Neonatal Hypoxic Ischemic Encephalopathy and its Lasting Effects

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This Senior Capstone Experience thesis has been submitted to, and approved by, my Psychology Department research advisor. Dr. Murphy, in partial fulfillment of the Bachelor of Arts degree requirements.

Acknowledgments

I would like to extend my deepest gratitude to my advisor, Dr. Murphy, for all of her guidance as I completed my Senior Capstone Experience. I would also like to thank the entirety of the Psychology Department at Washington College for sharing their knowledge with me throughout my four years here. Thank you to my parents for all they have done to make my Washington College education possible and for all of their support throughout this process, as well as to Connor and Gam for their consistent encouragement. Finally, I am very grateful for Dori McMenamin, Emma Parker-Watt, Olivia Payne, and Stephen Hook for always expressing their belief in me and interest in my work; I could not ask for better roommates.

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Abstract

Hypoxic ischemic encephalopathy is a neonatal condition of reduced blood and oxygen supply to the brain. Therapeutic hypothermia has been used to treat moderate and severe HIE and lowers rates of death in HIE patients. When infants do survive, though, they often face developmental impairments. The purpose of this study was to determine if infants affected by HIE during the perinatal period can overcome these impairments so that later in childhood and adolescence, they are developmentally on track with their healthy peers. Because there is limited knowledge on the effects of HIE into adolescence, potentially because these effects are minimal and thus, overlooked, and other groups facing developmental impairments such as preterm infants do eventually overcome these early challenges, I hypothesize that infants affected by HIE do look similar to their healthy peers later in childhood and adolescence. Although this hypothesis was not supported, regardless of whether infants received therapeutic hypothermia or not, these findings give parents of children who have experienced HIE a better idea of what to expect throughout their child's development, allowing them to better support their child.

Keywords: Hypoxic ischemic encephalopathy, therapeutic hypothermia, development

Neonatal Hypoxic Ischemic Encephalopathy and its Lasting Effects

The flow of oxygen and blood to the brain is essential for life. However, in neonates, a condition called hypoxic ischemic encephalopathy (HIE) (Allen & Brandon, 2011) does not allow sufficient amounts of oxygen and blood to reach the brain. Infants are unable to fully recover from the damage caused by this condition(Fattuoni et al., 2015). HIE is caused by perinatal asphyxia, which is when the oxygen supply to the fetus is reduced, often due to maternal or fetal hemorrhage, umbilical cord compression, or uterine rupture, among other events that could occur around the time of birth (Fattuoni et al., 2015). However, there are instances where the specific cause is unknown (Glass, 2018). Infants typically make a full recovery from this lack of oxygen. However, when they don't, they face HIE (Fattuoni et al., 2015). In developed countries, incidence of HIE is estimated to be 1.5 cases per 1,000 live births, while in middle- and low-income countries, it is estimated to be between 10 and 20 cases per 1,000 live births (Lee et al., 2022). Unfortunately, HIE can have devastating outcomes for the neonate, with HIE claiming nearly one million neonatal lives around the world annually (Lee et al., 2021). While current guidelines recommend therapeutic hypothermia, or the cooling of the brain, as a treatment for infants with moderate to severe HIE, it does not prevent infants from facing developmental impairments later in life (Davies et al., 2019).

However, regardless of whether or not therapeutic hypothermia is administered, developmental impairments depend on both the severity of HIE and the pattern of injury (Steinman et al., 2009). Deficits in infancy and throughout childhood are well understood, but there has been limited research on the effects of HIE into adolescence. It is possible that one reason why there is less knowledge on outcomes of HIE in adolescence is because the impairments are not as evident as those in infancy and early childhood and thus, they are

overlooked. I aim to determine if infants affected by HIE during the perinatal period eventually overcome the early challenges they face and look similar to their peers who were not affected by HIE later in childhood and adolescence. A similar pattern is seen in other neonatal groups such as preterm infants; it is known that while neonates born prematurely have delayed developmental milestones, they often get back on course with their full-term peers over time (Wilson & Cradock, 2004). Because other groups, such as preterm neonates, have the ability to overcome their early challenges, and it is possible that the outcomes of HIE in adolescence are overlooked because they are not significant, I hypothesize that infants affected by HIE do look similar to their peers who were not affected by HIE in adolescence.

Defining Hypoxic Ischemic Encephalopathy

Hypoxic ischemic encephalopathy occurs in three phases. The first phase, primary energy failure, is characterized by deceased cerebral blood flow and anaerobic cellular metabolism (Allen & Brandon, 2011; Piešová & Mach, 2020). When less oxygen is available, the electron transport train cannot drive the production of adenosine triphosphate (ATP) as efficiently, as oxygen is the final electron acceptor, and because ATP is necessary for cells to carry out their metabolic functions, less ATP inhibits their ability to do so (Piešová & Mach, 2020); ATP levels are further reduced by the low glucose levels consequent to diminished blood flow (Allen & Brandon, 2011). Low ATP levels can reduce or halt the action of the sodium/potassium pump and trigger a cascade of events that result in elevated intracellular calcium levels, which, in turn causes vascular damage in the brain. The impairment to these blood vessels leads to necrosis, apoptosis, or both (Allen & Brandon, 2011).

Furthermore, given the amount of lactate produced during anaerobic cellular metabolism, the tissue acidifies, hindering the ability of their cells to survive (Piešová & Mach, 2020). This

also increases the amount of reactive oxygen species in the brain (Piešová & Mach, 2020). These reactive oxygen species interfere with the stability of the membrane of cells, harm the blood vessels in the brain, and cause apoptosis (Piešová & Mach, 2020).

Following reperfusion and reoxygenation, there is the latent period, where there is a restoration of cerebral blood flow (Cotten & Shankaran, 2010; Allen & Brandon, 2011). During the latent period, neurons are able to completely heal, or at least make progress towards fully healing (Davidson et al., 2018). The length of the latent period varies depending on the severity of HIE, with a decreased latent period in cases of more severe HIE (Allen & Brandon, 2011). However, typically the latent period lasts from anywhere between one and six hours (Sechi et al., 2021). Therapeutic interventions are most effective during this time (Allen & Brandon, 2011).

The final phase of HIE is secondary energy failure, which occurs anywhere from six hours to two days following the hypoxic-ischemic insult (Allen & Brandon, 2011). The severity of secondary energy failure is dependent upon the severity of primary energy failure (Cotten & Shankaran, 2010). During secondary energy failure, the production of free radicals is excessive, resulting in continued oxidative stress, and due to low concentrations of antioxidants in the neonatal brain, neonates are unable to combat against the excess free radicals as well as an adult would (Allen & Brandon, 2011). Additionally, an increased amount of glutamate present causes increased stimulation of excitatory receptors and therefore excess sodium and calcium to enter the neural cells (Allen & Brandon, 2011). This differs from the accumulation of calcium during primary energy failure because it is not accompanied by acidosis (Lorek et al., 1994). As glutamate plays a key role in many pathways, including learning and memory, this excitotoxicity contributes to later developmental effects of HIE (Allen & Brandon, 2011). Furthermore, there is additional apoptosis during secondary energy failure (Cotten & Shankaran, 2010). This apoptosis

has a drastic impact on the infant's cognitive abilities when they are older (Rothstein & Levison, 2005). Some infants also experience tertiary brain damage following HIE (Nair & Kumar, 2018). In these cases, because some of the cells producing myelin died and were thus, unable to mature, there is less myelin and the brain is not as capable of changing based on the infant's experiences; the number of cells is affected as well (Davidson et al., 2018; Nair & Kumar, 2018).

Clinically, the severity of HIE is graded by the Sarnat score: mild (stage I), moderate (stage II), and severe (stage III) (Cotten & Shankaran, 2010). Factors including level of consciousness, spontaneous activity, posture, tone, suck and Moro reflexes, and autonomic nervous system activity are evaluated (Pavageau et al., 2020). An overactive sympathetic nervous system and hyperalertness are typically indicative of mild HIE while lethargy and hypotonia distinguish moderate HIE (Bonifacio & Hutson, 2021). Infants with severe HIE are usually flaccid and stuporous (Bonifacio & Hutson, 2021). As the Sarnat score will determine if the infant can receive therapeutic hypothermia or not, the severity of HIE must be determined within the first six hours following birth (Finder et al., 2020). Often, though, infants do not score with the same level of severity in each category and could be considered mild in some, but moderate or severe in others (Bonifacio & Hutson, 2021). In these cases, therapeutic hypothermia should be administered if the infant scores in the moderate or severe category in at least half of the six categories (Bonifacio & Huston, 2021). As the original Sarnat scoring system published in 1976, was based upon a small sample of patients (n = 21) and was not developed with HIE in mind, instead focusing on disruptions to the brain in general; a modified Sarnat scoring system is now typically used to determine the severity of HIE (Table 1) (Mrelashvili et al., 2020; Chalak et al., 2018). Following mild HIE, children tend to face cognitive impairments later in life (Finder et al., 2020), while infants suffering from severe HIE are at greater risk for

cerebral palsy, drastic cognitive impairments, and even death (Cotten & Shankaran, 2010). Unfortunately, in these cases, it is most common for infants to face a diagnosis of severe disability or death within the first two years of life (Allen & Brandon, 2011). The impairments associated with moderate HIE impact memory, school readiness, and vision; however, they are not as extreme as those associated with severe HIE (Cotten & Shankaran, 2010).

Modified Sarnat scoring system for categorizing encephalopathy.

Each of the six main categories is assigned a score based on severity (0–3). When findings are common or overlapped in a category (Spontaneous activity and Suck overlap for mild and moderate HIE), the score assigned is one that corresponds to the level of consciousness.

Category	Normal (0)	Mild(1)	Moderate (2)	Severe(3)
Level of consciousness	Alert(responsive to external stimuli)	Hyper-alert (responsive to minimal stimuli)	Lethargic	Stupor/Coma
Spontaneous activity	Normal	Normal or decreased	Decreased	None
Posture	Predominantly flexed	Mild flexion of distal joints	Distal flexion or complete extension	Decerebrate
Tone	Strong flexor tone in all extremities	Normal or slightly increased	a. Hypotonia (focal or general)	Flaccid
			b. Hypertonia	Rigid
Primitive reflexes				
Suck	Strong, easily illicit	Weak or Incomplete	Weak or incomplete and/or bite	Absent
Moro	Complete	Intact (low threshold)	Incomplete	Absent
Autonomic Nervous System (ANS)				
Pupils	Normal	Mydriasis	Myosis	Variable or Nonreactive
Heart rate	100–160 bpm	Tachycardia	Bradycardia	Variable
Respirations	Regular respirations	Hyperventilation	Periodic breath	Apnea or need ventilation

Table 1

A modified Sarnat scoring system to determine the severity of HIE. Mild HIE is primarily characterized by an overactive sympathetic nervous system and hyperalertness, moderate HIE is primarily characterized by lethargy and hypotonia, and severe HIE is primarily characterized by flaccidity and stupor. Because infants often score differently in different categories, therapeutic hypothermia should be administered if the infant scores as moderate or severe in at least three of the six total categories.

Adapted from Chalak et al. (2018).

There are two patterns of injury typically seen following neonatal HIE, the watershed distribution and the basal ganglia pattern of injury (Steinman et al., 2009). The watershed distribution is comprised of white matter in the intervascular boundary-zone (Steinman et al., 2009). In severe HIE, gray matter in the cortex is also involved (Steinman et al., 2009). The basal ganglia pattern of injury affects the perirolandic cortex, hippocampi, and deep gray matter (Steinman et al., 2009). The perirolandic region includes the pre-central gyrus, post-central

gyrus, central sulcus, and the paracentral lobule (Zuo et al., 2020). In severe HIE, the extent to which the cortex is involved is even greater (Steinman et al., 2009).

Treatment of Hypoxic Ischemic Encephalopathy

While it is evident a treatment for HIE is necessary, finding the best approach can be difficult. Ideally, it seems as though treatment should target primary energy failure, and thus, prevent or mitigate subsequent damage. However, it is a rare that a physician would be able to focus treatment efforts specifically on primary energy failure because the exact moment when primary energy failure begins is often challenging to identify (Cotten & Shankaran, 2010). Although there may be instances when the healthcare team is able to identify a cause of HIE, they often need to first deliver the baby before they can begin resuscitative efforts, thus lengthening the duration of primary energy failure (Cotten & Shankaran, 2010). It can also be unclear whether or not what neonatologists perceive to be the initial injury is actually the initial injury, as it is possible that the flow of blood and oxygen had previously been jeopardized (Cotten & Shankaran, 2010). As a result, the goal of treatment is to prevent, or at least lessen the devastating effects, of secondary energy failure through the initiation of treatment in the latent phase (Cotten & Shankaran, 2010).

Currently, therapeutic hypothermia (TH) is the only treatment for moderate and severe HIE (Laptook et al., 2017). The goal of therapeutic hypothermia is to alleviate secondary energy failure and reduce the risk of death and disability (Cotten & Shankaran, 2010; Shankaran et al., 2012). One way through which it does this is by combatting excitotoxicity through lowering the amount of glutamate released (Thoresen et al., 1995). Typically, it is administered through the use of cooling blankets placed on the baby's body and it lowers the infant's brain temperature to 33.5°C (92.3°F) for six hours until rewarming begins (Davies et al., 2019). Although the use of

therapeutic hypothermia as a treatment for HIE is well understood, more information is necessary to determine the optimal method of rewarming (Davies et al., 2019). It is understood that if rewarming is done too quickly, though, infants may begin to experience seizures (Davies et al., 2019). Therefore, it is recommended that rewarming begins after three days of hypothermia and the temperature increases by 0.5°C/hour (Davies et al., 2019).

However, while therapeutic hypothermia does reduce the risk of death and cerebral palsy, there are limitations and drawbacks to this treatment. First, therapeutic hypothermia must be initiated within six hours following birth (Cotten & Shankaran, 2010). Though some research suggests a moderate benefit of therapeutic hypothermia initiated between six and 24 hours after birth, more research is needed to determine its effectiveness (Laptook et al., 2017). Furthermore, therapeutic hypothermia can only be used to treat HIE in term infants (Koehn et al., 2020). Although the treatment of HIE using therapeutic hypothermia has been investigated in infants born between 34-35 weeks gestational age, these infants were more likely than their full-term peers to face complications from treatment such as hyperglycemia, which negatively impacts infants' neurodevelopment (Rao et al., 2017). As a result, more research is necessary to determine if therapeutic hypothermia is safe to administer as treatment for HIE in preterm infants (Rao et al., 2017). As cited in Yates et al., 2021, Walsh et al., 2022 is evaluating the treatment of moderate and severe HIE in infants born between 33-35 weeks gestational age in their Preemie Hypothermia for Neonatal Encephalopathy trial, however their results have yet to be published. The greatest limitation of therapeutic hypothermia, though, is that it does not prevent the developmental impairments infants may face due to HIE later in life.

Developmental Outcomes of HIE without Therapeutic Hypothermia

Early Childhood

As therapeutic hypothermia must be initiated within six hours after birth, treatment with therapeutic hypothermia is not always available to every child who develops HIE. If infants are born in hospitals that do not have access to therapeutic hypothermia and need to be transferred, for example, it may not be possible to both identify HIE and transfer the infant to another hospital with the ability to provide therapeutic hypothermia within the first six hours following birth (Laptook et al., 2017). Thus, it is important to study the effects of HIE when therapeutic hypothermia has not been used for treatment. Robertson and Finer (1985) studied children who were born at 37 weeks' gestation or later and who were diagnosed with mild (n = 66), moderate (n = 94), or severe HIE (n = 7) and treated according to the standards of care at the time. Three to five years later, the children were given a full physical and their neurodevelopment was assessed (Robertson & Finer, 1985). The Stanford-Binet Intelligence Scale (SB) and Visual-Motor Integration Test (VMI) were both conducted by a trained psychologist. Speech and language were evaluated by a speech pathologist, an audiological evaluation was completed by a clinical audiologist, and fine motor and gross motor skills were tested by an occupational therapist, physiotherapist and developmental pediatrician (Robertson & Finer, 1985). The results from the Peabody Picture Vocabulary Test (PPVT) were indicative of receptive language ability, especially auditory receptive vocabulary and the mean length of utterance (MLU), which demonstrated the child's expressive language ability (Robertson & Finer, 1985).

Their results showed that children in the severe HIE group scored significantly lower on every evaluation than children in the mild and moderate HIE groups (Robertson & Finer, 1985). When comparing children in the moderate HIE group to children in the mild HIE group, the

same pattern was observed with children in the moderate HIE group performing significantly worse (Robertson & Finer, 1985). Children who were affected by mild HIE during the perinatal period did not have any disabilities, demonstrated minimal developmental impairments, and performed at an average level on standardized tests (Robertson & Finer, 1985).

The average score on the Stanford-Binet Intelligence Scale is 100 with a standard deviation of 16 ("Understanding the Stanford Binet Intelligence Scale," 2023). Results from this study indicated that the average score on the SB was a 37.1 for children in the severe HIE group (Robertson & Finer, 1985). Because all children in the severe HIE group scored over three standard deviations below the mean, they were all considered to be handicapped (Robertson & Finer, 1985). The average score on the SB was a 92.3 for children in the moderate HIE group and 101.5 for children in the mild HIE group (Robertson & Finer, 1985). Thus, these children were considered to be of average intelligence. On the VMI, children in the mild HIE group scored within the average range of scores, however, children in the moderate HIE group scored an average of 4.7 months below their chronological age (Robertson & Finer, 1985). The most drastic effects of HIE on VMI score were observed in the severe HIE group, with these children scoring an average of 25.7 months below their chronological age (Robertson & Finer, 1985). Even if these children did not score low enough for their visual motor integration abilities to be considered developmentally delayed, their scores certainly indicate that they face additional challenges with visual motor integration that their healthy peers do not. Furthermore, the average score on the PPVT is 100 with a standard deviation of 15 (*Peabody Picture Vocabulary Test – Revised (PPVT-R)*, n.d.). Children affected by mild HIE had a mean score of 104.1 and children affected by moderate HIE had a mean score of 92.8 (Robertson & Finer, 1985). As both groups were within one standard deviation of the mean, it appears that in the cases of mild and moderate

HIE, receptive language ability is unaffected by HIE. However, children in the severe HIE group had a mean score of 71.7 (Robertson & Finer, 1985). Because these children are nearly within three standard deviations below the mean, it seems that severe HIE does negatively impact receptive language ability in early childhood. Finally, results from the MLU indicated that children in the mild HIE group scored 0.99 standard deviations above the expectation for their chronological age, while children in the moderate HIE group scored 0.04 standard deviations below the expectation for their chronological age (Robertson & Finer, 1985). Both groups are within one standard deviation of what would be expected for their chronological age, suggesting that HIE did not impair their expressive language ability. In contrast, the severe HIE group scored 3.32 standard deviations below the expectation for their chronological age (Robertson & Finer, 1985). Due to this large difference from the expectation, it appears that severe HIE led to impairments in expressive language ability.

Based on these results, overall, it seems as though children affected by mild HIE are developmentally on track with their healthy peers. Following moderate HIE, although children perform significantly worse than children affected by mild HIE, they are still of average intelligence and have average receptive language ability. Children affected by severe HIE are developmentally delayed in cognition and have difficulty with visual motor integration and receptive language ability.

Middle Childhood

Marlow et al. (2005) investigated the neurocognitive and behavioral outcomes of seven-year-old children who had been known to have moderate or severe HIE but were not treated with therapeutic hypothermia (n = 65). They were compared to children who had not been affected by HIE and the children in each group were matched for sex, ethnicity, first language, and age

within three months (n = 49) (Marlow et al., 2005). At school, both groups of children were given the British ability scales (BAS-II) school age battery, which evaluates the overall cognitive abilities of children, in addition to their specific abilities in verbal, spatial, and non-verbal reasoning, as well as the NEPSY, which evaluates children in the areas of attention and executive function, language, sensorimotor abilities, visuospatial processing, and memory and learning (Marlow et al., 2005). The strengths and difficulties questionnaire was given to both teachers and parents to evaluate the child's behavior (Marlow et al., 2005). Teachers were also given an opportunity to share the specific educational needs of that child as well as the child's performance in English and math relative to particular goals within those subjects based on the national curriculum (shape size and measurement, numbers and algebra, using and applying skills, spelling, writing, reading, and speaking and listening) (Marlow et al., 2005). Parents reported the everyday memory skills of their child and modifications were made to the movement of ABC to evaluate laterality and manual dexterity (Marlow et al., 2005). A pediatrician assessed the motor abilities of each child and determined if the child had cerebral palsy or not (Marlow et al., 2005).

It was concluded that 15 children in the HIE group had cerebral palsy; these children were excluded from the following results (Marlow et al., 2005). For children affected by moderate HIE, there was no significant difference between their overall cognition and the overall cognition of children in the comparison group; there was also no significant difference between their scores on the cognitive subscales (Table 2) (Marlow et al., 2005). Children affected by severe HIE, though, had significantly lower overall cognition and significantly lower scores on the cognitive subscales than children in the comparison group (Table 2) (Marlow et al., 2005). When compared to children in the moderate HIE group, children in the severe HIE group scored

worse in all aspects of cognition, including general cognitive ability (Table 2) (Marlow et al., 2005). Despite a lower verbal scale score, though, this difference was not large enough to be of significance (Table 2) (Marlow et al., 2005). On the NEPSY, children who had experienced moderate HIE had significantly lower language and sensorimotor abilities than children in the comparison group, whereas children who had experienced severe HIE had lower scores in all areas of the assessment (Table 2) (Marlow et al., 2005). Each of these scores was significantly worse, with the exception of the sensorimotor domain (Table 2) (Marlow et al., 2005). Children with severe HIE are at a greater risk than children with moderate HIE for cerebral palsy (Cotten & Shankaran, 2010), in which they face challenges with sensorimotor abilities, perhaps the sensorimotor development of children affected by severe HIE is observed more carefully by parents and pediatricians. As a result, challenges within this domain are more likely to be addressed sooner, contributing to why children affected by moderate HIE show impairments in sensorimotor development, but children affected by severe HIE do not. Furthermore, children who were affected by severe HIE had significantly worse attention and executive function as well as significantly worse memory than children who were affected by moderate HIE (Table 2) (Marlow et al., 2005). Although their overall score in the memory domain of the NEPSY was similar to the overall score of children unaffected by HIE, children in the moderate HIE group had significant impairments in the areas of narrative memory and sentence repetition; children in the severe HIE group had impairments in all aspects of memory (memory for faces, memory for names, narrative memory, sentence repetition, and orientation) (Table 2) (Marlow et al., 2005). Despite scoring lower in memory for faces and sentence repetition, these differences in scores were not great enough to reach significance (Table 2) (Marlow et al., 2005). The overall memory scores on the NEPSY were consistent with the results seen from the assessment of everyday

memory reported by parents, as no difference was observed between children in the moderate HIE group and children in the comparison group; however, children in the severe HIE group had worse memory than both groups (Table 2) (Marlow et al., 2005).

Test	Group with Significantly Worse Score		
	Comparison vs. Moderate HIE	**Comparison vs. Severe HIE**	**Moderate HIE vs. Severe HIE**
BAS-II			
Overall cognition	None	Severe HIE	Severe HIE
Special non-verbal composite	None	Severe HIE	Severe HIE
Verbal scale score	None	Severe HIE	None
Non-verbal reasoning score	None	Severe HIE	Severe HIE
Spatial scale score	None	Severe HIE	Severe HIE
NEPSY			
Attention & executive domain	None	Severe HIE	Severe HIE
Language domain	Moderate HIE	Severe HIE	None
Sensorimotor domain	Moderate HIE	None	None
Visuospatial domain	None	Severe HIE	None
Memory & learning domain	None	Severe HIE	Severe HIE
NEPSY memory domain			
Memory for faces	None	None	None
Memory for names	None	Severe HIE	Severe HIE
Narrative memory	Moderate HIE	Severe HIE	None
Sentence repetition	Moderate HIE	None	None
Orientation	None	Severe HIE	Severe HIE

Everyday memory impairment score	None	Severe HIE	Severe HIE

Table 2

Significant differences in scores on the British ability scales (BAS-II) and the NEPSY given to children seven years of age, as well as in their everyday memory impairment. Scores were compared between the comparison group composed of children unaffected by HIE (n = 49) and the moderate HIE group (n = 32), the comparison group and the severe HIE group (n = 18), and the moderate HIE group and the severe HIE group.

Data taken from Marlow et al. (2005).

Results from the strengths and difficulties questionnaire indicated that there were no significant differences between children in the moderate HIE group and children in the comparison group, exhibiting that there are no behavioral effects of moderate HIE in middle childhood (Marlow et al., 2005). Children in the severe HIE group, though, had significantly higher behavioral scores as reported by both parents and teachers than children in the moderate HIE group and comparison group, thus suggesting that these children were thought to exhibit more signs of behavioral problems (Marlow et al., 2005). Both parent and teacher reports found that more children in the severe HIE group had abnormal scores than children in the moderate HIE group and comparison group (Marlow et al., 2005). While parents and teachers also both reported significantly greater hyperactivity in children who had been affected by severe HIE when compared to the two other groups, only teachers reported significantly greater emotional problems and a significantly greater impact on daily life (Marlow et al., 2005). The teacher report also indicated that children in the severe HIE group exhibited significantly less pro-social behavior than children in the comparison group. However, this decrease in pro-social behavior was not significant in comparison to the moderate HIE group (Marlow et al., 2005). Both parent and teacher reports suggested that moderate HIE did not affect children's levels of emotional problems, peer problems, and pro-social behavior (Marlow et al., 2005).

Finally, in terms of academic achievement, children who were affected by HIE had lower levels of attainment than children who were not, and children in the severe HIE group had even lower levels of attainment than children in the moderate HIE group (Marlow et al., 2005). Children who had experienced severe HIE were significantly below the attainment goals expected for children their age, failing to reach any of them, while children who had experienced moderate HIE significantly underachieved only in spelling and reading (Marlow et al., 2005). Therefore, overall, children who had experienced HIE performed worse on cognitive, neuropsychological, educational, and behavioral evaluations than children who had not experienced HIE, with greater effects of HIE seen in children in the severe HIE group than in the moderate HIE group (Marlow et al., 2005).

Adolescence

Halpin et al. (2022) studied the neuropsychological and behavioral effects of mild and moderate HIE in adolescence as well as the impact of HIE on school performance at this age. Adolescents with a mean age of 14.45 years old who were classified as having either mild (n = 11) or moderate HIE (n = 12) in infancy were compared to a control group comprised of their sibling who was closest in age to them (n = 13) and peers who did not face any health issues (n = 14) (Halpin et al., 2022). Aspects of their cognition, including attention/executive functioning, verbal reasoning, non-verbal reasoning, visual and verbal memory, sensory-motor ability, language, and speed of information processing, were evaluated through the tests listed and described in Table 3 (Table 3) (Halpin et al., 2022). The tests were administered by a clinical psychologist in training and two students earning their master's degrees in psychology following training from two senior clinical neuropsychologists (Halpin et al., 2022). The Strengths and

Difficulties Questionnaire and the competency subscales of the Child Behavior Checklist (CBCL) and Youth Self-Report (YSR) were used to assess their behavior (Halpin et al., 2022).

Neuropsychological Outcome	Subtest Description
Verbal Reasoning – Similarities[a]	Measures the ability to think logically, verbal concept formation, and verbal abstract reasoning.
Non-verbal reasoning – Matrix Reasoning[a]	Measures abstract reasoning, spatial perception, and visual processing.
Speed of Information Processing	
Symbol Search[a]	Measures visual perception, fine-motor speed and accuracy, and recognition.
Coding[a]	Measures visual-motor and fine-motor dexterity and speed.
Attention/Executive Functioning	
Letter Fluency[b]	Measures the ability to generate words within specific initial letter categories.
Digit Span[a]	Measures attention and short-term auditory memory.
Visual Scanning[c]	Measures attentional ability to rapidly locate objects on a page.
Number Sequencing[c]	Measures numerical processing and mental sequencing.
Letter Sequencing[c]	Measures letter processing and mental sequencing.
Switching[c]	Measures complex mental processes of cognitive flexibility, multi-tasking, and divided attention.
Motor[c]	Measures visuomotor speed.
Rey Complex Figure Copy[d]	Measures attentional and planning abilities.
Visual Memory	
Memory for faces Immediate[b]	Measures encoding of facial features, face discrimination, and recognition.
Memory for faces Delay[b]	Measures delayed retrieval of facial recognition.
Verbal Memory	
List Learning Immediate[e]	Measures verbal learning and memory, and the role of interference in recall for verbal items.
List Learning Delay[e]	Measures delayed recall of verbal items.
Sensory Motor	
Finger Tap Sequencing[b]	Measures finger dexterity and motor speed.

Neuropsychological Outcome	Subtest Description
Language	
Speeded Naming[b]	Measures quick semantic access to and production of names of letters.
Spelling[f]	Measures written spelling of letter sounds and single words.
Reading[f]	Measures speed and accuracy of word recognition.
Receptive Vocabulary[g]	Measures oral language and receptive vocabulary.

a Wechsler Intelligence Scale for Children – 5th Edition (WISC-V)

b Neuropsychological Assessment Tool – 2nd Edition (NEPSY-II)

c Delis-Kaplan Executive Function System Trail Making tests (DKEFS)

d Rey Complex Figure Test - Copy test (RCFT)

e Children's Memory Scale (CMS)

f Wechsler Individual Achievement Test – 3rd Edition (WIAT-III)

g British Picture Vocabulary Scale – 3rd Edition (BPVS-III)

Table 3

Neuropsychological tests administered to adolescents affected perinatally by mild or moderate HIE, a healthy sibling who was closest in age to them, and a group of their healthy peers. Their cognition was assessed in the areas of attention/executive functioning, verbal reasoning, non-verbal reasoning, visual and verbal memory, sensory-motor ability, language, and speed of information processing.

Adapted from Halpin et al. (2022).

Overall, the scores of both the mild and moderate HIE groups on each of the tests were below normal, however, the moderate HIE group did not perform any worse than the mild HIE group (Halpin et al., 2022). Overall, the HIE group had lower scores than their unaffected peers on 19 out of the 21 total tests (Halpin et al., 2022). However, the scores were only significantly worse on the verbal reasoning (similarities) test, the visual scanning and letter sequencing tests, and the finger tap sequencing test, suggesting that the attention and executive function as well as the sensory motor domains were affected by HIE (Halpin et al., 2022). Interestingly, it appeared

that the HIE group also had lower scores on the speeded naming, spelling, and reading tests within the language domain, however, following statistical corrections, it was determined that the effect was not significant (Halpin et al., 2022). Furthermore, when the HIE group was compared to the group of healthy siblings, the HIE group only scored worse on 13 out of the 21 total tests and no effect was significant (Halpin et al., 2022). Results from the Strengths and Difficulties Questionnaire indicated that behavioral outcomes were similar, regardless of the severity of HIE (Halpin et al., 2022). Based on the SDQ responses from parents, it was determined that the HIE group had significantly worse scores than their healthy peers overall, and significantly worse scores than their siblings in prosocial behavior (Halpin et al., 2022). The HIE group had significantly worse scores than both their healthy peers and siblings in peer problems as well (Halpin et al., 2022). The difference between the scores of the HIE group and each of the other groups was moderate to large in these areas (Halpin et al., 2022). Both parental and youth responses on the SDQ also indicated that there were no differences between the HIE group and their siblings and healthy peers in hyperactivity or conduct problems (Halpin et al., 2022). On the competency scales of the CBCL, ratings from parents suggested that children in the HIE group were significantly worse at adaptive functioning than those in the healthy control group (Halpin et al., 2022). Not only was their competence worse overall, but they had reduced activities, poorer social competencies, and worsened abilities to function at school; each of these deficits were significant with a large effect size (Halpin et al., 2022). However, parental scores on each domain of the CBCL were similar for children in the HIE group and their siblings, and comparisons between scores on the YSR indicated that the HIE group did not differ from neither the healthy control group nor their siblings (Halpin et al., 2022). Because children affected by HIE were similar to their healthy siblings in their results on both the CBCL and YSR, this

suggests that perhaps their lower overall competence, poorer social competencies, and worsened abilities to function at school were not due to HIE, but rather, were due to some other genetic component. Lastly, school interventions such as assistance in the classroom, remediation, or repeating a grade were required for 38% of children in the HIE group, 18% of their siblings, and 0% of their healthy peers (Halpin et al., 2022).

Summary

In early childhood when children have not been treated with therapeutic hypothermia, it appears that the severity of HIE affects the presence of developmental delays in children. Following mild HIE, most children are not affected developmentally by HIE at all, while following moderate HIE, children tend to face impairments only in the sensorimotor domain (Table 5). However, despite their normal cognitive development, children affected by moderate HIE still have significantly worse cognition than children affected by mild HIE. Thus, while their cognition is not impaired, they do score in the lower range of normal scores due to the increased severity of HIE. When children have been affected by severe HIE, though, they tend to face true developmental delays in cognition as well as deficits in language and sensorimotor abilities (Table 5).

Like in early childhood, without treatment using therapeutic hypothermia, during middle childhood, the developmental impairments of children affected by HIE seem to depend on the severity of HIE. For children impacted by moderate HIE, the impairments seen in sensorimotor abilities continue into middle childhood, with setbacks in language appearing during this time as well (Table 5). Although their overall cognition does not seem to be impacted by HIE, it does seem as though aspects of their memory are worse than their healthy peers (Table 6). Together, all of these impairments appear to set these children back in school in the areas of spelling and

reading. Like in early childhood, language and cognitive impairments seem to persist into middle childhood for children affected by severe HIE with significant deficits specifically in attention, executive functioning, learning, visuospatial abilities, and memory (Table 6). However, these children do seem to be able to overcome some of the challenges they face in cognition in early childhood because these impairments are no longer significant enough to indicate developmental delay as they were in early childhood (Table 5). It also seems as though impairments in social and emotional development as well as hyperactivity and signs of behavioral issues begin to appear in middle childhood for children impacted by severe HIE (Table 5). When these effects are combined, they result in a failure to meet attainment levels in school typical for children their age.

Finally, in contrast to early and middle childhood, the presence of impairments does not seem to depend on the severity of HIE in adolescence, as children affected by both mild and moderate HIE tend to face setbacks in the same aspects of development and children affected by moderate HIE do not perform any worse than those affected by mild HIE. Both groups seem to experience deficits in specific aspects of cognition, such as impairments in attention and executive function (Table 6), as well as in sensory motor skills (Table 5). Additionally, mild and moderate HIE appear to impact the social development of children who did not receive therapeutic hypothermia, but only in terms of peer problems. Thus, although children affected by mild HIE do not display any effects of HIE in early childhood, by adolescence, the presence of these deficits indicates that HIE does eventually have an effect on their development, and these adolescents do not remain developmentally similar to their healthy peers (Table 5). Moderate HIE continues to impact children's sensorimotor and cognitive impairments in adolescence, just as it did in middle childhood. Within the cognitive domain, challenges in attention and executive

function, which were not previously noticed in early and middle childhood, begin to appear in adolescence. Furthermore, while they did have lower scores than their healthy peers, they did not perform significantly worse on assessments of visual and verbal memory (Halpin et al., 2022). This suggests that while their memory abilities may be on the lower end of what is typical of other children their age, these children are able to overcome the impairments they face in aspects of memory in middle childhood so that their memory is no longer significantly worse than that of their unaffected peers by adolescence. Similarly, while these children do still struggle in terms of language, as they score lower than their healthy peers, they are able to compensate for the previous significant impairment in this domain observed in middle childhood for children affected by moderate HIE so that this effect is no longer significant in adolescence. Together, all of these impairments may lead to an increased chance of requiring school interventions. Just as in middle childhood, the behavioral development of adolescents who had been affected by mild and moderate HIE is still in line with that of their healthy peers (Table 5).

Developmental Outcomes of HIE Treated with Therapeutic Hypothermia

Early Childhood

Álvarez-García et al. (2022) compared outcomes of children between three and six years of age who experienced moderate or severe HIE and were treated with therapeutic hypothermia (n = 14) to children who were unaffected by HIE (n = 15), particularly in terms of socio-emotional effects and mood disorders. All children were born at 35 weeks gestational age or later and the infants in the control group were matched to those in the HIE group based on gestational age, birth weight, sex, and date of birth (Álvarez-García et al., 2022). The development of the children was evaluated based on parental responses to the Ages and Stages Questionnaire 3 (ASQ-3), which assesses development in the areas of communication, fine and gross motor

skills, problem solving, and personal-social skills (Álvarez-García et al., 2022). Additionally, parents completed the Montgomery-Asberg Depression Rating Scale (MADRS), which indicates whether or not a child is exhibiting symptoms of depression and if so, the intensity of those symptoms (Álvarez-García et al., 2022). Lastly, parental responses to the Child Behavior Checklist (CBL) designed for children between one and a half and five years of age from the Archenbach System of Empirically Based Assessment (ASEBA) and children's responses to the Preschool Symptom Self-Report (PRESS) were used together to evaluate the socio-emotional status of the children (Álvarez-García et al., 2022). On the ASEBA, the child is rated according to the challenges they face with emotionally reactive, anxious/depressed, withdrawn, and aggressive behaviors, as well as somatic complaints and issues with sleep or attention, among other problems (Álvarez-García et al., 2022). These responses are categorized as either Internalizing Problems or Externalizing Problems (Álvarez-García et al., 2022). In the PRESS, children indicate whether or not they identify with images in order to determine if the child is demonstrating symptoms of depression (Álvarez-García et al., 2022).

It was found that despite having significantly lower scores than children in the control group on every aspect of the ASQ-3, the mean scores of children in the HIE group were not low enough to indicate developmental delay in the areas of communication, fine and gross motor skills, and personal-social skills (Álvarez-García et al., 2022). Their problem solving abilities were also significantly lower than the healthy control group (Álvarez-García et al., 2022). This suggests that their cognitive development is affected by HIE. Based on the PRESS, it was determined children in the HIE group were experiencing significantly more depressive symptoms than in the control group, however, children in the HIE group scored similarly to children in the control group on the MADRS (Álvarez-García et al., 2022). This discrepancy

between the reports of children and their parents could indicate that while the children are experiencing depressive symptoms, these symptoms are going unnoticed by parents. Lastly, results from the CBCL indicated that children who had experienced neonatal HIE had significantly higher scores in one area of internalization, anxious/depressed symptoms, and in one area of externalization, aggressive behavior, than children who were unaffected by HIE (Álvarez-García et al., 2022). Although no children in the control group had symptoms severe enough to be of a concern, in the HIE group, three children exhibited concerning levels of anxious/depressive symptoms and two children exhibited concerning levels of aggressive behavior (Álvarez-García et al., 2022).

Middle Childhood

Cainelli et al. (2021) investigated the differences between the neurodevelopment of children with moderate to severe HIE who were treated with TH (n = 40) and their peers who did not suffer from HIE (n = 33) during middle childhood. To participate in the study, children were required to be at least five years old; the average age in the HIE group was 6.25 years, while the average age in the healthy control group was 8.8 years (Cainelli et al., 2021). Over the span of two days, several assessments were administered by a child psychologist and a child neurologist who were blind to whether the child had HIE as a neonate or not (Cainelli et al., 2021). First, an evaluation of general intelligence was conducted using either the Wechsler Preschool and Primary Intelligence Scale III (WPPSI-III) or the Wechsler Intelligence Scale for Children IV (WISC-IV) (Cainelli et al., 2021). The WPPSI-III and WISC-IV also determined the level of executive functions such as planning through the use of the coding test, the semantic verbal fluency test, and the Tower of London task (Cainelli et al., 2021).The NEPSY-II was given to evaluate attention, via the visual and auditory tests, as well as social skills, via both the theory of

mind A and B and affect recognition tests (Cainelli et al., 2021). To study learning and long-term verbal memory, participants were given a list of words and asked to recall them (Cainelli et al., 2021). Short-term visuospatial memory was assessed as well, using the Corsi test (Cainelli et al., 2021). Furthermore, a naming test was used to evaluate language and the Visual-Motor Integration Test was used to evaluate visual-motor skills (Cainelli et al., 2021). Parents also played a role in gathering neurodevelopmental information by completing the Child Behavior Checklist (CBCL), in which characteristics of the child over the last six months were utilized to detect emotional, behavioral, and social issues, and the Conners Rating Scales-Revised (CRS-R), in which child behaviors that are indicative of problems with opposition, inattention, hyperactivity, anxiety, shyness, and perfectionism as well as social and psychosomatic issues are measured based on parents' perceptions (Cainelli et al., 2021). Lastly, parents were also given the Short-Form Parent Stress Index (PSI-SF) and if their stress was great enough to indicate clinical issues, their child's neurodevelopmental outcomes were no longer included in the analyses (Cainelli et al., 2021).

Their results indicated that children who had HIE early in life and were treated with therapeutic hypothermia, scored significantly lower in the tests of intelligence, visuomotor skills, and auditory attention, as well as on the coding test, evaluating executive functions (Table 4) (Cainelli et al., 2021). Additionally, the number of children in the HIE group with psychopathological problems was significantly greater than that of children in the control group (Cainelli et al., 2021). The observed symptoms of psychopathy in children in the HIE group included oppositional behavior, issues with attention, hyperactivity, and anxiety (Cainelli et al., 2021). Lastly, the IQ of children in the HIE group was significantly lower than the IQ of the children in the control group, and IQ could be used to distinguish between the children in the two

groups (Cainelli et al., 2021). However, for the majority of participants, total IQ could not be determined, and as a result, only IQ from each subtest was taken into consideration (Cainelli et al., 2021). Thus, their results do not indicate that children with HIE are generally less intelligent, but rather, that they score lower in different domains of intelligence than their healthy peers (Cainelli et al., 2021). As there were no significant differences in the results from the naming test and the theory of mind A, theory of mind B, and the affect recognition tests, it was determined that the language development and social skills of the HIE group were similar to those of the control group (Table 4) (Cainelli et al., 2021).

Group characteristics by neuropsychological tests.

Characteristics	**Controls, *N* = 33** [1]	**HIE, *N* = 40** [1]	***p*-Value** [2]	**Difference (95%CI)**
Intelligence Quotient	105 (100, 115)	100 (87, 110)	0.031	8.7 (1.5, 16)
Coding	10.0 (8.0, 13.0)	8.0 (6.8, 10.0)	0.024	1.6 (−0.04, 3.2)
Semantic Fluency	−0.12 (−0.66, 0.63)	−0.25 (−1.06, 0.50)	0.4	0.23 (−0.28, 0.74)
Naming	0.12 (−0.27, 0.71)	0.00 (−1.04, 0.50)	0.3	0.33 (−0.13, 0.79)
Words list	0.19 (−0.15, 1.02)	0.22 (−1.02, 0.81)	0.4	0.50 (−0.12, 1.1)
Recall list	0.81 (0.00, 1.27)	0.14 (−0.57, 0.89)	0.052	0.53 (-0.01, 1.0)
Corsi	0.25 (−0.27, 0.78)	0.12 (−0.27, 1.11)	>0.9	−0.03 (−0.50, 0.44)
Visual-Motor integr.	13.00 (11.00, 15.00)	10.00 (9.00, 13.00)	0.016	1.9 (0.53, 3.3)
Tower of London	0.18 (−0.99, 0.66)	−0.72 (−1.46, 0.30)	0.079	0.67 (−0.02, 1.4)

Characteristics	Controls, *N* = 33 [1]	HIE, *N* = 40 [1]	*p*-Value [2]	Difference (95%CI)
Visual attention	11.00 (10.00, 12.00)	11.00 (9.00, 12.00)	0.3	1.0 (−0.36, 2.3)
Auditory Attention			0.004	
<2°	0 (0%)	1 (2.5%)		
2–5°	2 (6.1%)	2 (5.0%)		
6–10°	0 (0%)	6 (15%)		
11–25°	26 (79%)	18 (45%)		
26–50°	2 (6.1%)	11 (28%)		
51–75°	3 (9.1%)	2 (5.0%)		
>76°	0 (0%)	0 (0%)		
Affect recognition	10.0 (9.0, 11.0)	9.5 (7.0, 11.8)	0.5	0.63 (−0.87, 2.1)
Theory of Mind A	0.07 (−0.82, 0.68)	0.21 (−0.77, 0.94)	0.5	−0.12 (−0.66, 0.42)
Theory of mind B	0.12 (−0.36, 0.49)	−0.04 (−0.77, 0.34)	0.3	0.32 (−0.15, 0.79)

Legend: HIE: hypoxic-ischemic encephalopathy; [1] Median (interquartile range, IQR); n (%); [2] Wilcoxon rank sum test; Fisher's exact test.

Table 4

Neuropsychological test scores of children in middle childhood who were either affected by moderate or severe HIE and treated with therapeutic hypothermia (n = 40) or who were in the healthy control group (n = 33). Children in the HIE group performed

> *significantly worse than their healthy peers on tests of intelligence, visuomotor skills, executive functions, and auditory attention.*
> Adapted from Cainelli et al. (2021).

Another study by Spencer et al. (2022) expanded on the previous findings by examining the differences in cognitive and motor development in children between the ages of six and eight in relation to their brain volume. Children with moderate to severe HIE treated with TH (n = 31) were compared to children who had not experienced HIE perinatally (n = 32); all children were born at a gestational age of 35 weeks or later and there was no difference in head circumference between the two groups (Spencer et al., 2022). Children in the control group were matched to children in the HIE group based on age, sex, and socioeconomic status (Spencer et al., 2022). When the children reached an age between six and eight years, their cognitive development was evaluated using the Wechsler Intelligence Scale for Children, Fourth Edition (Spencer et al., 2022). The psychologists who administered the assessments were unaware of whether the child they were assessing was in the HIE group or the control group (Spencer et al., 2022). The subscales of working memory, processing speed, verbal comprehension, and perceptual reasoning were included (Spencer et al., 2022). Their motor development was also evaluated using the Movement Assessment Battery for Children, Second Edition (MABC-2) to determine if they were at risk for motor impairment (Spencer et al., 2022). Videos were taken of the children during the assessment, reviewed by each researcher, and scored, after discussion to ensure that all researchers were in agreement, (Spencer et al., 2022). The three subscales of manual dexterity, aiming and catching, and balance were included; the total score was a combination of these three scores (Spencer et al., 2022). To study brain volume, each child underwent an MRI scan (Spencer et al., 2022).

Findings indicate that the total IQ of children in the HIE group was significantly less than that of children in the control group (Spencer et al., 2022). Additionally, a significantly greater proportion of children in the HIE group were at risk for motor impairment than children in the control group (Spencer et al., 2022). The total brain volume of both gray matter and white matter in children previously affected by HIE was less than in the healthy children (Spencer et al., 2022). Although the pallidi, hippocampi, and thalami had significantly lower volumes in children in the HIE group than in children in the control group, when considered with total brain volume, the decrease in volume was not significant for any of the structures (Spencer et al., 2022). However, findings indicate that IQ score was significantly correlated with both hippocampi volume and thalami volume in children in the HIE group (Spencer et al., 2022).

Based on these results, it is suggested that the lower scores in perceptual reasoning, verbal comprehension, working memory, and total IQ for children who had previously experienced HIE could be a result of the decreases in hippocampal volume. Consequently, cognitive development is also affected by reduced volume of the hippocampi (Spencer et al., 2022). Similarly, lower scores in manual dexterity, aiming and catching, and MABC-2 total could be a result of the decreases in thalamic volume seen in the children in the HIE group (Spencer et al., 2022). The results of these two studies indicate that during middle childhood, children who were affected perinatally by HIE do have impaired cognitive and motor development.

Adolescence

Unfortunately, there is limited knowledge on the impacts of HIE in adolescence when therapeutic hypothermia had been administered during infancy for treatment. As therapeutic hypothermia first began being used as a treatment for moderate and severe HIE in the early

2000s, it is possible that the individuals who did receive therapeutic hypothermia are just entering adolescence and their long-term development is currently being assessed.

Summary

When children affected by moderate or severe HIE have received treatment with therapeutic hypothermia, it appears that in early childhood, severity of HIE does not impact their development (Table 5). Experiencing HIE, regardless of severity, seems to lead to the presence of deficits in social development as well as in one aspect of sensorimotor development, fine and gross motor skills (Table 5). However, these deficits are not severe enough for these children to be considered developmentally delayed in these areas. Children affected by moderate or severe HIE are also at a greater risk for psychopathy such as depression and anxiety disorders during early childhood. As some children may demonstrate levels of aggressive behavior that are great enough to be considered a concern, it seems as though behavior can be impacted as a result of HIE during early childhood as well (Table 5).

During middle childhood, it is revealed that moderate and severe HIE treated with therapeutic hypothermia impact the cognitive development of children (Table 5), not only in their overall intelligence, demonstrated by Spencer et al. (2022), but also in various aspects of their intelligence and attention as seen in the results from Cainelli et al. (2021) (Table 6). The impact of HIE on motor development is more widespread than just fine and gross motor skills seen in early childhood, and these children are at a greater risk for overall motor impairment in middle childhood (Table 5). The increased risk for psychopathy such as anxiety disorders observed in early childhood seems to persist into middle childhood as well. Because some symptoms of known psychopathies that affect these children include oppositional behavior and hyperactivity, the behavior of children during middle childhood continues to be affected as it was

in early childhood (Table 5). However, the social impairments children face in early childhood seem to dissipate by middle childhood and the social development of these children appears to be on track with that of their healthy peers (Table 5).

Study	Therapeutic Hypothermia	Age	Severity of HIE	Cognitive Development	Language Development	Sensorimotor Development	Social/Emotional Development	Behavior
Robertson & Finer (1985)	No	Early Childhood	Mild	None	None	None	N/A	N/A
			Moderate	None	None	Impairments	N/A	N/A
			Severe	Developmental delay	Impairments	Impairments	N/A	N/A
Marlow et al. (2005)	No	Middle Childhood	Moderate	Mixed Results	Impairments	Impairments	None	None
			Severe	Impairments	Impairments	None	Impairments	Impairments
Halpin et al. (2022)	No	Adolescence	Mild	Impairments	None	Impairments	Mixed Results	None
			Moderate	Impairments	None	Impairments	Mixed Results	None
Álvarez-García et al. (2022)	Yes	Early Childhood	Moderate	Impairments	N/A	Impairments	Impairments	Impairments
			Severe	Impairments	N/A	Impairments	Impairments	Impairments
Cainelli et al. (2021)	Yes	Middle Childhood	Moderate	Impairments	None	Impairments	None	Impairments
			Severe	Impairments	None	Impairments	None	Impairments
Spencer et al. (2022)	Yes	Middle Childhood	Moderate	Impairments	N/A	Impairments	N/A	N/A
			Severe	Impairments	N/A	Impairments	N/A	N/A

Table 5

Effects of neonatal HIE on the cognitive development, language development, sensorimotor development, social/emotional development, and behavior of children in early childhood, middle childhood, and adolescence, based on severity of HIE and whether or not the infant received treatment with therapeutic hypothermia. N/A indicates that the study did not perform any tests to assess that area of development and mixed results indicates that there were conflicting results between different measures used to assess the same aspect of development.

Data taken from Álvarez-García et al. (2022); Cainelli et al. (2021); Halpin et al. (2022); Marlow et al. (2005); Robertson & Finer (1985); and Spencer et al. (2022).

Study	Therapeutic Hypothermia	Age	Severity of HIE	Intelligence	Memory	Attention	Executive Functioning
Robertson & Finer (1985)	No	Early Childhood	Mild	Average	N/A	N/A	N/A
			Moderate	Average	N/A	N/A	N/A
			Severe	Developmentally Delayed	N/A	N/A	N/A
Marlow et al. (2005)	No	Middle Childhood	Moderate	N/A	Narrative memory impaired	Average	Average
			Severe	N/A	Everyday memory, memory for names, & narrative memory impaired	Impaired	Impaired
Halpin et al. (2022)	No	Adolescence	Mild	N/A	Average	Impaired	Impaired
			Moderate	N/A	Average	Impaired	Impaired
Álvarez-García et al. (2022)	Yes	Early Childhood	Moderate	N/A	N/A	N/A	N/A
			Severe	N/A	N/A	N/A	N/A
Cainelli et al. (2021)	Yes	Middle Childhood	Moderate	Impaired	Average	Auditory attention impaired	Impaired
			Severe	Impaired	Average	Auditory attention impaired	Impaired
Spencer et al. (2022)	Yes	Middle Childhood	Moderate	Impaired	Working memory impaired	N/A	N/A
			Severe	Impaired	Working memory impaired	N/A	N/A

Table 6

Developmental outcomes in aspects of cognitive development including intelligence, memory, attention, and executive functioning following neonatal HIE based on the severity of HIE and whether or not the infant received treatment with therapeutic hypothermia. N/A indicates that the study did not perform any tests to assess that aspect of cognitive development. "Impaired" indicates an overall impairment; specific impairments within aspects of cognitive development are listed.

Data taken from Álvarez-García et al. (2022); Cainelli et al. (2021); Halpin et al. (2022); Marlow et al. (2005); Robertson & Finer (1985); and Spencer et al. (2022).

Discussion

My goal was to determine if infants affected by HIE are able to overcome their early challenges so that by adolescence, they are on track developmentally with their healthy peers. Based on the success of other groups, such as preterm neonates, in achieving this and due to the little understanding of the effects of HIE in adolescence, I hypothesized that the development of these infants looks similar to that of their healthy peers in adolescence. I found that my hypothesis was not supported when infants did not receive therapeutic hypothermia to treat HIE. While those affected by severe HIE are able to overcome the developmental cognitive delays they tend to face in early childhood by the time they reach middle childhood, these children still face cognitive impairments in middle childhood. Therefore, their cognitive development is not at the same level as their healthy peers.

Although no adolescents, regardless of whether they experienced mild or moderate HIE, face true developmental delays, many still live with impairments in aspects of their development including cognition and sensorimotor abilities. While their language abilities are worse than those of other children who were unaffected by HIE in middle childhood, they are able to overcome the setbacks they experience in middle childhood so that this effect is no longer significant in adolescence. As language is used daily in all aspects of life, it is possible this improvement occurs because these children are consistently using these skills and thus have extensive practice in this domain. During middle childhood, children also begin attending school, where individuals who are specifically trained to help children develop language, such as teachers, speech-language pathologists, and reading specialists, begin working with them. Perhaps it is through this targeted aid from more knowledgeable individuals that these children are able to overcome the developmental delay seen in early childhood.

My hypothesis was also unsupported in cases when children were treated with therapeutic hypothermia. While the effects of HIE following treatment with therapeutic hypothermia in adolescence are not yet known, when comparing the long-term impacts between early childhood and middle childhood, these children continue to face setbacks due to HIE in their cognition, behavior, and sensorimotor development. This lends further support to the idea that therapeutic hypothermia does not prevent children from facing developmental impairments following HIE (Shankaran et al., 2012). Despite its inability to protect against later developmental effects of HIE, therapeutic hypothermia is still beneficial due to its reduction in rates of death and severe disability. These children were, however, able to overcome the impairments they encountered in social and emotional development in early childhood so that they were on track developmentally in this domain by middle childhood. Their ability to overcome this impairment could be explained by findings from Johnson et al. (2000) suggesting that children with more positive social skills are more likely to be accepted by their peers. In order to ensure that other children want to play with them, perhaps these children quickly learn which social skills are desirable and then adapt and improve their own social skills so that by middle childhood, their social skills no longer present an issue for peer acceptance. Therefore, although these children did not look similar to their healthy peers in middle childhood, they were able to overcome impairments in one aspect of development. In order to gain a more comprehensive understanding of the long-term effects of HIE, it is imperative that future research evaluates the development of adolescents who experienced HIE during infancy but were treated with therapeutic hypothermia.

Regardless of whether these children received therapeutic hypothermia or not, the persistence of cognitive and sensorimotor impairments is in line with the current understanding of the two patterns of injury resulting from HIE. The watershed pattern of injury is known to

affect cognition, while the basal ganglia pattern of injury is known to predominantly affect motor skills (Miller et al., 2005). However, when the watershed pattern of injury dominates, it is common for the basal ganglia pattern of injury to exist as well, leading to deficits in both cognition and motor abilities (Miller at al., 2005). Overall, it is important to note that these children have reduced neuroplasticity due to lower levels of myelin and fewer cells (Davidson et al., 2018; Nair & Kumar, 2018). Therefore, it follows that they would require more practice than their healthy peers in order to attain the same level of performance in various domains of development. Without additional opportunities to strengthen their cognition and sensorimotor skills, these children may not be able to overcome the developmental impairments they face. Future research should evaluate therapies that have helped children overcome developmental effects of HIE.

Although this study provides further insight into the long-term effects of HIE from early childhood through adolescence, it does have some limitations. First, when therapeutic hypothermia was not administered, not every study looked at each severity of HIE. Thus, observations were unable to made regarding how certain severities of HIE affected development at each age range. For example, while the effects of mild HIE were observed in early childhood and adolescence, no study was included in which children's development following mild HIE was analyzed during middle childhood. Other studies included the long-term impacts of severe HIE in early and middle childhood when therapeutic hypothermia was not administered, but not in adolescence, thus inhibiting any conclusions about whether or not individuals in this group were able to overcome any impairments they faced earlier in life by adolescence. Additionally, while nearly every study excluded children with a cerebral palsy diagnosis from their results or separated the results of children diagnosed with cerebral palsy from those who were not, in the

study by Robertson & Finer (1985) analyzing the effects of HIE in early childhood without treatment using therapeutic hypothermia, their results included children both with and without a cerebral palsy diagnosis together. As a result, it is possible that the developmental effects of HIE without administration of therapeutic hypothermia in early childhood are worse than in middle childhood and adolescence due to some children also having cerebral palsy. Furthermore, studies used different measures to assess domains of development. Differences in these tests could have led to varying conclusions about each developmental domain and could have contributed to the mixed results seen in cognitive and social/emotional development following mild or moderate HIE without therapeutic hypothermia. Future research using a longitudinal study in which aspects of development are measured using the same tests, although appropriate for each age range, in early childhood, middle childhood, and adolescence would be helpful in gaining a more comprehensive understanding of the specific effects of HIE through adolescence. As many studies also had small sample sizes, including more studies so that a greater number of samples could be compared would help to improve this study in the future.

As a result of this study, parents of children affected perinatally by HIE can better understand the effects of HIE at various points in their child's life, whether their child was treated using therapeutic hypothermia or not. They can work together with teachers to provide enrichment opportunities for their child in domains of development that they know have a greater chance of impairment due to HIE. Because they are also aware that their child is at a greater risk for psychopathy such as depression or anxiety disorders, they are more likely to notice if their child starts demonstrating symptoms of these disorders and can provide them support and treatment sooner. Overall, this study provides a wholistic view of the effects of HIE from early childhood through adolescence, and by granting parents an increased understanding of the long-

term impacts of HIE, parents will be able to better support their child, potentially ameliorating these effects.

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