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The Impact of High Oxygen Levels on Cerebral Perfusion

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23 MAR 2022

Cleared, 88PA, Case # 2019-1752, 01 May 2019.

Disclosure Information

Dr. Ryan Mayes

- I have no conflicts to report.
- I have no financial relationships to disclose.
- I will not discuss off-label use and/or investigational use in my presentation.
- The views expressed are those of the author and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, or the U.S. Government.

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Background

- Tactical aviation presents many environmental challenges to physiology
  - Hypobaria → Hypoxia
  - Secondary: VGEs, DCS
- To combat the threat of hypoxia, modern US military fighter jets employ oxygen schedules that deliver O_2 at relatively high levels
  - Sea-level $ppO_2 \approx$ 160 mmHg.
    - At 8000 ft, ambient $ppO_2 \approx$ 120mmHg
  - US Military Fighters fly with FiO_2 (fraction of inspired oxygen) ranging from 40-100%
    - At 8000 ft, military O_2 schedules deliver $ppO_2 \approx$ 230-574 mmHg
- These military O2 schedules are built to protect against hypoxia, but hyperoxia is not without consequence.
  - Previous small studies have shown drops in cerebral perfusion due to hyperoxia
- Hypoxia has been studied extensively, but hyperoxia has not been well-studied
  - Defining the impact of hyperoxia-induced reductions in CBF is necessary to develop strategies providing maximal neuroprotection without conferring incidental risk

Courtesy of Dr. Ryan Mayes

Lambertsen, C.J., *et al*. Oxygen toxicity; effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. *J Appl Physiol* **5**, 471-486 (1953).

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Study Objectives

Goal: characterize duration and specificity of precipitous hyperoxia-related reductions in CBF

Approach: in the absence of other flight-related operational stresses, we:

1) employed magnetic resonance imaging (MRI) with arterial spin labeling (ASL) during exposure to 21% FiO2 and at four time points during a sustained 30 minute exposure to 100% FiO2.
2) Measured ventilation and circulatory acid-base status to inform our data analyses and interpretations.
3) Measured cognitive performance and cortical electroencephalographic activity at both 21% and 100% FiO2.

Courtesy of Dr. Michael Decker

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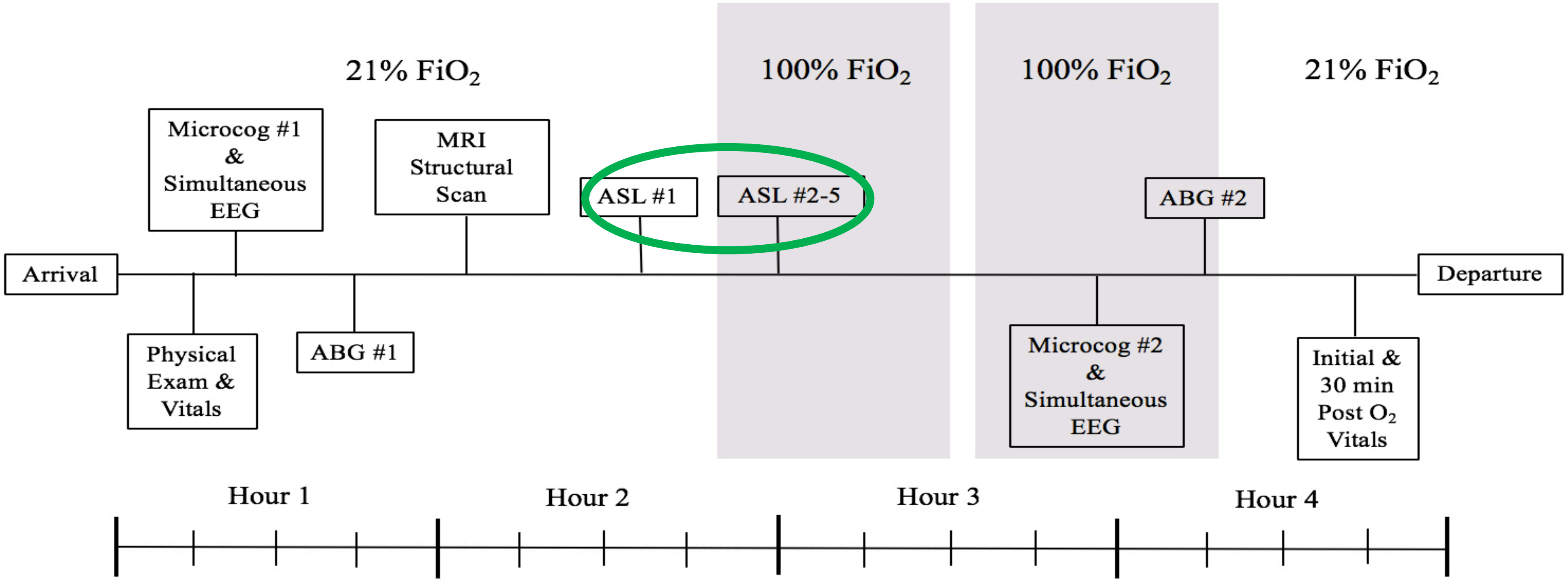
Study Design

- **Cerebral Blood Flow (CBF)**



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Results: Subject Demographics

- Sample consisted of:
  - Altitude-experienced DoD Active Duty officers & enlisted
  - Altitude-experienced civilians
  - Altitude-naïve subjects

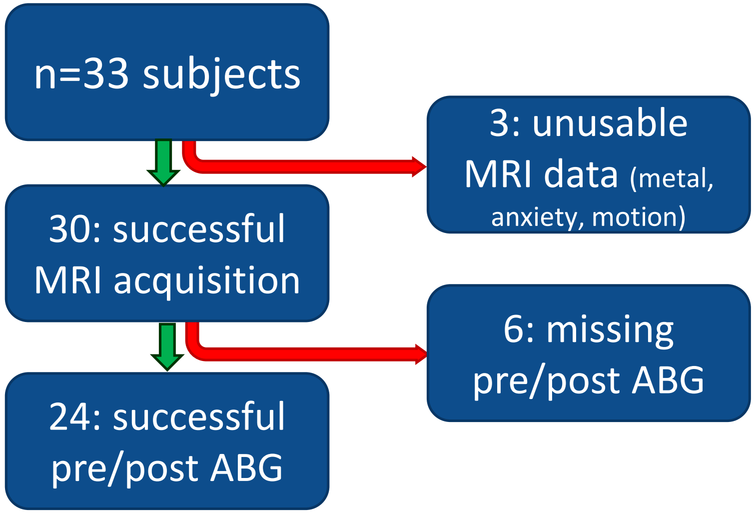

Table 1

Sex	Age	BMI	Occupational status AD = Active Duty Military; C= Civilian	Hypobaria with hyperoxia	Hypobaria with hypoxia	Hypobaria exposure with both hyperoxia and hypoxia	No history of hypobaria or hypoxia
Males n =17	43.29 ± 2.78	27.04 ± 0.66	AD=8, C=9	N=6	N=3	N=5	N=3
Females n =13	33.08 ± 4.04	25.83 ± 1.61	AD=5, C=8	N=4	N=1	N=1	N=7
2 tailed significance	p=0.04	p=NS					

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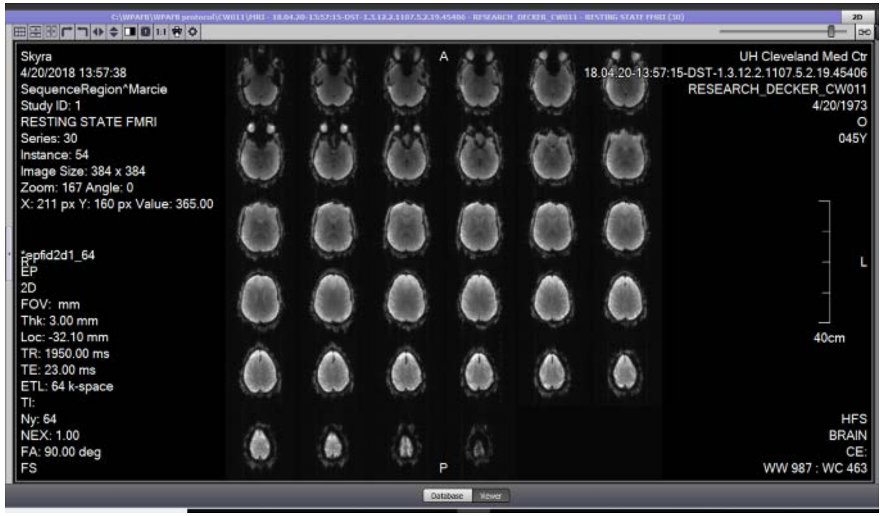
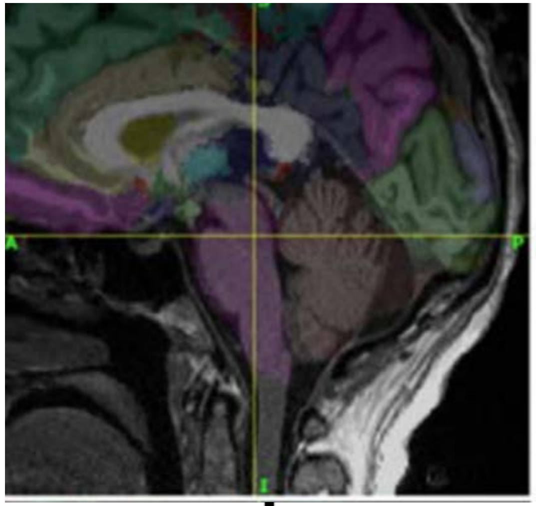
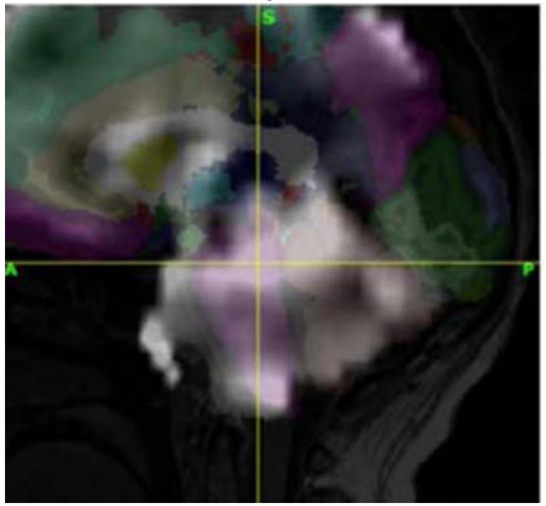
Arterial Spin Labeling Methodology

Courtesy of Dr. Michael Decker

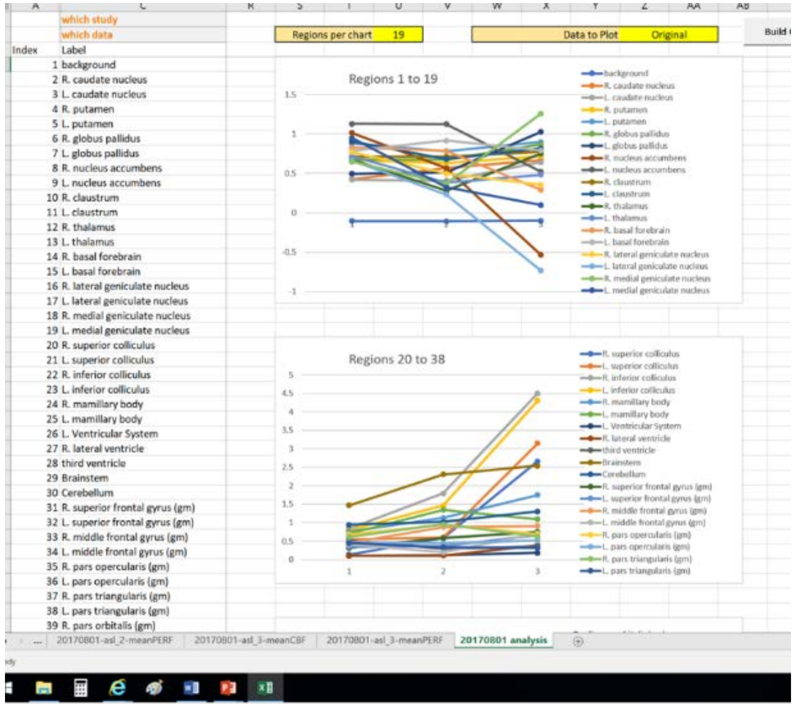


The cerebral perfusion images produced by Scanner





Perfusion image co-registered with anatomical image



Changes in perfusion are quantifiable between baseline and experimental conditions

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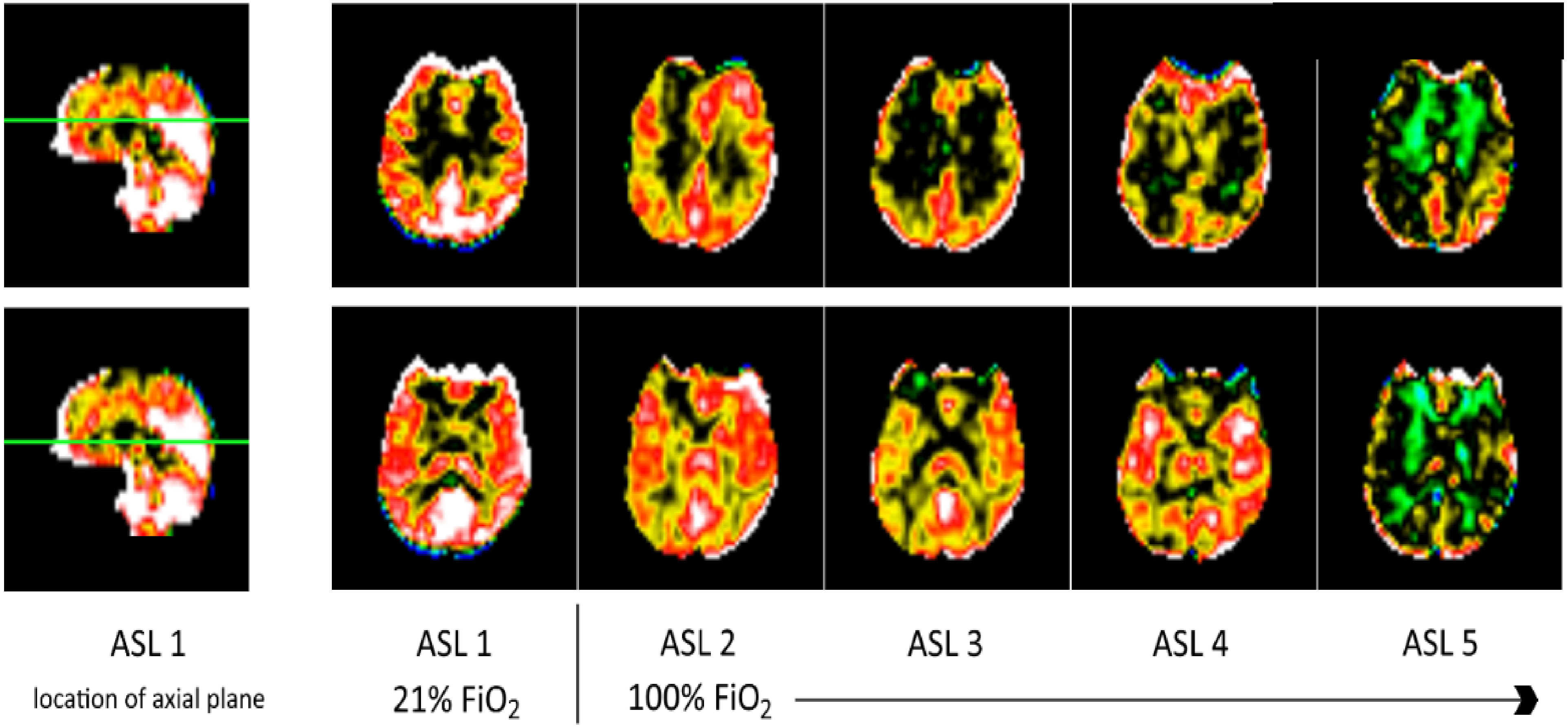
Results: Translating ASL to CBF



- These maps reveal reductions in CBF between PASL #1 @ 21% FiO2 and subsequent serial PASL sequences following onset of 100% FiO2.
- ASL 1-location of axial plane – is a sagittal cross section illustrating the neuroanatomical location of the coronal sections of ASL 1-ASL 5.
- This figure is positioned under the chart to facilitate comparisons of mean CBF values with actual changes we observed.

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Results – Cerebral Perfusion with 100% O_2

I. With 21% O_2: Group values (N=30) of CBF at 21% FiO2

ASL #1: 48.84 ± 2.35 milliliters per minute per 100 grams of tissue (ml/min/100g),

II. With 100% O_2: Marked reduction in CBF in <u>every study participant</u> (30/30). Following onset of 100% FiO2

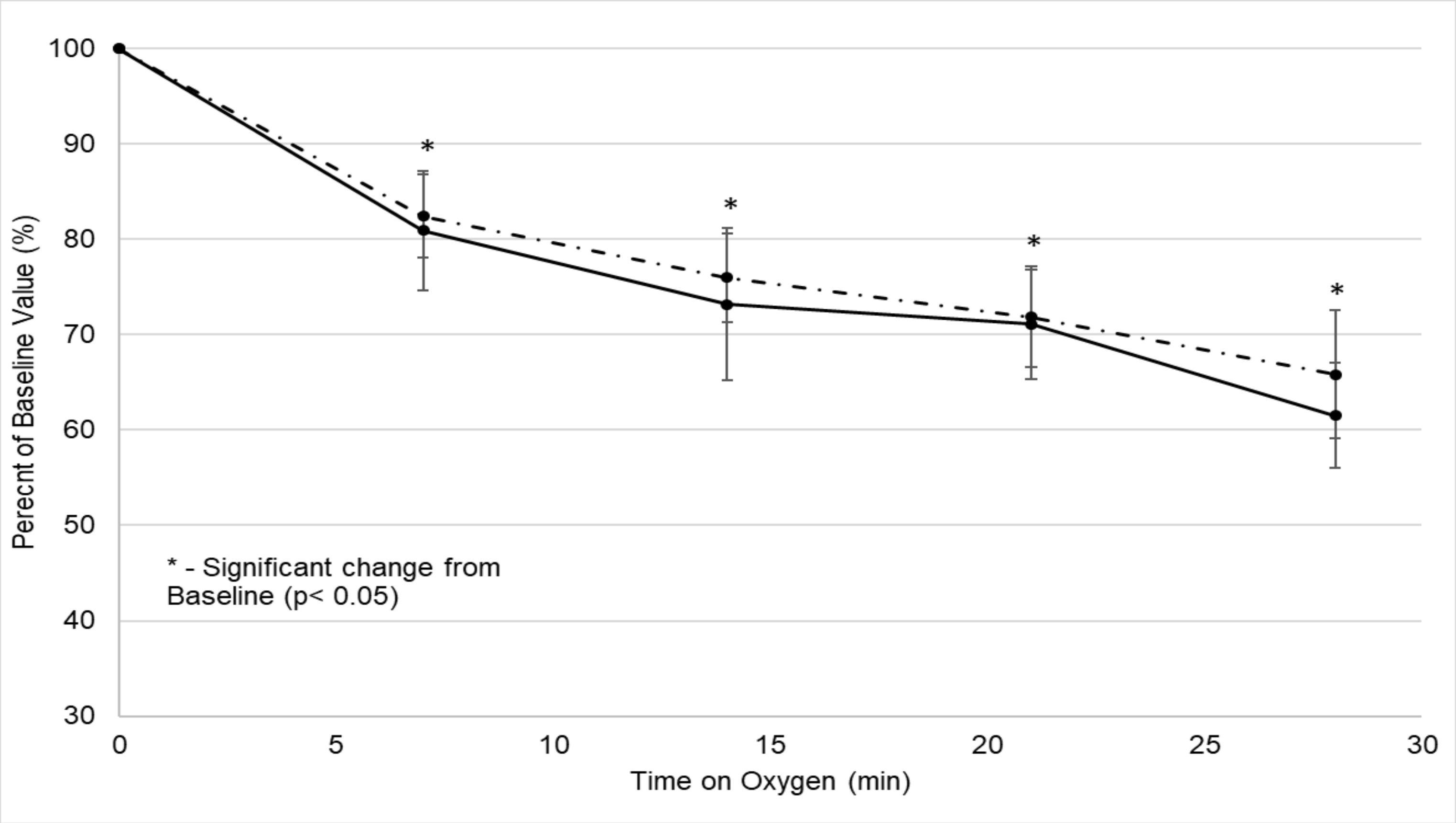
a) ASL #2: mean CBF values had fallen by 18%

b) ASL#5: CBF continued to fall to 63% of baseline at the final measurement (28-minute time point).

Percent change in cerebral perfusion during inspiration of 100% oxygen at 1 ATM.

Each ASL measurement required ~ 5 ½minutes, followed by a 1 ½ minutes in which EEG was acquired.

Data points are at 7 minute intervals



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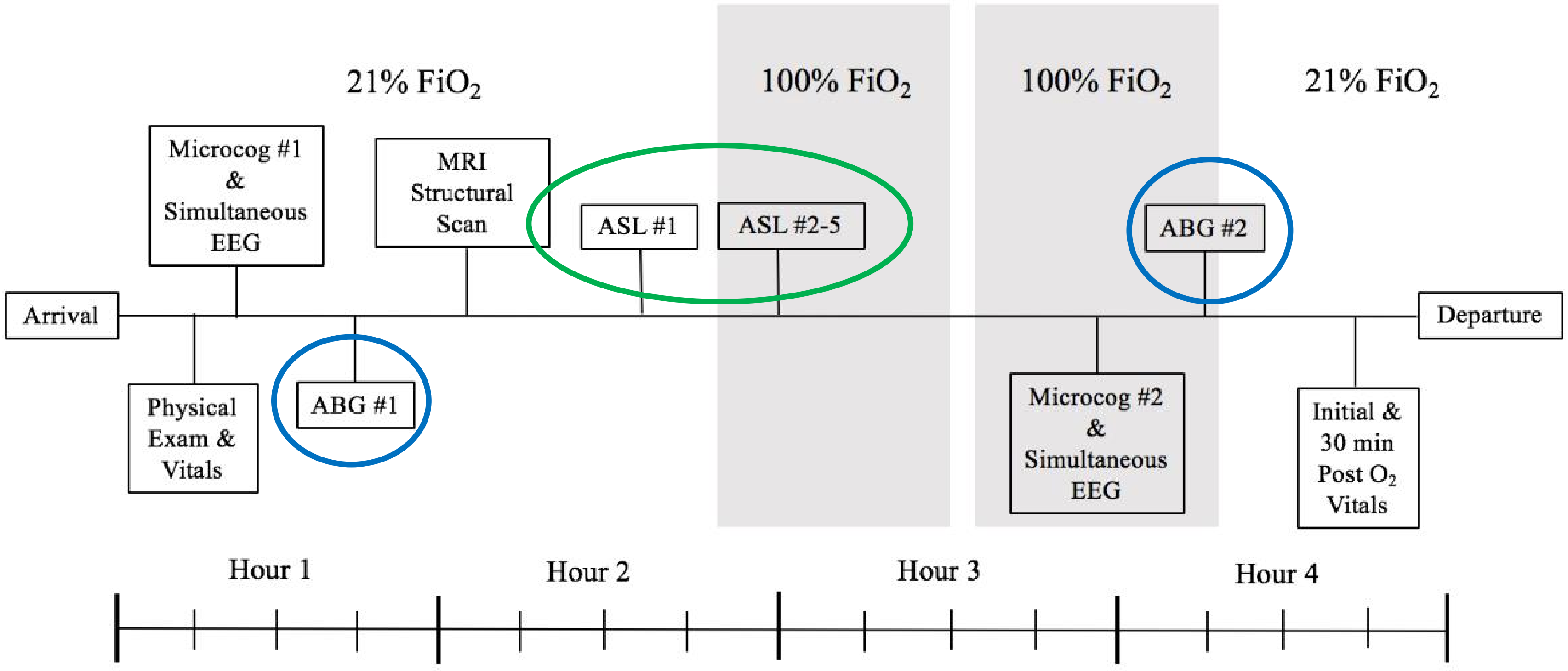
Study Design

- Outcomes discussed:
  - ABG values to determine acid-base physiology with ASL derived values of CBF
  - Heart Rate
  - Respiratory Rate

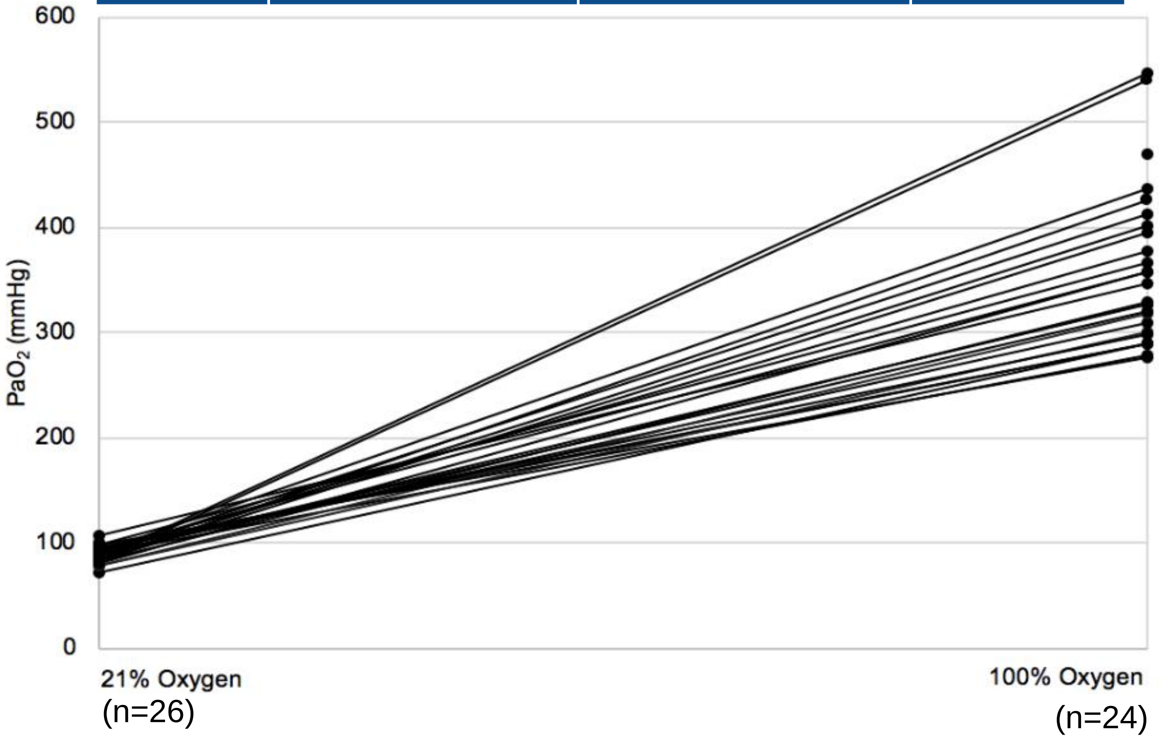


Source: Decker Lab

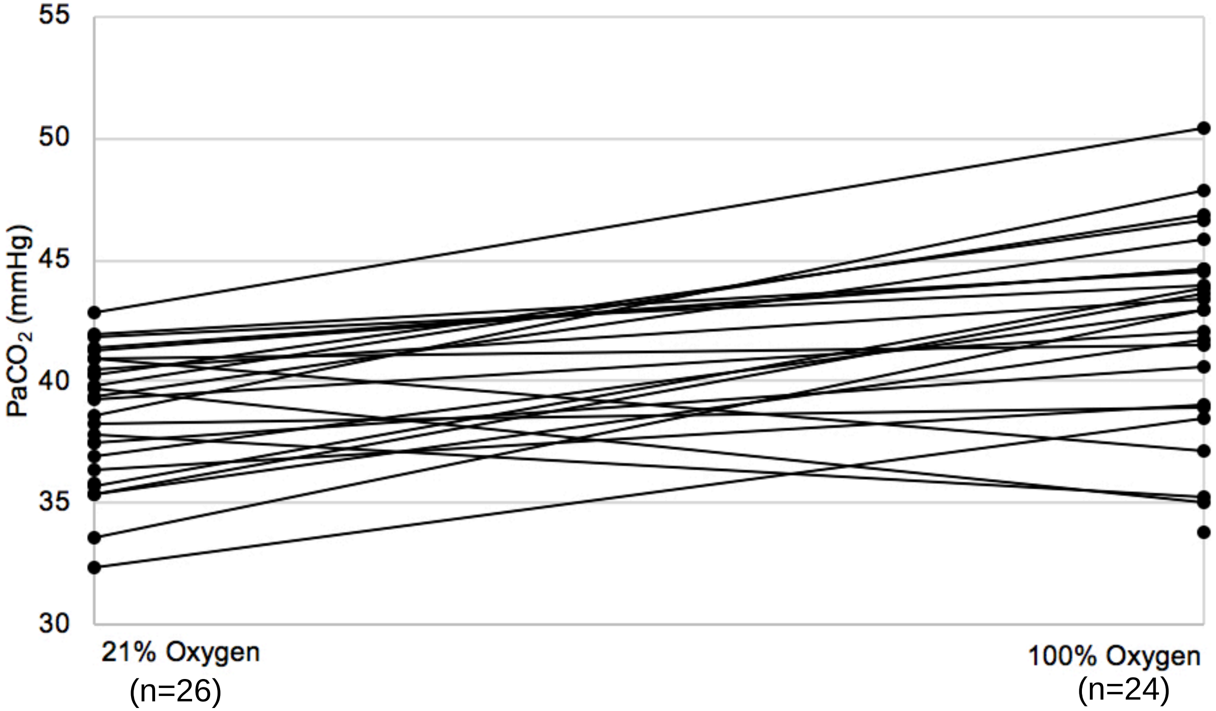
Arterial blood gases obtained in n=26 pre-MRI and n=24 post MRI.

Not all attempts at ABG were successful

PaO_2	21% FiO2 88.96 ± 1.55	100% FiO2 358.38 ± 15.24	$p < 0.001$



$PaCO_2$	21% FiO2 38.67 ± 0.57	100% FiO2 42.58 ± 0.79	$p < 0.001$



PaO_2 values significantly increased during 100% FiO_2

$PaCO_2$ increased in many participants, decreased in some or remained almost unchanged in others.

No impact of sex upon $Pa0_2$ or $PaC0_2$

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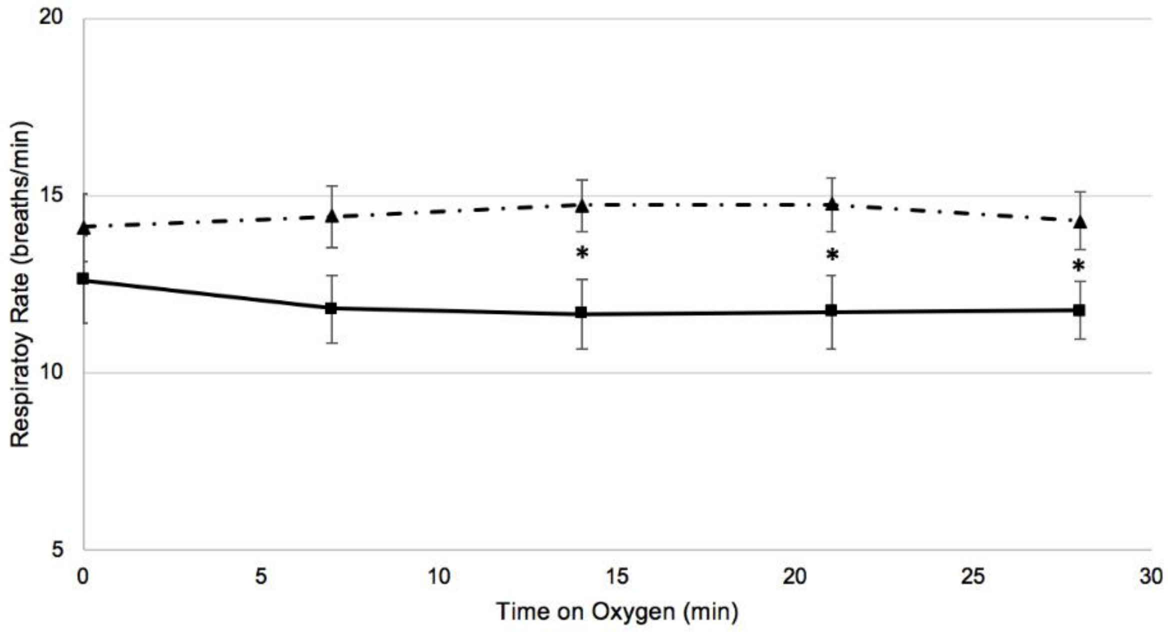
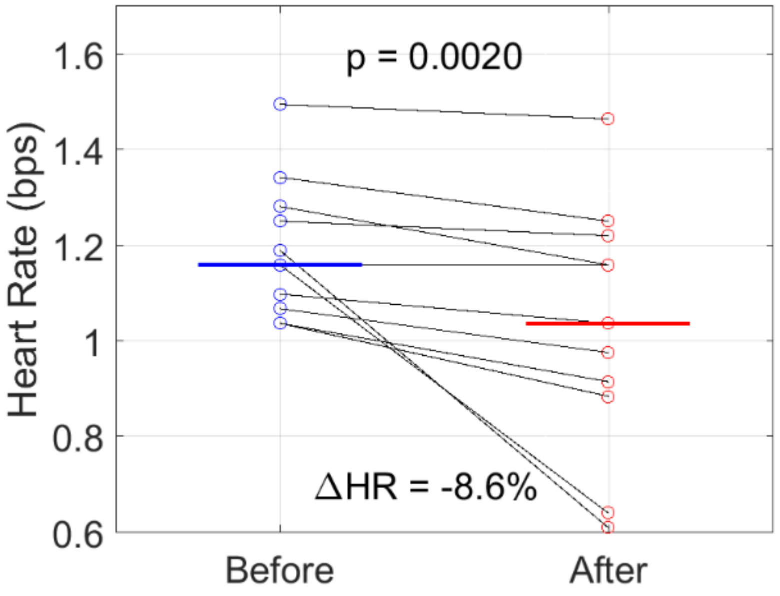
Cardiac and ventilatory functions are impacted by 100% FiO_2





Respiratory rates (n=13 female and n=13 males) did not differ while breathing 21% FiO_2 (Time 0). During 100% FiO_2, male respiratory began to drop and became significantly lower.

Heart rate decreased following transition from 21% FiO_2 (63.54 ± 1.79 beats/min) to 100% FiO_2 (61.40 ± 1.61 beats/min). Heart returned to baseline values at the 15 minute time mark.

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Calculations of systemic oxygen content

To determine systemic oxygen content (CaO_2) during exposure to 21% FiO_2 and again at 100% FiO_2, we used variables obtained from ABG samples.

$$CaO2\ ml\ O_2/\ 100\ ml\ =\ Hb_{avg}\ x\ 1.34\ x\ \left(\frac{O_2sat}{100}\right) + (PaO_2\ x\ 0.0031)$$

Hb_{avg}= mean of Hemoglobin measured in ABG #1 & ABG #2 to account for sample variation
1.34 = the amount of oxygen (ml at 1 atmosphere) bound per gram of hemoglobin.
0.0031 = is a constant that represents the amount of oxygen dissolved in plasma
normative values of CaO_2, at 21% FiO_2, range from 16-22

DaO_2 is the product of total blood flow and the oxygen content of arterial blood (Ca_{O2})

MRI arterial spin labeling provided a quantitative measure of cerebral perfusion during both 21% and 100% FiO_2,

$$DaO_2\ ml\ O2/min\ =\ CaO_2\ x\ CBF\ ml/min/100g$$

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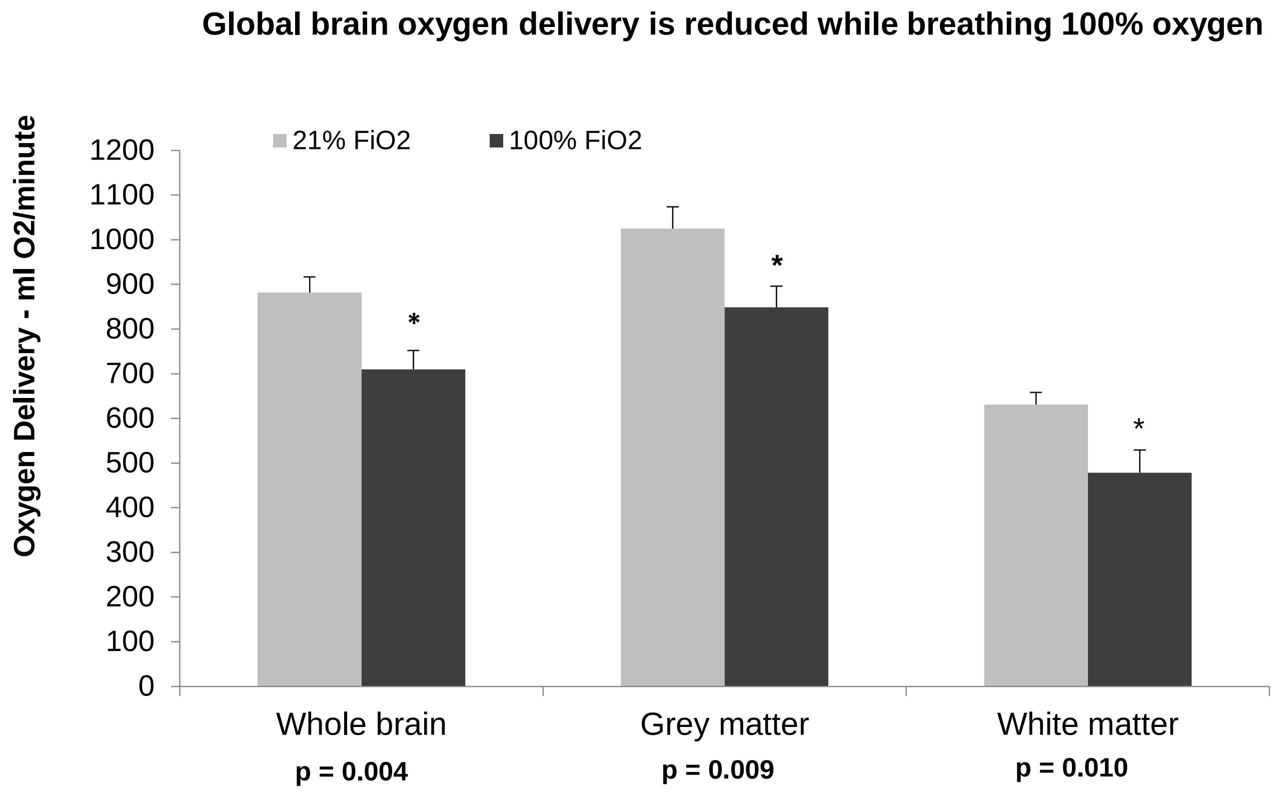
Hyperoxia led to a *global* reduction in cerebral oxygen delivery



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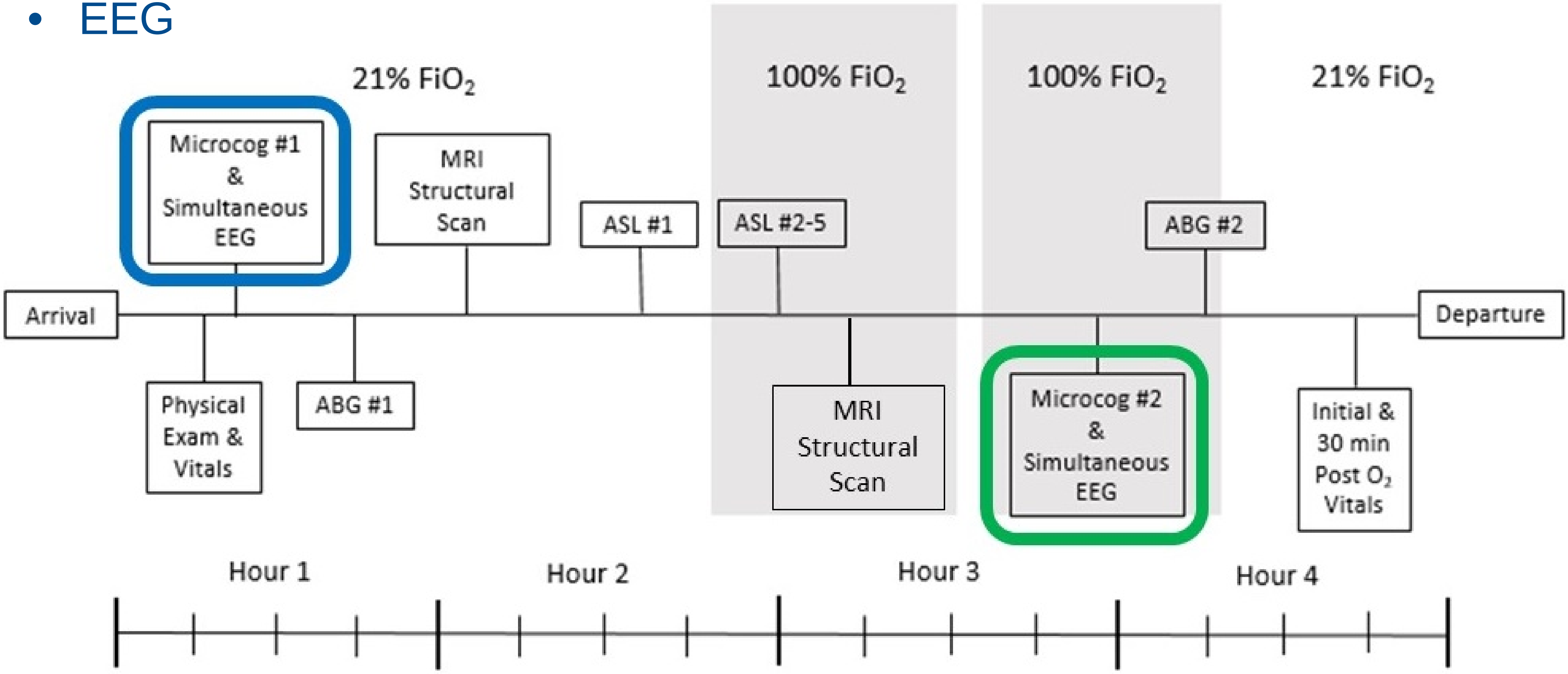
Study Design

- Microcog
- EEG



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Cognitive Testing

MicroCog™ Cognitive Domains Assessed

1. General Cognitive Function
2. General Cognitive Proficiency
3. Information Processing Speed
4. Information Processing Accuracy
5. Attention/Mental Control
6. Reasoning/Calculation
7. Memory
8. Spatial Processing
9. Reaction Time

Image courtesy of Dr. Lisa Damato

MicroCog Analysis

- Windows-based computerized neuropsychological battery
- Automated computer scoring
- Short form (30 minutes)
- Nationally normed on a representative sample of 810 adults ages 18-89
- Age-specific norms for nine age groups; adjusted for three education levels (< high school, high school, > high school)
- Raw scores are converted to scaled scores, corrected for age and education adjusted norms

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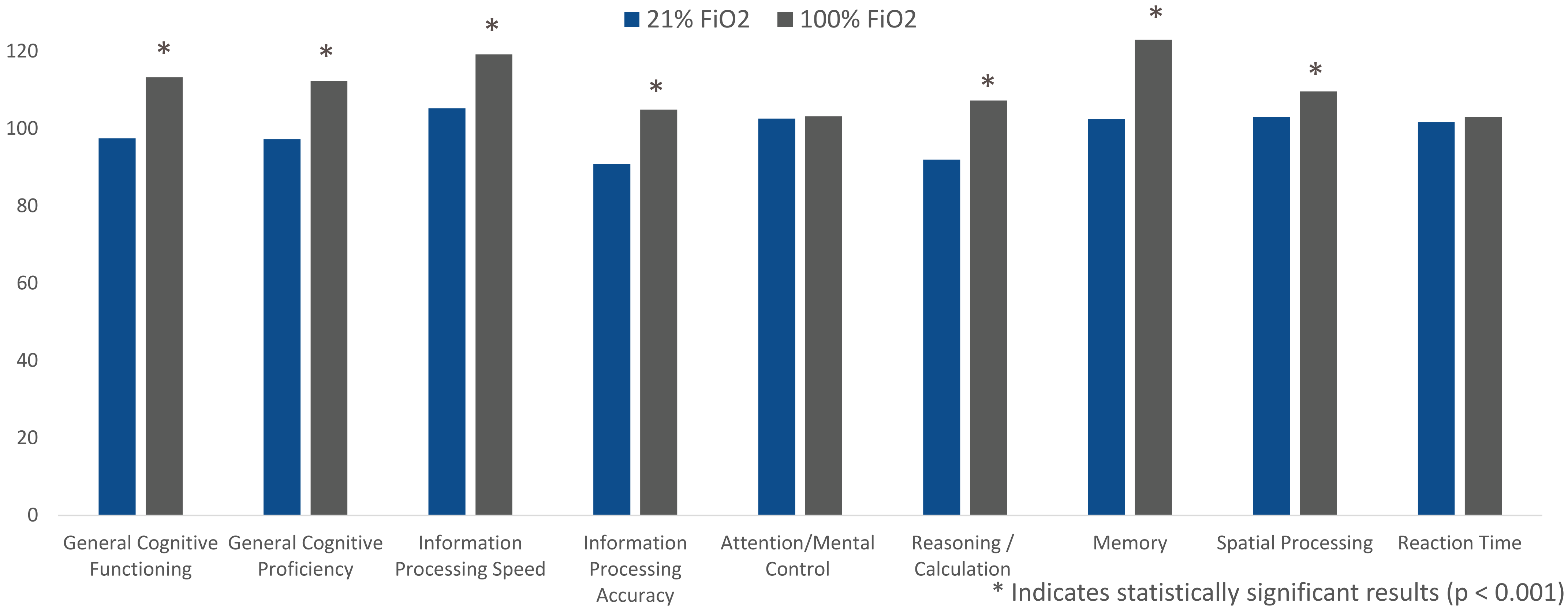
Hyperoxia resulted in enhanced performance



MicroCog mean scores in 21% versus 100% FiO_2

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Methods: 64-Channel High Density – EEG

Brain Regions

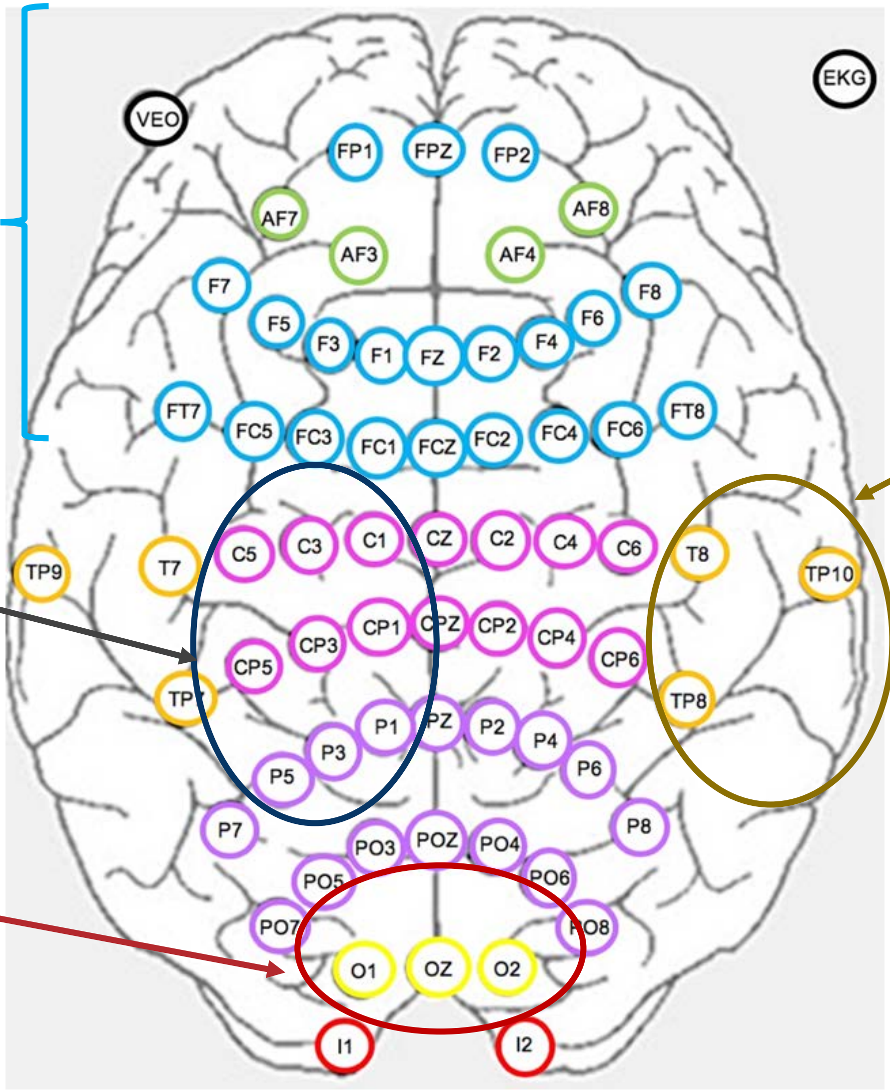
- Frontal Pole (FP)
- Anterior Frontal (AF)
- Frontal (F)
- Frontal Central (FC)
- Temporal (T)
- Central (C)
- Central Parietal (CP)
- Parietal (P)
- Parietal Occipital (PO)
- Occipital (O)
- Inion (I)

Frontal Lobe: Executive function

Parietal Lobe: spatial awareness, perception

Occipital Lobe: Vision

Temporal Lobe: memory, emotions, facial recognition



EEG Processing

Signal Processing

- DC offset removed using a 1-Hz high-pass filter
- Electrical power noise removed using a 60-Hz notch filter
- 0.5-1 second windows excluded for eye blinks & movement-related artifact; channels with > 3% noisy signals excluded from analyses
- Distinct frequency bands identified: theta (4.0-7.99 Hz), alpha (8.0-13.99 Hz), and beta (14.0-30.0 Hz)

Data Analysis

- Bandpass filter applied for each frequency band (theta, alpha, beta)
- Computation of the absolute value of the Hilbert transform performed to extract the envelope of each signal channel
- Clean analysis windows summarized as the average of the integral of the Hilbert envelope signal to produce the "mean Hilbert integral."

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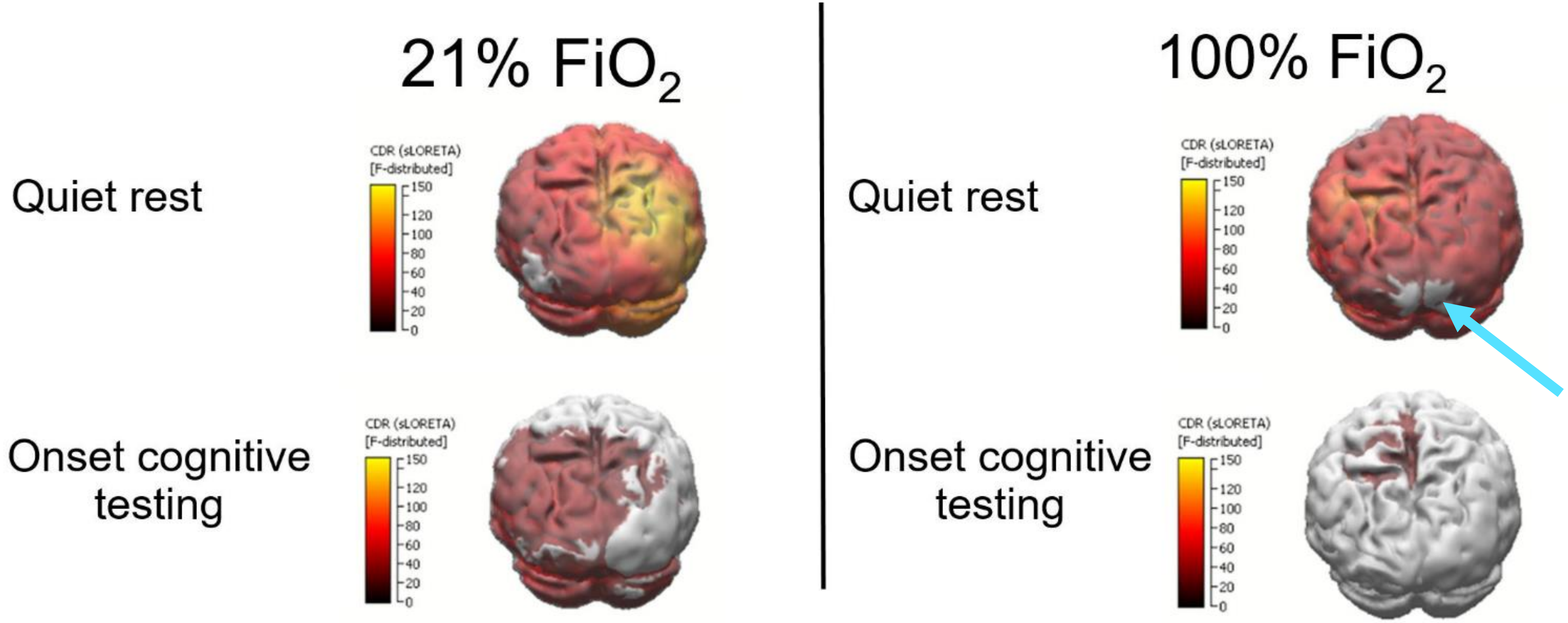
Alpha EEG activity enhanced during cognitive testing at 100% FiO_2

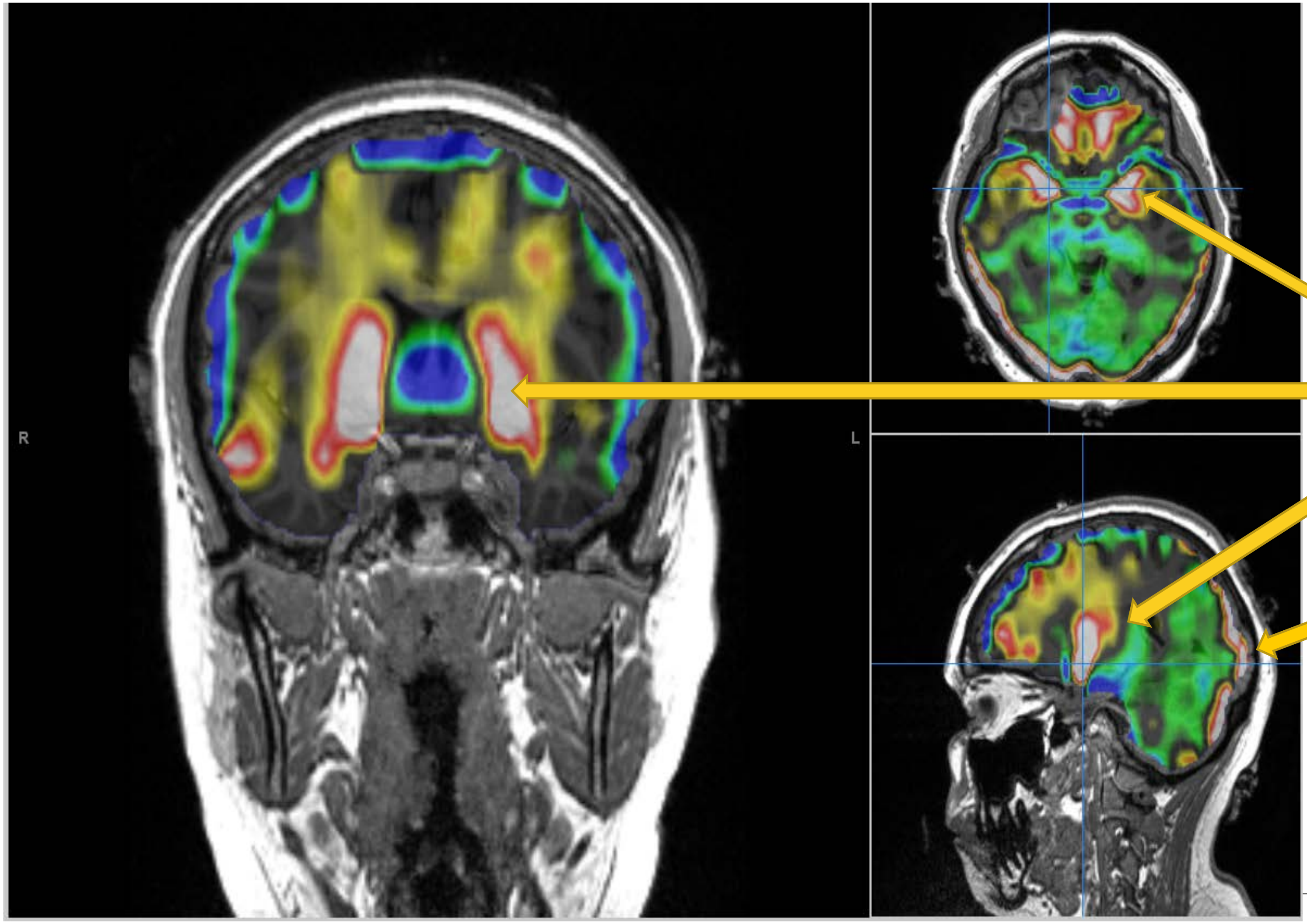
Maroon-yellow coloring reveals brain areas with synchronous alpha activity.

Reduced maroon-yellow coloring reveals areas with de-synchronized alpha activity (grey colored areas), suggestive of enhanced alertness.



Contradictory Findings + Anecdote = Re-Examination of Data

Anecdotal observations from pilots may be supported by hyperoxia-related increased cerebral perfusion within the Visual Cortex and motor output areas



- Developed new analysis tools to look at specific "regions of interest" in the brain (105 total)
  - New approach / cutting edge of neuroimaging research
- 4 cortical/subcortical regions showed marked INCREASE in local perfusion (29/30 subjects)
  - Globus Pallidus (bilateral)
    - Motor output (voluntary movement)
  - Middle and Superior Occipital Gyri
    - Visual Processing
  - Angular Gyrus (not shown)
    - Processing of visually-perceived words (also number processing and spatial cognition)

Summary of EEG Changes during Transition from Quiet Rest to Onset of MicroCog at 100% FiO_2

Cognitive testing in 100% FiO_2 led to changes in alpha activity that were significantly different in only a few cortical regions.

Those cortical regions included those that showed increased perfusion with 100% FiO_2

Frequency Band	Brain Region	MicroCog 21% FiO_2 M ± S.E.M. (Range)	MicroCog 100% FiO_2 M ± S.E.M. (Range)	2 tailed significance
Alpha	C	4.69 ± 0.31 (2.23-10.38)	5.08 ± 0.44 (2.41-14.88)	p=0.040
	P	6.07 ± 0.35 (3.13-9.90)	6.54 ± 0.46 (3.28-13.25)	p=0.049
	T	6.15 ± 0.34 (3.40-11.44)	6.75 ± 0.45 (3.75-15.30)	p=0.006

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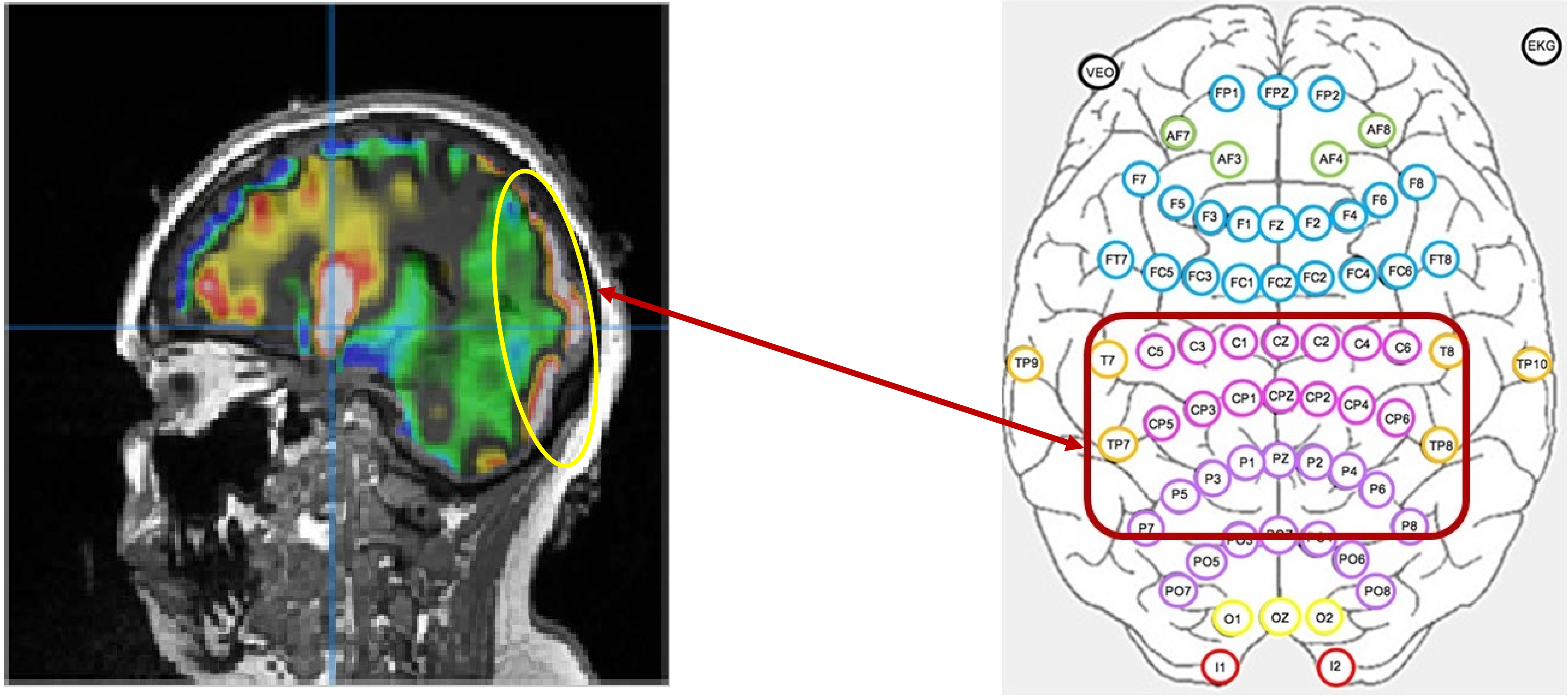
Cortical Regions with Significant Changes in Alpha Activity Corresponded to Areas with Increased Cerebral Perfusion



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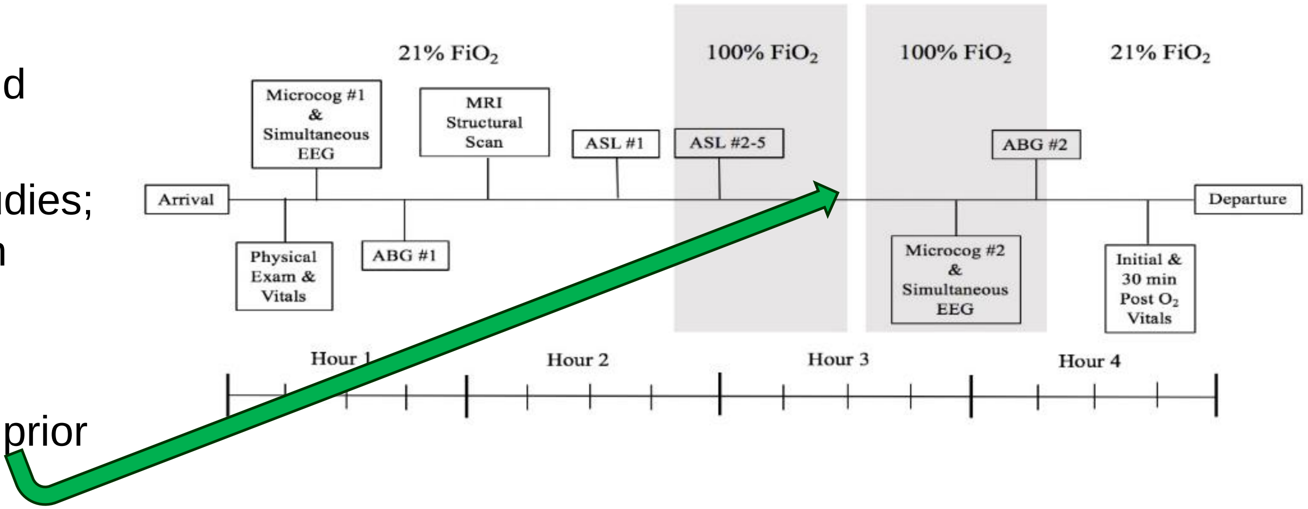
Limitations

Study design limitations:

- Simultaneous measures of CBF with cognitive performance and EEG within the MR scanner would have been preferable.
  - Ultimately did not do so due to preliminary studies; sessions of 90+ minutes were associated with significant subject burden, increased motion artifact and discomfort.
- In retrospect, would have taken an additional ABG prior to the end of the MRI session
- Extrapolation to operational environment. Study did not include:
  - Altitude
  - Gz
  - Vibration
  - Positive Pressure Breathing
  - Mask dead space replication



Summary of Findings

1) Exposure to 100% FiO_2 within our MR scanner led to a rapid and sustained reduction in CBF.

2) This was accompanied by reduced global oxygen delivery to the brain.

3) Despite reduced CBF and DaO_2, cognitive performance was enhanced while breathing 100% FiO_2.

4) Cortical alpha EEG patterns suggest enhanced vigilance/attentiveness transition from quiet rest to onset of cognitive testing. Those alpha EEG changes were greater while breathing 100% FiO_2.

5) Regions of the brain involved in visual processing and motor control experienced increased local perfusion (29/30 subjects).

6) Brain areas with increased CBF also showed corresponding EEG changes.

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Acknowledgments

Investigative Team

- Michael Decker, PhD
- Lisa Damato, PhD
- Tod Flak, PhD
- Kingman Strohl, MD
- Chris Flask, PhD
- Joseph LaManna, PhD

Collaborators

- Lt. Col. Justin Elliott
- Lt. Col. Kevin Hall
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Photo Credits

- Lt. Col. Kevin Hall

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Thank You!

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