Neonatal surgery in the past: Can it affect pain response in the future?

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OUTLINE

1. Early life experience and pain
   - preterm birth ± neonatal surgery
     - long-term outcome
   - somatosensory processing

2. Preterm born children and young adults
   - modulation of pain response
   - pain experience

3. Translational laboratory studies
   - impact of neonatal surgery
   - mechanisms and prevention
Long-term impact of pain in early life

**early life stress / adversity**
- neglect or abuse
  - physical, emotional, sexual
- exposure
  - trauma, infection, toxins
- pain: procedures; surgery

**health in adulthood**
- mental health
  - mood and anxiety disorders
- medical conditions
  - heart disease, bowel disorders
- chronic pain

Preterm birth

- high risk group
- global health care priority

  **WHO Global Action Report 2012**
  - largest cause of neonatal death worldwide
    - ~ 3/4 neonatal deaths
    - ~ 1/3 infant death
  - >10% born preterm

<table>
<thead>
<tr>
<th>GRADE</th>
<th>GESTATIONAL AGE (wks)</th>
<th>PROPORTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>32 to &lt;37</td>
<td>84.3%</td>
</tr>
<tr>
<td>Very</td>
<td>28 to &lt;32</td>
<td>10.4%</td>
</tr>
<tr>
<td>Extreme</td>
<td>&lt;28</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

- extreme preterm ~ 0.5% of all births

  Blencowe et al. *Lancet* 2012
Preterm birth

- UK & Scandanavia
  - < 10%
  - increasing in UK
  - stable in Sweden

- 2010
  - Sweden: 10-50,000
  - UK: 50-100,000

- mortality higher in UK
  - ? differences in coding
  - socioeconomic inequality
  - not neonatal care

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Why do young children die in the UK? A comparison with Sweden
Tambe et al., Arch Dis Child 2015

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>UK</th>
<th>SWEDEN</th>
<th>RATIO</th>
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<tbody>
<tr>
<td>Prematurity</td>
<td>138.5</td>
<td>10.1</td>
<td>13.7 x</td>
</tr>
<tr>
<td>Neonatal respiratory</td>
<td>34.2</td>
<td>8.9</td>
<td>3.8 x</td>
</tr>
<tr>
<td>Necrotosing enterocolitis</td>
<td>16.2</td>
<td>5.4</td>
<td>3.0 x</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>112.1</td>
<td>88.6</td>
<td>1.3 x</td>
</tr>
</tbody>
</table>
Preterm birth

- cost of ongoing care
  - adverse neurodevelopmental outcome & disability
    - Blencowe et al. Lancet 2012
  - impact on future health and well-being
    - respiratory; cardiac
    - ? pain

- susceptibility vs resilience
  - reduced risk taking
    - less smoking, drinking
    - peer group / social withdrawal
    - anxiety / introversion

Common mental disorders in young adults born preterm

Preterm : Procedural pain & NICU

- pain and stress in intensive care
  - painful procedures
    - median 10 (0–62) per day
  - use of analgesia increasing

- recommendations
  - guidelines to prevent / minimize
  - assessment
  - non-pharmacologic strategies
  - pharmacology

- research gaps
  - long-term neurodevelopmental, behavioural, cognitive outcomes
  - acute and long-term efficacy and safety of analgesic interventions
Preterm: Procedural pain & NICU

- **sensory processing in infancy**
  - periphery: sensitivity, hyperalgesia
  - brain: altered EEG response

- **brain structure and connectivity in childhood**
  - higher numbers painful procedures: greater change
  - ? impact on function
    - Ranger & Grunau. *Pain Manage* 2014

- **coping style / behavioural response**
  - child: catastrophizing; internalizing
  - parent: solicitousness; stress

Preterm: Impact of Surgery

- **neonatal surgery**
  - adverse cognitive outcome
    - Bayley score: 12-24 months age
    - **preterm**: higher risk

- **MRI 7 days post surgery**
  - $n=32$ preterm (30-36 wks)
  - $n=69$ full-term
  - overall abnormalities
    - 75% preterm
    - 58% full-term
  - preterm
    - parenchymal lesions > haemorrhagic
Preterm : Long-term impact of Surgery

- **extreme preterm**
  - 298; born < 28 wk; assess 2, 5, 8, 18 yrs
  - 26% require surgery

- **biological variables**
  - surgery
    - 5 yrs
      - worse neurosensory outcomes
    - 8 & 18 yrs
      - lower academic outcome
      - especially maths

- **social variables**
  - social class
  - maternal education
    - increasing effect at older ages

Is pain sensitivity altered following NICU?

**Range of clinical studies**

- **source of initial pain/injury**
  - NICU: procedures ± surgery

- **time interval before evaluation**
  - days, weeks, months, years

- **subsequent experience**
  - psychological, sex/gender
  - social and environmental factors

- **subsequent stimulus**
  - intensity: threshold or noxious stimulus
  - experimental stimulus; procedure; repeat surgery

- **outcome**
  - pain score / current pain report
  - behavior / stress response
  - neurophysiology
    - Quantitative Sensory Testing / EEG / Imaging
Quantitative Sensory Testing (QST)
standardised protocol: range of stimulus modality and intensity

- **thermal**
  - computer controlled thermode (C fibre)
  - baseline 32°C ± 1°C per second: 10-50°C limits

- **mechanical detection**
  - von Frey hairs (A-β): light touch: up-down
  - **punctate probes (A-δ)**: 8, 16, 32, 64, 128, 256, 510 mN
  - threshold and wind-up ratio

- **pressure sensitivity**
  - algometer: visual feedback for standardized slope

- **cold pressor test**

Are sensory thresholds in childhood altered?

- **preterm** (29±2wks) NICU or **term** (39±2wks) NICU vs healthy term
  - n=19-20; 9-14 yrs
  - decreased thermal sensitivity
    - hand and face
  - no difference in mechanical threshold
    - punctate probe

- **cardiac surgery + NICU** (3 prem, 6 term) vs healthy term
  - n=9; 9-12 yrs
  - decreased thermal sensitivity
    - localized at scar; not hand
  - mechanical detection: von Frey
    - decreased hand and scar


Hermann et al. Pain 2006
**EPI Cure: Extreme Preterm Infant Cohort**

- born <26 weeks gestation in 1995 in UK
  - longitudinal follow-up
    - Marlow et al. NEJM 2005

- pain and sensory testing
  - 11 years  
    - Walker et al. Pain 2009
  - 19-20 years  
    - Walker et al. (in prep)

- Quantitative Sensory Testing
  - generalized: thenar eminence
  - localized: neonatal thoracic scars

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**Generalized decreased thermal sensitivity in preterm group**

- **hand:** same pattern at 11 years and at 19 years
- overall increase in threshold with age

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![Graphs showing thermal sensitivity comparison between extreme preterm and term control groups at 11 and 19 years.](image)
More prolonged stimulus unmaskes increased sensitivity

- **prolonged cold stimulus**: 17-18 yrs
  - preterm ≤28wks (n=31)
  - healthy term (n=29)
- **cold pressor test**
  - 180 secs in ice water
  - reduced tolerance
  - preterm
  - females

Verderhus et al. / Pain 2012

More prolonged stimulus unmaskes increased sensitivity

- **prolonged heat stimulus**
  - QST
    - 9-14 years preterm NICU vs term NICU vs healthy controls, n=20/21 per group
    - healthy controls: habituation
    - sensitisation in ex-NICU
    - Hermann et al. Pain 2006
  - fMRI
    - 11-16 years preterm NICU vs term NICU vs healthy controls, n=9 per grp
    - 30sec heat: increased to VAS > 5
    - NICU preterm vs control
    - higher activation in somatosensory cortex, anterior cingulate and insula
    - brainstem: periaqueductal gray
    - Hohmeister et al. Pain 2010
QST and Neuropathic Pain

- **range of stimuli**
  - different units: normalize to values for controls
- **neuropathic pain**
  - mixed patterns of sensory gain and sensory loss
- **clusters**
  - sensory loss
  - thermal sensitivity
  - mechanical sensitivity

QST & paediatric pain

- Sethna & Berde
- Hermann
- Zernikow

Is descending modulation of pain altered?

stimulus location, intensity & modality

periaqueductal gray

PAG

rostroventral medulla

RVM
Conditioned Pain Modulation

- **evaluate endogenous pain modulation**
  - inhibition ↔ facilitation
- **influenced by**
  - sex / gender
  - psychological factors
- **less efficient**
  - pain populations vs healthy individuals
- **reduced CPM pre-op**
  - associated with increased acute and chronic post-surgical pain
- **potential clinical biomarker**
  - ? predict development of persistent / chronic pain
  - ? predict individual differences in treatment response


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Is descending modulation of pain altered?

**CONDITIONED PAIN MODULATION**

<table>
<thead>
<tr>
<th>TEST STIMULUS</th>
<th>CONDITIONING STIMULUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal</td>
<td>Thermode HOT</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Water bath Immersion</td>
</tr>
<tr>
<td>VON FREY HAIR ALGOMETER</td>
<td>COLD</td>
</tr>
<tr>
<td>Electrical</td>
<td>HOT</td>
</tr>
<tr>
<td>WITHDRAWAL REFLEX</td>
<td></td>
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</tbody>
</table>

**OUTCOME**

change post vs pre-conditioning
fixed stimulus: PAIN SCORE
variable stimulus: PAIN THRESHOLD

Nir & Yarnitsky.
Curr Opin Support Palliat Care 2015

Tsao et al. J Pain 2013
Binns et al. Pain Manag 2014
**Conditioned Pain Modulation**

- **efficacy varies with age**
  - more robust in late adolescence
  - 8-11 yrs: 9.2% decrease VAS
  - 12-17 yrs: 30.6%
  - Tsao et al. J Pain 2013

- **reduced CPM**
  - 7-12 year old girls
  - irritable bowel syndrome
  - Williams et al. J Pain 2013
  - 10-17 year old
  - functional abdominal pain

- **no difference**
  - 10-17 year olds
  - new-onset or chronic musculoskeletal pain

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**Preterm: Is descending modulation of pain altered?**

- preterm ≤32 wks vs healthy term (n=13): 7-11 years
  - **test stimulus**
    - fixed thermal: 46ºC for 5 secs: report VAS
  - **conditioning stimulus**
    - cold pressor: 3 min at 13ºC

- **“low-pain”**
  - shorter NICU stay (mean 65 days, n=6)
  - inhibition more marked

- **“high-pain”**
  - longer NICU stay (mean 91 days, n=7)
  - higher procedural pain exposure
  - no inhibition

Preterm birth: risk of chronic pain in later life?

**Different approaches:**

- **Population epidemiology**
  - Need large numbers to sample high risk groups
  - 1958 British birth cohort
    - Widespread musculoskeletal pain at 45 yrs: 12% (n=8,572)
    - Preterm birth (<37wks): minor increase risk: RR 1.26 (0.95-1.67)
    - \( n = 7382 \) \( n = 288 \) preterm < 37wks
      - \( n = 104 \): LBW (1.5-2.5kg); \( n = 9 \): VLBW (<1.5kg)
  - Norway
    - \( n = 7373 \) 13-18 years (78% response rate)
    - Chronic non-specific pain: 44.4%
    - Perinatal data: 1988-1994
    - ‘No consistent association between preterm birth and chronic pain’
    - \( n = 6850 \)
      - \( n = 80 \) preterm < 34wks
      - ‘Relatively few with low birthweight, low gestational age
        - \( n = 9 \): LBW (1.5-2.5kg); \( n = 60 \): VLBW (<1.5kg)

- **Self-reported current pain in high risk cohorts**
  - No difference
    - EP (17-18 yrs; n=31)
    - VLBW (20 yrs; n=43)
    - Lund et al. Health QoL Outcomes 2012
  - Increased
    - ELBW (23 yrs; n=140)
      - Saigal et al. Pediatrics 2006
    - VLBW (26 yrs; 29±2 wks; n=62)
      - Moderate to severe pain in last month
      - 24% vs 12% in term control

**Difficulties**

- Variable inclusion
- Small sample size
- Variable outcomes
  - Component of health/QoL (e.g., SF36; HUI)
  - Specific questionnaire
- Pain history


**Does early life pain alter the likelihood or risk of chronic pain?**
- multiple contributing / modulating factors

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**NEONATAL EXPERIENCE**
- preterm birth
- intensive care
- pain and tissue injury
  - procedures / surgery
  - type / severity / frequency

**BIOLOGICAL FACTORS**
- gestational age / sensitive periods
- sex / genetic vulnerability
- stress
- intercurrent illness: type and severity
- drugs: beneficial → adverse effects

**PSYCHOSOCIAL FACTORS**
- NICU environment
- handling → skin-to-skin contact
- non-pharmacological pain interventions

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**PAIN OUTCOMES IN LATER LIFE**
- persistent pain
  - risk / prevalence / severity
  - pain related disability
  - response to treatment
  - health care utilization

**BIOLOGICAL FACTORS**
- age / sex
- somatosensory function and sensitivity
- stress vulnerability → resilience
- epigenetic changes / neuroinflammation
- intercurrent illness

**PSYCHOSOCIAL FACTORS**
- gender
- cognitive function
- catastrophizing → adaptive coping
- anxiety → self-efficacy
- parental response / social support

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**Do changes in nociceptive pathways alter sensory response to future surgery?**

- **Does injury unmask increased sensitivity?**
  - repeat surgery in same dermatome as neonatal surgery
    - increased intra-op fentanyl and post-op morphine requirement
    - higher pain scores
  - one third of GOSH acute pain service: repeat patients

- Are effects specific to neonatal injury?
- What are the underlying mechanisms?
- Can we prevent or selectively target altered sensitivity?
**Surgical injury**

- **plantar hindpaw incision**
  - Brennan et al. Pain 1996

- **acute hyperalgesia at all ages**
  - Ririe et al. Anesthesiol 2003; Walker et al Pain 2009

**FIRST POSTNATAL WEEK**

P3 : POSTNATAL DAY 3

~ PRETERM NEONATE

**6 – 8 WEEKS AGE**

P40 – P60

~ YOUNG ADULT

**Neonatal hindpaw incision alters baseline sensitivity in adult**

**nIN**: adult with prior incision
- decreased sensitivity
- generalized

- altered descending modulation
- shift balance towards inhibition
- generalized effect
  - neonatal incision
    - same paw
    - contralateral hindpaw
    - forepaw

**nINa**: neonatal incision + analgesia
- sciatic nerve local anaesthetic block
- prevents long-term change
- activity-dependent

Walker, Fitzgerald, Hathway. Anesthesiology 2015
Adult injury un masks enhanced sensitivity

**Mechanical hyperalgesic index** (AOC 0-14 days)

- Enhanced injury response extends beyond site of initial incision

**Mechanical withdrawal threshold** (% of baseline)

- Enhanced sensitivity to re-incision

Neonatal analgesia prevents altered injury response

**Neonatal analgesia** (sciatic block)

- Specific developmental effect
  - Injury in first postnatal week
  - Activity-dependent mechanism

**Reflex response** (AUC EMG)

- No enhanced sensitivity to re-incision
Enhanced injury response: mechanisms

**neonatal incision**
- acute and long-term changes at spinal synapses
- specific to neonatal injury
  - prevent with local anaesthetic

Mark Baccei; University of Cincinnati

**ALTERED SYNAPTIC FUNCTION**

- strengthened input to lamina I projection
- ↑ glutamatergic signaling
- ↓ phasic and tonic glycinergic inhibition

Walker, Beggs, Baccei; Exp Neurol 2016

Enhanced injury response: role of spinal microglia

- microglial reactivity
- increase neuronal excitability

Salter & Beggs. Cell 2014

**Sublime Microglia: Expanding Roles for the Guardians of the CNS**
Enhanced injury response: role of spinal microglia

- nIN-IN
  - microglial reactivity
    - increased degree and duration
  - Iba1, phospho-p38
    - Beggs et al. Brain 2012
    - Schwaller et al. Anesthesiol 2015

nIN-IN: increased microglial reactivity following adult incision
Enhanced injury response: role of spinal microglia

- inhibit spinal microglia
  - minocycline; p38 inhibitor
  - block effect of prior incision

ADULT MALE

nIN-IN: increased microglial response following adult incision

ADULT INCISION: IN
NEONATAL + ADULT INCISION: nIN-IN

Iba1 fluorescence
(mean pixel intensity)

minocycline: prevents enhanced sensitivity in nIN-IN

Does the cortical response to surgical injury differ in early life?

Intracortical activity: somatosensory cortex
- spontaneous activity
  - suppressed by anaesthetic (isoflurane) in younger ages

- evoked response
  - not suppressed in younger

- after hindpaw incision
  - sensitized response
  - neonate > adult

- time-frequency spectral analysis
  - Y: frequency band: 1-100Hz
  - X: time: seconds
  - colour: energy

Impact of neonatal incision in brain

Intracortical recordings: somatosensory
- hindpaw incision: acutely sensitizes response to noxious stimulus
- need analgesia

Ex-vivo imaging mouse
- high resolution MRI imaging
- prior neonatal incision
  - alter degree and distribution of response to adult incision
  - identify ROI for tissue analysis

EPICure preterm young adults
- structural and RS-fMRI

PAIN EXPERIENCE

sensory

emotional

sex / gender

pain and injury in early life

pain in adulthood

Translational studies identify long-term impact of prior neonatal pain experience

Staatsen M, Walker*