UiO : Universitetet i Oslo

Systemic Inflammation Negates Hypothermic Neuroprotection in a Neonatal HIE-model

Mari Falck

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Mari Falck and co-authors

have documented no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.

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Background

- 1 million new cases of neonatal encephalopathy each year[1].

- Encephalopathy from HI alone is caused by sentinel events such as
  - placental abruption
  - uterine rupture
  - cord prolapse
  - shoulder dystocia[2]

Blencowe et al, Pediatr Res. 2013
Fleiss et al. Dev Med Child Neurol. 2015

Therapeutic hypothermia (TH) is somewhat neuroprotective: poor outcome 66% ⟶ 50%.[1]

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Edwards et al. BMJ. 2010

Neonatal HIE is Likely To Be a Multifactorial Condition With Complex Aetiology

Sensitisation → **Perinatal insult** → **Exacerbation**

- Antenatal factors
  - inflammation
  - maternal stress
  - hypoxia
  - malnutrition
  - genetic factors

- Perinatal factors
  - hypoxia-ischaemia
  - glutamate
  - inflammation
  - oxidative stress
  - genetic factors

- Postnatal factors
  - pain
  - drugs
  - ongoing inflammation
  - genetic factors

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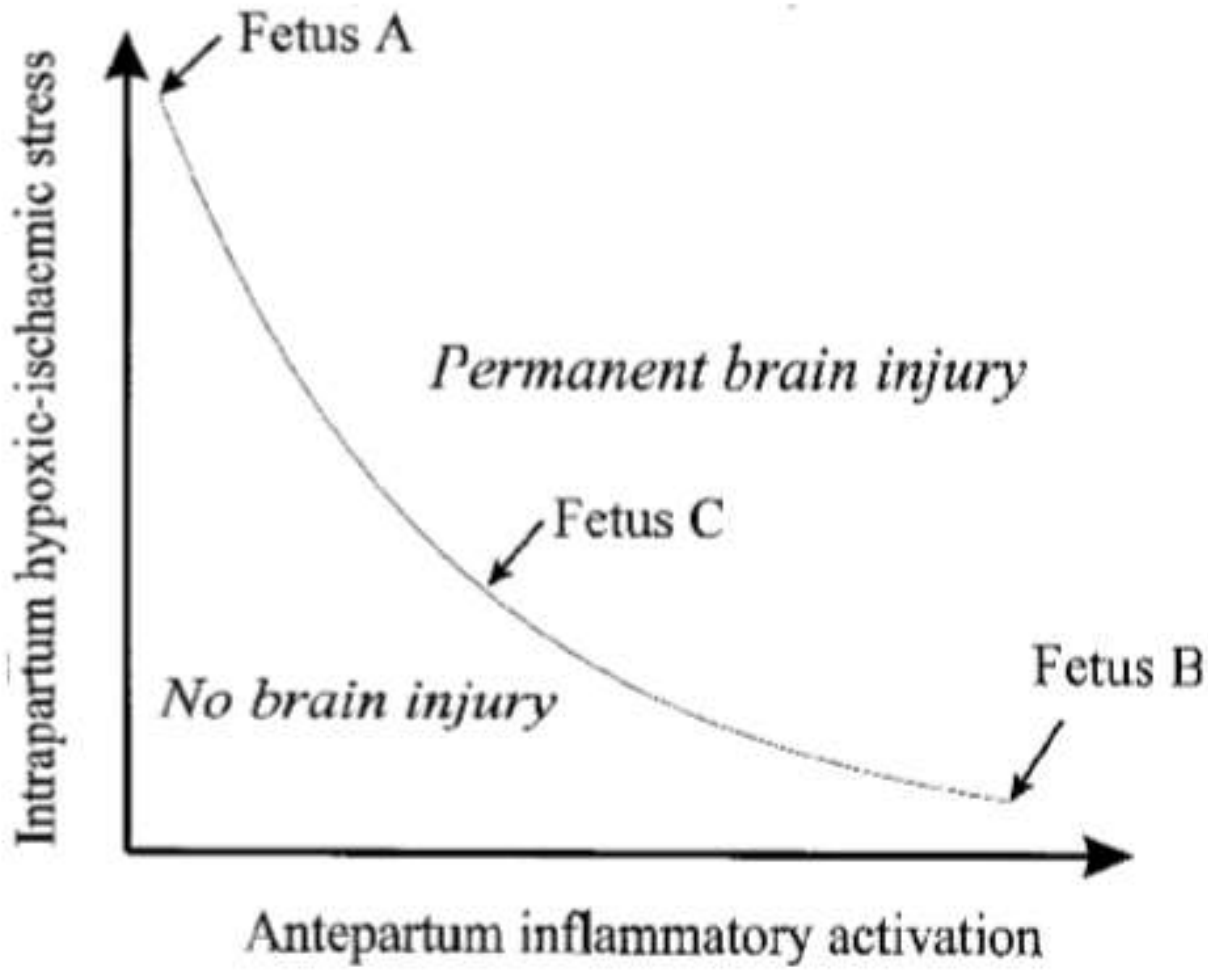
Modified from Fleiss et al. Dev Med Child Neurol. 2015

Fetal Exposure to Infection Contributes to the Risk of Hypoxic-Ischemic Encephalopathy.[1]



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Peebles et al. BJOG. 2002

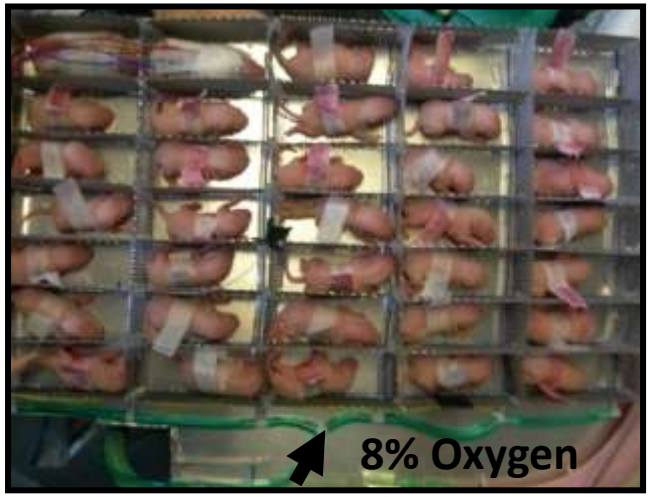
Experimental Design

7 day old rat pups (n=153)

Intraperitoneal injections
NaCl or LPS

4 hrs

Unilateral Ligation



Hypoxia (8% O_2 for **50** min at 36°C)

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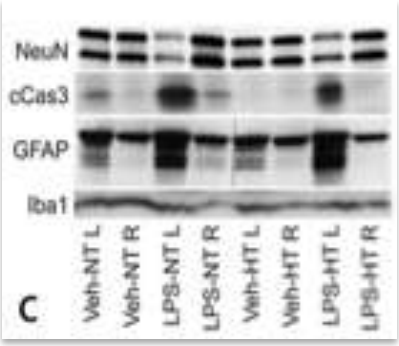
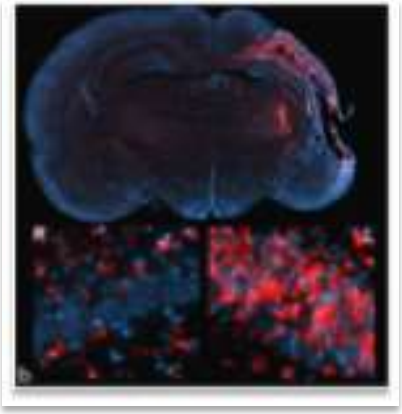
5 hrs NT
37°C
Veh=40, LPS=40

5 hrs HT
32°C
Veh=38, LPS=35

24 hrs survival OR 1 week survival



Western blots



Immunohistochemistry

Pathology – Area Loss (P14)

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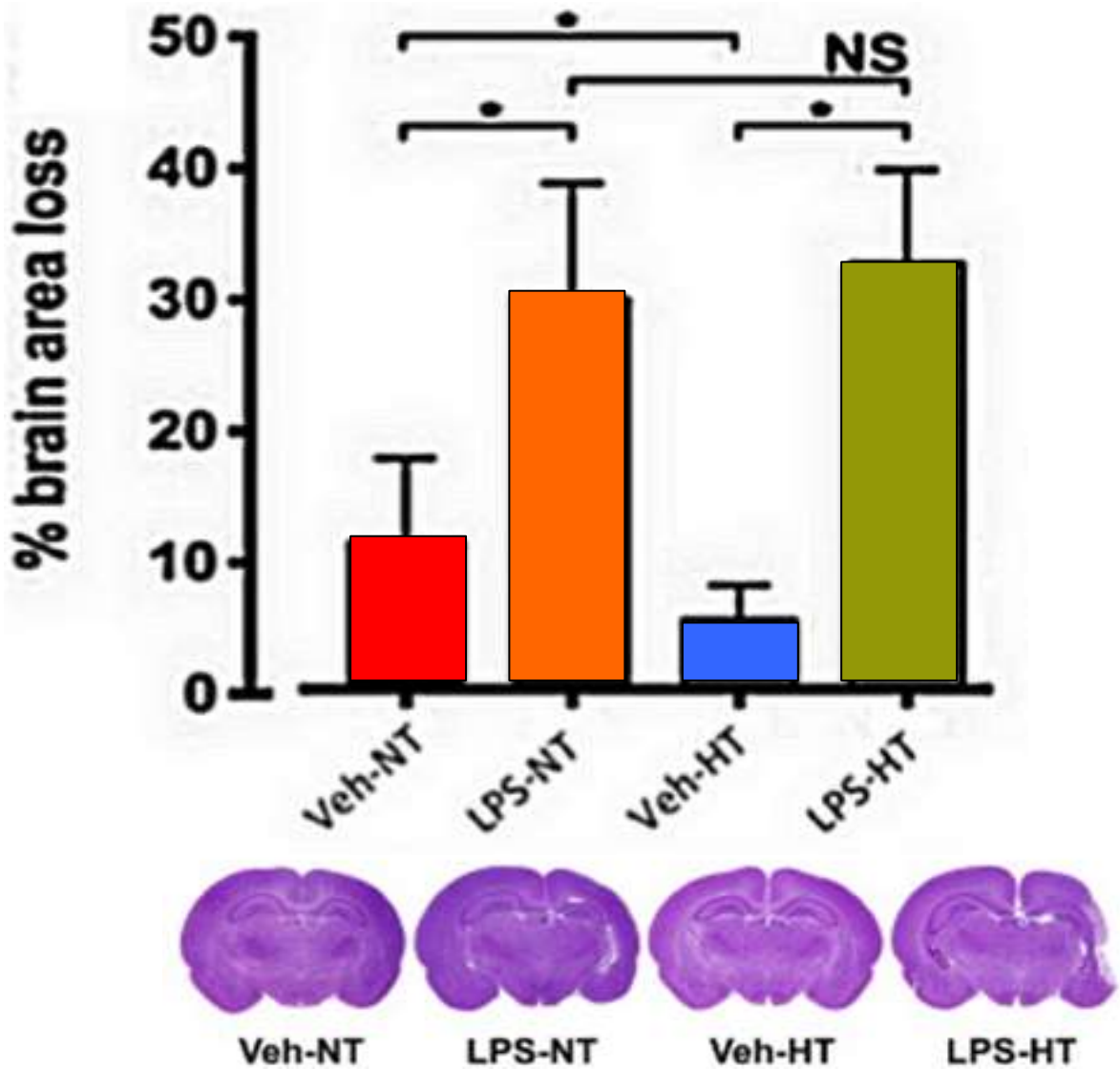
Hypothermia Did Not Offer Any Neuroprotection After LPS+HI



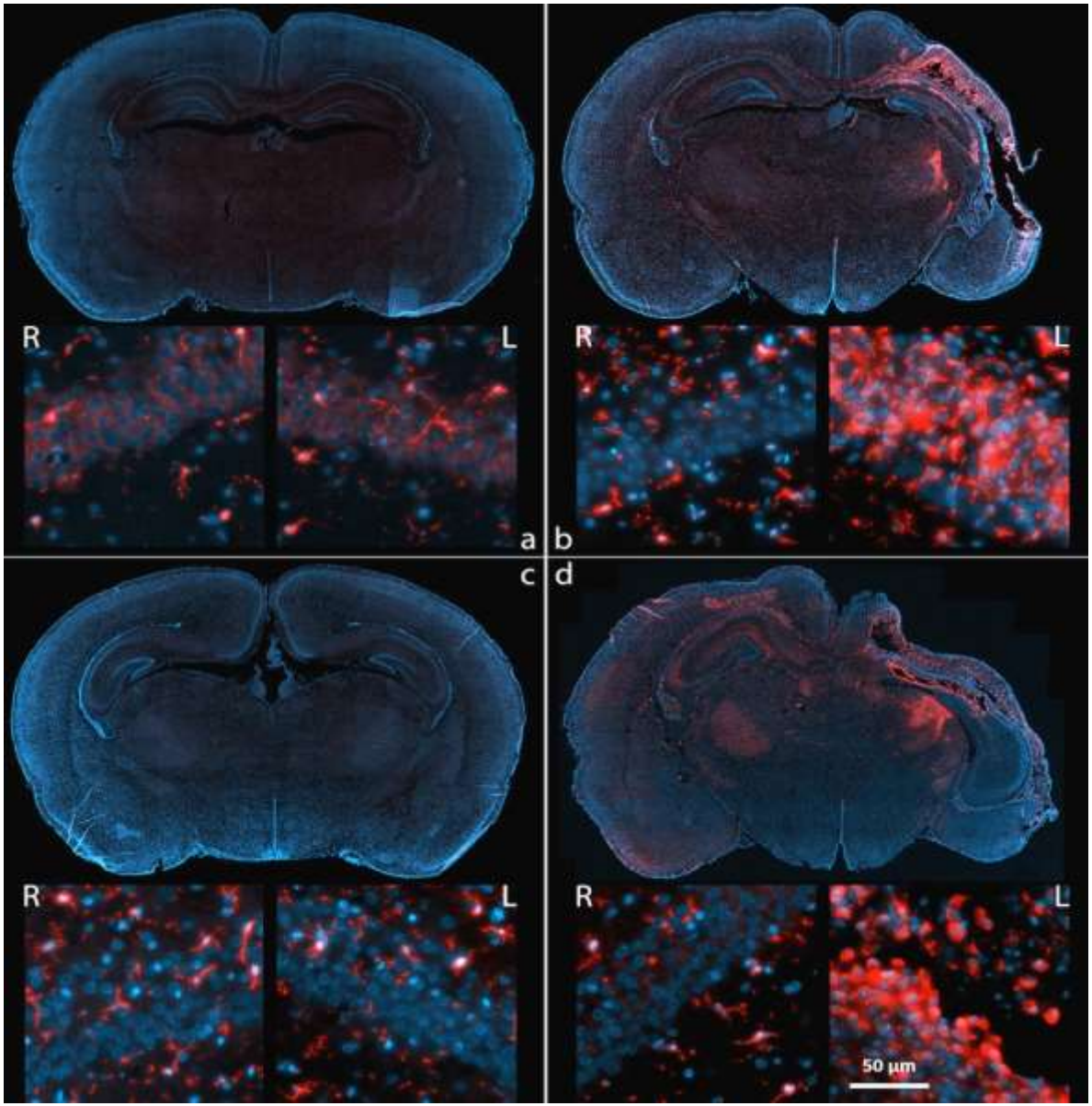
Osredkar et al. Resuscitation. 2014

Increased Microglial Activation After LPS+HI

Veh LPS

NT 37°C

HT 32°C



= Dapi, nuclei in general

= Iba1, microglia specific

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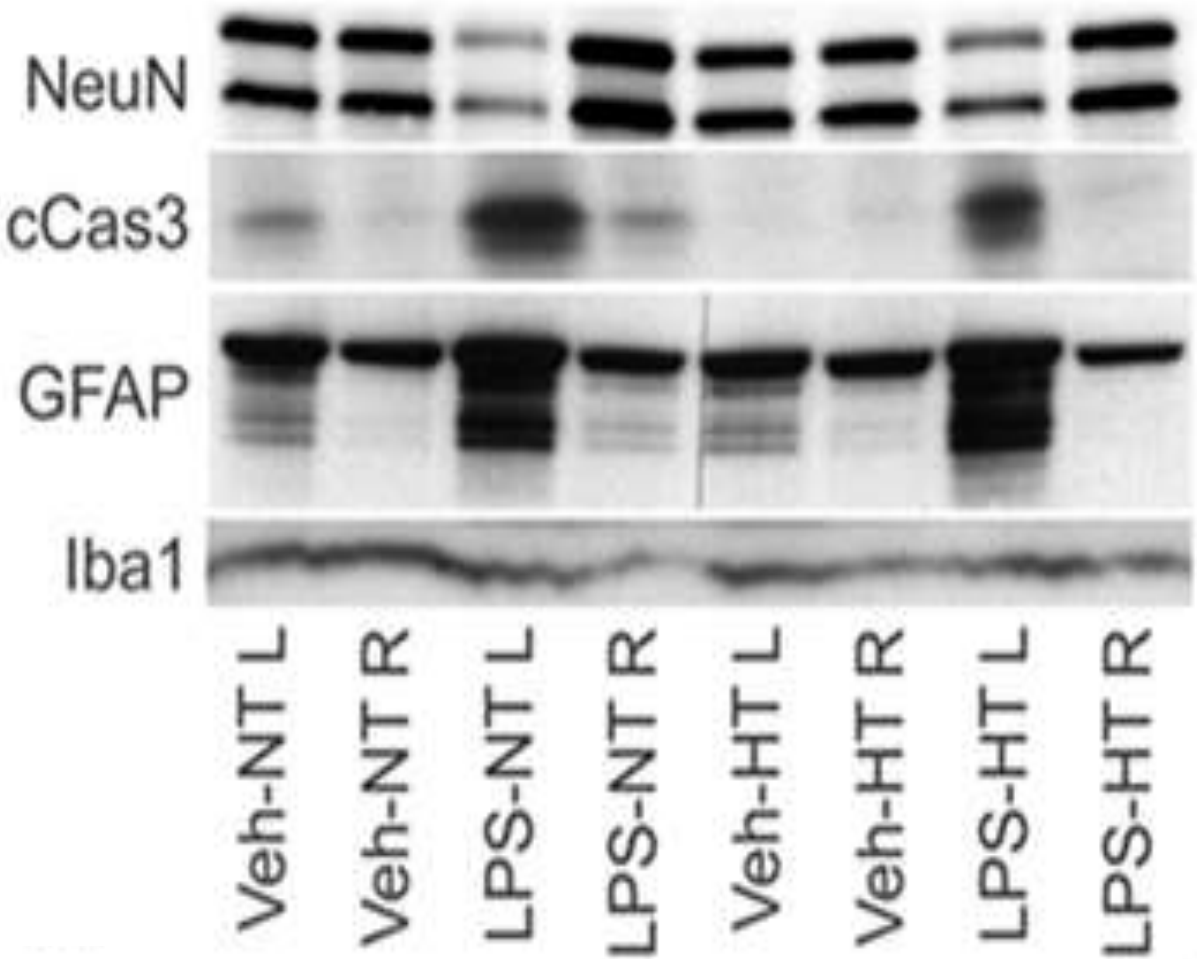
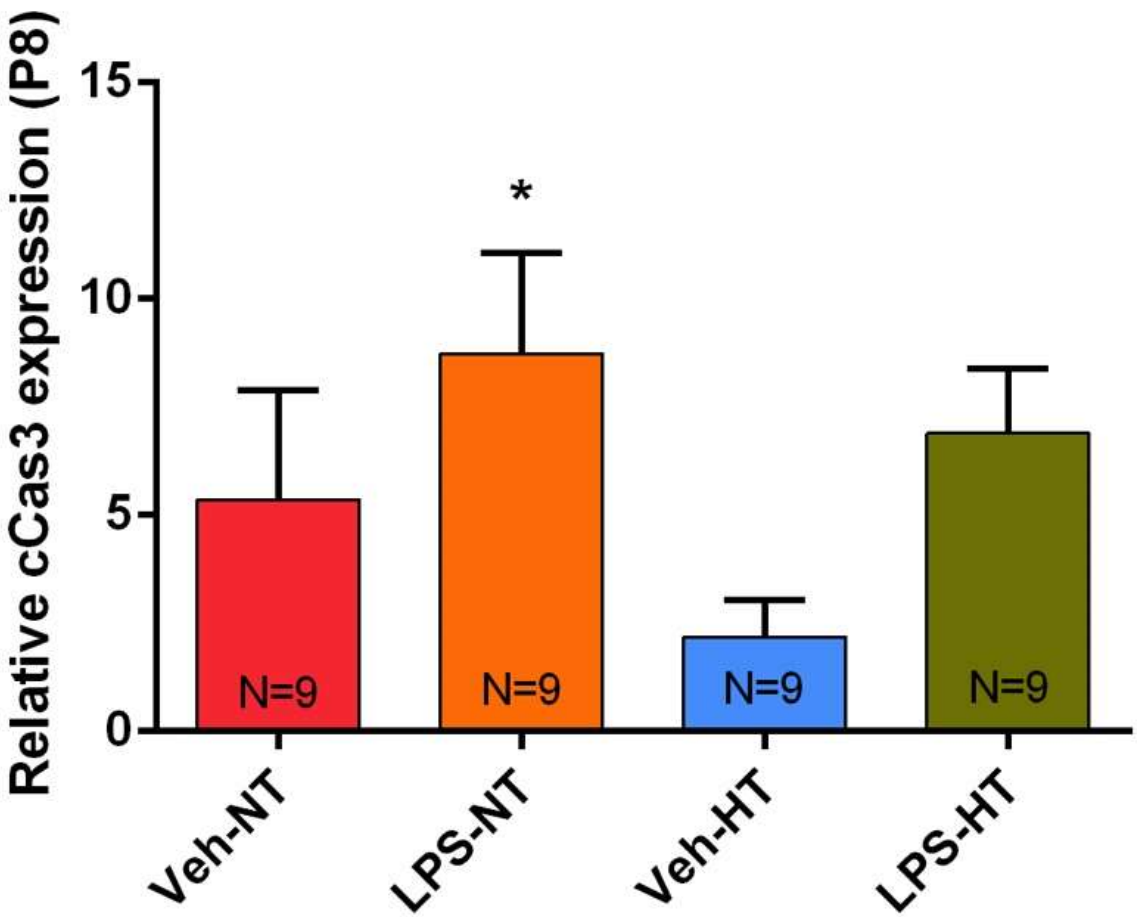
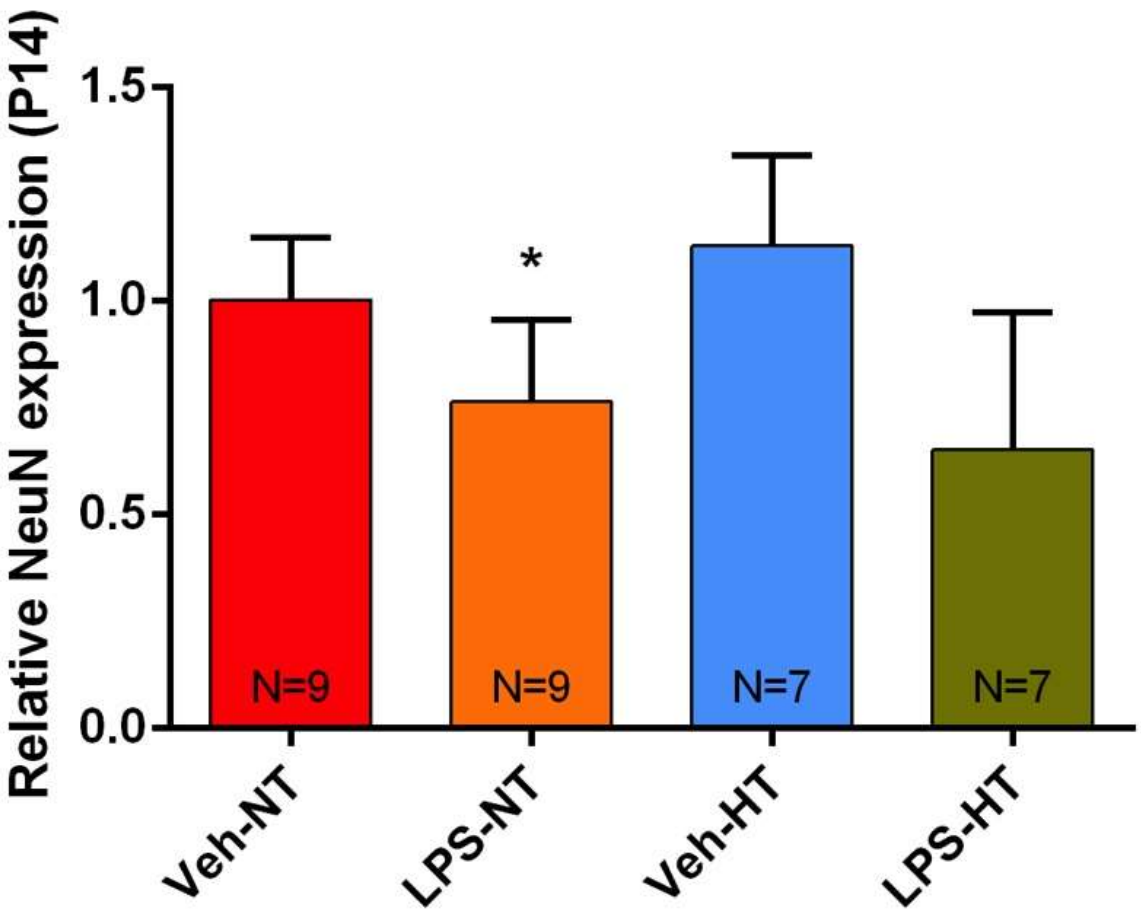
Western Blots



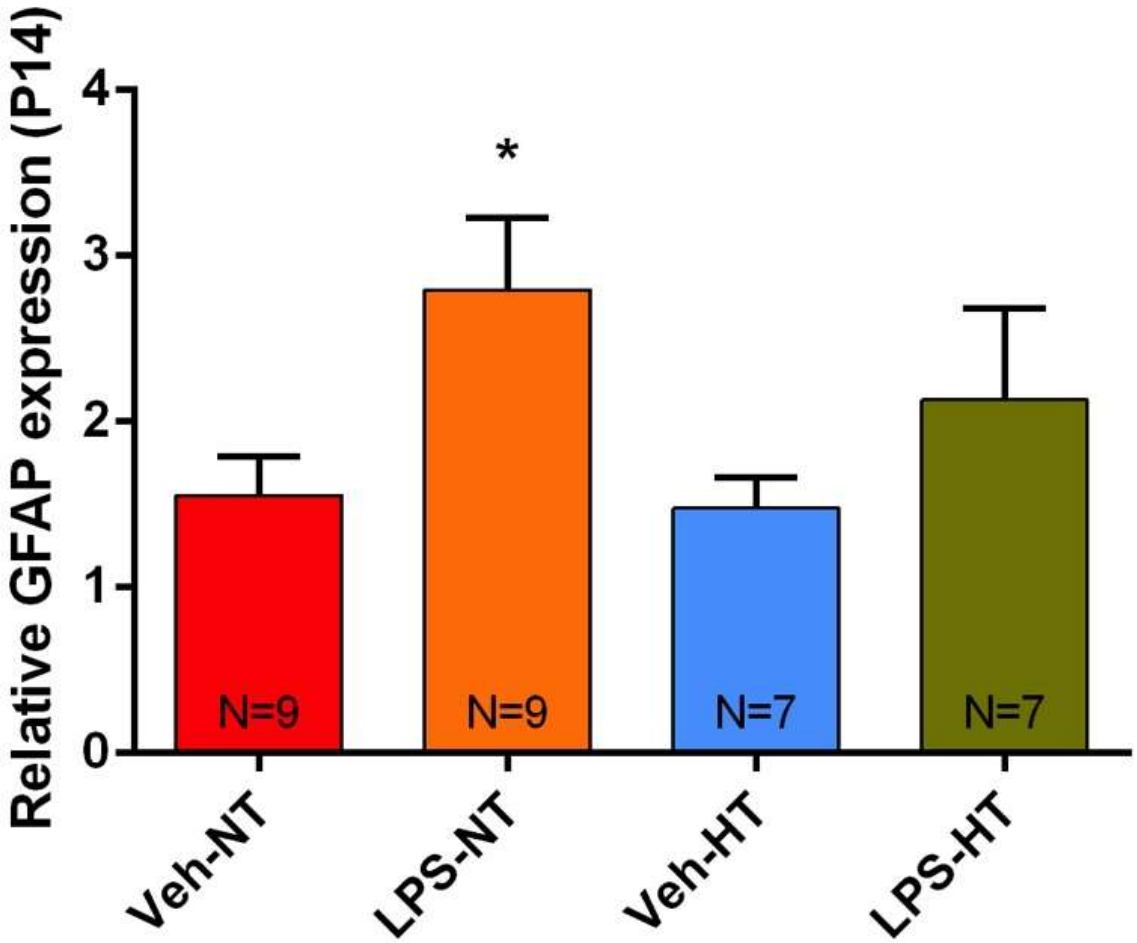
LPS Sensitisation Increases Apoptosis



LPS Sensitisation Exacerbates Neuronal Loss



LPS Sensitisation Enhances Astrogliosis



Clinical Relevance

- Are we cooling the right cohort?
- Should we cool, when there is substantial degree of systemic inflammation?
- Further research (pre-clinical and clinical) is needed

Conclusion

In a P7 HI rat model with systemic inflammation therapeutic hypothermia is not neuroprotective neither macroscopically, nor on a cellular level.

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Thoresen group, Oslo, Norway

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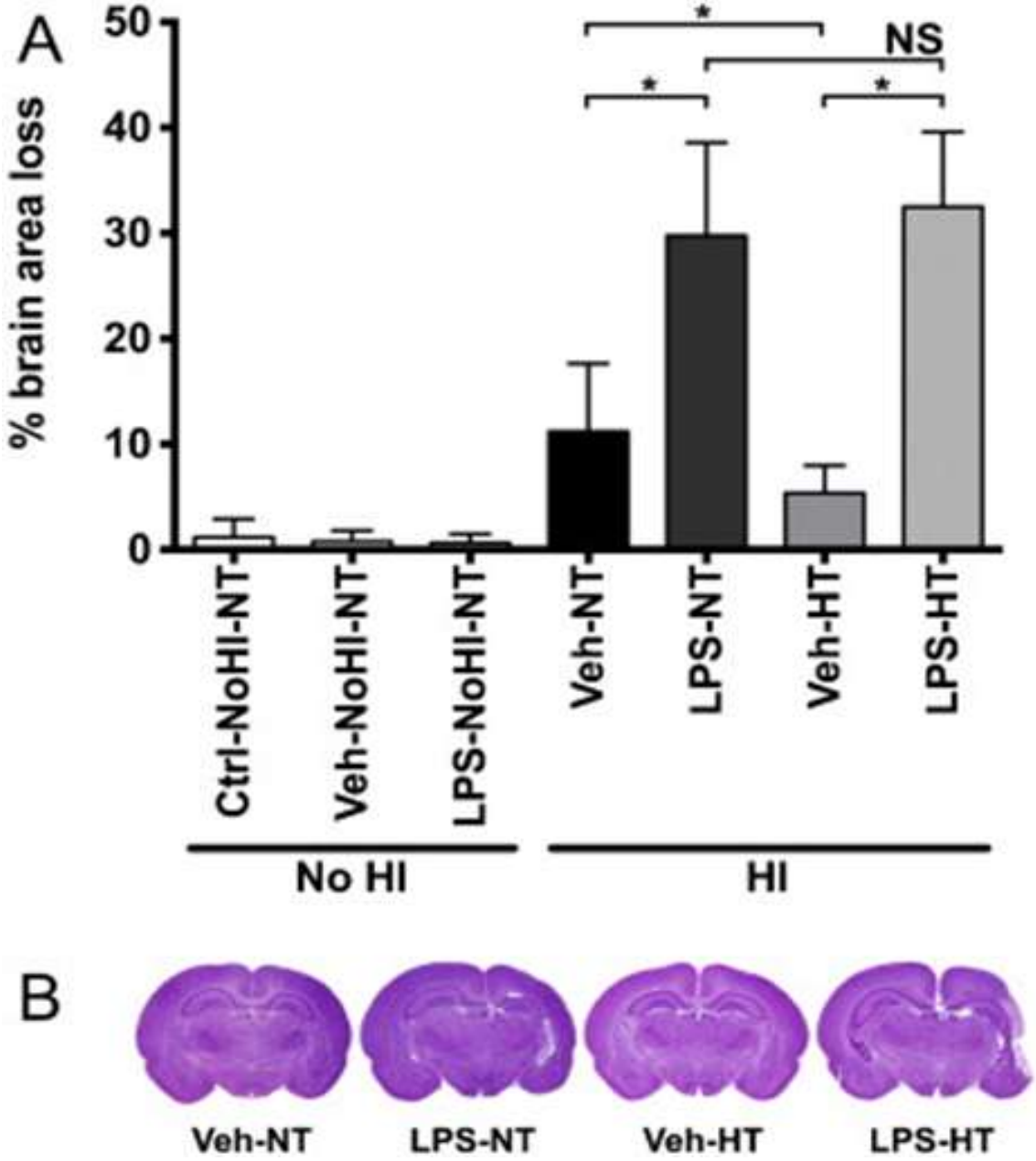
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% brain area loss
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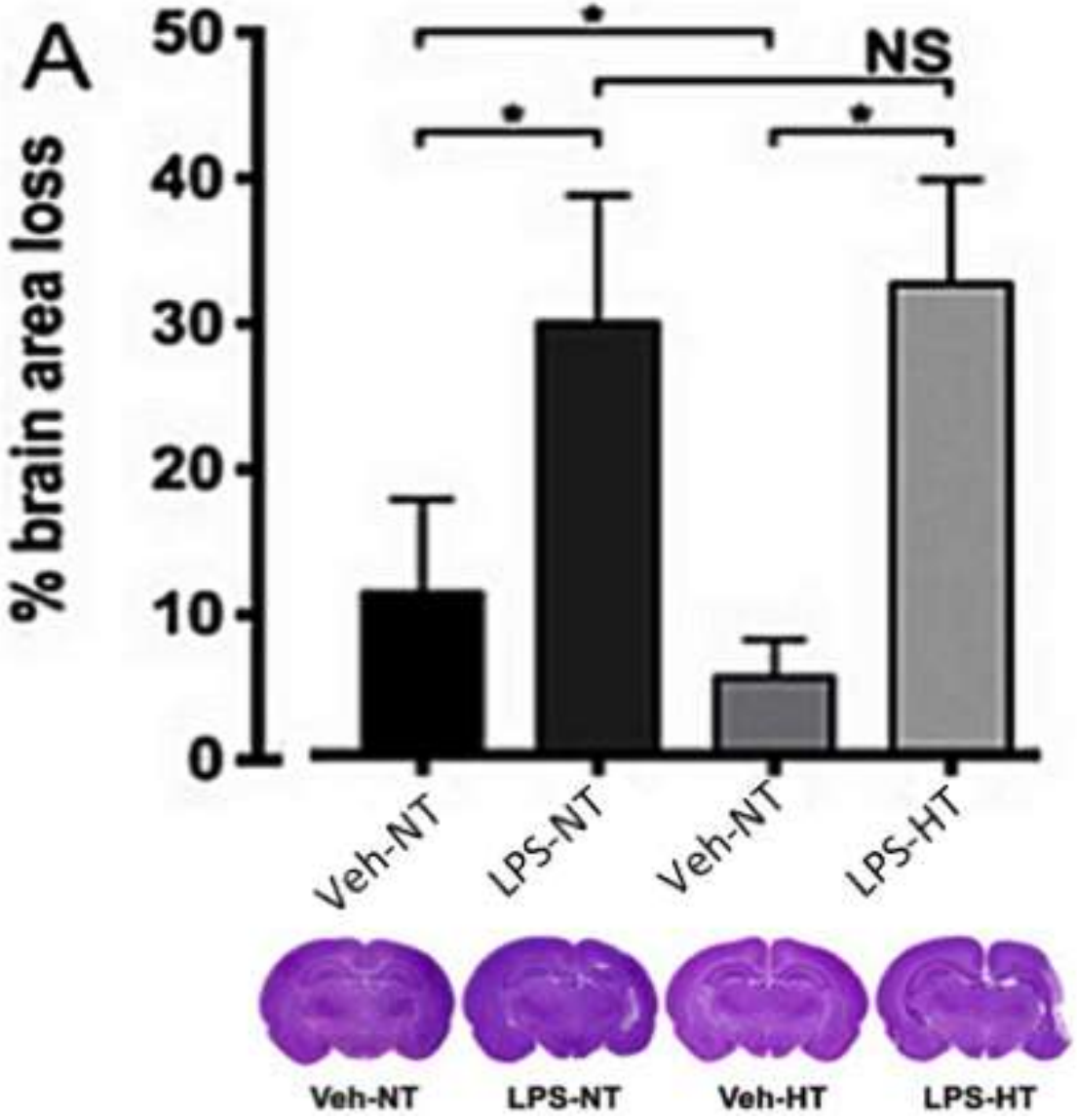
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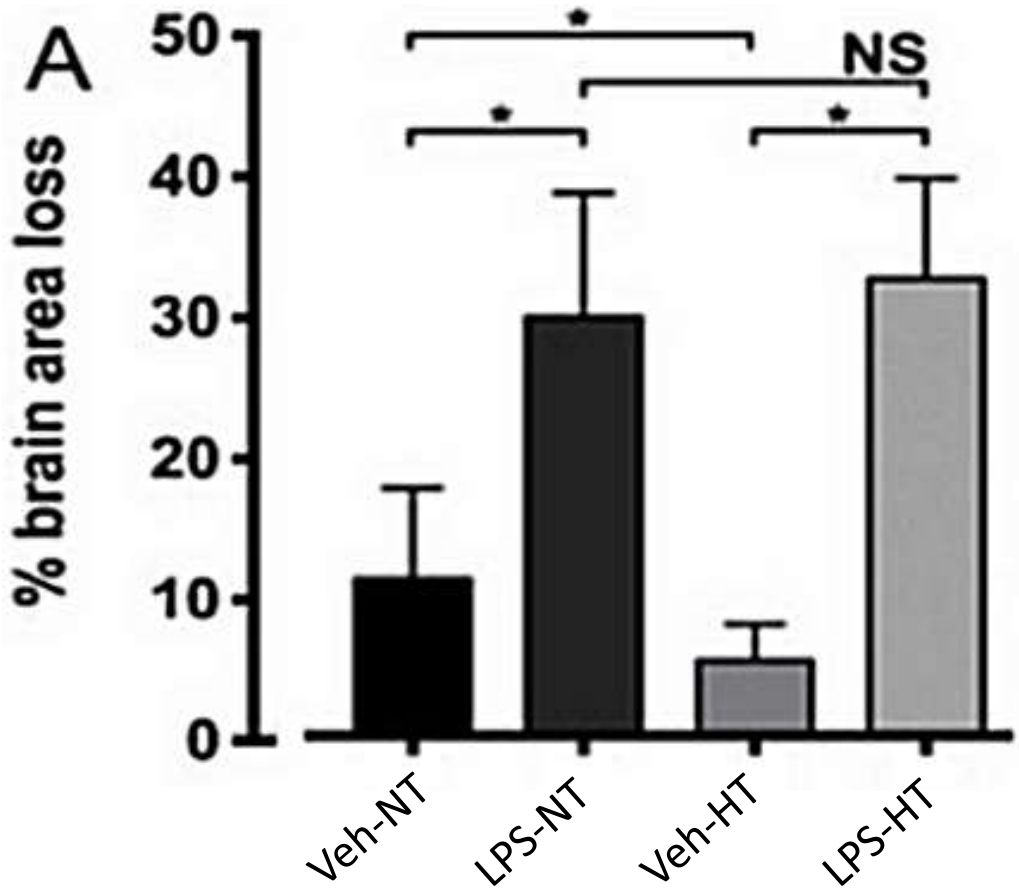
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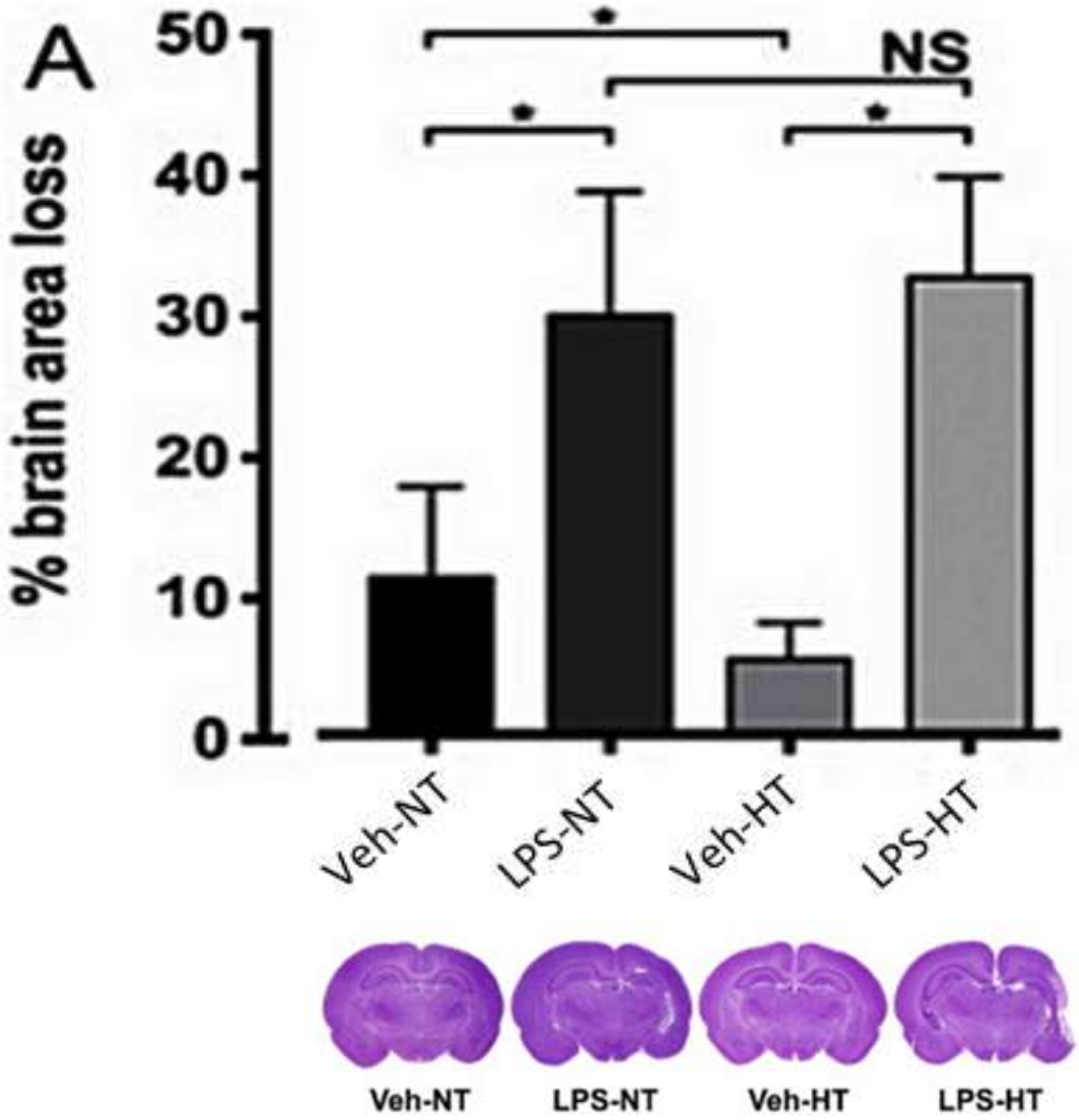
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1. Lee et al. Pediatr. Res 2013.

2. Fleiss et al, *Inflammation-induced sensitization of the brian in term infants*, Dev. Med. Child Neurol. 2015

3. Edwards et al, *Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data*, BMJ 2010

4. Peeples et al, *Synergy between antenatal exposure to infection and intrapartum events in causation of perinatal brain injury at term*, BJOG 2002

5. Osredkar et al, *Hypothermia Does Not Reverse Cellular Responses Caused by Lipopolysaccharide in Neonatal Hypoxic-Ischaemic Brain Injury*, Dev. Neuroscience 2015

6. Osredkar et al, *Hypothermia is not neuroprotective after infection-sensitized neonatal hypoxic-ischemic brain injury, Resuscitation*, 2014

7. asdfkjad

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2. Fleiss et al. Dev Med Child Neurol. 2015 Apr;57 Suppl 3:17-28. doi: 10.1111/dmcn.12723.
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6. Osredkar et al. Dev Neurosci. 2015;37(4-5):390-7. doi: 10.1159/000430860.
7. Osredkar et al. Resuscitation. 2014 Apr;85(4):567-72. doi: 10.1016.

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It has even been shown evidence that elective caesarean section was associated with a highly significant reduction in neonatal encephalopathy. This was in a large Australian case-control study of Badawi et al, published in BMJ in 1998.

that what we refer to as neonatal hypoxic-ishcemic encephalopathy

Developmental Medicine & Child Neurology
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http://onlinelibrary.wiley.com/doi/10.1111/dmcn.12723/full#dmcn12723-fig-0001

Discussion

1. Up-regulation of the innate immune system with early initiation of inflammatory processes by hypoxia leading to glial activation and release of cytotxic cytokines?

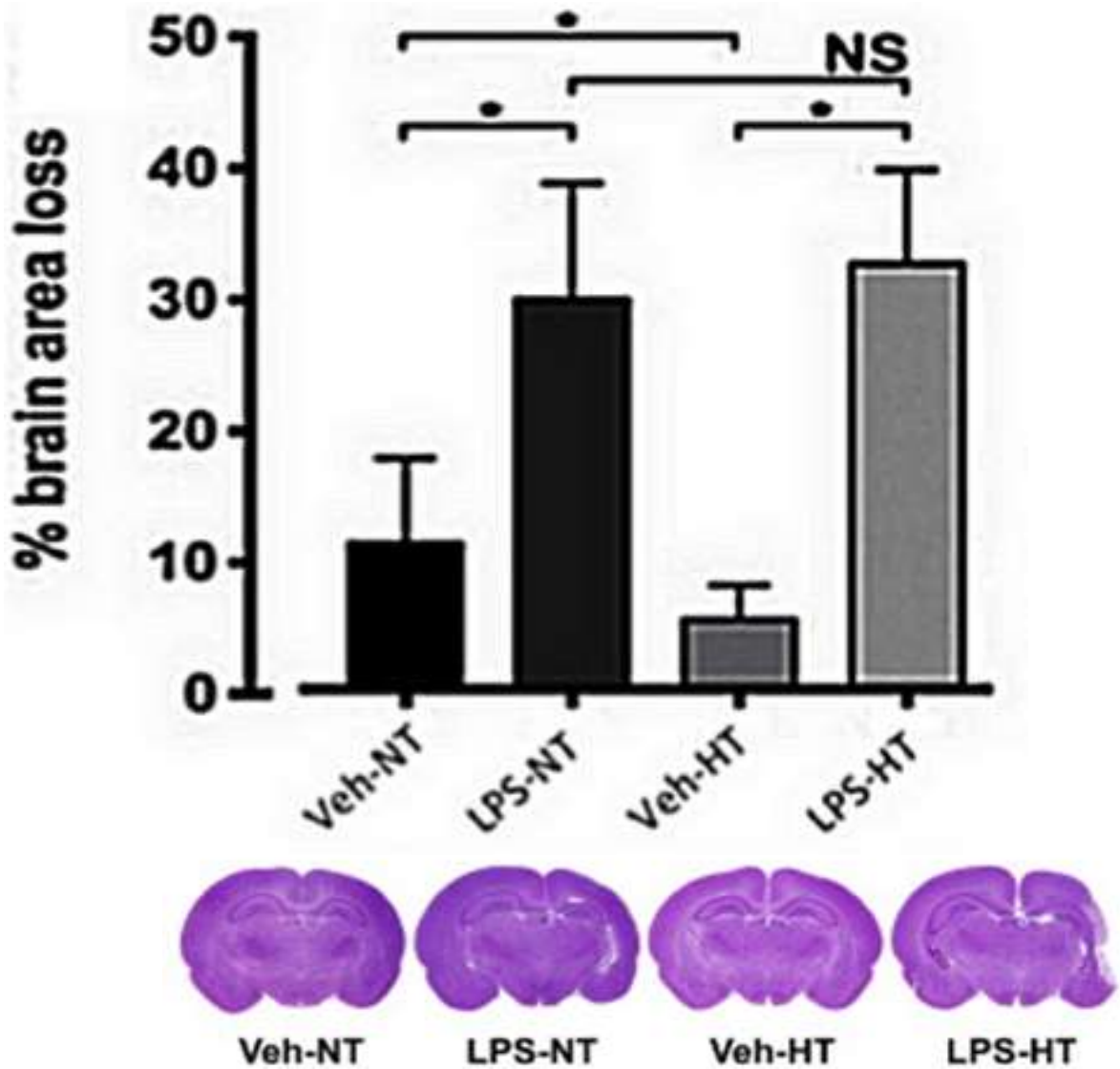
2. Increased NO production leading to mitochondrial dysfunction and failure of oxidative phosphorylation?

3. Endotoxin-induced hypoglycaemia impairing the metabolic response to hypoxia?

4. Exacerbation of local tissue ishcaemia via activation of procoagulant molecules and release of casoactive substances such as PAF and endothelial damage?

5. Increased espression of pro-apaptotic molecules such as Fas ligand or TNF?

Hypothermia did not offer any neuroprotection after LPS+HI



Osredkar et al. Resuscitation. 2014