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ORIGINAL ARTICLE

Executive function and behaviour problems in school-age children born at risk of neonatal hypoglycaemia

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Abstract

Aim: To examine the relationship between neonatal hypoglycaemia and specific areas of executive function and behaviour in mid-childhood.

Method: Participants in a prospective cohort study of infants born late preterm or at term at risk of neonatal hypoglycaemia were assessed at 9 to 10 years. We assessed executive function using performance-based (Cambridge Neuropsychological Tests Automated Battery) and questionnaire-based (Behavior Rating Inventory of Executive Function) measures and behaviour problems with the Strengths and Difficulties Questionnaire. Data are reported as adjusted odds ratio (aOR) with 95% confidence intervals, and standardized regression coefficients.

Results: We assessed 480 (230 females, 250 males; mean age 9 years 5 months [SD 4 months, range 8 years 8 months–11 years 0 months]) of 587 eligible children (82%). There were no differences in performance-based executive function between children who did and did not experience neonatal hypoglycaemia (blood glucose <2.6 mmoL/L). However, children who experienced hypoglycaemia, especially if severe or recurrent, were at greater risk of parent-reported metacognition difficulties (aOR 2.37–3.71), parent-reported peer (aOR 1.62–1.89) and teacher-reported conduct (aOR 2.14 for severe hypoglycaemia) problems. Both performance- and questionnaire-based executive functions were associated with behaviour problems.

Interpretation: Neonatal hypoglycaemia may be associated with difficulties in specific aspects of parent-reported executive functions and behaviour problems in mid-childhood.

Neonatal hypoglycaemia is a common metabolic problem affecting 5% to 15% of all infants.[1,2] Neuroimaging studies of infants who experience severe or symptomatic hypoglycaemia commonly report acute abnormalities in the occipital cortex and white matter injury.[3,4] Follow-up studies have also reported reduced mental and motor functioning at 18 months,[5] and adverse neurocognitive, motor, educational, and behavioural outcomes in later childhood.[6–8] However, few studies have examined the associations between neonatal hypoglycaemia and specific aspects of neurocognitive and behavioural functioning in childhood.[6,9] Enhanced understanding of these relationships may uncover subtle difficulties of children who experienced neonatal hypoglycaemia and inform timely intervention.

Abbreviations: CHYLD, Children with Hypoglycaemia and their Later Development; SDQ, Strengths and Difficulties Questionnaire.

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Neonatal hypoglycaemia has been reported to be associated with executive dysfunction. The Children with Hypoglycaemia and their Later Development (CHYLD) study assessed a cohort of 614 infants born at risk of neonatal hypoglycaemia, and reported that hypoglycaemia was associated with a twofold increased risk of performance-based executive function difficulties at age 4 years 6 months.[10] Children exposed to severe, recurrent, and clinically undetected hypoglycaemia were at greater risk of poor executive function. However, in this cohort hypoglycaemia was not associated with altered overall executive function at age 9 to 10 years.[11]

Previous findings about behavioural outcomes of children exposed to hypoglycaemia have been mixed. Children of diabetic mothers who experienced neonatal hypoglycaemia were more often reported to be hyperactive, impulsive, and easily distracted at age 8 years than matched comparison individuals.[7] However, another small study has reported no significant differences in behaviour problems between children who experienced neonatal hypoglycaemia and their matched comparison individuals at age 7 to 9 years.[6]

Specific domains of executive function play important roles in contributing to behavioural outcomes. For example, greater inhibitory control and sequencing abilities predicted reduced externalizing problems 2 years later in typically developing children aged 6 to 9 years.[12] Further, executive function mediated the relationships between preterm birth and behaviour problems at age 13 years.[13]

These findings suggest that neonatal hypoglycaemia may be linked with later executive dysfunction and behaviour problems. However, there is limited information on which specific executive functions and behaviours are affected, and how they may interact. We therefore examined a range of specific executive functions and behaviour problems in school-age children born at risk of neonatal hypoglycaemia. We aimed to investigate whether specific difficulties in these domains were related to the frequency or severity of hypoglycaemia or clinically undetected hypoglycaemia, and to test whether specific executive functions might mediate the relationship between neonatal hypoglycaemia and behaviour problems.

What this paper adds

- Neonatal hypoglycaemia associates with parent-reported but not performance-based executive function in mid-childhood.
- Neonatal hypoglycaemia associates with increased risks of peer and conduct problems.
- Specific aspects of performance-based and questionnaire-based executive function associate with behaviour problems.

METHOD

Participants

The CHYLD study is a prospective cohort study following the development of children born at 32 weeks' gestation or later with one or more risk factors for neonatal hypoglycaemia (diabetic mother, preterm [<37 weeks], small [<10th centile or < 2500 g], large [>90th centile or > 4500 g], or other risk such as poor feeding).[10,14] Participants in the CHYLD cohort were born between 2006 to 2010 at Waikato Hospital, Hamilton, New Zealand. Characteristics of the cohort, glycaemic management, and outcomes at age 2 years and 4 years 6 months have been reported elsewhere.[10,14] Infants underwent regular blood glucose monitoring using a glucose oxidase method and masked continuous interstitial glucose monitoring. Hypoglycaemia was treated with extra feeding, buccal dextrose gel, and intravenous dextrose to maintain blood glucose concentrations of at least 2.6 mmoL/L.

When the children were at a corrected age of 9 to 10 years, families were invited to participate in this mid-childhood outcomes study. Assessments of cognitive, motor, visual–perceptual, learning, and behaviour functioning were conducted by trained assessors at school or at home.[11] This study was approved by the Northern B Health and Disability Ethics Committee (16/NTB/208). Parents provided written consent and children provided written assent for all assessments.

Measures

Performance-based executive function was assessed using four tasks of the Cambridge Neuropsychological Tests Automated Battery (Cambridge Cognition, Cambridge, UK), chosen because it has good psychometric properties and can assess various components of executive function with child-friendly computerized tasks.[15] The Spatial Working Memory task requires children to search for blue tokens by touching the boxes to open them but not return to a box where a token has been found previously. The outcome measure was the total between errors (total number of times the child revisited a box in which a token had previously been found). The One Touch Stockings of Cambridge task assesses planning skills. Children must state the number of moves needed to make the lower display of three coloured balls copy the pattern shown in the upper display. The outcome measure was the number of problems solved on the first attempt. The Attention Switching task requires children to press the button corresponding to the direction or location of an arrow on screen. The outcome measure was the switching median response latency in milliseconds. The Stop Signal task assesses response inhibition. Children are asked to press the left- or right-hand button according to the direction of the arrows following a visual stimulus, but to withhold their response after an auditory signal. The outcome measure

was the mean stop-signal reaction time. Higher scores on Attention Switching, Spatial Working Memory, and Stop Signal tasks as well as lower scores on the One Touch Stockings of Cambridge task indicate poorer executive function. All raw scores were converted into z-scores and reverse coded for Attention Switching, Spatial Working Memory, and Stop Signal tasks. Low performance was defined as z-scores more than one standard deviation below the mean.

For questionnaire-based executive function assessing the behaviour manifestations of executive function, parents and teachers were asked to complete the Behavior Rating Inventory of Executive Function.[16] This questionnaire comprises 86 items within eight clinical scales that can yield two indexes: the Metacognition Index (including initiate, working memory, plan/organize, organization of materials, and monitor) and the Behavioral Regulation Index (including inhibition, shift, and emotional control). The sum of the two indexes generates the global executive composite score. All scores are reported as T scores with a mean of 50 and a standard deviation of 10. Higher scores indicate more executive function difficulties. Low performance was defined as indexes and a global executive composite greater than 65.

To assess behaviour problems, we used parent- and teacher-versions of the Strengths and Difficulties Questionnaire (SDQ). This screening tool comprises 25 items assessing four symptoms scales (emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationships) and a prosocial behaviour scale.[17] A total difficulties score is generated by summing the scores of the four symptoms scales. Higher symptoms scores indicate more behaviour problems. Problem behaviour was defined as a total difficulties score reaching the clinical range (SDQ – Parent ≥14 or SDQ – Teacher ≥12); emotional problems score SDQ – Parent ≥4 or SDQ – Teacher ≥5; conduct problems score SDQ – Parent or Teacher ≥3; hyperactivity problems score SDQ – Parent or Teacher ≥6; peer problems score SDQ – Parent ≥3 or SDQ – Teacher ≥4; and prosocial score SDQ – Parent or Teacher ≤5.

Neonatal and maternal characteristics were obtained from medical records. Parental questionnaires were used to obtain information on the home and family environment. Maternal ethnicity was self-defined and prioritized using Ministry of Health Guidelines.[18] Socioeconomic status was assessed using the New Zealand Deprivation Index, a decile scale ranging from 1 to 10, where 1 represents least deprivation.[19]

Analysis

A hypoglycaemic episode was defined as at least one consecutive blood glucose concentration less than 2.6 mmoL/L (mild ≥2.0 mmoL/L to <2.6 mmoL/L; severe <2.0 mmoL/L). Interstitial episodes were defined as interstitial glucose concentrations less than 2.6 mmoL/L for at least 10 minutes. Hypoglycaemic events referred to the sum of non-current hypoglycaemic and interstitial episodes more than 20 minutes apart. Hypoglycaemia was defined as at least one hypoglycaemic event in the first week after birth. Clinically undetected hypoglycaemia was defined as at least one hypoglycaemic event but no hypoglycaemic episodes.

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Descriptive data are presented as mean (standard deviation) or number (%). We used independent *t*-tests for continuous outcomes and χ^2 tests for dichotomous outcomes to compare the neonatal and demographic variables of participants and non-participants, and participants who did or did not experience neonatal hypoglycaemia.

Generalized linear models were fitted to investigate the differences in executive function and behaviour problems between hypoglycaemic and non-hypoglycaemic groups. Potential confounders including the New Zealand Deprivation Index, sex, primary risk factor for neonatal hypoglycaemia, and Full-Scale IQ at age 4 years 6 months measured by the Wechsler Preschool and Primary Scale of Intelligence were treated as covariates. Logistic and multivariable regression models were fitted to examine the relationships between hypoglycaemia, executive function, and behaviour problems after adjusting for the covariates. The indirect effects of hypoglycaemia on behavioural outcomes through executive function were determined using the bootstrapping method and the PROCESS macro for SPSS.

RESULTS

Neonatal and demographic characteristics

Of the 614 infants who took part in the neonatal studies, three died and 24 withdrew, leaving 587 children eligible for the mid-childhood follow-up study, of whom 480 (82%) were assessed at 9 years of age (230 females, 250 males; mean age 9 years 5 months [SD 4 months, range 8 years 8 months–11 years 0 months]). Children who were not assessed at 9 years were more likely to be of 'other' ethnicity but had otherwise similar demographic, maternal, and neonatal characteristics to those who were assessed (Table 1).

Neonatal hypoglycaemia had occurred in 304 (63%) of the 480 participants in the 9-year assessment, of whom 165 (54%) had at least three hypoglycaemic events, 128 (42%) had at least one severe hypoglycaemic event, and 29 (10%) were exposed to clinically undetected hypoglycaemia. Children who had experienced hypoglycaemia had shorter gestation length and lower birthweight than those who did not and were less likely to be an infant of a diabetic mother, but more likely to have received neonatal intensive care (Table 1).

Association between hypoglycaemia, executive function, and behaviour problems

Children who were or were not exposed to neonatal hypoglycaemia had similar risks of difficulties in performance-based

TABLE 1 Characteristics of participants in the Children with Hypoglycaemia and Their Later Development (CHYLD) study

	Assessed at 9–10 years			
	Total (*n* = 480)	**Neonatal hypoglycaemia (*n* = 304)**	**No neonatal hypoglycaemia (*n* = 176)**	**Not assessed at 9–10 years (*n* = 107)**
Maternal characteristics				
Number of females	447	280	167	100
Age, years:months	30:2	30:1	30:4	29:0
Diabetes in pregnancy				
None	275 (61)	179 (64)	96 (58)	58 (58)
Gestational	138 (31)	76 (27)	62 (37)	33 (33)
Pre-gestational	34 (8)	25 (9)	9 (5)	9 (9)
Socioeconomic status				
Most deprived decile[a]	192 (40)	124 (41)	68 (39)	51 (48)
Educational level				
Schooling incomplete	32 (9)	18 (8)	14 (11)	
High school >3 years	84 (23)	58 (24)	26 (19)	
Technical or trade	143 (35)	82 (34)	50 (38)	
University	124 (33)	81 (34)	43 (32)	
Neonatal characteristics				
Age-corrected at follow-up, years:months	9:5	9:5	9:5	
Males	250 (52)	153 (50)	97 (55)	58 (54)
Singletons	397 (83)	247 (82)	150 (85)	91 (85)
Gestational age (weeks)	37.3 (2.1)	37.1 (2.1)[b]	37.7 (2.0)	37.4 (1.9)
Birthweight (g)	3005 (877)	2937 (848)[b]	3123 (917)	3023 (852)
5-minute Apgar score <7	10 (2)	8 (3)	2 (1)	1 (1)
Admitted to neonatal intensive care unit	239 (50)	173 (57)[c]	66 (38)	42 (39)
Ethnicity[d]				
Māori	149 (31)	98 (33)	51 (29)	25 (25)
Pacific Island	9 (2)	4 (1)	5 (3)	4 (4)
Other[e]	22 (5)	15 (5)	7 (4)	14 (14)
New Zealand European	292 (62)	182 (61)	110 (64)	58 (57)
Primary risk factor[b]				
Infant of diabetic mother	175 (36)	103 (34)	72 (41)	42 (39)
Preterm	170 (35)	116 (38)	54 (31)	40 (37)
Small	71 (15)	50 (17)	21 (12)	14 (13)
Large	47 (10)	22 (7)	25 (14)	6 (6)
Other[f]	17 (4)	13 (4)	4 (2)	5 (5)
Neonatal hypoglycaemia				
Continuous glucose monitoring	377 (79)	250 (82)	127 (72)[b]	75 (70)
Hypoglycaemia				
None	176 (37)	0	176 (37)	40 (37)
1 or 2 events	139 (29)	139 (29)	0	41 (38)
≥3 events	165 (34)	165 (34)	0	26 (24)
Mild events	176 (37)	176 (37)	0	45 (42)

TABLE 1 (Continued)

	Assessed at 9–10 years			
	Total (*n* = 480)	Neonatal hypoglycaemia (*n* = 304)	No neonatal hypoglycaemia (*n* = 176)	Not assessed at 9–10 years (*n* = 107)
Severe events	128 (27)	128 (27)	0	33 (21)
Clinically undetected hypoglycaemia	29 (7)	29 (7)	0	10 (11)

Data are mean (SD) or *n* (%). Hypoglycaemia defined as at least one hypoglycaemic event, defined as the sum of non-concurrent hypoglycaemic and interstitial episodes more than 20 minutes apart; a hypoglycaemic episode is defined as at least one consecutive blood glucose concentration <2.6 mmoL/L, and an interstitial episode as interstitial glucose concentrations <2.6 mmoL/L for 10 minutes; a mild hypoglycaemia event is defined as mild hypoglycaemic events ≥2.0–2.5 mmoL/L only; a severe hypoglycaemia event is defined as at least one severe hypoglycaemic event <2.0 mmoL/L; clinically undetected hypoglycaemia is defined as at least one hypoglycaemic event but no hypoglycaemic episodes.

[a]Most deprived is defined as New Zealand Deprivation Index 8–10.

[b]$p < 0.05$ for comparison between children with and without neonatal hypoglycaemia.

[c]$p < 0.01$ for comparison between children with and without neonatal hypoglycaemia.

[d]$p < 0.01$ for comparison between children who were and were not assessed at 9–10 years.

[e]Other includes Chinese, Indian, Dutch, Japanese, Tokelauan, and other unspecified ethnicity.

[f]Other includes sepsis, haemolytic disease of the newborn, respiratory distress, congenital heart disease, and poor feeding.

executive function (adjusted odds ratio [aOR] 1.21–1.33, Table 2). However, exposure to neonatal hypoglycaemia was associated with a twofold increased risk of parent-reported metacognition difficulties (aOR 2.37, 95% confidence interval [CI] 1.13–4.99, $p = 0.023$), but no difference in teacher-reported executive function. Furthermore, exposure to neonatal hypoglycaemia was associated with a 1.5-fold increased risk of parent-reported peer problems (aOR 1.62, 95% CI 1.00–2.63, $p = 0.049$) but was not associated with increased teacher-reported behaviour problems (Table 2).

Further exploration of a possible dose–response relationship showed that children exposed to at least three hypoglycaemic events had a nearly threefold increased risk of parent-reported metacognition difficulties, and a nearly twofold increased risk of parent-reported peer problems (Figure 1 and Table S1). Children exposed to at least one severe hypoglycaemic event(s) had an approximately 2.5- to 3.5-fold increased risk of parent-reported metacognition difficulties and overall executive function difficulties, and a twofold increased risk of parent-reported peer problems and teacher-reported conduct problems (Figure 1 and Table S2). However, children who were exposed to mild hypoglycaemic events had a reduced risk of teacher-reported peer problems. There was no significant difference in executive function and behaviour problems between the clinically undetected hypoglycaemic group and the normoglycaemic group (Table S3).

Association between executive function and behaviour problems

Overall, better executive function was associated with reduced behaviour problems. Performance-based executive function explained 7% to 25% of variance and questionnaire-based executive function explained 10% to 72% of variance of behaviour problems (Table 3). Furthermore, specific aspects of executive function were associated with specific behaviour problems. Better spatial working memory, as assessed by the Spatial Working Memory task, associated with reduced hyperactivity problems reported by parents and teachers. Better planning skills, as assessed by the One Touch Stockings of Cambridge task, were associated with reduced emotion problems reported by parents and teachers. Parent-reported behaviour regulation was significantly associated with all behaviour problems scales except teacher-reported hyperactivity problems. Teacher-reported behaviour regulation was significantly associated with all aspects of behaviour problems.

Results of mediation analyses suggested that parent-reported metacognition difficulties did not mediate the relationships between neonatal hypoglycaemia, increased frequency, and severity of hypoglycaemic events and behaviour problems (Table S4). However, when IQ score at age 4 years 6 months was excluded from the model, metacognition difficulties seemed to mediate the relationship between frequency and severity of hypoglycaemic events and parent-reported peer problems ($B = 0.09$, standard error = 0.05, 95% CI = 0.01–0.19 for frequency; $B = 0.06$, standard error = 0.01, 95% CI = 0.04–0.08 for severity), although the effect sizes were small (Figure 2).

DISCUSSION

Neonatal hypoglycaemia, especially when severe or recurrent, is associated with increased difficulties with parent-reported metacognition and peer and conduct behaviour problems, but not with performance-based measures of executive function, at 9 to 10 years of age. Performance-based and questionnaire-based executive function were independently associated with behaviour problems. Metacognition difficulties did not mediate the relationships between hypoglycaemia and peer and conduct problems independent of early IQ.

Neonatal hypoglycaemia was modestly associated with increased risk of questionnaire-based but not performance-based executive function difficulties. This was different from our previous findings in this cohort at age 4 years

TABLE 2 Executive function and behaviour problems of children with and without neonatal hypoglycaemia

Measures	Hypoglycaemia	*n*	No hypoglycaemia	*n*	Adjusted mean difference or OR[a]	95% CI	*p*
Cambridge Neuropsychological Tests Automated Battery							
AST	842 (179)	298	833 (173)	173	1.1	−33 to 35	0.950
OTS	7.6 (3.2)	299	7.6 (3.3)	173	0.6	−0.5 to 0.6	0.291
SWM	18.4 (7.0)	297	17.5 (7.0)	172	1.2	−0.2 to 2.5	0.098
SST	339 (78)	295	332 (84)	171	9.3	−7 to 25	0.252
AST $z<-1$	47 (16)	298	24 (14)	173	1.22	0.66–2.23	0.527
OTS $z<-1$	62 (21)	299	30 (17)	173	1.33	0.73–2.42	0.358
SWM $z<-1$	38 (13)	297	21 (12)	172	1.21	0.63–2.30	0.570
SST $z<-1$	54 (18)	295	27 (16)	171	1.25	0.70–2.23	0.458
Behavior Rating Inventory of Executive Function – Parent							
BRI	51.1 (11.8)	258	50.6 (11.8)	146	−0.5	−3.0 to 1.9	0.492
MI	53.2 (12.1)	258	51.7 (11.2)	146	0.9	−1.5 to 3.4	0.463
GEC	52.3 (11.8)	258	51.1 (11.0)	146	0.4	−2.0 to 2.7	0.394
BRI > 65	31 (12)	258	15 (10)	146	1.11	0.53–2.31	0.780
MI > 65	46 (18)	258	14 (10)	146	2.37	1.13–4.99	0.023
GEC > 65	39 (15)	258	13 (9)	146	1.90	0.88–4.13	0.104
Behavior Rating Inventory of Executive Function – Teacher							
BRI	55.6 (12.4)	287	56.2 (12.6)	160	−0.6	−3.1 to 2.0	0.665
MI	58.6 (13.6)	287	59.5 (13.7)	160	−0.8	−3.5 to 2.0	0.571
GEC	57.9 (14.2)	287	58.8 (14.3)	160	−0.8	−3.6 to 2.1	0.602
BRI > 65	66 (23)	287	38 (24)	160	0.93	0.54–1.58	0.776
MI > 65	80 (28)	287	51 (32)	160	0.83	0.50–1.38	0.472
GEC > 65	81 (28)	287	51 (32)	160	0.82	0.50–1.36	0.823
Strength and Difficulties Questionnaire – Parent							
Total difficulties	10.8 (7.1)	262	10.3 (6.8)	145	0.6	−0.8 to 2.0	0.726
Hyperactivity	3.8 (2.6)	262	3.8 (2.6)	145	0.1	−0.4 to 0.7	0.673
Conduct	1.9 (2.1)	262	1.7 (1.7)	145	0.1	−0.3 to 0.5	0.645
Emotion	2.8 (2.3)	262	2.7 (2.6)	145	0.1	−0.4 to 0.7	0.613
Peer	2.3 (2.1)	262	2.1 (2.0)	145	0.3	−0.2 to 0.7	0.241
Prosocial	8.4 (1.8)	262	8.3 (1.7)	145	−0.02	−0.4 to 0.3	0.910
Total difficulties ≥14	79 (30)	262	38 (26)	145	1.21	0.72–2.04	0.475
Hyperactivity ≥6	61 (23)	262	35 (24)	145	1.08	0.62–1.88	0.779
Conduct ≥3	77 (29)	262	38 (26)	145	1.09	0.65–1.85	0.740
Emotion ≥4	86 (33)	262	49 (34)	145	0.92	0.57–1.49	0.732
Peer ≥3	116 (44)	262	50 (35)	145	1.62	1.00–2.63	0.049
Prosocial ≤5	20 (8)	262	11 (8)	145	1.12	0.45–2.81	0.811
Strength and Difficulties Questionnaire – Teacher							
Total difficulties	8.6 (6.7)	285	8.5 (6.8)	162	0.2	−1.1 to 1.5	0.723
Hyperactivity	3.5 (3.1)	285	3.6 (2.9)	162	0.01	−0.6 to 0.6	0.987
Conduct	1.3 (1.9)	285	0.98 (1.5)	162	0.3	−0.02 to 0.7	0.068
Emotion	2.0 (1.9)	285	2.11 (2.4)	162	−0.1	−0.5 to 0.4	0.761
Peer	1.8 (1.9)	285	1.9 (2.0)	162	−0.03	−0.5 to 0.4	0.878
Prosocial	7.5 (2.4)	285	7.3 (2.3)	162	0.2	−0.2 to 0.7	0.351
Total difficulties ≥12	84 (30)	285	49 (30)	162	1.05	0.64–1.72	0.853

TABLE 2 (Continued)

Measures	Hypoglycaemia	*n*	No hypoglycaemia	*n*	Adjusted mean difference or OR[a]	95% CI	*p*
Hyperactivity ≥6	74 (26)	285	42 (26)	162	1.12	0.66–1.89	0.671
Conduct ≥3	63 (22)	285	24 (15)	162	1.75	0.95–3.21	0.071
Emotion ≥5	38 (13)	285	27 (17)	162	0.77	0.43–1.41	0.403
Peer ≥5	47 (17)	285	35 (22)	162	0.74	0.42–1.30	0.299
Prosocial ≤5	59 (21)	285	39 (24)	162	0.74	0.43–1.27	0.277

Data are mean (SD), *n* (%), adjusted mean difference, adjusted odds ratios (OR), 95% confidence intervals (CI).

Abbreviations: AST, Attention Switching task; BRI, Behavioral Regulation Index; GEC, Global Executive Composite; MI, Metacognition Index; OTS, One Touch Stockings of Cambridge; SST, Stop Signal task; SWM, Spatial Working Memory.

[a]Adjusted for New Zealand Deprivation Index, sex, primary risk factor for neonatal hypoglycaemia, and IQ at 4 years 6 months.

6 months, when neonatal hypoglycaemia was associated with increased risk of low scores on performance-based measures of executive function.[10] These two measures assess different aspects of executive function.[20] Cognitive-based performance tasks assess children's efficiency of cognitive abilities, whereas questionnaire-based measures reflect children's goal-directed behaviours. Our findings suggest that the executive function difficulties of 9- to 10-year-old children who had experienced neonatal hypoglycaemia are apparent at a behaviour level and related to goal formulation and execution.

Furthermore, we found that neonatal hypoglycaemia was associated with reduced parent-reported metacognition. Metacognition is a higher-order thinking process which helps children to plan, monitor, and evaluate their behaviours.[21] Improved metacognition is associated with better academic performance and well-being.[22] Our recent report in the same cohort of 9- to 10-year-old children found no differences between hypoglycaemic and normoglycaemic groups for overall questionnaire-based executive function.[11] However, the current findings suggest that children who experienced neonatal hypoglycaemia may show later difficulties in specific skills related to initiation, planning, organization, and self-monitoring, rather than global executive dysfunction. Future studies should use both performance-based and questionnaire-based assessments of specific areas of executive function and should involve multiple informants to detect more subtle later consequences of neonatal hypoglycaemia.

We also found that children who experienced neonatal hypoglycaemia had increased risk of later peer and conduct problems as perceived by parents and teachers. This is consistent with previous findings of higher levels of hyperactivity and impulsivity for 8-year-old children born to diabetic mothers who experienced neonatal hypoglycaemia compared with those who did not.[7] However, it contrasts with another study that reported no significant differences in behaviour difficulties between children exposed to moderate to severe neonatal hypoglycaemia aged 7 to 9 years and their typically developing siblings aged 3 to 16 years.[6] Maternal diabetes is associated with an increased risk of attention-deficit/hyperactivity disorder among offspring.[23] However, in our study, only one-third of participants were infants of diabetic mothers, so the increased risk of behaviour problems is unlikely to be explained by maternal diabetes.

This study found associations between neonatal hypoglycaemia and specific areas of behaviour difficulties. We previously found no differences in overall behavioural difficulties between the hypoglycaemic and normoglycaemic groups in this cohort.[11] The current findings emphasize the importance of examining different aspects of behaviour in different contexts in future studies. In particular, children who had experienced neonatal hypoglycaemia were more likely to have parent-reported social difficulties, and children who had experienced severe hypoglycaemia showed increased risk of teacher-reported conduct problems. These different behavioural difficulties may be related to the varied behaviour expectations in different environments. Teachers may be concerned about whether students can follow instructions, whereas parents may be concerned about whether children get along well with peers.

Previous studies have reported that specific executive functions are associated with specific behaviours. For example, working memory was associated with inattention and impulsivity in children with a history of institutional rearing and those without at aged 12 years.[24] We also found that working memory was associated with hyperactivity problems. Children with low working memory may have difficulties in storing and processing multiple sources of information, which may further impede them to stay on tasks and accomplish their work.[25]

Our study suggests that metacognition difficulties no longer mediated the relationship between neonatal hypoglycaemia and peer problems after controlling for IQ at age 4 years 6 months. This is consistent with previous reports that intelligence is associated with the mediator (executive function) in children aged 11 to 12 years[26] and outcomes (behaviour problems) in preterm-born children aged 9 to 16 years.[27]

Our study has several strengths, including the prospective design, large sample size, and the use of standardized and validated neuropsychological measures. There are also several limitations. First, results of this cohort study describe the relationships between neonatal hypoglycaemia, executive function, and behaviour problems but we cannot conclude that these relationships are causal. Second, the

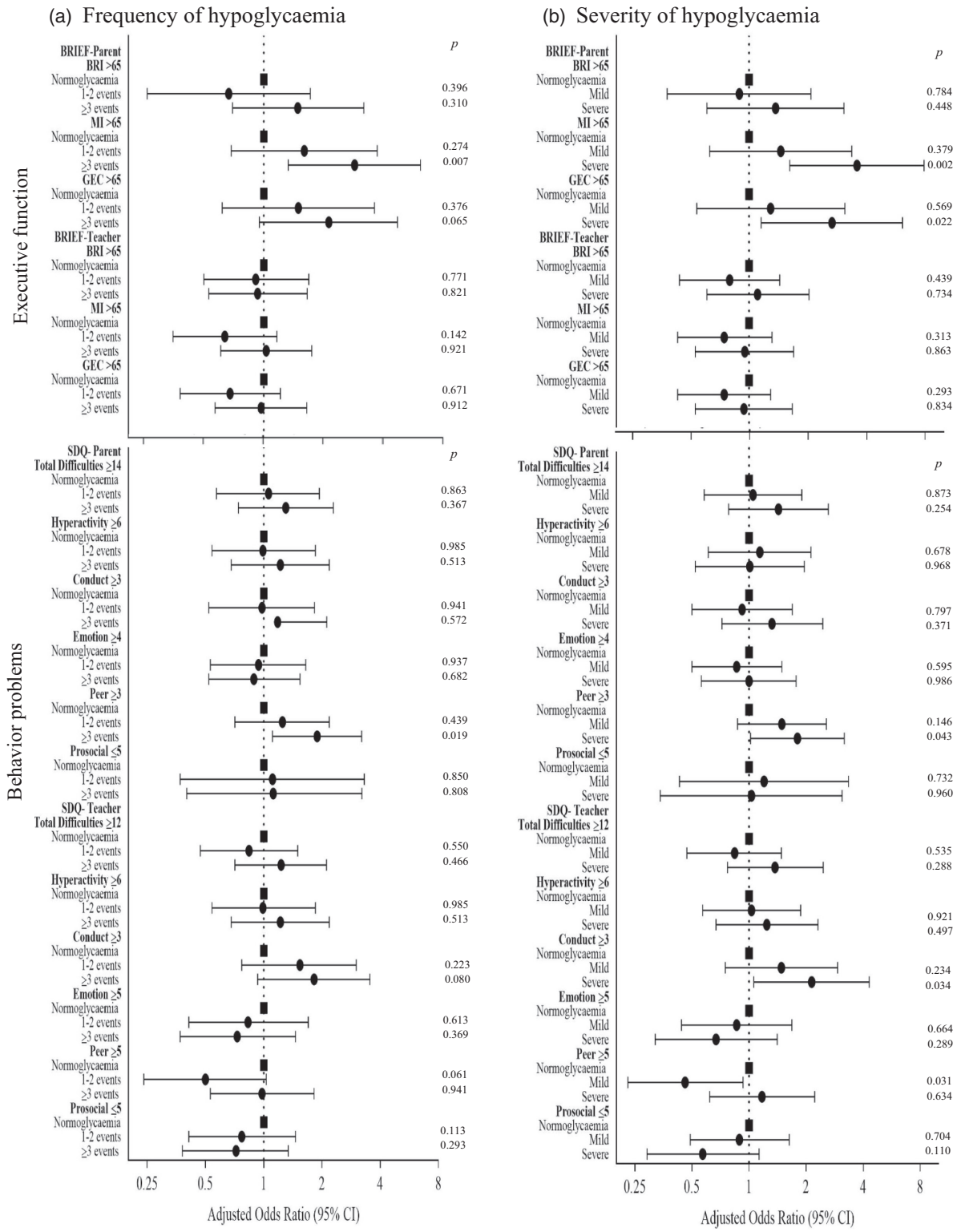

FIGURE 1 Relationships between (a) frequency and (b) severity of neonatal hypoglycaemia, and questionnaire-based executive function and behaviour problems at 9 years of age. Odds ratios and 95% confidence intervals (CI) are shown using the normoglycaemia group as the comparator and are adjusted for New Zealand Deprivation Index, sex, primary risk factor for neonatal hypoglycaemia, and IQ at 4 years 6 months. Hypoglycaemia is defined as at least one hypoglycaemic event, defined as the sum of non-concurrent hypoglycaemic and interstitial episodes more than 20 minutes apart; a hypoglycaemic episode is defined as at least one consecutive blood glucose concentration <2.6 mmoL/L, and an interstitial episode as interstitial glucose concentrations <2.6 mmoL/L for 10 minutes; a mild hypoglycaemia event is defined as mild hypoglycaemic events ≥2.0–2.5 mmoL/L only; a severe hypoglycaemia event is defined as at least one severe hypoglycaemic event <2.0 mmoL/L; clinically undetected hypoglycaemia is defined as at least one hypoglycaemic event but no hypoglycaemic episodes. Abbreviations: BRI, Behavior Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function; GEC, Global Executive Composite; MI, Metacognition Index; SDQ, Strengths and Difficulties Questionnaire

TABLE 3 Association between performance-based and questionnaire-based executive function and behaviour problems

	Total difficulties		Hyperactivity		Conduct		Emotion		Peer		Prosocial	
Strength and Difficulties Questionnaire – Parent												
Predictors[a]	β	p	β	p	β	p	β	p	β	p	β	p
AST	0.009	0.868	−0.013	0.801	0.022	0.681	0.043	0.440	−0.025	0.645	−0.097	0.076
OTS	−0.115	0.051	−0.048	0.408	−0.150	0.013	−0.155	0.013	−0.005	0.929	0.086	0.160
SWM	0.052	0.957	0.126	0.020	0.027	0.624	−0.016	0.780	0.008	0.888	0.011	0.850
SST	−0.004	0.934	0.015	0.769	−0.627	0.531	−0.039	0.478	0.043	0.419	0.028	0.608
	$R^2 = 0.16$	<0.001	$R^2 = 0.18$	<0.001	$R^2 = 0.13$	<0.001	$R^2 = 0.07$	0.002	$R^2 = 0.12$	<0.001	$R^2 = 0.08$	<0.001
BRIEF-P MI	0.130	0.006	0.399	<0.001	0.008	0.889	−0.028	0.662	−0.050	0.455	−0.001	0.991
BRIEF-P BRI	0.674	<0.001	0.286	<0.001	0.665	<0.001	0.630	<0.001	0.552	<0.001	−0.466	<0.001
	$R^2 = 0.68$	<0.001	$R^2 = 0.53$	<0.001	$R^2 = 0.51$	<0.001	$R^2 = 0.38$	<0.001	$R^2 = 0.36$	<0.001	$R^2 = 0.28$	<0.001
BRIEF-T MI	0.037	0.826	0.239	0.154	−0.245	0.166	0.193	0.305	−0.180	0.313	0.347	0.062
BRIEF-T BRI	0.333	0.048	0.142	0.392	0.550	0.002	−0.009	0.961	0.447	0.012	−0.502	0.007
	$R^2 = 0.26$	<0.001	$R^2 = 0.28$	<0.001	$R^2 = 0.20$	<0.001	$R^2 = 0.09$	<0.001	$R^2 = 0.19$	<0.001	$R^2 = 0.12$	<0.001
Strength and Difficulties Questionnaire – Teacher												
Predictors[a]	β	p	β	p	β	p	β	p	β	p	β	p
AST	−0.094	0.051	−0.103	0.031	−0.089	0.072	0.001	0.979	−0.087	0.092	0.029	0.557
OTS	−0.074	0.180	−0.047	0.394	−0.010	0.865	−0.124	0.040	−0.041	0.486	−0.029	0.615
SWM	0.099	0.053	0.113	0.025	0.053	0.341	0.074	0.178	0.038	0.486	−0.027	0.611
SST	0.154	0.002	0.075	0.120	0.125	0.012	0.170	0.001	0.120	0.021	−0.046	0.356
	$R^2 = 0.22$	<0.001	$R^2 = 0.25$	<0.001	$R^2 = 0.18$	<0.001	$R^2 = 0.09$	<0.001	$R^2 = 0.11$	<0.001	$R^2 = 0.17$	<0.001
BRIEF-P MI	0.101	0.155	0.281	<0.001	−0.079	0.289	−0.029	0.725	0.020	0.797	0.026	0.733
BRIEF-P BRI	0.324	<0.001	0.107	0.125	0.382	<0.001	0.307	<0.001	0.274	<0.001	−0.264	<0.001
	$R^2 = 0.31$	<0.001	$R^2 = 0.34$	<0.001	$R^2 = 0.24$	<0.001	$R^2 = 0.10$	<0.001	$R^2 = 0.16$	<0.001	$R^2 = 0.23$	<0.001
BRIEF-T MI	0.250	0.011	0.511	<0.001	−0.445	<0.001	0.614	<0.001	−0.181	0.215	0.135	0.365
BRIEF-T BRI	0.550	<0.001	0.237	0.019	1.007	<0.001	−0.123	0.437	0.736	<0.001	−0.560	<0.001
	$R^2 = 0.72$	<0.001	$R^2 = 0.69$	<0.001	$R^2 = 0.48$	<0.001	$R^2 = 0.24$	<0.001	$R^2 = 0.36$	<0.001	$R^2 = 0.34$	<0.001

Data are R^2 of regression models for subtests of performance-based and questionnaire-based executive function, β (standardized regression coefficient) for individual predicators.

Abbreviations: AST, Attention Switching task; BRI, Behavior Regulation Index; BRIEF-P, Behavior Rating Inventory of Executive Function – Parent; BRIEF-T, Behavior Rating Inventory of Executive Function – Teacher; MI, Metacognition Index; OTS, One Touch Stockings of Cambridge; SST, Stop Signal task; SWM, Spatial Working Memory.

[a]Adjusted for New Zealand Deprivation Index, sex, primary risk factor for neonatal hypoglycaemia, and IQ at 4 years 6 months.

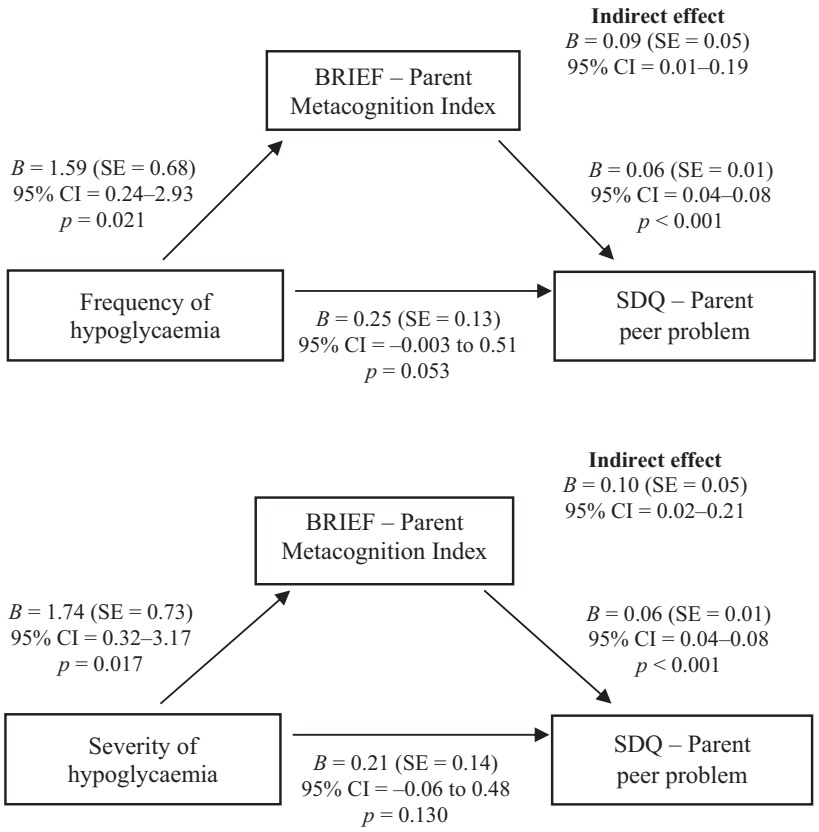

FIGURE 2 Mediation models of the indirect effect of frequency and severity of hypoglycaemic events on behaviour problems through executive function without adjustment for Full-Scale IQ at 4 years 6 months. Measures of the indirect effect include the bootstrapped 95% confidence intervals (CI). *B*, unstandardized regression coefficient; SE, standard error. Hypoglycaemia is defined as at least one hypoglycaemic event, defined as the sum of non-concurrent hypoglycaemic and interstitial episodes more than 20 minutes apart; a hypoglycaemic episode is defined as at least one consecutive blood glucose concentration <2.6 mmoL/L, and an interstitial episode as interstitial glucose concentrations <2.6 mmoL/L for 10 minutes; a mild hypoglycaemia event is defined as mild hypoglycaemic events ≥2.0–2.5 mmoL/L only; a severe hypoglycaemia event defined as at least one severe hypoglycaemic event <2.0 mmoL/L. Adjusted for New Zealand Deprivation Index, sex, and primary risk factor for neonatal hypoglycaemia. Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; SDQ, Strengths and Difficulties Questionnaire

large number of analyses undertaken may pose a risk of type I error, although we had prospectively hypothesized that executive function and behaviour problems were related to hypoglycaemia on the basis of our findings at age 4 years 6 months.[10] The relationship between executive function and behaviour problems has also been established in children with other clinical conditions.[29] Third, to keep the assessment to a manageable length, and because we had found no association between cognitive assessments and hypoglycaemia at earlier ages in this cohort,[10,14] we did not include a concurrent assessment of overall cognitive ability. Since IQ may change over time particularly during early to mid-childhood,[28] it may have been optimal to assess children's IQ at the same time as the other assessments, but in the current analyses adjustment for IQ measured at 4 years 6 months had little effect on the findings. Fourth, the Behavior Rating Inventory of Executive Function has been reported to have low to moderate interrater reliability[16] and to be susceptible to responder bias,[30] which may affect its reliability and validity.

This study demonstrates the importance of assessing specific aspects of neurocognitive functioning and behaviour in children exposed to neonatal hypoglycaemia to avoid missing important difficulties that these children may face in later childhood.

CONCLUSION

Neonatal hypoglycaemia is associated with specific difficulties in metacognition skills and peer and conduct problems as reported by parents and teachers at 9 to 10 years of age, but not with performance-based executive function. Both performance-based and parent-reported executive function difficulties are associated with behaviour problems.

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CONFLICT OF INTEREST

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Data and associated documentation are available to other users under the data sharing arrangements provided by the Maternal and Perinatal Research Hub, based at the Liggins Institute, University of Auckland (https://wiki.auckland.ac.nz/researchhub). The data dictionary and metadata will be published on the University of Auckland's data repository Figshare, which allocates a DOI and thus makes these details searchable and available indefinitely. Researchers are able to use this information and the provided contact address (researchhub@auckland.ac.nz) to request a deidentified data set through the Data Access Committee of the Liggins Institute. Data will be shared with researchers who provide a methodologically sound proposal and have appropriate ethical approval, where necessary, to achieve the research aims in the approved proposal. Data requestors are required to sign a Data Access Agreement that includes a commitment to using the data only for the specified proposal, not to attempt to identify any individual participant, a commitment to secure storage and use of the data, and to destroy or return the data after completion of the project. The Liggins Institute reserves the right to charge a fee to cover the costs of making data available, if needed, for data requests that require additional work to prepare.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1 Executive function and behaviour problems of children with different frequencies of neonatal hypoglycaemia
Table S2 Executive function and behaviour problems of children with different severity of neonatal hypoglycaemia
Table S3 Executive function and behaviour problems of children with and without clinically undetected neonatal hypoglycaemia
Table S4 Mediating effect of parent-reported metacognition on relationship between neonatal hypoglycaemia and behaviour problems
Appendix S1

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