

WMRF Grant Final Report: Vision and visual processing in children who experienced neonatal hypoglycaemia

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BACKGROUND

Neonatal hypoglycaemia is a common metabolic condition in newborns which is believed to affect 5-15% of infants in the first week of life (Cornblath and Naeye 1965; Harris, Battin et al. 2009; Harris, Weston et al. 2009). While mild hypoglycaemia may represent normal metabolic adaptation to life outside the womb, severe hypoglycaemia has been associated with reduced intelligence, mental retardation, cerebral palsy, motor development deficits, seizures, visual impairments and learning difficulties. Despite being common, little is known about the long-term consequences of neonatal hypoglycaemia and controversy exists around the definition of low blood glucose in infants, significance of acute symptoms and management. The over-arching aim of the Children with Hypoglycaemia and their Later Development (CHYLD) study was to determine the impact of neonatal hypoglycaemia on development at two- and 4½-years of age. In particular, this grant supported the investigation of vision and visual processing in a large cohort of children who were all born at risk of developing neonatal hypoglycaemia.

Retrospective studies have demonstrated that severe neonatal hypoglycaemia can cause abnormal visual development, but the effect of moderate hypoglycaemia on vision and visual processing was unknown. This grant supported work on the investigation of visual development in a large cohort (n = 403) of children who were all born at risk of neonatal hypoglycaemia as part of the CHYLD study.

A number of studies have found that the dorsal visual stream, which is responsible for the detection and processing of motion, may be particularly vulnerable to developmental disorders. Therefore global motion processing, a function primarily mediated by this pathway, was explored as part of this study as it was postulated that motion detection may provide a sensitive marker for any effect that neonatal hypoglycaemia had on cortical visual development.

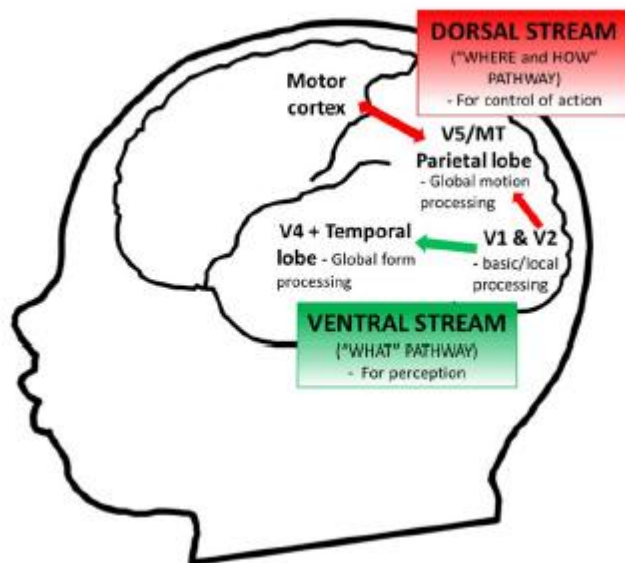


Figure 1: Summary of the ventral and dorsal stream model of cortical visual processing. The ventral stream is concerned with object recognition (for example colour and form processing) for the purpose of perception. The dorsal stream runs predominantly through the parietal cortex and is concerned with visuospatial and motion processing for the purpose of controlling actions.

OBJECTIVES

1. To develop and validate a method of assessing global motion coherence thresholds suitable for use with two year old children.
2. To investigate the effects of neonatal hypoglycaemia on vision and visual motion processing.

OBJECTIVE 1: Validating the method for assessing visual motion processing in two year old children.

Little is known about the global motion capabilities of children from seven months to three years of age due to poor cooperation, short attention span and the inability to give reliable subjective responses in children this age. The method developed for use in this study utilized the Optokinetic Reflex (OKR) an involuntary eye movement which has been successfully used to measure visual acuity(Gorman, Cogan et al. 1957) and motion perception(Banton and Bertenthal 1996) in infants. The OKR provides a reliable alternative to behavioural responses by allowing video recording on eye movement responses to global motion stimuli (see Figure 2) which were then analysed by a trained observer. A validation of this technique was undertaken on both adults (n = 10) and control children (n = 15). These validation studies showed that:

1. motion coherence thresholds measured by OKR are related to behavioural responses in adult participants, so that the two thresholds can be predicted from one another
2. subjective grading of the OKR eye movements is repeatable in both adults and two year old children.
3. test-retest variability of this method in both adults and children is low.

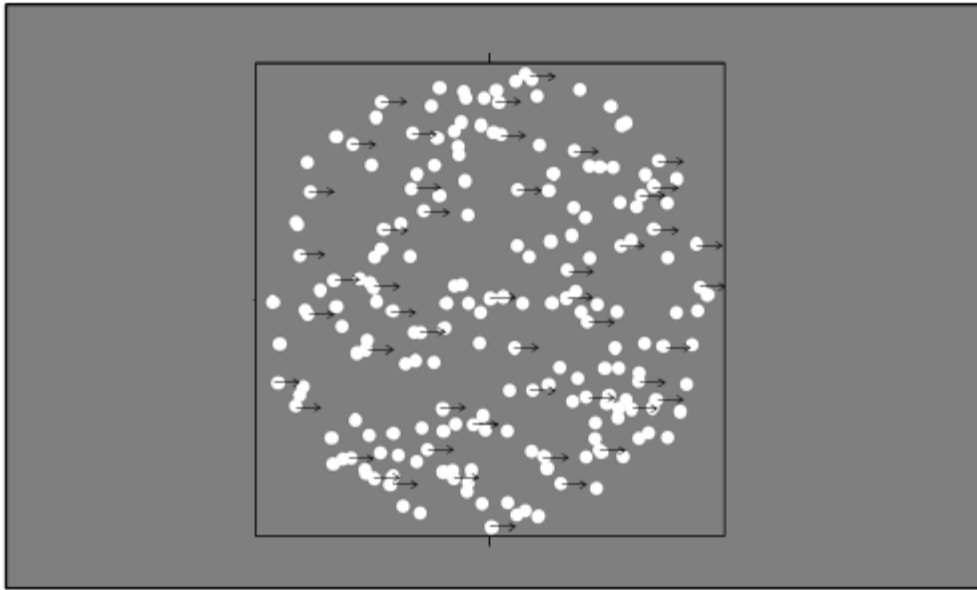


Figure 2: Random dot kinematogram (RDK) stimulus display layout for global motion threshold measurement. Dots with arrows are signal dots which all move in the same direction (signal dots). Dots without arrows are noise dots that move in a random direction. The proportion of signal to noise dots are altered until the threshold of global motion detection is found.

In CHYLD study participants, global motion detection thresholds were attempted on 371 children, and successfully measured on 335 children in the cohort (90.3%). This success rate is similar to many age-appropriate clinical tests, with the success rate of optometric evaluations ranging from 100% (when attempting external ocular inspection) to 19.8% (when attempting measurement of monocular unaided visual acuities). Only 9% of two-year old children were able to provide behavioural responses (active identification of right and left motion) to the global motion stimulus which supports the finding that the use of OKR responses is the most appropriate method in this age group (Figure 3).

This data has been recently published in *Investigative Ophthalmology and Vision Science* (Yu, Jacobs et al.) as well as presented at a number of national and international conferences, which are listed at the end of this report.

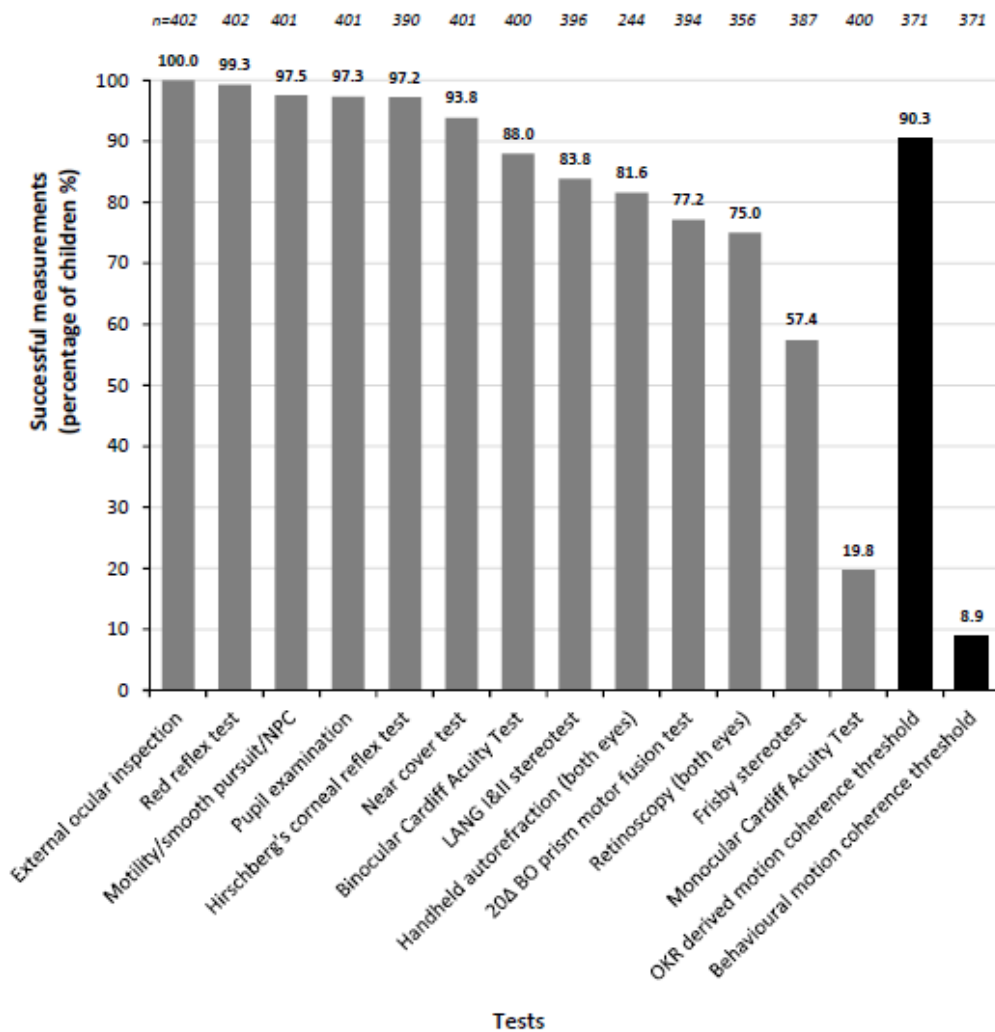


Figure 3: Percentage of successful measurement for each of the vision tests and global motion measurements for two-year old children enrolled in the CHYLD study. Grey bars represent testability of clinical optometric tests and black bars testability of measures used to assess global motion processing. The numbers above each bar represent the number of children for which each test was attempted (*italics*) and the number of children that were successfully tested (**bold**).

OBJECTIVE 2: To investigate the effects of neonatal hypoglycaemia on vision and visual motion processing.

Neonatal hypoglycaemia was defined using the blood glucose cut of level of 2.6 mmol/L because this was the threshold that clinicians at Waikato Hospital used and because this level is the most widely accepted clinical definition in Australia and New Zealand(Harris, Weston et al. 2009). Children who experienced blood glucose levels of < 2.6 mmol/L were treated according to standard clinical guidelines in place at Waikato Hospital.

Children who experienced one or more episodes of hypoglycaemia did not have any significant differences in performance in global motion processing ($p = 0.294$), unaided vision ($p = 0.139$), stereopsis (3D vision; $p = 0.137$) or manifest refractive error (long- or short-sightedness; $p = 0.551$) compared with children who remained euglycemic (normal blood sugar level).

	Neonatal blood glucose group	n	M±SD	MR	U	p
OKR derived motion coherence threshold (%)	Hypoglycaemia (<2.6mmol/L)	177	41±13	162.8	13054.0	0.294
	Euglycaemia	158	42±13	173.9		
Behavioural motion coherence threshold (%)	Hypoglycaemia (<2.6mmol/L)	16	60±20	21.1	70.0	0.017
	Euglycaemia	17	43±17	13.1		
Binocular unaided vision (logMAR)	Hypoglycaemia (<2.6mmol/L)	184	0.07±0.17	183.5	13987.0	0.139
	Euglycaemia	167	0.05±0.16	167.8		
Monocular unaided vision (logMAR)	Hypoglycaemia (<2.6mmol/L)	50	0.09±0.11	44.9	971.5	0.314
	Euglycaemia	44	0.14±0.16	50.4		
Lang I & II stereopsis (log sec of arc)	Hypoglycaemia (<2.6mmol/L)	181	2.54±0.21	172.6	12376.5	0.137
	Euglycaemia	150	2.50±0.20	158.0		
Frisby stereopsis (log sec of arc)	Hypoglycaemia (<2.6mmol/L)	113	2.44±0.26	106.3	5566.0	0.249
	Euglycaemia	108	2.49±0.23	116.0		
Retinoscopy mean RE SER (D)	Hypoglycaemia (<2.6mmol/L)	144	0.76±0.83	138.7	8762.5	0.551
	Euglycaemia	127	0.69±1.01	133.0		
Autorefraction mean RE SER (D)	Hypoglycaemia (<2.6mmol/L)	121	1.15±0.55	108.1	5703.5	0.923
	Euglycaemia	95	1.20±0.70	109.0		

Table 1: Comparison of visual outcomes for the CHYLD study cohort when grouped into those children who experienced hypoglycaemia and those that remained euglycaemic.

Children who became hypoglycaemic were no more likely to have visually significant ocular findings than children who remained euglycaemic. In the CHYLD study cohort 10 children were found to have strabismus (6 in the hypoglycaemic group and 4 in the euglycaemic group) and 47 children were found to have significant refractive errors (20 in the hypoglycaemic group and 27 in the euglycaemic group). No children were found to have cataracts, nystagmus or retinal pathology, which have been identified in some published case reports in children who have suffered severe neonatal hypoglycaemia (Burns, Rutherford et al. 2008). In summary results from this study suggest neonatal hypoglycaemia was not associated with any anomalies of visual function, global motion processing, prevalence of ocular anomalies or testability of visual function in the CHYLD study cohort at two-years of age.

CONCLUSIONS

The method developed for measuring global motion processing for this thesis, using involuntary OKR eye movements, avoided the need for behavioural responses for participants. This method was validated in adults and health (control) two year old children and these validation studies showed that OKR-derived motion thresholds provide a valid and highly repeatable measure of motion processing. When this method was applied to a large cohort of children (CHYLD study participants) it was found to have a high success rate that was comparable to the testability of many standard age-appropriate optometric tests.

The CHYLD study found that neonatal hypoglycaemia, which was treated according to clinical guidelines in place at the Waikato hospital, had no significant effects on vision or

visually processing at two-years of age. The results of this study provide clinicians with reassurance that the current management of newborns found to have a blood glucose level of < 2.6mmol/L appears to negate any potentially harmful effects hypoglycaemia may have on vision. Data collection is currently taking place for the CHYLD study participants at age 54-months to further assess the long-term outcomes of neonatal hypoglycaemia. Further research will provide stronger evidence-based guidelines for the clinical management of this common neonatal disorder and will help improve outcomes for children at risk of adverse effects.

PUBLICATIONS AND PRESENTATIONS SUPPORTED BY THIS GRANT

Yu, T.Y., Jacobs, R.J., Anstice, N.S., Paudel, N., Harding, J.E. & Thompson, B. (2013) Global motion perception in 2-year-old children: a method for psychophysical assessment and relationship with monocular and binocular visual function. *IOVS*; published ahead of print November 26, 2013,doi:10.1167/iovs.13-13051

Yu, T.Y., Ansell, J., Anstice, N.S., Jacobs, R.J., Paudel, N., Wouldes, T. Harding, J.E. & Thompson, B. (2013). Global motion detection, stereopsis and motor development are related at the age of 2-years. *Front. Hum. Neurosci.*, doi: 10.3389/conf.fnhum.2013.212.00186

Yu, T.Y., Jacobs, R.J., Anstice, N.S., Paudel, N., Harding, J.E. & Thompson, B. (2013) Global motion perception in 2-year-old children: a method for psychophysical assessment and relationship with monocular and binocular visual function. *Investigative Ophthalmology & Visual Science*, IOVS-13.

Yu, T.Y., Jacobs, R., Anstice, N.S., Paudel, N., Harding, J.E. and Thompson B. on behalf of the CHYLD study group. (2013). Global motion processing is related to motor and cognitive development at 2 years of age. *Children's Vision Research Society Meeting, Toronto, Canada, June 2013.*

Yu, T.Y., Jacobs, R., Anstice, N.S., Paudel, N., Harding, J.E. and Thompson B. on behalf of the CHYLD study group. A method of assessing global motion perception in two-year old children using the optokinetic reflex. *ARVO Annual Meeting, Seattle USA, May 2013.*

Yu, T.Y., Jacobs, R., Anstice, N.S., Paudel, N., Harding, J.E. and Thompson B. on behalf of the CHYLD study group. The effects of neonatal hypoglycaemia on vision and visual development at the age of 2-years'. *Biannual Waikato Medical Research Seminar, Waikato Clinical School, March 2012*

Yu, T.Y., Jacobs, R., Anstice, N.S., Paudel, N., Harding, J.E. and Thompson B. on behalf of the CHYLD study group Global motion psychophysics in two-year-old children for early detection of dorsal visual stream deficits. *New Zealand Applied Neurosciences Conference, Auckland, September 2012*

Yu, T.Y., Jacobs, R., Anstice, N.S., Paudel, N., Harding, J.E. and Thompson B. on behalf of the CHYLD study group Early detection of visual deficits in children at risk of neonatal hypoglycaemia. *14th Scientific and 8th Educators' Meeting in Optometry, Melbourne, August 2012*

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Gorman, J. J., D. G. Cogan, et al. (1957). "An apparatus for grading the visual acuity of infants on the basis of opticokinetic nystagmus." Pediatrics **19**(6): 1088-92.

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Yu, T. Y., R. J. Jacobs, et al. "Global motion perception in 2-year-old children: a method for psychophysical assessment and relationships with clinical measures of visual function." Invest Ophthalmol Vis Sci **54**(13): 8408-19.