



## Relationship between volumetric differences in the brain in children with hypoxic ischemic encephalopathy after therapeutic hypothermia.

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### Abstract

#### Background

Therapeutic hypothermia (TH) is the standard neuroprotective treatment for moderate-to-severe hypoxic-ischemic encephalopathy (HIE) in neonates. Although TH reduces mortality and severe disability, many survivors develop subtle cognitive, memory and motor impairments later in childhood.

#### Objective

This systematic review synthesizes evidence on volumetric brain differences detected using magnetic resonance imaging (MRI) in children with HIE treated with therapeutic hypothermia and evaluates associations with neurodevelopmental outcomes.

#### Methods

A structured search of PubMed/MEDLINE, Embase, Scopus, Web of Science and Google Scholar identified peer-reviewed studies including term or near-term infants with HIE treated with TH that reported quantitative volumetric MRI data and neurodevelopmental outcomes. Study selection followed PRISMA guidelines. Data on imaging timing, segmentation methods, regional brain volumes and outcome correlations were extracted. Methodological quality was appraised using validated tools for observational studies.

#### Results

Across included cohorts, consistent volumetric alterations were reported in deep gray matter structures, hippocampus, cerebellum, brainstem and global brain volume. In a neonatal cohort, brainstem volume reduction ( $p < 0.05$ ) and ventricular enlargement ( $p < 0.01$ ) were associated with abnormal neurodevelopment after TH. At 5-year follow-up, hippocampal volumes were significantly smaller in HIE survivors compared with controls ( $p = 0.02$ ), with positive correlations between hippocampal volume and memory performance ( $r = 0.66$ ,  $p = 0.038$ ). In school-age children without cerebral palsy, reduced hippocampal and thalamic volumes correlated with full-scale IQ (hippocampus  $r = 0.477$ ,  $p = 0.010$ ; thalamus  $r = 0.452$ ,  $p = 0.016$ ) and motor performance ( $p < 0.01$ ).

#### Conclusions

Despite therapeutic hypothermia, measurable regional brain volume differences persist in children with HIE and show statistically significant associations with cognitive and motor outcomes. Volumetric MRI represents a promising quantitative biomarker for injury severity and long-term prognosis; however, methodological standardization and longitudinal validation remain necessary.

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**Keywords:** Hypoxic-ischemic encephalopathy; Therapeutic hypothermia; Magnetic resonance imaging; Volumetric analysis; Neurodevelopmental outcomes; Brain injury biomarkers

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## Introduction

Hypoxic-ischemic encephalopathy (HIE) is a major cause of neonatal mortality and long-term neurodevelopmental disability worldwide. It results from impaired cerebral blood flow and oxygen delivery during the perinatal period, typically due to intrapartum asphyxia or compromised placental function [1]. The global incidence of HIE ranges from 1–3 per 1,000 live births in high-income countries and may exceed 10 per 1,000 in low-resource settings [2]. Despite advances in perinatal care, HIE remains a leading contributor to cerebral palsy, epilepsy, intellectual disability and behavioral impairments [3,4].

The burden of HIE extends beyond infancy, with survivors frequently demonstrating subtle cognitive, executive and memory deficits even in the absence of overt motor impairment [5,6]. Given its lifelong consequences and substantial healthcare impact, HIE remains a critical focus of neonatal neurology research.

### *Neuroimaging Methodologies in HIE Research: Emphasis on Volumetry*

Neuroimaging has become central to understanding brain injury patterns and predicting outcomes in HIE. Magnetic resonance imaging (MRI) is considered the gold standard for assessing neonatal brain injury due to its high spatial resolution and ability to characterize both acute and chronic injury [7,8]. Conventional MRI sequences identify characteristic injury patterns, including basal ganglia–thalamic and watershed cortical injuries [9].

Beyond qualitative assessments, quantitative neuroimaging techniques have gained prominence. Volumetric MRI allows for objective measurement of total and regional brain volumes, including cortical grey matter, white matter, hippocampi, thalami and cerebellum [10,11]. Automated segmentation tools and atlas-based approaches further enable reproducible volumetric analysis across developmental stages [12].

Recent studies have demonstrated that volumetric reductions in deep grey matter and hippocampal regions correlate strongly with cognitive and motor outcomes, even among children treated with therapeutic hypothermia [13,14]. These findings highlight volumetry as a potential biomarker for long-term prognosis and a critical outcome measure for neuroprotective trials.

### *Mechanisms Underlying Brain Injury in HIE*

The pathophysiology of HIE unfolds in distinct but overlapping phases. The initial hypoxic-ischemic insult

leads to primary energy failure due to depletion of adenosine triphosphate (ATP), resulting in membrane depolarization, excitotoxic glutamate release and intracellular calcium influx [15].

A secondary phase occurs hours later, characterized by mitochondrial dysfunction, oxidative stress, inflammation and apoptotic cell death [16,17]. The selective vulnerability of regions such as the basal ganglia, thalamus and hippocampus reflects differences in metabolic demand and receptor distribution [1].

More recently, tertiary injury processes—including chronic inflammation, impaired myelination and altered neurogenesis—have been recognized as contributors to long-term structural abnormalities [18]. These evolving mechanisms underpin the structural changes detectable on volumetric imaging and explain the persistence of neurodevelopmental impairments.

### *Therapeutic Hypothermia as a Neuroprotective Strategy*

Therapeutic hypothermia (TH) is currently the standard of care for moderate to severe neonatal HIE. Large randomized controlled trials—including the TOBY, NICHD and CoolCap trials—demonstrated that controlled cooling to 33–34 °C for 72 hours significantly reduces mortality and severe disability [19–21].

The neuroprotective effects of TH are attributed to its capacity to attenuate secondary energy failure, reduce excitotoxicity, suppress inflammation and limit apoptotic pathways [22,23]. Follow-up studies have shown sustained benefits into middle childhood [5].

However, while TH improves survival and reduces severe disability, it does not fully prevent subtle structural brain alterations detectable on MRI [24]. This has prompted increasing investigation into quantitative imaging markers, including volumetric measures, to better understand residual brain differences.

### *Long-Term Neurodevelopmental Outcomes*

Survivors of HIE demonstrate a broad spectrum of outcomes. Severe cases may develop cerebral palsy, epilepsy and global developmental delay [25]. However, even children without overt motor impairment may exhibit impairments in executive function, attention and memory during school age [26,27].

Neuroimaging studies suggest that reduced volumes in hippocampal and subcortical regions are associated with poorer cognitive outcomes [28]. Importantly, some deficits may not emerge until later childhood when



higher-order cognitive demands increase, underscoring the need for longitudinal imaging studies [5].

#### *Gaps in Knowledge and Future Directions*

Despite advances in therapeutic hypothermia and neuroimaging, several gaps remain. First, variability in imaging protocols and segmentation methodologies limits comparability across studies. Standardization of volumetric approaches is needed to enable meta-analytic synthesis [12].

Second, most studies focus on early neonatal imaging, with fewer examining longitudinal volumetric changes across childhood. The trajectory of brain growth following hypothermic treatment remains incompletely understood.

Third, while volumetric differences correlate with functional outcomes, causative relationships and mechanisms of ongoing neurodevelopmental vulnerability require further elucidation. Integration of multimodal imaging—including diffusion tensor imaging and functional connectivity—with volumetric data may offer deeper insight [10].

Finally, there is a need to determine whether volumetric biomarkers can guide individualized prognostication or serve as surrogate endpoints in emerging neuroprotective interventions beyond hypothermia.

This systematic review aims to comprehensively synthesize existing evidence on volumetric brain differences in children with hypoxic-ischemic encephalopathy (HIE), with particular emphasis on those treated with therapeutic hypothermia. Specifically, the review will evaluate reported alterations in global and regional brain volumes across developmental stages, examine the neuroimaging methodologies and segmentation techniques used to derive volumetric measures and assess the associations between structural volume changes and long-term neurodevelopmental outcomes. In addition, it will explore sources of methodological heterogeneity across studies, including differences in imaging timing, analytic approaches and outcome assessment tools. By integrating current findings, this review seeks to clarify the role of quantitative volumetric MRI as a biomarker of injury severity, recovery trajectory and functional prognosis in HIE, while identifying critical gaps that may inform future research and emerging neuroprotective strategies.

## Methodology

### Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Scopus, Web of Science and Google Scholar. All databases were searched from inception until 31 January 2026 and no filters other than language (English) and human studies were applied. The final search for each database was performed on 31 January 2026 to ensure inclusion of the most recent eligible studies.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to hypoxic-ischemic encephalopathy, therapeutic hypothermia, magnetic resonance imaging, volumetric analysis and neurodevelopmental outcomes. Reference lists of included articles and relevant reviews were manually screened on the same date to identify additional eligible studies.

### Study Selection

All identified records were exported to a reference management software and duplicates were removed prior to screening. Two reviewers independently screened titles and abstracts for eligibility. Full-text articles of potentially relevant studies were retrieved and assessed independently by the same two reviewers against predefined inclusion and exclusion criteria. Discrepancies at any stage were resolved through discussion and consensus. No automation tools were used in the screening process.

### Effect Measures

Given the heterogeneity in study design, imaging timing and outcome reporting, effect measures were extracted as reported by the original studies.

For volumetric comparisons, extracted measures included:

- Absolute or relative brain volumes (mean  $\pm$  standard deviation)
- Volume differences between groups
- p-values for between-group comparisons
- Correlation coefficients (Pearson's  $r$  or Spearman's  $\rho$ ) between regional volumes and neurodevelopmental outcomes
- Regression coefficients and adjusted odds ratios when available



For neurodevelopmental outcomes, effect measures included:

- Standardized test scores (e.g., Bayley Scales, IQ scores)
- Motor classification outcomes (e.g., presence of cerebral palsy)
- Correlation statistics between volumetric measures and functional outcomes

Because of methodological heterogeneity and variable reporting metrics, pooled effect estimates were not calculated.

### Reporting Bias Assessment

Due to the absence of meta-analysis and the limited number of homogeneous studies per outcome, formal statistical assessment of publication bias (e.g., funnel plot asymmetry or Egger's regression test) was not feasible.

To mitigate potential reporting bias, the following steps were undertaken:

- Comprehensive multi-database search strategy without restriction by outcome direction
- Screening of reference lists of relevant studies
- Inclusion of both positive and negative volumetric findings were reported
- Evaluation of selective outcome reporting within included studies during risk-of-bias assessment

Where studies lacked complete statistical reporting or selectively presented regional findings without full volumetric data, this was noted during qualitative synthesis.

## Results

### Study Selection

The database search identified 312 records. After removal of duplicates (n = 74), 238 titles and abstracts were screened. Of these, 198 were excluded for irrelevance, including non-volumetric imaging studies, animal experiments, review articles and studies without therapeutic hypothermia cohorts.

Forty full-text articles were assessed for eligibility. Twenty-nine were excluded for the following reasons: absence of quantitative volumetric MRI (n = 11), lack of therapeutic hypothermia subgroup (n = 6), case series with fewer than 10 participants (n = 4), absence of neurodevelopmental outcome assessment (n = 5) and review articles (n = 3).

Eleven studies met inclusion criteria and were included in the qualitative synthesis.

### Study Characteristics

The included studies comprised prospective cohort studies (n = 6), retrospective cohorts (n = 3) and secondary analyses of randomized controlled trials (n = 2). Sample sizes ranged from 10 to 50 participants in individual cohorts. MRI acquisition timing varied from the neonatal period (within the first 7–14 days of life) to school age (6–10 years).

Volumetric approaches included manual tracing and automated segmentation methods. Brain regions most frequently analyzed were the hippocampus, thalamus, basal ganglia, total brain volume, white matter, cerebellum, brainstem and ventricular volume.

Neurodevelopmental outcomes were assessed using standardized tools including the Bayley Scales of Infant Development, full-scale IQ testing, memory assessments, motor performance batteries (e.g., MABC-2) and diagnosis of cerebral palsy.

**Table 1. Characteristics of Included Volumetric MRI Studies in HIE Treated with Therapeutic Hypothermia**

Author (Year)	Study Design	Sample Size	Age at MRI	Brain Regions Assessed	Outcome Measures
Im et al., 2024	Cohort	TH + controls	~10 days	Total brain, cerebrum, cerebellum, brainstem, ventricles	ND outcome categories
Pfister et al., 2023	Cohort	10 HIE, 8 controls	5 years	Total brain, hippocampus	Memory, cognition
Spencer et al., 2023	Cohort	31 HIE, 32 controls	6–8 years	Grey matter, white matter, hippocampus, thalamus	IQ, MABC-2
Annink et al., 2021	Cohort	50	10 years	Hippocampus, mammillary bodies	IQ, memory

Parikh et al., 2009	RCT secondary analysis	NICHD cohort	Neonatal	Relative tissue volumes	Bayley PDI
Massaro et al., 2010	Retrospective	47	Neonatal	Basal ganglia, thalamus (quantitative signals)	CP, death
O’Kane et al., 2021	Prospective cohort	49	Early vs late neonatal	Injury scoring	15–30 month outcomes

### Risk of Bias Within Studies

Using the Newcastle–Ottawa Scale for observational studies, overall methodological quality was moderate.

Selection bias was moderate in smaller cohorts due to limited sample size. Most studies used clearly defined inclusion criteria and appropriate comparison groups. Six studies adjusted analyses for age, sex and total brain volume when evaluating regional volumes. Outcome assessment bias was low in studies employing standardized neuropsychological instruments. Attrition bias was present in several longitudinal cohorts due to incomplete follow-up at school age. No study was judged to be at critical risk of bias.

### Results of Individual Studies

#### Deep Gray Matter Structures

Volumetric reductions in thalamus and basal ganglia were consistently associated with adverse neurodevelopmental outcomes. In a neonatal cohort, reduced brainstem volume ( $p < 0.05$ ) and increased ventricular volume ( $p < 0.01$ ) were observed in infants with abnormal neurodevelopment following therapeutic hypothermia. Severe HIE without hypothermia demonstrated significantly reduced cerebral ( $p < 0.01$ ), cerebellar ( $p < 0.05$ ), brainstem ( $p < 0.001$ ) and total brain volumes ( $p < 0.01$ ).

At school age, reduced thalamic volumes correlated positively with full-scale IQ ( $r = 0.452$ ,  $p = 0.016$ ) and motor performance scores ( $p < 0.01$ ). Subcortical volume reductions were often not independent of total brain volume, indicating global growth effects.

Quantitative signal intensity ratios in basal ganglia and thalamus were significantly associated with adverse neurological outcomes in cooled neonates, with T2 intensity ratios demonstrating predictive value comparable to qualitative MRI assessment.

#### Hippocampal Volume

Selective hippocampal vulnerability was a consistent finding across neonatal and school-age cohorts. At 5-year follow-up, children treated with therapeutic hypothermia exhibited significantly smaller hippocampal volumes compared with controls ( $p = 0.02$ ). Within the HIE cohort, hippocampal volume positively correlated with memory performance ( $r = 0.66$ ,  $p = 0.038$ ).

In school-age cohorts without cerebral palsy, hippocampal volume was significantly associated with full-scale IQ ( $r = 0.477$ ,  $p = 0.010$ ) and motor performance ( $p = 0.004$ ). Reduced hippocampal volume and mammillary body atrophy were also associated with lower IQ and episodic memory scores at 10 years of age.

Total brain volume did not always differ significantly between groups, suggesting region-specific vulnerability.

**Table 2. Summary of Volumetric Findings and Effect Estimates**

Study	Key Volumetric Finding	Effect Estimate	Precision
Im 2024	↓ Brainstem volume in abnormal ND	$p < 0.05$	—
	↑ Ventricular volume	$p < 0.01$	—
Pfister 2023	↓ Hippocampal volume	$p = 0.02$	—
	Hippocampus vs memory	$r = 0.66$	$p = 0.038$
Spencer 2023	Hippocampus vs IQ	$r = 0.477$	$p = 0.010$
	Thalamus vs IQ	$r = 0.452$	$p = 0.016$
Annink 2021	↓ Hippocampus & MB → ↓ IQ	Significant	—



Parikh 2009	Relative TBV → impairment	Significant	—
Massaro 2010	↑ T2 ratio → adverse outcome	Significant	—

## Global Brain and White Matter Volume

Global volumetric reductions were reported in several cohorts. Enlarged ventricles were observed in infants with abnormal neurodevelopment, consistent with ex vacuo dilation secondary to parenchymal loss.

Relative total brain volume was significantly associated with death or neurosensory impairment at 18–22 months in randomized trial cohorts. Relative cortical grey matter and subcortical white matter volumes correlated with Bayley Psychomotor Development Index scores. Whole-brain grey and white matter volumes were reduced at school age in children treated with therapeutic hypothermia, particularly in those with neonatal cortical injury.

## Cerebellum and Brainstem

Cerebellar volume reduction was reported in neonatal severe HIE and in selected follow-up cohorts, although findings were less consistent than deep gray matter changes. Brainstem volume reduction was significantly associated with abnormal neurodevelopment in early neonatal imaging ( $p < 0.05$ ). However, few longitudinal studies specifically evaluated posterior fossa growth trajectories.

## Results of Syntheses

Across studies examining hippocampal volume ( $n = 4$ ), findings consistently demonstrated reduced volume associated with memory and IQ outcomes. Certainty of evidence was considered moderate due to consistent direction of effect but limited sample sizes.

Deep gray matter synthesis ( $n = 6$ ) demonstrated reproducible associations between thalamic volume reduction and motor impairment. Certainty was moderate.

Global brain volume findings ( $n = 4$ ) were directionally consistent but methodologically heterogeneous due to differences in normalization approaches; certainty was low to moderate. Cerebellar findings were inconsistent across studies and limited by small sample sizes; certainty was low. Due to heterogeneity in imaging timing, analytic pipelines and outcome metrics, quantitative meta-analysis was not performed.

## Reporting Bias Assessment

Formal statistical assessment of publication bias was not feasible given the limited number of studies per outcome and absence of pooled meta-analysis. Selective reporting was suspected in a small number of studies that reported only significant regional findings without complete volumetric datasets. Most observational cohorts lacked publicly registered protocols, limiting evaluation of outcome reporting bias.

## Certainty of Evidence

Using GRADE principles adapted for observational studies:

- Hippocampal volume and memory outcomes: Moderate certainty
- Thalamic volume and motor outcomes: Moderate certainty
- Global brain volume and cognitive outcomes: Low to moderate certainty
- Cerebellar volume and executive outcomes: Low certainty

Certainty was downgraded primarily for small sample size, heterogeneity in imaging methodology and variable follow-up duration.

## Discussion

This systematic review examined volumetric brain differences in children with hypoxic-ischemic encephalopathy (HIE) treated with therapeutic hypothermia (TH), synthesizing findings across MRI-based studies and contextualizing them within the broader neuroimaging literature. Overall, although TH has reduced mortality and severe disability, volumetric MRI studies consistently demonstrate residual alterations in deep gray matter, limbic structures, cerebellum and global brain growth in a subset of survivors. These structural differences frequently correlate with later cognitive, memory and motor impairments, underscoring the importance of quantitative neuroimaging as a biomarker of injury and recovery.

## Hippocampal Volume: Vulnerability and Memory Outcomes



Across included studies, reduced hippocampal volumes were among the most consistently reported findings in children with HIE following TH. This aligns with prior observational and cohort studies demonstrating hippocampal susceptibility to hypoxic-ischemic injury due to its high metabolic demand and glutamate receptor density [38-40].

#### *Significance and mechanisms:*

The hippocampus plays a central role in episodic memory and learning. Selective vulnerability of CA1 pyramidal neurons to hypoxia likely explains long-term volume reduction even when early MRI appears reassuring. Although TH mitigates acute cytotoxic injury, delayed apoptotic pathways and disrupted neurogenesis may still impair hippocampal growth. Animal models [17] suggest that hypothermia attenuates but does not fully prevent delayed neuronal loss in limbic regions.

#### *Neurodevelopmental implications:*

Reduced hippocampal volumes correlate with deficits in memory and executive function at school age [26,41]. Studies outside the hypothermia era [39] and in cooled cohorts [13,32] both demonstrate that smaller hippocampi are associated with poorer performance on verbal memory and working memory tasks.

#### *Consensus and gaps:*

There is broad agreement that hippocampal injury may be underrecognized in the neonatal period. However, discrepancies exist regarding laterality (bilateral vs unilateral reductions) and whether hippocampal volume normalizes partially over time. Longitudinal volumetric data remain limited.

### **Thalamus and Basal Ganglia: Deep Gray Matter and Motor Outcome**

Volumetric reductions in the thalamus and basal ganglia (particularly the putamen and globus pallidus) were strongly associated with adverse motor outcomes across reviewed studies. This is consistent with earlier qualitative MRI literature identifying basal ganglia–thalamus (BGT) injury as predictive of cerebral palsy [8,20].

#### *Significance and mechanisms:*

The thalamus and basal ganglia are highly metabolically active and particularly vulnerable to acute profound hypoxia. Injury to these structures disrupts motor circuitry and corticothalamic connectivity. Although TH reduces the incidence of severe BGT injury [19] volumetric studies reveal that even mild reductions in deep gray matter volume can persist in survivors.

#### *Outcome correlations:*

Multiple studies [36,42,43] show strong correlations between reduced thalamic volume and abnormal motor scores on the Bayley Scales and later Gross Motor Function Classification System (GMFCS) levels. Quantitative thalamic volume often performs comparably to qualitative grading for predicting motor impairment, but offers greater objectivity.

#### *Discrepancies:*

Some cohorts report preserved deep gray matter volumes in children with normal early MRI but subtle motor dysfunction later in childhood, suggesting that volumetric loss may not capture microstructural or connectivity deficits detectable by diffusion tensor imaging (DTI). This highlights the complementary value of multimodal imaging.

### **Cerebellar Volume: Beyond Motor Coordination**

Cerebellar volume reduction was identified in several studies, though less consistently than deep gray matter injury. Historically, cerebellar involvement was underappreciated in HIE, but emerging evidence indicates its role in cognitive and affective regulation [44,45].

#### *Mechanisms:*

Hypoxic injury may disrupt cerebellar Purkinje cells and afferent pathways. Additionally, diaschisis from supratentorial injury may impair cerebellar growth. TH may not fully protect posterior fossa structures due to differential cooling gradients.

#### *Functional implications:*

Reduced cerebellar volume has been associated with deficits in coordination, processing speed and executive function [32,46]. These findings support the concept of the cerebellum as a modulator of higher-order cognition.

#### *Knowledge gaps:*

Few longitudinal volumetric studies have isolated cerebellar growth trajectories in cooled HIE cohorts, limiting conclusions about its long-term contribution to neurodevelopmental outcomes.

### **Brainstem Volume: Autonomic and Developmental Implications**

Brainstem volumetric alterations were less frequently reported but, when present, correlated with more severe neonatal encephalopathy and adverse early outcomes. Given the brainstem's role in autonomic regulation and arousal, injury here may contribute to feeding difficulties,



respiratory instability and global developmental delay [45].

Prior diffusion and spectroscopy studies [40,47] have demonstrated metabolic abnormalities in the brainstem even when structural MRI appears normal. Volumetric MRI may underestimate subtle injury in this region.

### Ventricular Enlargement and Global Brain Volume

Enlarged lateral ventricles and reduced total brain volume were common findings in children with moderate-to-severe HIE despite TH. Ventricular enlargement likely reflects ex vacuo dilation secondary to parenchymal loss.

#### *Clinical significance:*

Reduced total brain volume correlates with global developmental delay and lower IQ scores at school age [26,41] Relative white matter volume reductions, particularly subcortical white matter, have also been linked to impaired psychomotor outcomes.[41]

#### *Consensus:*

There is general agreement that global volumetric reduction reflects cumulative injury burden. However, variability in normalization methods (absolute vs intracranial volume-adjusted measures) complicates comparisons across studies[44].

### Correlation with Cognitive, Memory and Functional Outcomes

Across studies, volumetric differences show region-specific functional correlations:

- Hippocampus → Memory and learning deficits
- Thalamus/Basal ganglia → Motor impairment and cerebral palsy
- White matter and total brain volume → Processing speed and global cognition
- Cerebellum → Executive and motor coordination deficits

Importantly, some children with apparently mild neonatal imaging exhibit later cognitive vulnerabilities, suggesting that early volumetric MRI may underestimate evolving network-level dysfunction [45].

### Strengths and Limitations of Volumetric MRI as a Biomarker

Volumetric MRI offers several important strengths as a biomarker in children with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia. First, it provides an objective and quantitative assessment of brain structure, reducing reliance on subjective qualitative interpretation. Second, volumetric techniques allow for regional specificity, enabling detailed evaluation of vulnerable structures such as the hippocampus, thalamus, basal ganglia, cerebellum and white matter. Third, regional brain volumes have demonstrated meaningful correlations with functional outcomes, including motor, cognitive and memory performance, supporting their clinical relevance. Finally, volumetric MRI facilitates longitudinal tracking of brain growth trajectories, allowing researchers and clinicians to monitor developmental changes over time [47-49].

Several limitations inherent to the review methodology should be acknowledged. Although a comprehensive multi-database search was conducted up to 31 January 2026, restriction to English-language publications may have resulted in language bias. Grey literature, conference abstracts and unpublished datasets were not systematically searched, which may increase susceptibility to publication bias. The included studies were predominantly observational with relatively small sample sizes and heterogeneous imaging protocols, limiting the feasibility of quantitative meta-analysis. Variability in MRI acquisition timing, segmentation techniques, normalization strategies and neurodevelopmental assessment tools introduced methodological heterogeneity that constrained direct cross-study comparability. Formal statistical assessment of publication bias was not possible due to the limited number of studies per outcome and absence of pooled effect estimates. In addition, most included studies lacked preregistered protocols, restricting evaluation of selective outcome reporting. These factors may influence the strength and generalizability of the synthesized conclusions.

### Methodological Considerations

Several methodological factors contribute to variability across studies. The timing of MRI acquisition is particularly critical: scans obtained within the first week of life may not fully capture delayed apoptotic processes and subsequent volume loss, whereas later imaging reflects injury evolution and secondary degeneration. Sample size remains a recurring limitation, as many



studies include fewer than 50 participants, thereby reducing statistical robustness [50].

Heterogeneity in injury severity also influences results. Studies that include infants with mild HIE alongside moderate-to-severe cases may dilute detectable volumetric differences and obscure structure–function relationships. Variations in analysis techniques further complicate comparisons; automated segmentation tools, such as FreeSurfer, may differ in reliability compared to manual tracing, especially in developing brains where anatomical boundaries are less distinct. Finally, follow-up duration plays a crucial role in interpreting outcomes. Neurodevelopmental assessments conducted at 18–24 months may fail to detect higher-order cognitive or executive deficits that emerge at school age. Standardization across imaging protocols, analytic pipelines and follow-up intervals is therefore essential to improve comparability and reproducibility.

### Future Directions

Future research should prioritize the development of standardized volumetric MRI protocols, including harmonized acquisition parameters, segmentation pipelines and normalization strategies. Large, multicenter longitudinal cohorts are needed to track brain growth trajectories from infancy through adolescence, thereby clarifying the long-term structural consequences of HIE despite therapeutic hypothermia.

Integration of multimodal imaging approaches—including volumetrics, diffusion imaging, spectroscopy and functional connectivity analyses—will likely provide a more comprehensive understanding of injury mechanisms and recovery patterns. Correlating imaging findings with detailed neuropsychological batteries that extend beyond early motor assessments will enhance characterization of cognitive and executive outcomes. Additionally, investigation of adjunctive neuroprotective strategies, such as erythropoietin, xenon, or stem-cell-based therapies, may help determine whether combined treatments further preserve brain growth. Finally, the development of predictive models that integrate imaging, clinical variables and biological biomarkers—potentially using machine learning techniques—holds promise for improving individualized prognostication in this high-risk population.

Volumetric MRI studies demonstrate persistent regional brain differences in children with HIE treated with therapeutic hypothermia, particularly affecting the hippocampus, thalamus, basal ganglia, cerebellum and global brain volumes. These structural alterations correlate meaningfully with memory, cognitive and motor

outcomes across early childhood and school age. While volumetric MRI provides valuable objective biomarkers of injury severity and prognosis, methodological variability and limited longitudinal data constrain definitive conclusions. Standardized imaging approaches and long-term follow-up studies are essential to refine prognostic models and optimize neuroprotective strategies in this vulnerable population.

### Conclusion

This systematic review demonstrates that measurable regional brain volumetric differences persist in children with hypoxic-ischemic encephalopathy (HIE) despite treatment with therapeutic hypothermia. While hypothermia has significantly improved survival and reduced severe disability, quantitative MRI studies reveal residual alterations in vulnerable structures, particularly the thalamus, basal ganglia, hippocampus, cerebellum and global brain volumes. These structural differences show meaningful and region-specific correlations with neurodevelopmental outcomes, including motor impairment, memory dysfunction, cognitive delay and executive deficits extending into school age.

Deep gray matter volume reductions remain strongly associated with adverse motor outcomes and cerebral palsy, whereas hippocampal volume loss appears more closely linked to memory and learning difficulties. Global brain volume reduction and ventricular enlargement reflect cumulative injury burden and correlate with broader cognitive and functional impairments. Importantly, some children with apparently mild early imaging findings may later demonstrate subtle neurocognitive vulnerabilities, highlighting the evolving nature of brain injury and development following HIE.

Volumetric MRI emerges from this review as a promising quantitative biomarker for assessing injury severity and predicting long-term outcomes. However, variability in imaging timing, segmentation methodologies, sample sizes and follow-up duration limits cross-study comparability. Furthermore, volumetric analysis captures structural dimensions but does not fully characterize microstructural, metabolic, or connectivity alterations, underscoring the need for multimodal imaging approaches.

Future research should focus on standardized imaging protocols, larger multicenter longitudinal studies and integration of advanced neuroimaging techniques with detailed neuropsychological follow-up. Such efforts will refine prognostic models, enhance individualized risk stratification and potentially guide the development of adjunctive neuroprotective strategies to complement



therapeutic hypothermia. Ultimately, improving our understanding of post-hypothermia brain growth trajectories is essential for optimizing long-term neurodevelopmental outcomes in this vulnerable population.

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### List of Abbreviations

ADC – Apparent diffusion coefficient  
BGT – Basal ganglia–thalamus  
CP – Cerebral palsy  
DTI – Diffusion tensor imaging  
GMFCS – Gross Motor Function Classification System  
HIE – Hypoxic-ischemic encephalopathy  
IQ – Intelligence quotient  
MB – Mammillary bodies  
MABC-2 – Movement Assessment Battery for Children, Second Edition  
MRI – Magnetic resonance imaging  
ND – Neurodevelopment  
NICHD – National Institute of Child Health and Human Development  
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
RCT – Randomized controlled trial  
TBV – Total brain volume  
TH – Therapeutic hypothermia

### Author Contributions

Dr. Priyadarshini Subramani contributed to study conceptualization, literature search strategy development, screening of studies, data extraction, interpretation of neuroimaging findings and manuscript drafting.

Dr. Karthik Shunmugavelu contributed to methodological design, independent screening and eligibility assessment, data verification, risk-of-bias assessment, critical revision of the manuscript for intellectual content and final approval of the version to be published.

Both authors approved the final manuscript and agree to be accountable for all aspects of the work.

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### Registration and Protocol

This systematic review was conducted in accordance with PRISMA 2020 guidelines. The review was not prospectively registered in PROSPERO or any other international registry. A formal protocol was not publicly registered prior to study initiation. The methodological framework was defined a priori by the authors before commencement of literature screening.

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This review did not receive external funding. No financial or non-financial sponsorship was obtained. The authors conducted this study as part of institutional academic research activities. The institution had no role in study design, data collection, data analysis, interpretation of findings, manuscript preparation, or the decision to submit for publication.

### Competing Interests

The authors declare that they have no competing interests, financial or non-financial, related to this work.

### Availability of Data, Code and Other Materials

All data analyzed in this review were extracted from publicly available peer-reviewed publications cited in the reference list

- Template data extraction forms: Available from the corresponding author upon reasonable request.



- Extracted data from included studies: Available from the corresponding author upon reasonable request.
- Data used for analyses: Derived from published sources; no individual patient data were generated.
- Analytic code: Not applicable, as no meta-analysis or statistical programming was performed.
- Additional materials: PRISMA checklist and risk-of-bias assessments are available from the corresponding author upon request.

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