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Review

What is the pathophysiology of inflammation-induced cortical injury in the perinatal brain?

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From the Contents

Abstract

Perinatal exposure to infection/inflammation is highly associated with neural injury, and subsequent impaired cortical growth, disturbances in neuronal connectivity, and impaired neurodevelopment. However, our understanding of the pathophysiological substrate underpinning these changes in brain structure and function is limited. The objective of this review is to summarize the growing evidence from animal trials and human cohort studies that suggest exposure to infection/inflammation during the perinatal period promotes regional impairments in neuronal maturation and function, including loss of high-frequency electroencephalographic activity, and reduced growth and arborization of cortical dendrites and dendritic spines resulting in reduced cortical volume. These inflammation-induced disturbances to neuronal structure and function are likely to underpin subsequent disturbances to cortical development and connectivity in fetuses and/or newborns exposed to infection/inflammation during the perinatal period, leading, in the long term, to impaired neurodevelopment. The combined use of early electroencephalography monitoring with neuroimaging techniques that enable detailed evaluation of brain microstructure, and the use of therapeutics that successfully target systemic and central nervous system inflammation could provide an effective strategy for early detection and therapeutic intervention.

Key Words: anti-inflammatory therapies; cerebral cortex; chorioamnionitis; electroencephalography; magnetic resonance imaging; neonatal sepsis; neurodevelopment; neuroinflammation; neurons

Infection/Inflammation Triggers Neurodevelopmental Impairment

Perinatal inflammation is strongly associated with neurodevelopmental impairments such as vision and hearing impairments, learning difficulties, autism spectrum disorder, attention deficit and hyperactivity, schizophrenia, and cerebral palsy (CP) (Wu and Colford, 2000; Honeycutt et al., 2004; Fleischmann et al., 2021). Indeed, the risk of CP is increased in preterm and term infants exposed to perinatal infection/inflammation (odds ratio: 2.5–9.3) (Grether and Nelson, 1997; Wu et al., 2003; Soraisham et al., 2013). The cumulative lifetime economic cost of CP in the USA was estimated to be over USD 11.5 billion in 2003 (Honeycutt et al., 2004), which equates to approximately USD 20 billion in 2024 after adjusting for changes in the CPI. The cost of disability associated with neurodevelopmental impairments continues to rise and prevention of such impairments would substantially reduce the socio-economic burden on affected individuals, their families, and society (Shih et al., 2018).

Human cohort studies show that exposure to infection/inflammation during the perinatal period is highly associated with brain injury and subsequent neurodevelopmental impairments in preterm and near-term/term infants (Wu et al., 2003; Pappas et al., 2014). Although there are multiple causes of perinatal inflammation, infection is a major trigger in the fetus and newborn globally (Becroft et al., 2010). In late preterm/near term infants, exposure to chorioamnionitis, defined as infection/inflammation of the chorion, amnion, and placenta, and funisitis, defined as inflammation of the umbilical cord, occurs in approximately 18% of cases (Lahra and Jeffery, 2004) and is associated with an increased risk of neurodevelopmental impairment. For example, in a study of 327 term/near-term infants, clinical chorioamnionitis defined by maternal fever, leukocytosis, tachycardia, uterine tenderness, and preterm rupture of membranes, was associated with a 4-fold increase in the risk of CP in early childhood (2 years of age) (Wu et al., 2003). 50%–70% of extremely preterm infants (birth before 28 weeks' gestation) are exposed to antenatal infection/inflammation (Lahra and Jeffery, 2004). In preterm infants, histological chorioamnionitis, defined by semiquantitative assessment of inflammatory cells in the placental disc, fetal membranes, and umbilical cord (Galinsky et al., 2013), was associated with an increased risk of cerebrovascular hemorrhage and cognitive impairment at 2 years of age (Pappas et al., 2014). Moreover, the combination of histological and clinical chorioamnionitis was associated with an increased risk of impaired cognition compared to histological chorioamnionitis alone, suggesting that increased severity of inflammation may augment adverse neurodevelopmental outcomes (Pappas et al., 2014).

Postnatal infection (including early or late onset sepsis) occurs in up to 40% of cases in extremely preterm infants and is associated with a greater risk of both grey and white matter abnormalities (Shah et al., 2008; Stoll et al., 2015; Fleiss et al., 2020). Furthermore, increased concentrations of circulating cytokines, including interleukin-1β, tumor necrosis factor, and interleukin-6 in preterm and term infants are associated with impaired neonatal brain function, and impaired cognition at 2–3 years corrected age (Sävman et al., 1998; Bartha et al., 2004; Wikstrom et al., 2008; O'Shea et al., 2012).

Inflammation-Induced Disturbances to Cortical Growth and Connectivity Play a Major Role in Abnormal Neurodevelopment

Overactivation of central nervous system inflammation is strongly implicated in disturbances to neuronal development and regional reductions

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in grey matter volumes that may underpin long-term behavioral, cognitive and motor disabilities seen in preterm and term infants (Nosarti et al., 2014; Kelly et al., 2024). Magnetic resonance imaging (MRI) studies have shown that exposure to antenatal infection/inflammation is independently associated with reduced sulcal depth and cortical volume, without evidence of overt grey matter injury (Hatfield et al., 2011; Jain et al., 2022). In a recent study in preterm fetal sheep exposed to progressive lipopolysaccharide (LPS)-induced inflammation, Kelly et al. (2023b) showed that systemic inflammation was associated with inflammation within the somatosensory cortex, as shown by increased microglial activation and interleukin 1β immunostaining. Cortical pyramidal neurons within the somatosensory cortex had reduced basal dendrite numbers, complexity, and length, and reduced numbers of dendritic spines (**Figure 1**). Moreover, the number of cortical neurons within the somatosensory cortex did not differ in LPS-exposed subjects compared to controls (Kelly et al., 2023b).

Similarly, postnatal inflammation, using daily intraperitoneal LPS injections in neonatal rats from P1–3, reduced dendritic arborization and spine formation in cortical pyramidal neurons and reduced cortical volume without causing overt neuronal loss (Prasad et al., 2021). Moreover, repeated intraperitoneal injections of inactivated group B Streptococcus to pregnant rats between gestational days 19 and 22 (term) led to thinning of the cerebral cortex and impaired motor function in the offspring at postnatal day 40 (Allard et al., 2019). Collectively, these observations suggest that cortical neuronal arborization and dendritic spine formation in the developing fetus are susceptible to inflammation.

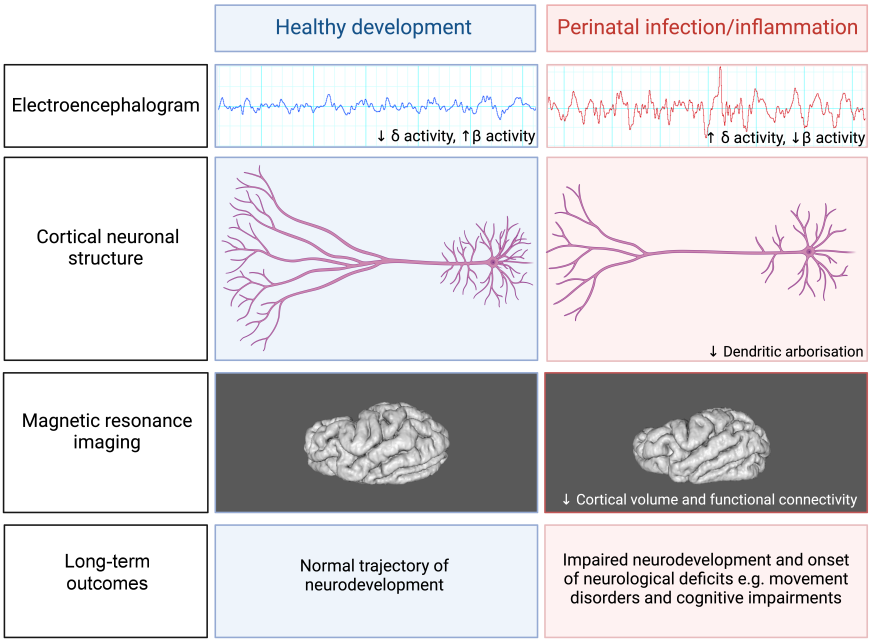

Figure 1 | Summary of the main findings of inflammation-induced effects on EEG activity, neuronal arborization, cortical growth, and neurodevelopmental outcomes.
The left panel shows the trajectory of healthy cortical development in the fetal sheep brain, including development of the EEG (with increased beta activity), growth and arborization of cortical dendrites, and increased cortical volumes, measured using high-field MRI. The right panel shows the trajectory of brain development in fetal sheep exposed to progressive systemic inflammation, including impaired electroencephalogram activity (with reduced beta activity), and reduced growth and arborization of cortical dendrites. A representative example of cortical reconstructions of a cerebral hemisphere from a fetal sheep exposed to progressive systemic inflammation, acquired using high-field MRI, shows a reduction in cortical volume. These observations are consistent with studies in human neonates that show reductions in cortical volume and functional connectivity after exposure to perinatal infection/inflammation. These disturbances to cortical development are likely to have a significant role in the pathophysiology of poor neurodevelopmental outcomes, including motor and cognitive impairments. Created with BioRender.com. Representative EEG traces and MRI cortical reconstructions are unpublished data from the Galinsky laboratory. EEG: Electroencephalography; MRI: magnetic resonance imaging.

Detecting Evolving Inflammation/Injury in the Perinatal Brain – A Role for Electroencephalography and Magnetic Resonance Imaging

Rapid detection of cerebral inflammation-induced injury/impaired neuronal function at the bedside would facilitate early treatment stratification and could provide an early indication of the patient's responsiveness to neuroprotective interventions. Electroencephalography (EEG) is commonly used to assess functional changes caused by encephalopathy in preterm and term infants (al Naqeeb et al., 1999; Tsuchida, 2013). However, the relationship between the electroencephalogram and development of the neuronal microstructure is poorly understood. In line with the inflammation-induced reduction in cortical neuronal complexity in the somatosensory cortex of late gestation fetal sheep, Kelly et al. (2023b) showed a transient increase in delta (slow wave) activity and a persistent reduction in beta (fast wave) activity, leading to an overall reduction in the spectral edge frequency of the electroencephalogram. These data indicate that inflammation promotes a loss of high-frequency activity, with a corresponding shift to lower-frequency activity (**Figure 1**). There were no differences in myelin density within the large white matter tracts of LPS-exposed fetuses (Kelly et al., 2021), which suggests the inflammation-induced changes in EEG activity were a functional consequence of changes in cortical neuronal development (**Figure 1**).

Consistent with these data, in mice, pre and postnatal immune activation increases slow wave sleep and promotes a shift in EEG spectral band power towards more low-frequency activity and less high-frequency activity (Missig et al., 2018). Moreover, in neonatal rat pups exposed to mild-moderate LPS-induced inflammation, reduced cortical neuronal complexity, increased delta activity, and reduced spectral edge frequency were observed at 7 and 14 days after LPS exposure. In the same subjects, high-field *ex vivo* MRI analysis was unable to detect inflammation-induced changes in cortical development after 7 and 14 days but could identify established changes in cortical microstructure 21 days after LPS exposure (White et al., 2024). Conversely, a study in preterm fetal sheep exposed to antenatal inflammation showed high-field *ex vivo* MRI was capable of detecting a reduction in cortical development (**Figure 1**) and inflammation within the large white matter tracts of the preterm brain as early as 10 days after exposure to progressive LPS-induced inflammation (Galinsky et al., 2020).

In preterm and term infants, reduced EEG frequency predicts subsequent brain injury and neurodevelopmental impairment. For example, reduced EEG frequency was associated with greater severity of neonatal white matter injury (Inder et al., 2003). Similarly, motor and cognitive impairments in early childhood were associated with depression of the EEG background pattern in neonates with evidence of neuroinflammation (Hayakawa et al., 1997; Sävman et al., 1998). Furthermore, in children with bilateral spastic cerebral palsy, an increased latency of somatosensory evoked potentials was reported, suggesting a reduction in the rate of cortical neuronal signaling (Teflioudi et al., 2011). Notably, the latency of somatosensory evoked potentials correlated with exposure to perinatal infection (Teflioudi et al., 2011).

Interestingly, MRI studies suggest there is a reduction in cortical functional connectivity in fetuses exposed to chorioamnionitis (Thomason et al., 2017). Moreover, reduced functional connectivity in the cerebral cortex was observed in preterm infants despite no overt evidence of cortical injury (Smyser et al., 2010; Smyser et al., 2013). Together, these observations suggest that reduced cortical functional connectivity in the fetal and newborn brain could be attributed to inflammation-induced reductions in cortical neuronal complexity and synaptic density (**Figure 1**).

If We Can Detect Adverse Cortical Development, How Do We Treat It?

Despite strong preclinical evidence that exposure to unbridled inflammation in the fetus and newborn triggers brain injury, and encouraging preclinical data from animal trials, no anti-inflammatory interventions have been trailed for the prevention of clinical perinatal brain injury. This most likely reflects uncertainty about the most appropriate drug targets.

Corticosteroids and antibiotics are among the most routinely used anti-inflammatory interventions in perinatology. In a recent systematic review, the corticosteroids betamethasone and dexamethasone were associated with the least promising outcomes in preclinical neuroprotection trials, with 63% of studies reporting either deleterious effects or no improvement to neurological outcomes in animal models of inflammation-induced perinatal brain injury (Kelly et al., 2023c). Indeed, in human trials, corticosteroids have been associated with an increased risk of adverse neurological outcomes, including peri/intraventricular hemorrhage, cerebral palsy, and hyperactivity in childhood (Barrington, 2001; French et al., 2004). The potential for corticosteroids to cause deleterious effects in the perinatal brain is likely to be multifactorial and has been linked to the dose and duration of exposure relative to the timing of the insult, the stage of neurodevelopment at the time of exposure, and their potential to cause hyperglycemia, which animal and human studies have shown is associated with exacerbation of encephalopathy (Lear et al., 2018; Tam et al., 2021).

Antibiotic therapy is a logical strategy to prevent against bacterial infection. Unexpectedly, in a meta-analysis, antibiotics given to women with ruptured fetal membranes and at risk of preterm labor were associated with an increased risk of neonatal death and disability (Flenady et al., 2013). This observation is supported by animal trials. For example, pregnant rabbits treated with antibiotics 24 hours after intrauterine *E. coli* administration had improved offspring survival but surviving kittens had increased white matter cell death (Debillon et al., 2000). The mechanisms for this are unclear, however, it is possible that antibiotic-induced lysis of bacteria releases bacterial fragments that promote inflammation-induced injury. Supporting this hypothesis, a preclinical study has shown increased neural injury with stand-alone antibiotic treatment (Muri et al., 2018). In contrast, combining antibiotics with trocade, a matrix metalloproteinase-9 inhibitor, was associated with improved neurological outcomes, suggesting that in cases of perinatal infection combined use of antibiotics with an anti-inflammatory intervention could be a more effective approach than antibiotics alone (Muri et al., 2018). Moreover, the use of anti-cytokine therapies targeting the primary effector cytokine interleukin-1 was most associated with improved outcomes in animal trials of infection and non-infection related inflammation (Kelly et al., 2023c). This suggests that the use of anti-cytokine therapies as an adjuvant to antibiotic therapy could be an effective approach to ameliorate inflammation-induced injury in the perinatal brain (Kelly et al., 2023a). These considerations supported the development of a phase 1 trial of the FDA-approved interleukin 1 receptor antagonist anakinra for the prevention of inflammatory disease in extremely preterm infants (Green et al., 2022).

In conclusion, there is growing evidence that exposure to perinatal inflammation impairs neuronal maturation and function. This could be the pathophysiological substrate that underpins the increased risk of disturbances in cortical development and connectivity in fetuses or newborns exposed to infection/inflammation during the perinatal period. Ultimately these structural and functional disturbances to cortical development are likely to play a significant role in the pathophysiology of impaired neurodevelopment in infants exposed to perinatal infection/inflammation. The combined use of early EEG monitoring with neuroimaging techniques that enable detailed evaluation of brain microstructure, and the use of therapeutics that successfully target systemic and central nervous system inflammation could provide an effective strategy for early detection and therapeutic intervention.

Search Strategy

Studies mentioned in this review were searched on PUBMED and OVID Medline databases using these keywords: preterm brain injury OR neonatal encephalopathy OR neonatal inflammation OR chorioamnionitis AND cerebral cortex OR cortical growth OR cortical connectivity. All years were included in the search.

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Data availability statement: *Not applicable.*
Open access statement: *This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.*

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围产期脑部炎症引起的皮层损伤的病理学机制是什么？
文章特色分析

一、文章重要性
1. 临床问题突出：
- 围产期感染/炎症是导致新生儿脑损伤和远期神经发育障碍（如脑瘫、自闭症、认知障碍等）的主要因素之一，具有高发病率和高社会经济负担。
- 文章强调了对这一问题的病理生理机制理解的缺乏，并指出当前缺乏有效的抗炎干预措施。
2. 跨学科整合：
- 文章综合了动物实验与人类队列研究的数据，从分子、细胞、电生理到影像学多个层面系统阐述炎症对大脑皮层发育的影响，具有高度的临床与基础科研结合价值。
3. 治疗策略探讨：
- 文章不仅揭示问题，还探讨了现有治疗手段（如糖皮质激素、抗生素）的局限性，并提出了联合抗细胞因子治疗等新型干预策略的前景。

二、创新性特色
1. 聚焦皮层结构与功能的微观改变：
- 不同于以往关注白质损伤的研究，本文强调炎症对皮层神经元树突复杂性、棘突密度、皮层体积和功能连接的影响，揭示了皮层微观结构异常是神经发育障碍的重要基础。
2. 电生理与影像学结合的早期诊断策略：
- 提出 EEG 高频活动减弱与低频活动增强可作为炎症性脑功能损害的早期电生理标志；
- 结合高场强 MRI 评估皮层微观结构变化，为早期识别脑发育异常提供了新思路。
3. 对治疗策略的批判性与前瞻性分析：
- 指出传统抗炎药物（如糖皮质激素）在围产期脑保护中的潜在危害；
- 提出抗生素联合抗炎治疗（如 IL-1 受体拮抗剂） 可能是更有效的神经保护策略，并已进入临床试验阶段。

三、对学科的启示
1. 推动机制研究向临床转化：
- 文章强调从“炎症→神经元结构/功能异常→神经发育障碍”这一连续过程的机制研究，为开发针对性的神经保护疗法提供了理论基础。
2. 倡导多模态早期评估体系：
- 提倡将 EEG 与 MRI 结合用于早期识别高危患儿，推动围产期神经监护从“结构影像”向“功能与微结构并重”转变。
3. 重新审视现有抗炎治疗策略：
- 呼吁在围产期感染管理中避免单一依赖抗生素或激素，应考虑联合靶向抗炎治疗，以减轻继发性神经损伤。
4. 促进跨学科合作：
- 本文整合了生理学、影像学、免疫学、神经发育学等多学科证据，为未来围产期脑损伤研究提供了多维度的研究框架。

总结
本文在围产期神经科学领域具有重要的学术与临床价值，其创新之处在于系统揭示了炎症对皮层发育的微观与功能影响，并提出了结合电生理、影像学与靶向治疗的早期诊断与干预策略，对未来研究方向和临床实践具有深远的启示意义。