Monitoring the developing brain in crisis

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The developing brain is expensive and privileged
The developing brain sustains injury quietly and on our watch
The developing brain is unforgiving when injured
Current neuromonitoring is limited

- mechanisms translating insult-to-injury are incompletely understood
- *the optimal target signals remain unclear*
Current neuromonitoring is limited

- mechanisms translating insult-to-injury are poorly understood
- the optimal target signals remain unclear
- insult-to-injury proceeds down multiple potential pathways
- monitoring has been mostly unimodal
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- neurodiagnostics have been largely static
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- insult-to-injury is a dynamic process
- neurodiagnostics have been largely static
- techniques have strengths and limitations
- tools are used without a clear understanding of their limitations
Pathways from insult to injury in the immature brain
Pathways from insult to injury in the immature brain

Two major pathways

Destructive

Developmental
Pathways from insult to injury in the immature brain

Major pathways
- Destructive
  - Hypoxia
  - Infection-inflammation
- Developmental
The multiple determinants of hypoxic brain injury

Hypoxia Pathway

- hypoxemic
- anemic
- ischemic
- cytotoxic
- hypoxic-ischemic
The multiple determinants of hypoxic brain injury
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Critical periods of development, vulnerability and plasticity
Insults may be well tolerated but once function fails structure soon follows.

- Onset of insult
- Loss of brain function
- Onset of irreversible brain injury
Post-insult cascades of brain injury
The fundamental goals for neuromonitoring are to open the therapeutic window, to enable preventive neuroprotection, and to guide brain-oriented neonatal care.
Endogenous neuroprotective systems

- Intrinsic Cerebral Autoregulation
- Systemic Cardiorespiratory System
Communication between systems is costly

Intrinsic Cerebral Autoregulation

Autonomic nervous system

Systemic Cardiorespiratory System
Intrinsic Cerebral Autoregulation

Graph showing the relationship between cerebral blood flow (CBF) and pressure (torr) with markers for PaO$_2$, PaCO$_2$, and CPP.
Intrinsic Regulation of Cerebrovascular Tone

Smooth muscle cell

Ca

Muscularis

Endothelium

Parenchyma

Circulation
Cerebral pressure-flow autoregulatory failure

- CBF
- CBV
- COE
- CMRO2

Falling Blood Pressure
Near Infrared Spectroscopy

Measures absolute change in cerebral concentration of:

- oxygenated hemoglobin (HbO₂) (900 nm)
- deoxygenated hemoglobin (Hb) (760 nm)

Derived indices of cerebral hemodynamics and oxygenation:

- \( HbT = HbO2 + Hb \) (~ CBV)
- \( HbD = HbO2 - Hb \) (~ CBF)
- \( HbO2/HbT \sim \) cerebral hemoglobin saturation
Near-infrared Spectroscopy

- Fiberoptic cable
- Detectors
- Laser diode

BRAIN
Cerebral pressure-flow autoregulatory failure

<table>
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Falling Blood Pressure
Multimodal Monitoring

Date/time

BR Function

CVR-CO₂

Routine procedures

MAWP

MAP

HR

ET-CO₂

HbD

EEG

Video

Δ‘CPP’

Autoregulation

Activation coupling
Pathway from insult to injury

Onset of insult

Onset of irreversible brain injury

Loss of brain function

Intrinsic brain compensatory mechanisms

Expanded therapeutic window
Destructive Lesions of the Immature Brain

Term

Preterm
Developmental disruptions are increasingly implicated in neurologic compromise after early-life neurologic insults.
Chronic, recurrent insults below the level of cellular destruction may cause developmental disruption of the immature brain.
Developmental disruption of the immature brain

- Chronic low-grade hypoxia
  - functional deafferentation, developmental diaschisis
- Allostasis ("stability through change") and allostatic load
  (Sterling and Eyer, 1988; McEwen, NEJM, 1998)
- Epigenetic mechanisms
- Developmental imprinting / programming
Neuronal activation consumes 60% of cerebral energy supply

Nerve action potentials are
- highly energy dependent
- critical for brain development
Hypoxia, adenosine and neuroprotection

ATP → ADP → AMP → Adenosine

Neuronal inhibition (Presynaptic)
- $A_1$ receptor
- $A_2$ receptor

Cerebral Vasodilation
‘Neurons that fire together wire together, those that don’t won’t’
Allostasis and Allostatic Load

Allostasis (‘stability through change’)
- steady state change keeping regulated variables stable
- compensatory and adaptive
- longterm trade-off (allostatic load) - “wear and tear”

Allostatic responses
- initiated by autonomic and adrenal catecholamines and glucocorticoids
- adaptive processes alter cell function and structure

McEwen, NEJM, 1998
Concluding remarks

- Preventive neuroprotection and brain-oriented care of the human fetus and newborn remains limited by the lack of effective neuromonitoring.

- Effective brain monitoring will demand:
  - an increased understanding of the pathophysiology
  - more precise targeting of the relevant causal pathways
  - an informed and appropriate response to signals

- Investment in development of effective neuromonitoring and preventive neuroprotection for the fetus and newborn is desperately needed.
The fundamental goal for neuromonitoring is to open the window for neuroprotection.

- **Onset of insult**
- **Onset of irreversible brain injury**
- **Loss of brain function**
- **Therapeutic window**
- **Secondary brain injury**