Hacking the fetal brain: Confessions of EEG and ECG

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Conflicts of interest

1. Maternal abdominal electrocardiogram (aECG) to record fetal ECG and analyze HRV: two patents pending

2. Fetal EEG monitor: US 9,215,999
Overview of the talk

• Intro: why, what and how
• Intrapartum monitoring of hypoxia/acidemia using EEG and ECG - comparisons to ultrasound-derived FHR
• Antepartum monitoring of inflammation and stress using ECG
• Quo vadis?
The problem

Information about fetal well-being is imprecise, outdated or invasive

1. Before birth: a black hole
2. During labor: fetal brain injury cannot be detected

The end result is a series of lifelong health sequelae
Solutions

1. Non-invasive monitoring of fetal health via maternal abdominal electrocardiogram (aECG)

2. Fetal EEG monitoring during labor
“Nature is not economical of structures - only of principles”
  Abdus Salam

• Can we discover rules governing brain’s complex patterns?
• Until recently, tackling data streams of 1,2 M data points per minute was impossible;
• Advancement in ML techniques;
• Enter the era of bioelectronic medicine
Can the Nervous System Be Hacked?

Bioelectronic medicine: a research roadmap

Bioelectronic medicines connect your vital organs, sensing and shaping your health. If we learn to use them, the future of medicine will be electric.
What is innervated by vagus nerve’s afferent fibers? (What isn’t?)

- Heart
- Lower airways
- Thymus
- Paraganglia (distributed sensor system in thorax and abdomen)
- Liver, portal vein, bile ducts
- GI tract
- Uterus
- Pancreatic islets
- (Spleen)
- (Gall bladder, adipose tissue)

What is being sensed?

**Chemoreceptors**
- Nutrients
- Nutrient-related compounds
  - glucose, amino acids, fatty acids, neuropeptides

**Mechanosensors**
- Touch
- Tension
- Serosal

**Temperature**

**Osmosensors**

**Nociception**

**Brain projections**
- Brainstem
- Hypothalamus
- Amygdala
- Insular cortex
Labor
Detecting fetal acidemia

• Positive Predictive Value for fetal acidemia intrapartum 50%

• FHR monitoring inconsistently detects fetal acidemia

• Reasons for FHR monitoring inconsistencies:
  – Non-specificity of FHR decelerations
  – Variation in observers and methods interpretation of FHR patterns
  – Uncertainty about which fetal heart rate variability measures to use

Labor simulation with EEG monitoring

Synchronized EEG – FHR pattern at \( \sim \text{pH}=7.2 \) and \( \sim 60 \text{ min} \) prior to pH drop to less than 7.00. EEG, electroencephalogram, uV; ECoG, electrocorticogram, uV; ABP, fetal systemic arterial blood pressure, mmHg; FHR, fetal heart rate, bpm; UCOs, umbilical cord occlusions, mmHg (rise in pressure corresponds to a UCO; note the increase in strength of the UCOs corresponding to mild, moderate and severe UCOs).
Labor simulation with EEG monitoring

Objectives:
- Feasibility to record spontaneous fetal EEG
- Detection of incipient acidemia

Recruiting for one year or until five acidemia cases observed

Frasch et al, Phys Rep 2015
Change point detection in fHRV during labour

Online detection of fetal acidemia in EEG-FHR during labour

• Fetal EEG – HR monitoring allows for an automated early detection of worsening hypoxic-acidemia with good accuracy.
Sympathetic Vagal
Sinus node cells

Heart rate variability \(\downarrow\)

RMSSD

Suprabulbar control
Cardiovascular control

From mathematics to physiology

RMSSD, Root Mean Square of Successive Differences in R-R intervals (estimate of short-term components of HRV)
Fetal HRV monitoring alerts to incipient fetal acidemia: FHR sampling rate matters

Sampling rate of heart rate variability impacts the ability to detect acidemia in ovine fetuses near-term

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![Graph showing pH changes with different sampling rates](image_url)

**FIGURE 2** | FHRV analysis of RMSSD changes during worsening acidemia (black) at 1000 Hz and (gray) 4 Hz sampling rates. Animals reached pH nadir <7.00 between the time points "severe UCO 40 min" and "severe UCO 100 min." Accordingly, sample sizes of these time points were lower where indicated. For other time points, N = 9. Mean ± SEM. *p < 0.05 versus baseline for 1000 Hz sampled fHRV; * versus baseline for 4 Hz sampled fHRV.
If information is encoded in the HRV signal, it must be sampled correctly for true representation to contain predictive information.

- Novel bioinformatics approach to fHRV derived from maternal abdominal ECG during labour predicted well acid-base status at birth. Further refinement and validation in larger cohorts are needed.

- Potential to predict fetal cardiovascular decompensation during labour and acid-base status at birth.
Intrapartum monitoring: Progress to date

Animal studies completed

- Fetal EEG proof-of-principle studies show early detection of fetal acidemia
- Fetal EEG device prototype

Clinical study at UW is in progress

- ClinicalTrials.gov Identifier: NCT03013569
- Fetal scalp electrode
- Labor EEG as evoked response

Eswaran 1999 AJOG 180(6 Pt 1):1422-6
Vagus nerve stimulation increases acetylcholine levels in the spleen and requires T lymphocytes to attenuate TNF-a in endotoxemia. Rosas-Ballina et al, Science 2011.
BRAIN INTEGRATION?
Neuroimmunological homunculus?
Plasticity? Recovery potential?
Biomodulation?
The multi-talented vagabond: how does it talk and can we talk back?

- Direct study of VENG / Vagotomy (Vx) / VNS
- Indirect analysis of multi-dimensional HRV properties in relation to outcome measures
- HRV / Vx / VNS / VENG studies yielded first insights into existence of vagus code and its amenability to manipulation
- Vagus signaling in fetus impacts
  - brain regional and gut blood flow
  - systemic glucose levels
  - peripheral (gut) and central (neuro) inflammation levels
  - microglial and astrocytes’ phenotype
  - the response patterns differ dramatically from those in adult organisms
- How does vagus nerve communicate? How is this information organized in the brain? (Immunological homunculus) Is this information reflected in HRV code?
The inverse and direct problems

Systemic inflammatory response coding

Durosier et al. 2015


Frasch et al. SRI 2018 (manuscript in preparation)


Frasch et al. SRI 2018 (manuscript in preparation)

Durosier et al. 2015

Within gut and brain, no fHRV measure correlated to several markers of inflammation at the same time; that is, there were no overlapping correlations of the fHRV measures.
Antepartum monitoring: Progress to date

Animal studies completed

- Heart rate variability (HRV) permits early detection of fetal infection and acidemia
- aECG is the pre-requisite for precise and continuous acquisition of HRV

Clinical study at UW is in progress

- ClinicalTrials.gov Identifier: NCT03111173
Outlook

- Is there future for fetal EEG monitoring intrapartum?
  - Long history
  - New medical device ancillary to current FHR monitors
  - Recruitment scale

- How can we make fetal ECG technologies more acceptable?
  - Price
  - Validation
  - Future uses at home and in clinic, antepartum and intrapartum
  - Joint mother-fetus monitoring
Maternal-fetal stress memory

- Maternal prenatal stress impacts the fetal heart rate reactivity to maternal heart rate.
- Joint m/f ECG monitoring!
- This impact can be detected non-invasively from maternal transabdominal ECG.
A complex multi-scale phenotype of the healthy or prenatally stressed individual.

- Can the rapidly advancing machine learning techniques help distinguish individual phenotypes based on all its features across the scales of observations, from microbiome, over to epigenetic landscape to the heart rate (HR) time series?
From Bioelectronics to Electroceutics

THE TARGET
Molecular biologists identify ‘targets’ of disease or health

THE SIGNAL
Neuroscientists identify the neural pathway to manipulate the target

THE DEVICE
Engineers and computer scientists design a device to modulate the appropriate pathway
Can the Nervous System Be Hacked?
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