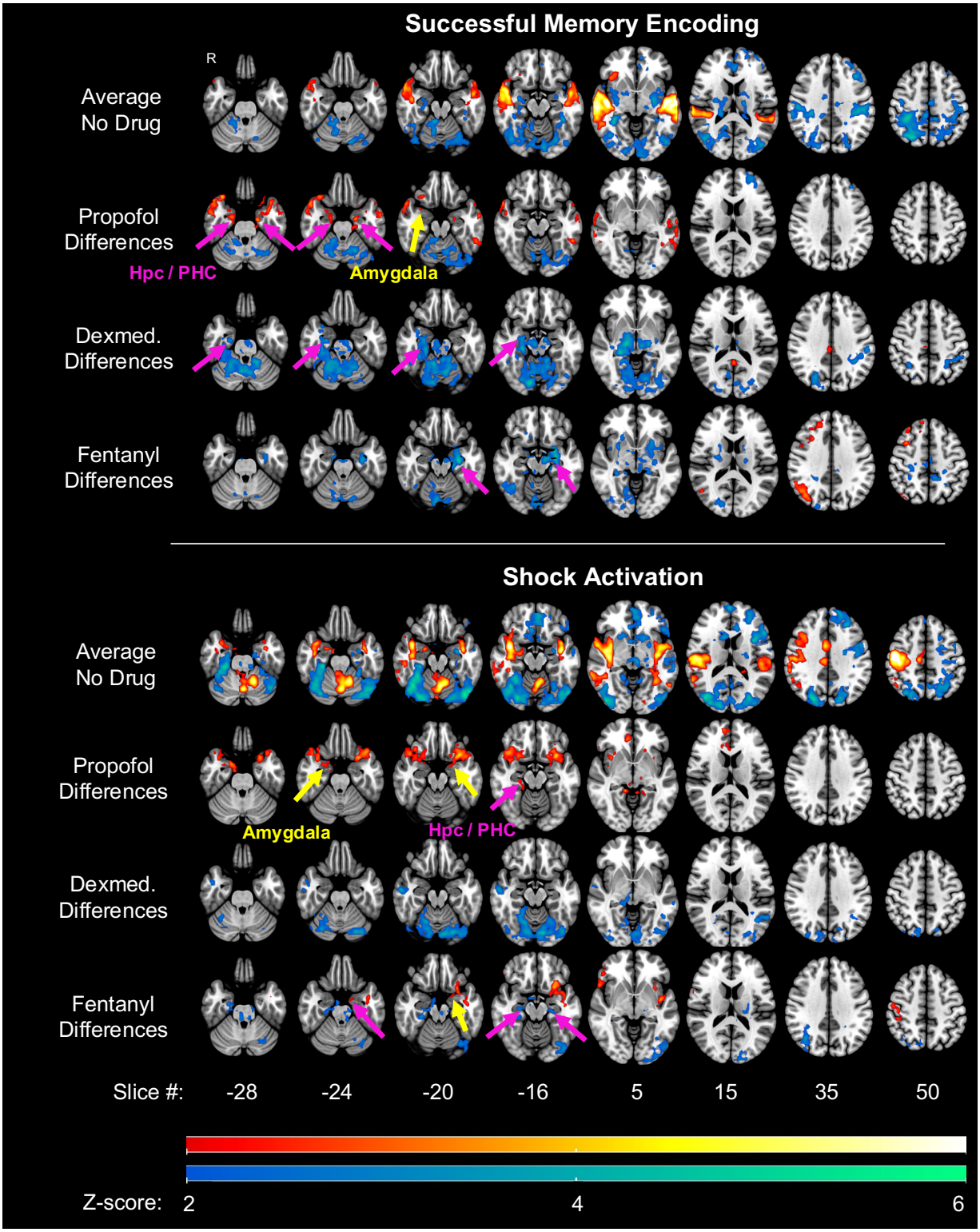

Fig. 2. All-subject average fMRI task activation for words successfully encoded (top) and during periods experiencing painful electric nerve stimulation (bottom) for selected axial slices (left brain on right side of figure), with MNI-152 slices shown. The color bar indicates Z-score, according to the scale shown. The top row in each sub-panel show brain with significant positive (warm colors) or negative (cool colors) correlation to the task under the no-drug condition. The subsequent rows display areas of significant differences under each drug condition (the no-drug vs. drug contrast). Warm colors indicate no-drug > drug and cool colors indicate drug > no-drug differences. Color-coded arrows indicate changes in key areas. Hpc= hippocampus, PHC= parahippocampus, Dexmed.= dexmedetomidine

A novel index for trending sepsis and inflammatory response using processed EEG and Heart Rate Variability.

Erik Weber Jensen[1], Jaume Millán[1], Carolina Frederico[2], Alexandra Caballero[3], Maria Alejandra Manjarrest[1], Montserrat Vallverdú[1], Gertrude Nieuwenhuijs-Moeke[4] , Michel Struys[4]

1. Biomedical engineering, School of Industrial Engineering of Barcelona (ETSEIB) - UPC, Barcelona, Spain
2.Anesthesiology department, Hospital Quirón Salud, Barcelona, Spain
3. Anesthesiology department, Clínica Interhospital, Guayaquil, Ecuador
4. Department of Anesthesiology, University Medical Center of Groningen, The Netherlands

INTRODUCTION:

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. It is frequently a final common pathway to death for many infectious diseases worldwide.

Systemic inflammatory response syndrome (SIRS) is an exaggerated defense response of the body to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy, to name a few) to localize and then eliminate the endogenous or exogenous source of the insult. Dysregulation of proinflammatory and anti-inflammatory pathway homeostasis lies at the heart of the clinical scenario with the dysregulated release of acute and chronic phase reactants. This activity reviews the evolution of the definition and the clinical relevance of systemic inflammatory response syndrome. It outlines appropriate evaluation and management strategies for the syndrome and reviews the role of the interprofessional team in improving care and clinical outcomes for patients with this condition

Electroencephalography (EEG) has been employed to assess the hypnotic effect and the level of nociception/antinociception during general anaesthesia. Furthermore, Heart Rate Variability (HRV) has been put forth as a potential monitoring tool for the nociception/antinociception balance. A number of studies have indicated that a reduction in HRV is linked to an elevated level of systemic inflammation or sepsis (4, 5). Nevertheless, it has been demonstrated that certain HRV parameters, such as the Root Mean Square of Successive Differences (RMSSD), may also undergo a reduction during the induction of general anaesthesia or sedation. It is therefore essential to isolate the effects of inflammation on HRV by accounting for the level of sedation, as assessed by processed EEG.

OBJECTIVE:

The objective of this study was to develop an index that would enable the accurate assessment of the inflammatory response based on processed electroencephalogram (EEG) and heart rate variability (HRV) data. The index was termed the "Trending Sepsis and Inflammation" (TSI) index.

METHODS:

The Trending Sepsis and Inflammation (TSI) index was developed using data collected from patients at Hospital Quirón Salud in Barcelona, Spain, and Clínical Interhospital in Guayaquil,

Ecuador. Both hospitals had obtained the approval of their local ethics committee, and the CoreSys One monitor (CoreSys Health S.L., Barcelona, Spain) was employed to record two EEG channels and one ECG channel simultaneously. A total of 63 patients were included in the study, comprising 54 patients from surgical procedures of durations ranging from 45 minutes to five hours, 4 patients in the ICU with confirmed sepsis and 5 healthy volunteers for baseline estimation. In total, 1,279,557 readings were collected at 0.25-second intervals.

The dataset was categorized into three levels of increasing inflammation. The healthy awake volunteers were assigned to Level 1, the perioperative patients to Level 2, and the patients with confirmed sepsis to Level 3. Subsequently, an Adaptive Neuro-Fuzzy Inference System (ANFIS) model was employed to train the index, with heart rate, root mean square of the successive differences (RMSSD), the ratio between low and high frequency components of heart rate variability (LF/HF), and the brain activity index (BA) as inputs. Heart rate variability (HRV) parameters were calculated at 3-minute intervals, with a 20-second increment.

The TSI index provides real-time data on a patient's inflammatory status, facilitating prompt clinical decision-making. The index indicates that values ranging from 0 to 25 indicate a normal state, 25 to 50 suggest a mild inflammatory response, 50 to 75 denote a strong inflammatory response and risk of sepsis, and 75 to 100 indicate a severe inflammatory response and risk of sepsis and septic shock.

RESULTS:

The TSI index vs the reference inflammatory scale resulted in a Pk(SE) value of 0.9862(0.001) and an R^2 Pearson correlation coefficient of 0.85. Figure 1 shows a boxplot of TSI vs the inflammatory scale.

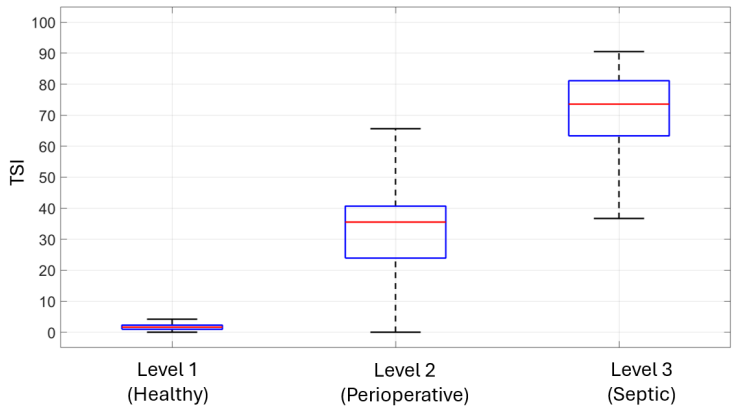

Figure 1 presents a boxplot depicting the distribution of TSI values among healthy volunteers, surgical cases, and septic cases.

CONCLUSIONS:

The prediction probability of the TSI of the reference inflammatory scale was high , however it should be taken into account that the Pk was calculated on the training data, the method should be validated in data set different from the training data. The TSI has the potential of detecting inflammatory states, however future studies, including inflammatory biomarkers, must be carried out to prove that the TSI is associated with systemic inflammation.

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Nitrous Oxide activates layer 5 prefrontal neurons via SK2 channel inhibition for antidepressant effect

Author list:

Joseph Cichon[1,2], Thomas T. Joseph[1], Andrzej Z. Wasilczuk[1], Max B. Kelz[1], Peter Nagele[3]

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Abstract:

Nitrous oxide (N_2O) induces rapid and durable antidepressant effects. The cellular and circuit mechanisms mediating this process are not known. Here we find that a single dose of inhaled N_2O induces rapid and specific activation of layer V (L5) pyramidal neurons in the prefrontal cortex of rodents exposed to chronic stress conditions. N_2O-induced L5 activation rescues a stress-associated hypoactivity state, persists following exposure, and is necessary for its antidepressant action. While NMDA-receptor antagonism has been N_2O's purported mechanism of action, L5 neurons activate independently from NMDA-receptor function and synaptic activity. By examining different molecular and circuit targets, we identify N_2O-induced inhibition of calcium-sensitive potassium (SK2) channels as a primary molecular interaction responsible for driving specific L5 activity along with ensuing antidepressant-like effects.

Stereoselective Population Pharmacokinetics and Pharmacogenomics of Intravenous Methadone

Presenting Author: Thomas K. Henthorn[1,]
Co-Authors: Evan D. Kharasch[2]

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Background/Introduction: Methadone is chiral and generally used clinically as a racemic mixture of R- and S- enantiomers. R-methadone mu-receptor binding affinity and analgesic potency are 30- to 50-fold greater than S-methadone, thus R-methadone is responsible for the majority of racemic methadone analgesia. There is an unmet need for a) a comprehensive population pharmacokinetic model of methadone and its major inactive metabolite 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) derived from dense, early sampling times extending to 4 days after a single dose, b) the influence of genetic CYP variants on disposition, and c) a more comprehensive evaluation of chiral effects on the disposition of methadone and EDDP.

Methods: R- and S-methadone and EDDP plasma concentrations were measured in 1214 blood samples obtained over 4 days from 64 healthy subjects, following a single 6 mg IV dose of racemic methadone. 5 *CYP2B6* genotypes and 7 *CYP2C19* genotypes were determined for each subject. Parameters for a 3-compartment population pharmacokinetic model were estimated using Phoenix NLME 8.4.3. Proportional links (S:R) between the 3-compartment models of S- and R-methadone were evaluated for volume, intercompartmental clearance and elimination clearance estimates. Demographic and genotype data were evaluated with a stepwise covariate analysis. Individual Bayesian estimates of the final methadone model were carried forward in a stepwise manner to model the population pharmacokinetics of EDDP.

Results: Figure 1 demonstrates the differential concentration versus time relationships for R- and S-methadone. Central, rapidly, and slowly equilibrating volumes of distribution of a 3-compartment model for S-methadone were estimated to be 46.1±7.0, 172.4±9.7, and 181.9±11.5 L, respectively; intercompartmental clearances to rapid and slow equilibrating peripheral compartments were11.0±2.0 and 0.44±0.06 L/min, respectively; and elimination clearance was0.078±0.01 L/min. Introduction of estimated proportionality constants (S:R) for distribution volumes (0.60±0.01), intercompartmental clearances (0.77±0.02) and elimination clearance (0.87±0.02) significantly reduced the OFV (-2LL) of the population pharmacokinetic model. Sex and *CYP2B6* genotype were significant covariates for elimination clearance and body weight was a significant covariate for the slow volume of distribution.

Conclusion: 3-compartment pharmacokinetics of R- and S-methadone differ and can be well described by proportionality constants applied separately to distribution volumes, intercompartmental clearances, and elimination clearance. These systematic differences among parameter estimates suggest the influence of chirality on protein binding and metabolism as well as the presence of significant rbc:plasma partitioning for methadone. *CYP2B6* genotype, but not that of *CYP2C19*, explains some of the interindividual variability in elimination clearance.

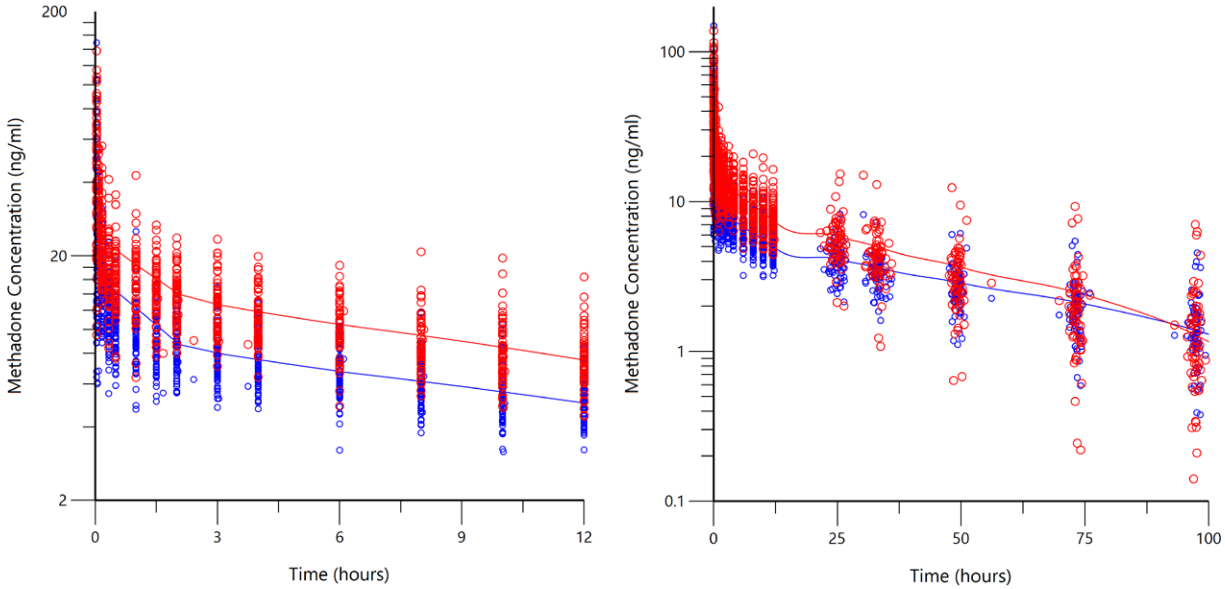

Figure 1. Observed plasma R-methadone (blue circles) and S-methadone (red circles) versus time for all 64 subjects. The left graph is for the first 0-12 hour, which highlights stereoselective differenecs in distribution and the right graph is for the full 0-96 hours. Red and blue solid lines represent the loess central tendencies.

Nitrous Oxide Exposure Alters Functional Connectivity in Medial Limbic Structures in Treatment-Resistant Major Depression

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Background

Nitrous oxide (N_2O) is an N-methyl-D-aspartate receptor (NMDAR) antagonist that has demonstrated promising therapeutic effects in several psychiatric disorders, including treatment-resistant major depressive disorder (TRMD). Similar to ketamine, N_2O's antidepressant effects are both rapid and sustained and often observed for days to weeks after a single dose, suggesting that N_2O produces lasting CNS changes that persist beyond its acute brain interactions. These lasting effects may be mediated via neural plasticity within brain networks and changes in correlated neural activity, i.e., functional connectivity. However, little is known how N_2O alters brain networks to confer antidepressant effects. This study employed serial resting-state functional magnetic resonance imaging (rs-fMRI) to compare the spatiotemporal effects of inhaled N_2O on brain functional connectivity in TRMD patients and non-depressed healthy controls (CNTL).

Methods

Approval was obtained from the Washington University School of Medicine Human Research Protection Office and registered on ClinicalTrials.gov (NCT02994433). Participant age range was 18-65, and exclusion criteria for TRMD/CNTL participants included severe medical/neurological disorders, psychosis, or severe personality disorders. The CNTL participants did not screen positive for MDD; TRMD participants had a ≥17 score on the Hamilton Depression Rating Scale (17 item) and failure to respond to ≥3 lifetime adequate dose/duration antidepressant treatments, with ≥1 nonresponse in the current episode. Employing serial resting-state functional magnetic resonance imaging (rs-fMRI), we compared spatiotemporal effects of inhaled N_2O on brain functional connectivity in TRD patients (n=14) and non-depressed healthy controls (n=16, CNTL). Participants received sequential, one-hour inhalations of either 50% N_2O/oxygen or air/oxygen (placebo), with sessions separated by at least one month in random cross-over order. BOLD-contrast rs-fMRI scans were acquired at three time points: pre-inhalation, 2 hours post-inhalation, and 24 hours post-inhalation. For rs-fMRI functional connectivity analyses, five *a priori* seeds in medial limbic structures targeted cortical networks implicated in major depression – the salience, anterior and posterior default mode, reward, and cingulo-opercular networks – and a dorsal nexus in the dorsal paracingulate region previously identified in MDD. Depression, dissociation, and psychosis assessments were made before and after inhalations.

Results

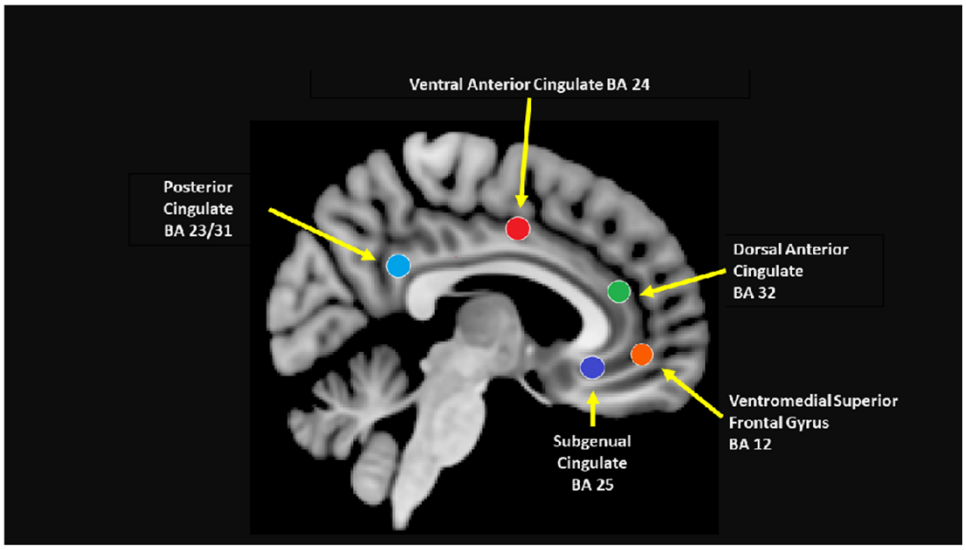
In TRMD patients, statistically significant functional connectivity *reductions* were observed in all seeded networks after N_2O exposure (**Fig 1**). N_2O progressively *decreased* connectivity in patients with TRMD but *increased* connectivity in healthy controls. In TRMD patients, each seeded network demonstrated post-exposure functional connectivity reductions in the dorsal paracingulate cortex ("dorsal nexus"). Of note, the subgenual cingulate seed in the TRMD cohort demonstrated considerably higher baseline connectivity vis-à-vis the CNTL cohort. However, following N_2O inhalation, this functional connectivity difference was reduced levels seen in the CNTLs. Further, a voxel-wise global analysis global correlation analysis (GCOR), which assessed functional connectivity changes across all brain regions, demonstrated changes in functional connectivity in medial prefrontal cortex, with exposure-related reductions in functional connectivity in TRMD participants and increases in CNTLs. There was a clinically significant greater reduction in depressive symptoms in the TRMD participants receiving N_2O, compared to placebo. Similar to other N_2O trials, significant placebo effects, as well as carry-over effects, were observed despite a minimal one-month separation between N_2O sessions.

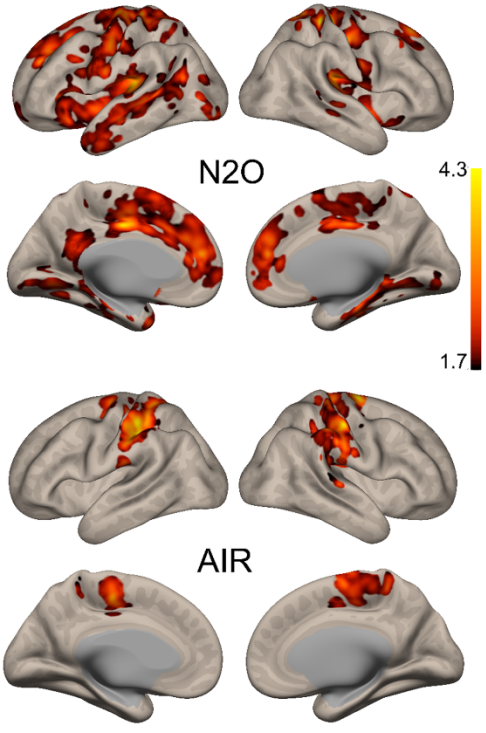
Conclusions

This study further elucidates neural mechanisms underlying the antidepressant properties of N_2O, supporting the notion that N_2O specifically alters mood-associated brain regions in the depressed brain state by reducing functional connectivity within these brain networks.

Figure 1. Seeds (top panel) and Changes in Functional Connectivity Observed Before and After N_2O (middle panel) and AIR (bottom panel).

Top Panel: *A priori* seeds were selected to compare pre-post exposure to N_2O and placebo. These five seeds targeting midline limbic structures probed networks known to be involved in mood regulation: the reward network (Brodmann's area BA 25), the cingulo-opercular executive network (midline dorsal cingulate, BA 24,red), the salience network (dorsal anterior cingulate, BA 32, green), and the anterior and posterior nodes of the default mode network (ventromedial prefrontal cortex, BA 12, orange, and posterior cingulate, BA31, cyan, respectively). Middle Panel: Changes in functional connectivity averaged across all 5 seeds comparing pre- to 2 and 24 hours post-N_2O exposure. There are notable changes in functional connectivity observed in the anterior and posterior portions of the cingulate cortex, hippocampal and parahippocampal regions, and insular cortex. Lower Panel: Changes in functional connectivity averaged across all 5 seeds comparing pre- to 2- and 24-hours post-placebo exposure. We observed markedly different spatial changes in functional connectivity, with changes limited to primarily parietal cortex and no involvement of the cingulate, hippocampus, insula or dorsal paracingulate gyrus.


Ventral Anterior Cingulate BA 24
Posterior Cingulate BA 23/31
Dorsal Anterior Cingulate BA 32
Ventromedial Superior Frontal Gyrus BA 12
Subgenual Cingulate BA 25


N2O
4.3
1.7
AIR

Opioids in treated and untreated obstructive sleep apnea: Remifentanil pharmacokinetics and pharmacodynamics

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Background: Patients with obstructive sleep apnea (OSA) are considered more sensitive to opioids and at increased risk of opioid-induced respiratory depression. Whether OSA treatment (continuous positive airway pressure, CPAP; or bilevel positive airway pressure, BIPAP) modifies this risk remains unknown. Greater opioid sensitivity may arise from altered pharmacokinetics or pharmacodynamics. This preplanned analysis of a previous cohort study of remifentanil clinical effects in OSA tested the hypothesis that pharmacokinetics and/or pharmacodynamics of remifentanil, a representative μ-opioid agonist, are altered in adults with treated or untreated OSA.

Methods: A single center, prospective, open-label, cohort study (ClinicalTrials.gov, NCT02898792) administered a stepped-dose, target-controlled remifentanil infusion (target effect-site concentrations 0.5, 1, 2, 3, 4 ng mL^{-1}) to awake adult volunteers (median 52 yr, range 23-70) without OSA (n=20), untreated OSA (n=33), and treated OSA (n=21). Type III (in-home) polysomnography verified OSA. Remifentanil plasma concentrations, end-expired CO_2, thermal heat tolerance, and pupil diameter (miosis) were assessed. Population pharmacokinetic (clearance, volume of distribution) and pharmacodynamic (miosis, thermal heat tolerance, end-expired CO_2) models were developed.

Results: Remifentanil clearance (median) was 147, 143, and 155 L h^{-1} (P=0.472), and volume of distribution was 19.6, 15.5, and 17.7 L (P=0.473) for subjects without OSA, untreated OSA, and treated OSA, respectively. Total body weight was an influential covariate on both remifentanil clearance and central volume of distribution. There were no statistically or clinically significant differences between the three groups in miosis EC_{50} or Emax, or the slopes of thermal heat tolerance or end-expired CO_2 vs remifentanil concentration. At a plasma remifentanil concentration of 4 ng mL^{-1}, in participants without OSA, untreated OSA, and treated OSA,

respectively model-estimated pupil area (12, 13, and 17% of baseline, P=0.086), thermal heat tolerance (50, 51 and 51°C, P=0.218) and end-expired CO_2 (47, 48, and 50 mmHg, P=0.257) were not statistically different between groups.

Conclusions: OSA (untreated or treated) did not influence remifentanil pharmacokinetics or pharmacodynamics (miosis, analgesia, respiratory depression). Results do not support the hypothesis that pharmacokinetics and/or pharmacodynamics of remifentanil, a representative μ-opioid, are altered in adults with treated or untreated OSA. Remifentanil dosing may not need adjustment for pharmacokinetic or pharmacodynamic considerations in OSA.

Intralipid in Action: A Case Study on Distinguishing Local Anesthetic Systemic Toxicity (LAST) from Serotonin Syndrome in Post-Operative Care

Presenting Author: Aishwary Adepalli, BA, University of Texas Health Science Center, San Antonio

Abstract:

Background/Introduction:

Local anesthetic systemic toxicity (LAST) and serotonin syndrome (SS) share overlapping symptoms, posing a diagnostic challenge. LAST arises from excessive local anesthetics, causing initial CNS excitation followed by cardiovascular collapse. SS results from serotonergic hyperactivity, leading to neuromuscular excitation, altered mental status, and autonomic instability. Distinguishing these conditions relies on understanding the temporal onset, associated medications/procedures, and subtle nuances in clinical presentation. Prompt differentiation is essential, as LAST treatment centers on supportive care and lipid emulsion therapy, while SS management may necessitate serotonin antagonists. Quick and accurate diagnosis can also help prevent unnecessary, potentially harmful, interventions.

Case Presentation:

We present the challenging case of a 70-year-old female patient who developed altered mental status, slurred speech, perioral numbness/tingling, severe shortness of breath, and hypotension in the post-anesthesia care unit (PACU) following left reverse total shoulder arthroplasty and open subpectoral biceps tenodesis. The patient had an interscalene peripheral nerve catheter in place infusing Ropivacaine 0.2% at 6 ml/hr. Initial concerns of LAST prompted cessation of the Ropivacaine infusion, and administration of 100 ml of Intralipid. Despite negative aspiration of catheter for blood, and a negative test dose for LAST, the patient's symptoms persisted, leading to further evaluations of differential diagnoses such as stroke, seizure, and pulmonary embolism.

Subsequent evaluations showed findings of large hiatal hernia and cardiomegaly, complicating the clinical picture with respiratory distress which necessitated management with CPAP. The case was further complicated by transient blood pressure elevations, and possible seizure activity suggested by facial and oral movements resembling tardive dyskinesia. However, it was confirmed that no medications known to cause tardive dyskinesia had been administered. Despite initial concerns for LAST, the administration of Intralipid, and removal of the interscalene catheter, the patient's symptoms persisted, leading to broader differential diagnoses including seizure, given the patient's history, and the potential for pharmacological interactions like serotonin syndrome suggested by the patient's collection of symptoms.

Discussion:

LAST is diagnosed when predisposed patients exhibit consistent symptoms. Risk factors include advanced age, pediatric status, hepatic dysfunction, cardiac conditions, pregnancy, and metabolic syndromes. Symptoms involve neurological changes (altered mental status, agitation, perioral

numbness, seizures) and cardiovascular instability (bradycardia, hypotension, arrhythmia, respiratory arrest).

Hypertension and tachycardia in this patient reduce the likelihood of LAST as the primary cause. Despite the presence of perioral numbness and respiratory distress, the multifaceted origins suggest other causes. Excluding LAST involves administering Intralipid, catheter aspiration, and an epinephrine test dose. In this case, these steps were properly conducted, but the patient's condition did not improve, suggesting another causative underlying mechanism.

The mainstay treatment of LAST includes supportive measures including airway management, cardiocirculatory support and seizure prevention. More recently, the administration of lipid emulsion via intravenous route has been theorized to improve outcomes. The hypothesized mechanism of using lipid emulsions in LAST include the shunting of local anesthetic from organs such as the heart and the brain to more peripheral organs involved in detoxification such as the liver and musculature. This is protective due to the decreased toxicity and the increased metabolism and sequestration of the local anesthetic away from vital organs. As such, lipid emulsions should be administered quickly when suspecting LAST in a patient.

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TITLE PAGE

Comparison of the qCON-qNOX and Bispectral Index (BIS) responses to anesthesia and noxious stimuli during surgery

AUTHORS:

Jason Hager MD[1], Ofelia Loani Elvir-Lazo MD[1], Roya Yumul MD, PHD, CHSE[1-2], Ruby Wang MD[1], Ashley Fejleh MD[1], Jason Hager MD[1], Paul F White PhD, MD. FANZCA[1,3]

ABSTRACT

BACKGROUND: Monitoring a patients' level of anti-nociception during surgery can minimize autonomic and muscular responses to intraoperative stimuli. Electroencephalogram (EEG)-based tools like Bispectral Index (BIS) (Covidien, Boulder CO. USA) and qCON (Quantium Medical, Spain) provide insights into depth of hypnosis, while qCON-qNOX is designed to assesses nociception during surgery. The purpose of this observational study was to evaluate the correlation between the qCON and BIS indices for evaluating the depth of hypnosis, and the qNOX as a monitor for assessing the responses to noxious surgical stimuli.

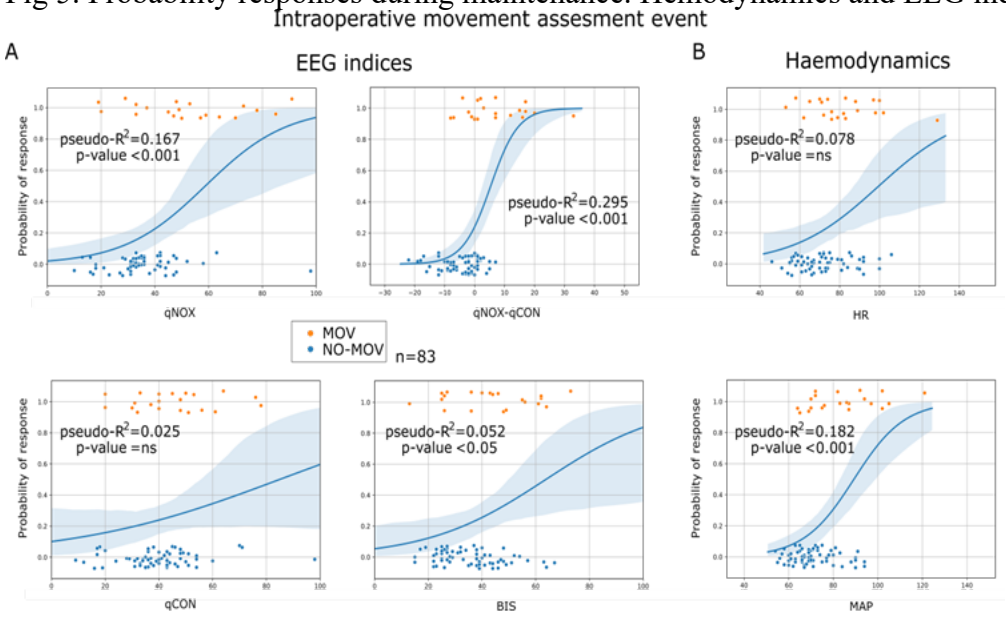
METHODS:
Prior to induction, 59 consenting adult patients undergoing general anesthesia with a laryngeal mask airway (LMA) were monitored using BIS and qCON-qNOX electrodes. Monitoring continued throughout surgery with the surgical and anesthetic teams both blinded to both the BIS and qCON-qNOX values. Responses to LMA insertion and removal, as well as noxious events related to surgery: skin preparation, local infiltration, incision, and suturing were recorded.

RESULTS:
The prediction probabilities (Pk) in the Bland-Altman analysis show significant concordance among comparisons of qCON vs BIS (Pk=0.821, $p<0.01$), qCON vs qNOX (Pk=0.827, $p<0.01$), and qNOX vs BIS (Pk=0.743, $p<0.05$) during anesthesia. During LMA insertion, there were no significant differences in heart rate (HR), mean arterial pressure (MAP), BIS, or qCON values in patients who moved vs. those who did not move; however, qNOX and qNOX-qCON values were significantly higher ($p<0.05$) in “movers” compared to “non-movers”. During the aforementioned stimulating intraoperative events there was not a significant difference in qCON when comparing movers and non-movers, but HR, MAP, BIS, qNOX, and qNOX-qCON were significantly higher ($p<0.05$) in movers compared to non-movers. These findings suggest that qNOX can accurately serve as a surrogate for sympathetically mediated responses to noxious stimuli. Probability response analysis showed that qNOX-qCON, followed by qNOX, was the most accurate predictor of intraoperative movement and the remaining aforementioned parameters were less predictive.

CONCLUSION:
This observational study confirms a strong correlation between BIS and qCON in monitoring hypnotic levels and validates qNOX for anti-nociception monitoring. qNOX appears sensitive to anti-nociception levels independently from qCON, suggesting increased qNOX levels may signal

inadequate analgesia. These findings underscore the importance of separately monitoring hypnosis and nociception throughout surgeries, particularly during noxious stimuli. Anesthesia providers should integrate hypnotic and anti-nociceptive monitoring alongside hemodynamic measures to ensure optimal anesthetic depth.

Fig 5. Probability responses during maintenance. Hemodynamics and EEG indices.



Morphine and Hydromorphone Pharmacokinetics in Human Volunteers: Population-based Modeling of Inter-individual and Opioid-related Variability

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ABSTRACT

Background: Morphine and hydromorphone have differing effect and side effect onset, magnitude, and duration. Differences between opioids in their interindividual variabilities in pharmacokinetics and pharmacodynamics may influence rational drug selection. Crossover drug studies can provide more informative interindividual variability data than parallel group studies. Using data from a crossover study of intravenous morphine and hydromorphone in healthy volunteers, we tested the hypothesis that morphine and hydromorphone differ in their inter-individual pharmacokinetic variability.

Methods: Arterial opioid and metabolite concentrations from a randomized crossover study in 51 volunteers receiving a 2-h IV infusion of hydromorphone (0.05or 0.1 mg kg^{-1}) or morphine (total 0.1 or 0.2 mg kg^{-1}) 1-2 weeks apart were evaluated with a three-compartmental model for parent opioid and incorporating glucuronides using population modeling (NONMEM). The primary outcome was interindividual variability in pharmacokinetics, based on the coefficient of

variation (%CV) of individual model parameters, calculated as $\sqrt{[\exp(\omega^2) - 1]} \times 100$ where ω^2 is the interindividual variability.

Results: Data were analyzed per drug and in a combined morphine-hydromorphone model. Both analyses indicate that interindividual variabilities for hydromorphone and morphine were comparable with %CV ranging from 9 to 31% for structural model parameters (combined analysis). Similarly, additive and relative residual errors had comparable variabilities, 20 to 40% and 72 to 87%, respectively for morphine and hydromorphone (combined analysis).

Conclusions: Morphine and hydromorphone did not differ significantly or clinically meaningfully in their interindividual pharmacokinetic variability. Interindividual pharmacokinetic variability does not appear a meaningful consideration in the choice between these two opioids.

Pain activation and resting-connectivity are altered by intravenous lidocaine: A functional MRI in healthy young adults

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Introduction: Intravenous lidocaine infusions have been increasingly employed as a means to provide opioid-sparing pain relief. Persistence of these effects for hours to days after termination of the infusion suggests the involvement of higher-brain processes rather than direct sodium channel blockade in the periphery as the mechanism for systemic lidocaine. Despite these unknowns, little attention has been focused on the brain response to systemic lidocaine administration in humans. This study aimed to quantify the effects of lidocaine infusion on functional MRI (fMRI) measures of the brain response to acute painful stimulation and functional connectivity.

Methods: Data is reported from 27 volunteers (13 male, range 20-55 years, mean 31.4 years) in an open-label observational study. An electric nerve stimulator was connected to the left index finger and titrated to a subjective pain rating of 7/10 intensity using a verbal numerical rating scale. After connection to standard monitors and initiation of a saline carrier infusion, participants underwent 3 T MRI. An acute pain task with five 10 s painful electric nerve stimulations was followed by an 8-minute resting-state scan. In both scans, blood oxygen-level dependent weighted fMRI images were obtained every 800 ms with 2.1 mm isotropic spatial resolution. Lidocaine was then dosed to achieve an effect site concentration of 1.5 mcg/mL using stanpumpR (//stanpumpr.io/). After steady-state was predicted, the pain task and resting-state fMRI scans were repeated under the lidocaine condition. Pain ratings obtained after each pain stimulation period were compared with the Related-Samples Wilcoxon Signed Rank Test. FMRI task analysis was done with FSL (//fsl.fmrib.ox.ac.uk/) using a paired mixed-effects model. Resulting group average maps were thresholded for an adjusted $p < 0.05$, after a cluster significance threshold of $Z > 2$, correcting for multiple comparisons. Connectivity analysis was performed with Conn toolbox (//web.conn-toolbox.org/) using a region-of-interest (ROI) to ROI approach. ROI-level inferences were based on parametric multivariate statistics, combining the connection-level random-effects statistics across all connections from each ROI with the familywise false-discovery rate set at $p < 0.05$.

Results: The total dose of lidocaine was 1.8 +/- 0.1 mg/kg (range 1.7 to 2.0 mg/kg) administered over a mean time period of 27 minutes (range= 21-33 min). No subjects experienced sedation or lasting side effects. Pain intensity scores (mean, standard deviation) at baseline (6.8, 0.8) were slightly higher than under lidocaine (6.4, 1.0), with a mean rating difference of 0.44 (95% confidence interval 0.01 to 0.88, p=0.045). Pain unpleasantness scores at baseline (6.3, 1.6) were higher than under lidocaine (5.7, 1.7), with a mean rating difference of 0.56 (95% confidence interval 0.11 to 1.0, p=0.016). Brain fMRI responses to pain were decreased under lidocaine (Fig. 1) in the insula, cingulate, left thalamus, bilateral primary somatosensory cortex, left cerebellum, bilateral putamen, right primary motor cortex, medial prefrontal cortex, and a small portion of the left hippocampus. Functional connectivity was predominantly decreased both within and between hemispheres (Fig. 2), with predominance of temporal lobe ROIs identified, However, connectivity changes were also seen in frontal, occipital, parietal, and cerebellar areas, as well as deeper brain structures such as the putamen, amygdala, hippocampus, and cingulate.

Conclusions: Intravenous lidocaine at an effect site-concentration of 1.5 mcg/mL significantly affected fMRI measures of brain function. Lidocaine was associated with broad reductions in fMRI response to experimental painful stimulation in regions commonly involved in acute pain processing. Lidocaine modulated whole-brain functional connectivity, predominantly decreasing long-range connectivity with some predominance in temporal lobe structures. Small but significant decreases in pain ratings were also observed. This suggests that lidocaine modifies the pain experience by modulating both primary sensory processing and affecting higher-level processing of the noxious stimulus. This work lays the foundation for better understanding of systems-level neuroscience changes that occur with lidocaine, working towards refining the clinical use of this important opioid-alternative analgesic agent.

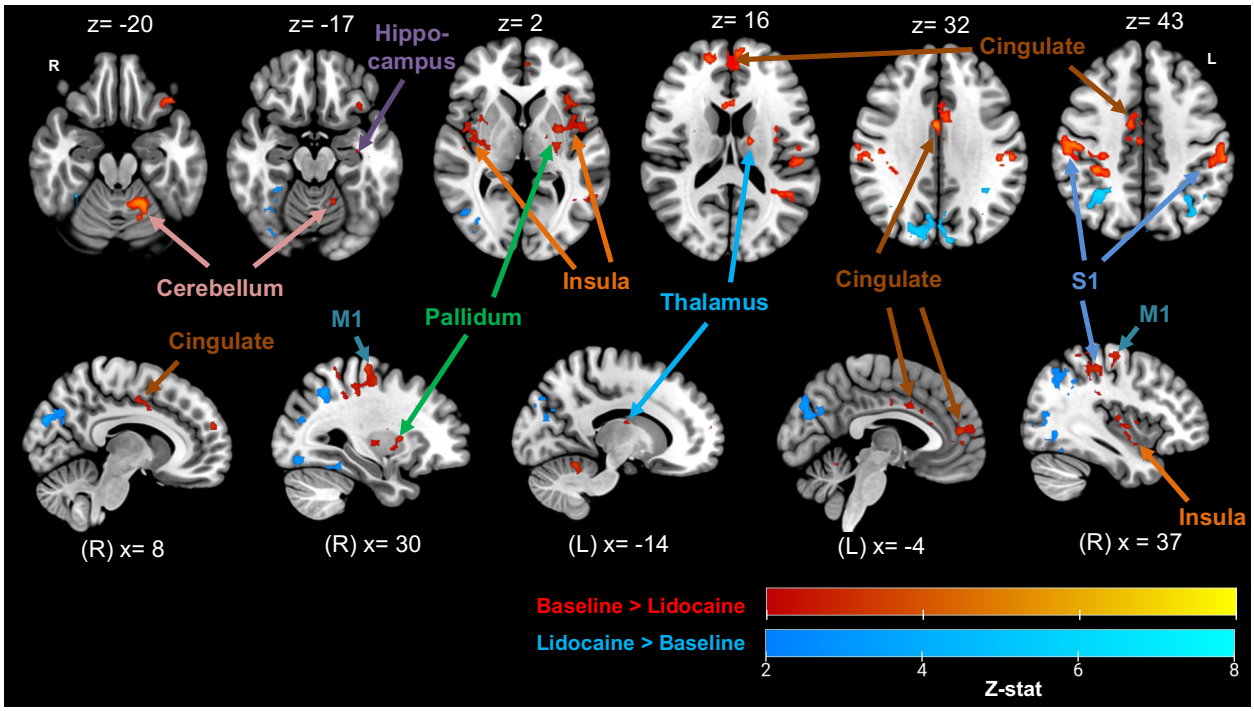

Fig. 1. Pain task functional MRI differences for baseline vs. lidocaine condition, averaged across subject. These are in radiologic orientation (right brain on left side of image). Color bars indicate strength of statistical difference, cluster corrected (for multiple comparisons) and thresholded at Z> 2, p< 0.05. Slice numbers refer to coordinates in the MNI-152 standard space template. S1= primary somatosensory cortex, M1= primary motor cortex, R= right, L=left

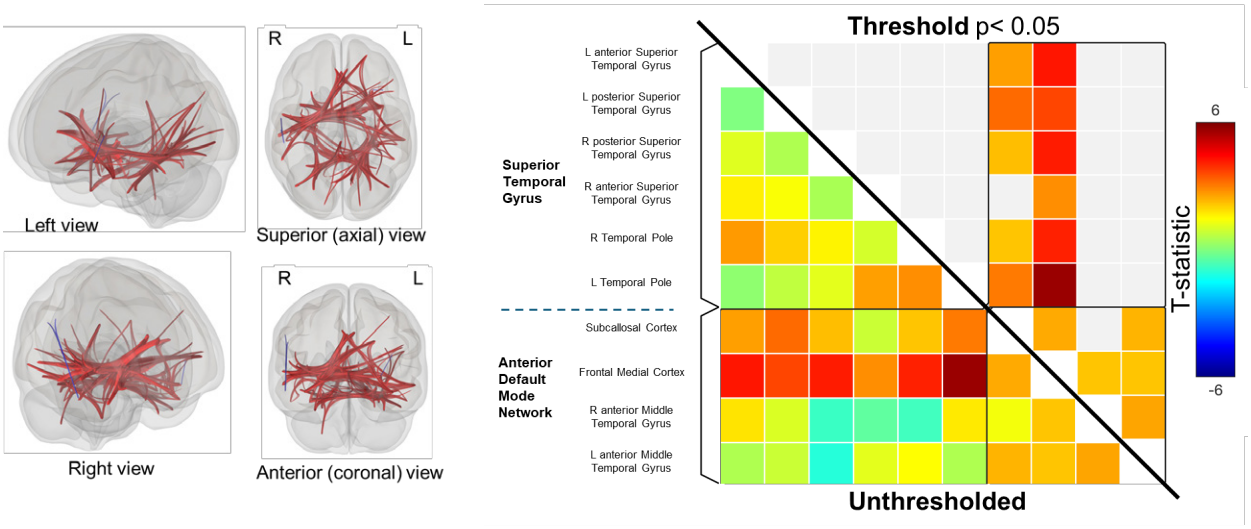

Fig 2. Group differences in resting connectivity, using hierarchical clustering with multivariate pattern analysis. Left panel shows anatomical locations; right panel shows strength of connectivity change, with unthresholded results in the bottom-left half of the grid and significant connectivity changes (FDR-p < 0.05) in the top-right half of the grid. L= left, R= right

Monitoring the effect of fentanyl on the Stress Activity (SA) index during general anaesthesia using EEG and Heart Rate Variability.

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Introduction: The surface electroencephalogram (EEG) is a non-invasive tool that allows for real-time assessment of brain electrical activity. Brain activity (BA) is derived from the EEG signal, allowing for the observation of the patient's neurological state, while stress activity (SA) is defined by parameters from both the EEG and heart rate variability (HRV), as the combination of these can reveal changes in brain function and the body's autonomic response that may not be evident if monitored in isolation. Variations in these indices may reflect the effects of anesthesia, the impact of the surgical procedure, and recovery in the post-anesthesia care unit (PACU).

Method: This analysis included data from 13 patients who participated in a randomized controlled trial ("Recovery of Ventilation after General Anesthesia for Robotic-Assisted Laparoscopic Nephrectomy or Prostatectomy: The Effect of Oxygen Supplementation"; Institutional Review Board, #63878) at Stanford Health Care, and were scheduled for surgery under general anesthesia. Surface EEG was recorded with the CoreSys One monitor (CoreSys Health, Barcelona, Spain) at five key points during the perioperative process: before anesthesia (awake), at the onset of anesthesia, at the end of the surgery, upon admission to the PACU, and at discharge from the PACU. From these data, two indices were calculated: BA and SA. The BA index assessed general neuronal activity, while the SA index measured the stress response. The values of both indices were recorded and **analyzed at each phase** to identify significant changes. Additionally, the exact time of the first dose of fentanyl administered during the surgery was recorded to evaluate its potential impact on SA.

The first dose of fentanyl administered during the surgery was identified, and the SA index was analyzed in a 5-minute interval before and 5 minutes after administration to **determine significant changes in SA following fentanyl administration**. The Jarque-Bera test was conducted to check if the data followed a normal distribution; if so, a Student's t-test was used, otherwise, the Wilcoxon test was applied **to evaluate significant differences between SA before and after fentanyl administration.** For the SA and BA indices, the Kruskal-Wallis statistical test was employed to identify significant differences **among the 5 perioperative states** and to assess the effects of anesthesia on brain activity and stress. Finally, to analyze the data related to BA, SA, and fentanyl administration, medians were calculated and results were presented in boxplots, determining the interquartile range to evaluate data dispersion.

Results: The results show that the data before and after the administration of fentanyl follow a normal distribution, according to the Jarque-Bera test. Therefore, a Student's t-test for dependent samples was performed, yielding a p-value <0.0001, which indicates a significant difference in SA before and after fentanyl administration. Additionally, the Kruskal-Wallis test revealed significant differences in the BA and SA index ($p < 0.0001$) among the five perioperative states.

Figure 1 shows the median of brain activity (BA) at different stages: while the patient was awake, at the onset of anesthesia, at the end of surgery, upon admission to the PACU, and at discharge from the PACU. During the awake state, BA was 95. At the onset of anesthesia, there was a significant decrease, reaching a minimum of 45, due to the effects of anesthetic agents that reduce neuronal activity. As the surgery progressed, BA increased slightly to 61, which could indicate a gradual decrease in the anesthetic effect or preparation for recovery. Upon admission to the PACU, brain activity recovered considerably to 93, approaching normal levels. Finally, at discharge from the PACU, BA stabilized at 89, indicating that brain function began to normalize as the effects of anesthesia wore off [1].

Figure 2 shows that SA decrease markedly at the onset of anesthesia (58) and reach their lowest point at the end of surgery (42), reflecting the suppression of the stress response by anesthesia. However, upon arrival at PACU, SA returns to maximum levels (99), remaining high at discharge from PACU, which could be due to factors such as postoperative pain, discomfort, or anxiety related to recovery [2]. Figure 3 shows that the median of stress activity (SA) was 98 five minutes before the administration of the first dose of fentanyl (100 mcg) and decreased to 63.5 five minutes after. This reduction indicates that fentanyl, by acting on opioid receptors in the brain and spinal cord, has been effective in relieving pain and providing sedation. Fentanyl not only reduces pain perception but also modulates the body's response to surgical stress, resulting in a decrease in SA and a calmer and more stable patient response during surgery. This pattern highlights the effectiveness of fentanyl in improving the overall patient condition and emphasizes the importance of continued monitoring of stress activity and other parameters to ensure that the surgery is effective and safe [3].

Conclusion: Monitoring of brain activity (BA) shows a significant decrease at the onset of anesthesia, followed by a recovery during the post-anesthesia care unit (PACU) phase. On the other hand, stress activity (SA) decreases significantly after the administration of the first dose of fentanyl. Statistical analyses confirm these observations, with significant differences in p-values (<0.05).

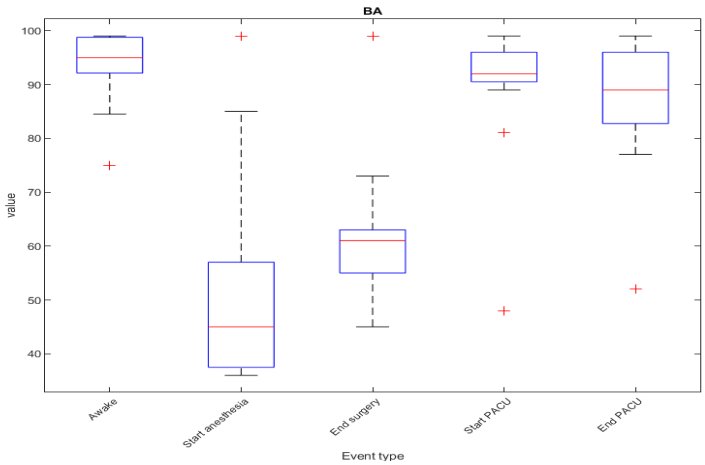

Figure 1. Brain Activity During the Perioperative Period

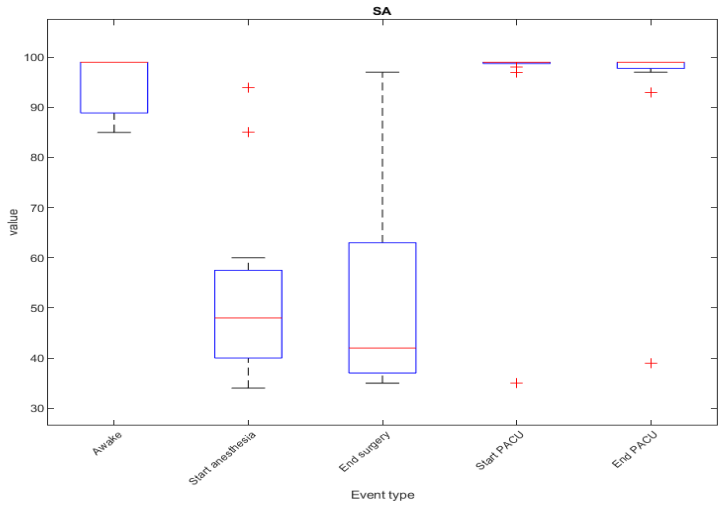

Figure 2. Stress Activity During the Perioperative Period

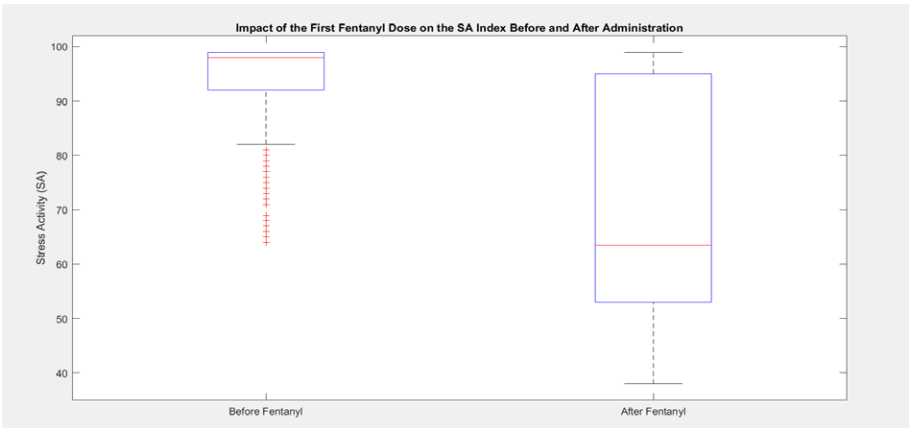

Figure 3. Effect of the First Dose of Fentanyl on Stress Activity During Surgery

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Pharmacological Effects of a New Inhaled Anesthetic in Fischer-344 Rats

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Background/Introduction: There are numerous characteristics of the ideal inhalational anesthetic, including potency, low blood:gas solubility, inflammability, and resistance to degradation and metabolism, among others. We have identified a novel compound that holds promise as an inhalational anesthetic. This compound is a member of the class of 1,3-dioxolanes, heterocyclic acetals which have a five-member ring structure, with two oxygens in the ring at the 1,3 positions. We studied *trans*-2,4,5-trifluoro-2-trifluoromethyl-1,3-dioxolane (EXP-GA-23A), a halogenated dioxolane that has saline:gas and oil:gas solubility characteristics similar to isoflurane. We determined the potency of EXP-GA-23A to produce immobility in response to noxious stimulation in rats, and its effects on blood chemistries and hematology (to determine any organ toxicity and fluoride levels to determine extent of metabolism). For comparison, we also studied a group of rats anesthetized with sevoflurane.

Methods: Fisher-344 rats (N=6) were anesthetized in acrylic cylinders using a calibrated vaporizer that delivered EXP-GA-23A. Anesthetic requirements were determined by adjusting the EXP-GA-23A concentration (measured using gas chromatography), and applying a tail clamp to elicit gross, purposeful movement. The EXP-GA-23A

concentration was adjusted in an up-and-down method to find the concentrations that permitted, and prevented, movement in response to the clamp; the minimum alveolar concentration (MAC) was the median concentration, as calculated using logistic regression. After 120 minutes of anesthetic exposure, a laparotomy was performed and the rat exsanguinated. Blood chemistry, hematology and fluoride levels were determined. Another group of rats (N=5) were anesthetized with sevoflurane for comparative purposes.

Results: Anesthetic requirements for EXP-GA-23A were 2.1 ± 0.1% (mean, SEM); sevoflurane requirements were 3.4 ± 0.1%. There were no clinically meaningful differences in blood chemistries or hematology values between the two groups. The fluoride concentrations in four of six EXP-GA-23A rats were below the limit of detection (0.05 µg/ml), while two rats had values of 0.051 and 0.057 µg/ml, respectively. The fluoride concentration was 0.24 ± 0.02 µg/ml in the sevoflurane-anesthetized rats. Spontaneous motor activity was not observed in any of the rats. Overall, the rats appeared to tolerate the two-hour exposure to EXP-GA-23A and sevoflurane.

Conclusions: EXP-GA-23A appeared to be well tolerated with no obvious organ toxicity after two-hour exposures. The fluoride concentrations were less than those found with sevoflurane, suggesting minimal metabolism. EXP-GA-23A shows potential as a new inhalational anesthetic.