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CLINICAL RESEARCH ARTICLE

Neurodevelopmental correlates of caudate volume in children born at risk of neonatal hypoglycaemia

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BACKGROUND: Neonatal hypoglycaemia can lead to brain damage and neurocognitive impairment. Neonatal hypoglycaemia is associated with smaller caudate volume in the mid-childhood. We investigated the relationship between neurodevelopmental outcomes and caudate volume and whether this relationship was influenced by neonatal hypoglycaemia.
METHODS: Children born at risk of neonatal hypoglycaemia ≥36 weeks' gestation who participated in a prospective cohort study underwent neurodevelopmental assessment (executive function, academic achievement, and emotional-behavioural regulation) and MRI at age 9–10 years. Neonatal hypoglycaemia was defined as at least one hypoglycaemic episode (blood glucose concentration <2.6 mmol/L or at least 10 min of interstitial glucose concentrations <2.6 mmol/L). Caudate volume was computed using FreeSurfer.
RESULTS: There were 101 children with MRI and neurodevelopmental data available, of whom 70 had experienced neonatal hypoglycaemia. Smaller caudate volume was associated with greater parent-reported emotional and behavioural difficulties, and poorer prosocial behaviour. Caudate volume was significantly associated with visual memory only in children who had not experienced neonatal hypoglycaemia (interaction $p = 0.03$), but there were no other significant interactions between caudate volume and neonatal hypoglycaemia.
CONCLUSION: Smaller caudate volume is associated with emotional behaviour difficulties in the mid-childhood. Although neonatal hypoglycaemia is associated with smaller caudate volume, this appears not to contribute to clinically relevant neurodevelopmental deficits.

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IMPACT:

- At 9–10 years of age, caudate volume was inversely associated with emotional-behavioural difficulties and positively associated with prosocial behaviour but was not related to executive function or educational achievement.
- Previous studies have suggested that neonatal hypoglycaemia may contribute to smaller caudate volume but exposure to neonatal hypoglycaemia did not appear to influence the relationship between caudate volume and behaviour.
- Among children not exposed to neonatal hypoglycaemia, caudate volume was also positively associated with visual memory, but no such association was detected among those exposed to neonatal hypoglycaemia.
- Understanding early-life factors that affect caudate development may provide targets for improving behavioural function.

INTRODUCTION

Neonatal hypoglycaemia is the most common metabolic disorder of the newborn infant.[1] It is associated with brain damage in infancy[2] and neurodevelopmental problems in childhood.[3] Neuroimaging studies of infants soon after they have experienced neonatal hypoglycaemia have generally reported injury to posterior regions of the brain,[2,4] although more widespread changes have also been observed.[5] A meta-analysis of follow-up studies conducted to investigate neurodevelopmental outcomes following neonatal hypoglycaemia has suggested that neonatal hypoglycaemia is associated with visual-motor impairment and executive dysfunction in early childhood and with neurodevelopmental impairment, low literacy and numeracy in mid-childhood.[3] Because increasingly complex demands are placed on the child as they transition through later developmental stages, more adverse effects of neonatal hypoglycaemia on neurodevelopmental outcomes may become apparent at older ages. However, the relationship between adverse neurodevelopment and brain imaging in childhood after exposure to neonatal hypoglycaemia has yet to be explored.

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In the recently completed Children with Hypoglycaemia and their Later Development (CHYLD) Mid-childhood Outcome Study, neonatal hypoglycaemia was not associated with educational attainment or other neurodevelopmental outcomes at 9–10 years,[6] despite an association with executive function and visual-motor integration at 4.5 years.[7] However, the cohort as a whole had poorer than average educational attainment. Furthermore, in mid-childhood neonatal hypoglycaemia was associated with a smaller caudate volume in a magnetic resonance imaging (MRI) sub-study.[8] This anatomical association is somewhat surprising in the context of no associations with neurodevelopmental outcomes at the same age. Furthermore, the association persisted even after adjusting for potential confounding and in various sensitivity analyses, suggesting a robust association.

The caudate is a subcortical C-shaped structure that receives afferent projections from nearly all regions of the cortex and is one of the main input nuclei, along with the putamen, to the basal ganglia.[9] It is important for both cognitive and emotional processing.[9,10] Smaller caudate volumes have been associated with lower intelligence quotient in children born preterm[11] and poorer cognitive control and verbal learning/recall in youth exposed to alcohol in utero.[12] These domains are critical for learning, and further investigation of the neurodevelopmental correlates of caudate volume in the CHYLD cohort is warranted. Our aim was to investigate the relationship between caudate volume and executive and emotional-behavioural function and educational achievement at 9–10 years in the CHYLD cohort and whether any relations were influenced by exposure to neonatal hypoglycaemia.

METHODS

Participants

Participants were drawn from the CHYLD Study. The CHYLD Study is a prospective cohort study of children who were born at or after 32 weeks' gestation with one or more risk factors for neonatal hypoglycaemia: maternal diabetes, preterm birth (<37 weeks' gestation), small (<10th centile or <2500 g) or large (>90th percentile or >4500 g) birthweight, or other illness. Recruitment took place between December 2006 and November 2010 at Waikato Hospital, Hamilton, New Zealand. Babies were screened and treated aiming to maintain blood glucose concentrations ≥2.6 mmol/L (47 mg/dL) and two-thirds had masked continuous glucose monitoring (CGM) (CGMS Gold; Medtronic MiniMed). Details of the cohort are available elsewhere.[7,13–15]

All eligible participants (had not previously withdrawn or died) were invited to undergo neurodevelopmental assessment at 9–10 years.[6] A subset of children born ≥36 weeks' gestation was randomly selected to be invited to consider MRI scanning, based on their experience of neonatal hypoglycaemia in four exposure groups: none, mild (1–2 hypoglycaemic events 2.0–2.6 mmol/L), severe (any hypoglycaemia events <2 mmol/L or ≥3 hypoglycaemic events) or clinically undetected hypoglycaemia (interstitial episodes only). Hypoglycaemic events were defined as the sum of nonconcurrent blood and interstitial (CGM-based) episodes more than 20 min apart.[6] A hypoglycaemic episode was defined as at least one consecutive blood glucose concentration <2.6 mmol/L and an interstitial episode was defined as at least 10 min of interstitial glucose concentrations <2.6 mmol/L.

The Health and Disability Ethics Committee (16/NTB/208/AM02) provided ethics approval for the study. Parents or primary caregivers provided written informed consent and the child provided assent.

Caudate volume

MRI scans were acquired at Midland MRI, Anglesea Imaging Centre, Hamilton or the Centre for Advanced MRI (CAMRI), Auckland, with a 3.0 Tesla Siemens Skyra using a 20-channel paediatric head coil. T1-weighted images were acquired with a magnetization-prepared rapid gradient-echo sequence [slice thickness = 0.85 mm; repetition time = 2000 ms; echo time = 3.51 ms; field of view = 210 mm; voxel size = 0.8 × 0.8 × 0.8 mm; flip angle = 9°].

Volumes of the caudate were extracted using the recon-all pipeline in FreeSurfer 6.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/), as described elsewhere.[16–18]

Neurodevelopmental measures

At age 9–10 years, children underwent a neurodevelopmental assessment that included measures of executive function, academic achievement, and social-emotional behaviour.[6]

Executive function was assessed using a tablet-based battery (Cambridge Neuropsychological Test Automated Battery). Measures of attention (Attention Switching Task [AST]), planning/memory (One-touch Stockings of Cambridge, Spatial Working Memory [SWM], Paired Associate Learning [PAL]) and inhibition (Stop Signal Task [SST]) were included. The AST measures a child's ability to switch their attention between the direction of an arrow and the location of an arrow in the presence of distracting information that is given during testing. The outcome measures were median switching and congruent response latency. The One-Touch Stocking of Cambridge task involves solving problems to position coloured balls in the correct sequence on the screen in two, three and four moves. The outcome measures were the number of problems solved on first choice and median latency to the first choice. The SWM task involves finding a blue token in each of four, six or eight boxes that appear on the screen by selection and process of elimination. Between errors (number of times the subject revisits a box in which a token has previously been found) and a measure of strategy were the outcome measures. The PAL task involves correctly locating patterns that were previously shown within boxes on-screen. The outcome measures were total errors (adjusted) and the first attempt memory score (number of correct box choices made on the first attempt). The SST involves responding to an arrow stimulus, by selecting the correct side of the screen depending on the direction of the arrow. The participant must withhold (inhibit) the response if an audio tone is present. The main outcome measure was the stop signal reaction time (length of time between the go stimulus and the stop stimulus (audio tone) at which the subject is able to successfully inhibit their response in 50% of the trials); two categorical outcomes were also assessed (failed stop reaction time less than go reaction time, and mean failed stop reaction time increases).

Academic achievement was assessed using the e-asTTle school achievement tests of Reading Comprehension and Mathematics in English or Māori.[19] Social-emotional behaviour was assessed using the Strengths and Difficulties Questionnaire (SDQ), both parent and teacher reported.[20] The SDQ assesses emotional and behavioural difficulties in children aged 4–17 years. The 25 items are divided into five subscales. We included the total difficulties score (range 0–40) which comprises four subscales (emotional symptoms, conduct problems, hyperactivity/inattention, peer problems) and the fifth subscale, prosocial behaviour, which represents the strengths of a child. Borderline and abnormal thresholds for the total difficulties score were defined as a parent-reported score of ≥14 or a teacher-reported score of ≥12.

Statistical analysis

All analyses were conducted on SAS version 9.4.

Associations between caudate volume and neurodevelopmental outcomes were assessed using general linear models conducted on the overall cohort, in the subgroups of those who did and did not experience neonatal hypoglycaemia, and including neonatal hypoglycaemia as an interaction term. The models were conducted unadjusted and then adjusted for gestational age at birth, sex, birthweight *z*-score and age at MRI scan; the adjusted models are presented in the text.

The main findings are reported for the total caudate volume. Additional analyses were conducted for the left and right hemisphere caudate volumes separately to explore the effect of laterality.

RESULTS

In total, 248 participants were randomly selected to be invited to consider MRI, of whom 170 parents (69%) agreed to be approached and 111 (65% of those approached) consented to MRI. Following exclusion due to head motion, there were 101 participants with MRI and neurodevelopmental data available; 70 who had experienced neonatal hypoglycaemia (37 mild, 17 severe and 16 undetected) and 31 who had not. Most of the mothers of included children had post-secondary education (59%) and 40% had gestational diabetes mellitus (Table 1). There was a similar number of boys and girls, approximately one-third of the cohort lived in an area with high deprivation at birth and half of the cohort was of non-European ethnicity. There were no significant differences between children who had and had not experienced

Table 1. Characteristics of the overall cohort and children who did and did not experience neonatal hypoglycaemia.

	Overall cohort	Neonatal hypoglycaemia	No neonatal hypoglycaemia
Maternal characteristics			
N	99	68	31
Parity, median (IQR)	1 (0–2)	1 (0–2)	1 (0–1)
Gestational diabetes mellitus	40 (40.4)	29 (42.7)	11 (35.5)
Smoking during pregnancy	26 (26.3)	18 (26.5)	8 (25.8)
Alcohol consumption during pregnancy	9 (9.1)	6 (8.8)	3 (9.7)
Education level			
Schooling incomplete	5 (5.1)	4 (5.9)	1 (3.2)
High school ≥3 years	19 (19.2)	14 (20.6)	5 (16.1)
Technical or trade	29 (29.3)	19 (27.9)	10 (32.3)
University	30 (30.3)	22 (32.4)	8 (25.8)
Neonatal characteristics			
N	101	70	31
Boys	49 (48.5)	33 (47.1)	16 (51.6)
Gestation, weeks	38.3 (1.5)	38.3 (1.6)	38.3 (1.4)
Birthweight	3213 (873)	3225 (858)	3184 (919)
Birthweight *z*-score	0.1 (1.8)	0.1 (1.7)	-0.004 (1.9)
Birth head circumference	34.4 (2.3)	34.4 (2.4)	34.3 (2.1)
Birth head circumference *z*-score	0.2 (1.6)	0.3 (1.7)	0 (1.6)
Twin	6 (5.9)	4 (5.7)	2 (6.5)
Afebrile seizures	2 (2.0)	1 (1.4)	1 (3.2)
Primary risk for hypoglycaemia[a]			
IDM	49 (48.5)	35 (50.0)	14 (45.2)
Preterm	17 (16.8)	14 (20.0)	3 (9.7)
Small	17 (16.8)	10 (14.3)	7 (22.6)
Large	12 (11.9)	7 (10.0)	5 (16.1)
Other	6 (5.9)	4 (5.7)	2 (6.5)
High deprivation[b]	33 (32.7)	21 (30.0)	12 (38.7)
Incidence of neonatal hypoglycaemia[c]	70 (69)	70 (100)	0
Severity of hypoglycaemia[c]			
None	31 (30.7)	0	31 (100)
Mild	37 (36.6)	37 (52.9)	0
Severe	17 (16.8)	17 (24.3)	0
Undetected	16 (15.8)	16 (22.9)	0
Frequency of hypoglycaemia[c]			
None	31 (30.7)	0	31 (100)
1–2 events	38 (37.6)	38 (54.3)	0
≥3 events	32 (31.7)	32 (45.7)	0
Characteristics at assessment			
Age (years)	9.4 (0.3)	9.4 (0.4)	9.3 (0.3)
Ethnicity			
Māori	29 (28.7)	22 (31.4)	7 (22.6)
Pacific	4 (4.0)	2 (2.9)	2 (6.5)
NZ European	51 (50.5)	34 (48.6)	17 (54.8)
Other	10 (9.9)	12 (17.1)	4 (12.9)
Need for additional learning support or older than expected for the year level[d]	51 (50.5)	38 (54.3)	13 (41.9)
Need for additional learning support or older than expected for year level or low educational achievement[d]	71 (70.3)	52 (74.3)	19 (61.3)

Data are presented as *n* (%), mean (standard deviation) or median (interquartile range).
IQR interquartile range, *IDM* infant of diabetic mother.
[a]Other risk = sepsis, haemolytic disease of the newborn, respiratory distress, congenital heart disease or poor feeding.
[b]High deprivation = New Zealand deprivation index decile 8 to 10.
[c]Incidence of hypoglycaemia = any hypoglycaemic events < 2.6mmol/L; none = no evidence of hypoglycaemic events; mild = 1 or 2 hypoglycaemic events between 2.0 to 2.6 mmol/L; severe = any hypoglycaemic events <2 mmol/L; undetected = interstitial episodes only.
[d]Older than expected for year level = child is ≥1 year older than 95% of children in their school year level.

Table 2. Associations between neurodevelopmental outcomes and caudate volume.

Outcome	*N* (%) or mean (SD)	Adjusted β^a	95% CI	Interaction term *p* value
Educational achievement				
e-asTTle				
Low educational achievement	42 (41.6)	−243	(−593 to 106)	–
Hypoglycaemia	30 (42.9)	−121	(−552 to 309)	0.48
No hypoglycaemia	12 (38.7)	−281	(−925 to 362)	
Low achievement in reading comprehension//Pānui	26 (25.7)	55	(−342 to 451)	–
Hypoglycaemia	18 (25.7)	106	(−380 to 591)	0.95
No hypoglycaemia	8 (25.8)	187	(−535 to 910)	
z-score for year and term of school in Reading Comprehension/Pānui	−0.05 (0.9)	−51	(−238 to 136)	–
Hypoglycaemia	−0.1 (0.9)	−60	(−285 to 166)	0.96
No hypoglycaemia	−0.02 (0.9)	−172	(−520 to 176)	
Low achievement in Mathematics/Pāngarau	29 (28.7)	−352	(−733 to 29)	–
Hypoglycaemia	21 (30)	−229	(−699 to 240)	0.42
No hypoglycaemia	8 (25.8)	−355	(−1096 to 387)	
z-score for year and term of school in Mathematics/ Pāngarau	−0.1 (0.8)	54	(−174 to 282)	–
Hypoglycaemia	−0.1 (0.8)	2	(−258 to 263)	0.44
No hypoglycaemia	−0.1 (0.6)	69	(−471 to 610)	
Executive function				
Attention/cognitive flexibility				
Attention switching task				
Switching median response latency (ms)	858 (167)	0.2	(−0.8 to 1.3)	–
Hypoglycaemia	851 (180)	0.04	(−1.2 to 1.2)	0.68
No hypoglycaemia	872 (137)	2	(−1 to 4)	
Congruent median response latency (ms)	730 (124)	0.3	(−1.2 to 1.7)	–
Hypoglycaemia	729 (136)	0.09	(−1.5 to 1.7)	0.69
No hypoglycaemia	732 (94)	3	(−1 to 6)	
Planning/working memory				
One-touch stockings of Cambridge				
Number of problems solved on first choice	7.7 (3.1)	48	(−6 to 102)	–
Hypoglycaemia	7.6 (3)	62	(−6 to 130)	0.47
No hypoglycaemia	8.0 (3.4)	17	(−73 to 108)	
Median latency to first choice—ms	12703 (6693)	−0.001	(−0.03 to 0.03)	–
Hypoglycaemia	12903 (7262)	−0.005	(−0.03 to 0.02)	0.26
No hypoglycaemia	12251 (5262)	0.02	(−0.04 to 0.08)	
Spatial working memory				
Between search errors	18.0 (7.3)	−22	(−46 to 2)	–
Hypoglycaemia	18.4 (7.2)	−30	(−59 to −1)*	0.16
No hypoglycaemia	17.1 (7.7)	6	(−37 to 48)	
Strategy score	9.0 (1.6)	−22	(−134 to 90)	–
Hypoglycaemia	9.0 (1.4)	−1	(−171 to 169)	0.86
No hypoglycaemia	8.8 (2)	−6	(−155 to 143)	
Visual memory/learning				
Paired associate learning				
First attempt memory score	13.4 (3.1)	37	(−19 to 93)	–
Hypoglycaemia	13.5 (2.9)	−23	(−99 to 54)	0.03
No hypoglycaemia	13.3 (3.6)	106	(28 to 184)	
Total errors (adjusted)	11.0 (9.3)	−12	(−31 to 7)	–
Hypoglycaemia	10.6 (8)	7	(−22 to 35)	0.11
No hypoglycaemia	11.9 (11.8)	−24	(−49 to 2)	

Table 2. continued

Outcome	*N* (%) or mean (SD)	Adjusted β^a	95% CI	Interaction term *p* value
Inhibitory control				
Stop signal task				
Stop signal reaction time (ms)	333 (79)	0.7	(–2 to 3)	–
Hypoglycaemia	337 (74)	1	(–2 to 4)	0.78
No hypoglycaemia	324 (89)	2	(–1 to 6)	
Failed stop reaction time less than go reaction time	0 (0)	–	–	–
Hypoglycaemia	0 (0)	–	–	–
No hypoglycaemia	0 (0)	–	–	
Mean failed stop reaction time increases	12 (11.9)	–106	(–637 to 424)	–
Hypoglycaemia	8 (11.4)	229	(–434 to 892)	0.09
No hypoglycaemia	4 (12.9)	–580	(–1489 to 330)	
Strength and Difficulties Questionnaire				
Parent (SDQ-P)				
Total Difficulties Score	10.8 (6.9)	–31	(–56 to –5)*	–
Hypoglycaemia	10.7 (6.7)	–21	(–54 to 12)	0.27
No hypoglycaemia	11.1 (7.2)	–56	(–89 to –23)**	
Prosocial Behaviour Score	8.3 (1.8)	109	(10 to 208)*	–
Hypoglycaemia	8.2 (1.8)	118	(–9 to 245)	0.53
No hypoglycaemia	8.5 (1.9)	99	(–61 to 259)	
Total Difficulties Score ≥14	27 (29)	–421	(–816 to –26)*	–
Hypoglycaemia	18 (27.7)	–428	(–933 to 78)	0.76
No hypoglycaemia	9 (32.1)	–584	(–1155 to –13)*	
Teacher (SDQ-T)				
Total Difficulties Score	7.6 (5.9)	–2	(–32 to 28)	–
Hypoglycaemia	7.4 (5.7)	–7	(–45 to 32)	0.70
No hypoglycaemia	8.2 (6.3)	–1	(–49 to 48)	
Prosocial Behaviour Score	7.9 (2.0)	32	(–59 to 123)	–
Hypoglycaemia	8.0 (2.0)	51	(–56 to 157)	0.49
No hypoglycaemia	7.6 (1.9)	–4	(–191 to 183)	
Total Difficulties Score ≥12	26 (26.5)	98	(–298 to 493)	–
Hypoglycaemia	15 (22.4)	–98	(–606 to 411)	0.30
No hypoglycaemia	11 (35.5)	219	(–424 to 863)	

Data for the cohort are mean (standard deviation) or *n* (%).
e-asTTle = assessment tools for teaching and learning; low educational achievement = e-asTTle score below or well below the normative curriculum level in reading comprehension or mathematics.
*$p < 0.05$; **$p < 0.005$.
[a]Adjusted for gestational age at birth, sex, birthweight *z*-score and age at MRI scan.

neonatal hypoglycaemia in any maternal or neonatal characteristics. Over 40% of children had low educational achievement, as assessed by the e-asTTle, and over 25% had parent- or teacher-reported emotional and behaviour difficulties (Table 2).

In the overall cohort, caudate volume was not significantly associated with executive function measures (Table 2; for unadjusted models see Supplementary Table 1). However, there was evidence that the association between caudate volume and memory score on PAL (associative memory) may be influenced by neonatal hypoglycaemia as there was a positive association between caudate volume and memory score in children who had not experienced neonatal hypoglycaemia but not in those who had experienced hypoglycaemia (*p* for interaction 0.03; Fig. 1 and Table 2). No other interaction terms in the executive function tasks were significant.

Caudate volume was associated with emotional-behavioural regulation. The parent-reported Total Difficulties score and the proportion with borderline or abnormal score (≥14) were negatively associated with caudate volume, corresponding to a 60-mm^3 decrease in caudate volume for every two-point increase in the Total Difficulties score. Parent-reported Prosocial score was positively associated with caudate volume (Table 2). There was no interaction between the caudate volume and neonatal hypoglycaemia for SDQ outcomes. However, in the subgroup analyses, among children who had not experienced neonatal hypoglycaemia SDQ, parent-reported total difficulties score and score ≥14 were negatively associated with caudate volume.

The analysis results were similar for left and right hemisphere caudate volume separately, although the associations between right caudate volume and SWM (between search errors) in the neonatal hypoglycaemia subgroup and with SDQ total difficulties score ≥14 in the no neonatal hypoglycaemia subgroup were not statistically significant (Supplementary Table 2).

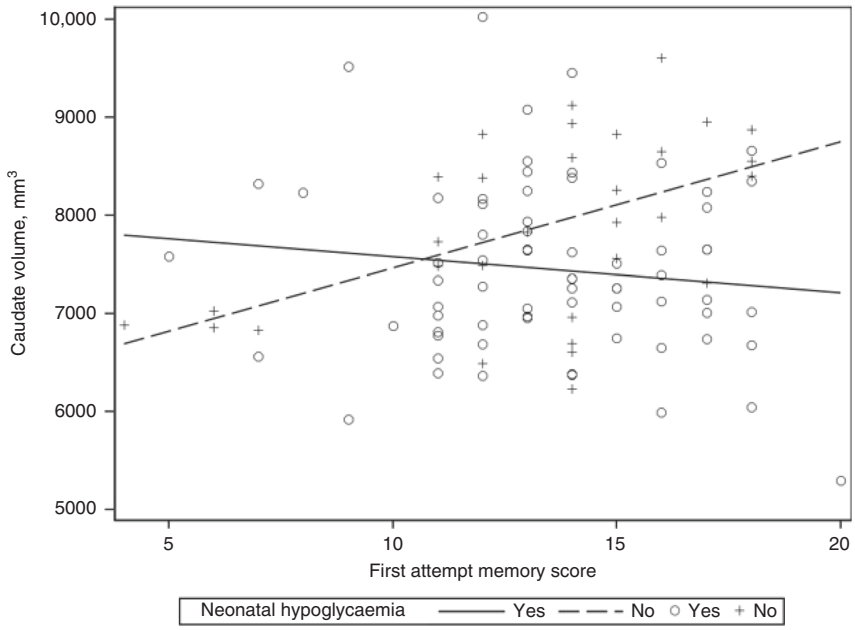

Fig. 1 Interaction between neonatal hypoglycaemia and paired associate learning. Neonatal hypoglycaemia β −23, 95% CI −99 to 54, $p = 0.56$. No neonatal hypoglycaemia β 106, 95% CI 28 to 164, $p = 0.01$. Interaction p value = 0.03.

DISCUSSION

In a cohort of children born at risk of neonatal hypoglycaemia, caudate volume was associated with emotional-behavioural difficulties. Specifically, smaller caudate volume was associated with a greater number of parent-reported emotional and behavioural difficulties, and poorer prosocial behaviour. Furthermore, we found that although neonatal hypoglycaemia is associated with smaller caudate volume,[8] it did not appear to influence the relationship between caudate volume and neurodevelopment, with the possible exception of associative memory.

The caudate is a key structure in cortical networks responsible for emotion regulation[10,21] and integration of emotional information.[22] We found that parent-reported social-emotional behaviour was related to smaller caudate volume, although teacher-reported behaviour was not. Discrepancies between these reports have been noted previously, possibly because teachers have a wider comparison to children of the same age and children may behave differently at home and at school.[23,24] The negative relationship observed between total difficulties and caudate volume is consistent with previous literature linking altered structure of the caudate to attention deficit hyperactivity disorder (ADHD).[25] It would be interesting to explore the relationship between ADHD and caudate volume in the current cohort. However, just five participants had parent-reported ADHD based on a single questionnaire item, which is too few for a reliable analysis.

There was just one significant interaction between the caudate volume and neonatal hypoglycaemia in the relationship with neurodevelopmental outcomes, indicating that smaller caudate volume may be associated with fewer correct choices on the first attempt at a visual associative memory task only in children who had not experienced neonatal hypoglycaemia. This interaction may be driven by the opposite direction of effect observed in children who had experienced neonatal hypoglycaemia. However, this association was not significant and any further discussion about the meaning of a negative relationship between caudate volume and visual memory in the neonatal hypoglycaemia group would be entirely speculative. The caudate nucleus has strong connections to higher-order association areas such as the dorsolateral prefrontal cortex[9] and has previously been linked with executive function in children.[11,12] Although we found associations between SWM and social-emotional behaviour difficulties and caudate volume in subgroups of children who had and had not experienced hypoglycaemia, the lack of an interaction effect for these outcomes necessitates caution when interpreting these findings. We performed 42 tests for the subgroup analyses and could therefore reasonably expect eight false-positive results. It is therefore possible that the hypoglycaemia subgroup findings are due to Type I error.

We have previously reported that neonatal hypoglycaemia is not associated with altered educational or other neurodevelopmental outcomes in mid-childhood,[6] and this study suggests that hypoglycaemia may not alter the relationship between caudate volume and neurodevelopmental outcomes. Together, these suggest that the observed association between neonatal hypoglycaemia and reduced caudate volume[8] may not be causal, or that if it is, it has little observable clinical relevance. However, all children in this cohort were tested and treated with the intention of maintaining blood glucose concentrations at or above 2.6 mmol/L, which may have minimized any potential effects on later outcomes. Randomized trials are needed to determine whether neonatal hypoglycaemia actually causes altered brain volumes and neurodevelopmental outcomes and at what glucose thresholds.

Strengths of the study include that children were assessed on a wide range of neurodevelopmental outcomes that included academic performance, executive functions and socio-emotional behaviour. In addition, there was a high percentage of low educational achievement and emotion and behaviour difficulties, which may have increased the power to detect associations with caudate volume. Low educational attainment in this cohort has been discussed comprehensively in our previous report[6]—briefly, we postulate that the risk factors for neonatal hypoglycaemia and their social determinants may themselves. have a negative effect on neurodevelopment. Examining the left and right hemisphere caudate volumes separately also did not change the findings. This is one of the few studies to conduct brain MRI in the mid-childhood following neonatal hypoglycaemia. However, the sample size was modest, particularly in the group that had not experienced neonatal hypoglycaemia, and the confidence intervals around many of the beta coefficients

were relatively wide, suggesting that these estimates of relationships between caudate volume and functional outcomes were imprecise. Furthermore, we focussed on caudate volume based on the most robust finding in our previous report of the MRI findings at 9–10 years related to hypoglycaemia in this cohort;[8] however, children who had experienced neonatal hypoglycaemia also had smaller thalamus and subcortical grey matter volumes as a percentage of total brain volume compared to children who had not. As these findings were not significant for the absolute volumes (mm^3), it is unlikely they are contributing to the association between caudate volume and emotional-behavioural problems. In addition, none of the included children underwent neonatal MRI; therefore, we have no information about any acute changes after neonatal hypoglycaemia. Two children had evidence of other changes on MRI scan (one a well-defined splenium lesion of the corpus callosum and the other posterior white matter injury, particularly in the parieto-occipital regions). However, as there were just two children with incidental findings, they are unlikely to have substantially influenced the results. Future studies with larger sample sizes would be beneficial to determine if differences in brain structure associated with neonatal hypoglycaemia have an effect on neurodevelopment.

In summary, smaller caudate volume is associated with increased emotional-behavioural difficulties in the mid-childhood. However, exposure to neonatal hypoglycaemia was not found to significantly influence this relationship.

DATA AVAILABILITY

Published data are available to approved researchers under the data sharing arrangements provided by the Clinical Data Research Hub, based at the Liggins Institute, University of Auckland (https://wiki.auckland.ac.nz/researchhub). Metadata, along with instructions for data access, are available at the University of Auckland's research data repository, Figshare (https://auckland.figshare.com). Data access requests are to be submitted to Data Access Committee via researchhub@auckland.ac.nz. Deidentified published data will be shared with researchers who provide a methodologically sound proposal and have appropriate ethical and institutional approval. Researchers must sign and adhere to the Data Access Agreement that includes a commitment to using the data only for the specified proposal, to refrain from any attempt to identify individual participants, to store data securely, and to destroy or return the data after completion of the project. The Clinical Data Research Hub reserves the right to charge a fee to cover the costs of making data available, if required.

REFERENCES

1. Harding, J. E., Harris, D. L., Hegarty, J. E., Alsweiler, J. M. & McKinlay, C. J. An emerging evidence base for the management of neonatal hypoglycaemia. *Early Hum. Dev.* **104**, 51–56 (2017).
2. Alkalay, A. L., Flores-Sarnat, L., Sarnat, H. B., Moser, F. G. & Simmons, C. F. Brain imaging findings in neonatal hypoglycemia: case report and review of 23 cases. *Clin. Pediatr. (Philos.).* **44**, 783–790 (2005).
3. Shah, R., Harding, J., Brown, J. & McKinlay, C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. *Neonatology* **115**, 116–126 (2019).
4. Filan, P. M., Inder, T. E., Cameron, F. J., Kean, M. J. & Hunt, R. W. Neonatal hypoglycemia and occipital cerebral injury. *J. Pediatr.* **148**, 552–555 (2006).
5. Burns, C. M., Rutherford, M. A., Boardman, J. P. & Cowan, F. M. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics* **122**, 65–74 (2008).
6. Shah, R. et al. Association of neonatal hypoglycemia with academic performance in mid-childhood. *JAMA* **327**, 1158 (2022).
7. McKinlay, C. J. D. et al. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. *JAMA Pediatr.* **171**, 972–983 (2017).
8. Nivins, S. et al. Associations between neonatal hypoglycaemia and brain volumes, cortical thickness and white matter microstructure in mid-childhood: an MRI study. *Neuroimage Clin.* **33**, 102943 (2022).
9. Grahn, J. A., Parkinson, J. A. & Owen, A. M. The cognitive functions of the caudate nucleus. *Prog. Neurobiol.* **86**, 141–155 (2008).
10. Graff-Radford, J., Williams, L., Jones, D. T. & Benarroch, E. E. Caudate nucleus as a component of networks controlling behavior. *Neurology* **89**, 2192 (2017).
11. Abernethy, L. J., Cooke, R. W. I. & Foulder-Hughes, L. Caudate and hippocampal volumes, intelligence, and motor impairment in 7-year-old children who were born preterm. *Pediatr. Res.* **55**, 884–893 (2004).
12. Fryer, S. L. et al. Caudate volume predicts neurocognitive performance in youth with heavy prenatal alcohol exposure. *Alcohol. Clin. Exp. Res.* **36**, 1932–1941 (2012).
13. McKinlay, C. J. D. et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. *N. Engl. J. Med.* **373**, 1507–1518 (2015).
14. Harris, D. L., Weston, P. J., Signal, M., Chase, J. G. & Harding, J. E. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. *Lancet* **382**, 2077–2083 (2013).
15. Harris, D. L., Battin, M. R., Weston, P. J. & Harding, J. E. Continuous glucose monitoring in newborn babies at risk of hypoglycemia. *J. Pediatr.* **157**, 198–202 (2010).
16. Dale, A. M., Fischl, B. & Sereno, M. I. Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage* **9**, 179–194 (1999).
17. Fischl, B., Liu, A. & Dale, A. M. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans. Med. Imaging* **20**, 70–80 (2001).
18. Fischl, B. et al. Sequence-independent segmentation of magnetic resonance images. *Neuroimage* **23**, 69–84 (2004).
19. Minister of Education. e-asTTle. http://e-asttle.tki.org.nz/. Accessed 15 Sept 2016.
20. Goodman, R. The Strengths and Difficulties Questionnaire: a research note. *J. Child Psychol. Psychiatry* **38**, 581–586 (1997).
21. Robinson, J. L. et al. The functional connectivity of the human caudate: an application of meta-analytic connectivity modeling with behavioral filtering. *Neuroimage* **60**, 117–129 (2012).
22. Haber, S. N. Neuroanatomy of reward: a view from the ventral striatum. *Neurobiol. Sensat. Reward* 255–282 https://doi.org/10.1201/b10776-19 (2011).
23. Crane, L., Sumner, E. & Hill, E. L. Emotional and behavioural problems in children with Developmental Coordination Disorder: exploring parent and teacher reports. *Res. Dev. Disabil.* **70**, 67–74 (2017).
24. Gritti, A. et al. Epidemiological study on behavioural and emotional problems in developmental age: prevalence in a sample of Italian children, based on parent and teacher reports. *Ital. J. Pediatr.* **40**, 19 (2014).
25. Tremols, V. et al. Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder. *Psychiatry Res.* **163**, 270–278 (2008).

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AUTHOR CONTRIBUTIONS

E.K.: conceptualization, formal analysis, resources, writing—original draft. S.N.: investigation, writing—review and editing. B.T.: funding acquisition, writing—review and editing. C.J.D.M.: conceptualization, funding acquisition, writing—review and editing. J.H.: conceptualization, supervision, funding acquisition, writing—review and editing.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT TO PARTICIPATE

Parents or primary caregivers provided written informed consent and the child provided assent.

ADDITIONAL INFORMATION

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