Cortical vision, MRI and developmental outcome in preterm infants

J Atkinson,[1] O Braddick,[2] S Anker,[1] M Nardini,[2] D Birtles,[1,2] M A Rutherford,[3] E Mercuri,[4] L E Dyet,[4] A D Edwards,[3,4] F M Cowan[4]

[1] Visual Development Unit, Department of Psychology, University College London, UK; [2] Department of Experimental Psychology, University of Oxford, Oxford, UK; [3] Department of Imaging Sciences, Medical Research Council Clinical Sciences Centre, Imperial College, Hammersmith Campus, London, UK; [4] Department of Paediatrics, Medical Research Council Clinical Sciences Centre, Imperial College, Hammersmith Campus, London, UK

Correspondence to: Professor J Atkinson, Visual Development Unit, Department of Psychology, University College London, Gower Street, London WC1E 6BT, UK; j.atkinson@psy.ox.ac.uk

Accepted 27 January 2008
Published Online First 11 March 2008

ABSTRACT

Objectives: To test two measures of visual cortical function in the first year of life as early markers of functionally significant brain damage in infants born preterm: orientation-reversal visual event-related potentials (OR-VERP) and a behavioural test of cortically controlled visual attention-fixation shifts under competition (FS). Also to examine how these measures relate to (1) perinatal brain insults identified by MRI, and (2) later neurodevelopmental status.

Patients and methods: After neonatal and term-age-equivalent MRI, 26 preterm infants (<32 weeks of gestational age, mean 28.1 weeks) were given the OR-VERP and FS tests before 12 months post-term age and a neurodevelopmental assessment (Griffiths Scales) at 2 years. MRI scans examined for parenchymal lesions, intraventricular haemorrhage, ventricular dilatation and diffuse excessive high signal intensity were classified into three categories of severity. Cortical visual test results were compared across these categories and examined as predictors of developmental status at 2 years.

Results: 26 infants were studied. 13/25 infants showed significant OR-VERP responses. 12/26 showed normal FS performance. On both tests, the proportion of infants meeting these criteria decreased significantly with MRI severity. As predictors of Griffiths developmental quotient $\leqslant$80, the FS test had a sensitivity of 100%, a specificity of 61%, and positive and negative predictive values of 50% and 100%, respectively; corresponding values for OR-VERP were 86%, 65%, 50% and 92% .

Conclusions: Visual cortical tests can provide early indicators of the functional impact of perinatal brain damage in the preterm infant.

Preterm birth is a major cause of childhood neurological and psychiatric impairment, including lifelong mental health problems.[1 2] Half of surviving infants born before 26 weeks show neurodevelopmental impairment by 30 months.[3] Among less premature infants, over one-third develop neurocognitive, motor and behavioural deficits.[4 5] All levels of childhood disability have great impact on individuals' and families' quality of life, and incur heavy healthcare costs.[6]

The feasibility of MRI in the neonatal intensive care unit (NICU) has now been established,[7] offering improved identification of perinatal cerebral lesions in the preterm infant.[8 9] Brain imaging around term has also identified characteristic anomalies of white matter and cerebral development in these children.[10 11] These early structural brain anomalies revealed by MRI can be related to infants' neurological condition. Many clinical assessments in the first few years have depended heavily on motor development, but recent studies[8] have increasingly attempted to relate structural measures to broader neurocognitive development and to investigate specific brain systems. Such measures may help to indicate early functional consequences of brain damage identified by MRI and provide early surrogates for later measures of neurological and cognitive outcome.

Cortical visual processing is an important, early-developing aspect of brain function.[12] Several investigators have used visual indicators of the neurological status of premature infants (eg, refs[13–15]). We have devised specific "markers" of visual cortical function in the first postnatal months, linked to a neurobiological model of normal visual development.[12] In particular, we have established tests of orientation-reversal visual event-related potentials (OR-VERP)[16–18 20] and cortical control of visual attention (fixation shifts under competition; FS),[18 19] with both typically[16–18 20] and atypically developing groups.[19 21–26] In full-term infants with perinatal brain insults,[22–24] these measures correlate with cerebral damage assessed by neonatal MRI, and also with later neurodevelopmental status.[27] Here we examine infants for whom neonatal and term MRI scans are available, to test whether these indicators are also diagnostic of early brain damage, and predict later outcome, in infants born preterm.

PATIENTS AND METHODS

Patients

The inclusion criterion was birth before 32 weeks of postmenstrual age. Infants were recruited either within a consecutive cohort study[11] or because they had neonatal MRI scans for clinical purposes. Families of children from the Hammersmith Hospital NICU meeting this criterion were invited to attend the Visual Development Unit (VDU) for further testing. Data on those who consented and attended the VDU assessments within the periods specified below were analysed.

Each infant had an assessment 2–11 months after term. Whenever possible, infants failing one or both tests on a first visit were retested later in the first year.

MRI of the brain

Most imaging used a dedicated 1.0 T MRI scanner (Oxford Magnets, Witney, Oxon, UK) in the NICU; a few scans were acquired using a Philips 1.5 T Eclipse and a 1.0 T HPQ scanner. Infants were sedated with orally administered chloral hydrate (20–50 mg/kg) and monitored with ECG

Table 1 Classification scheme of MRI scans

Rating	Description
Normal/mild (0)	No neonatal lesions
	Any neonatal IVH resolved without ventricular dilatation at term equivalent
	Isolated mild DEHSI or none, at term equivalent
Moderate (1)	Any of:
	Moderate or severe DEHSI Moderate DEHSI with ventricular dilatation
	Ventricular dilatation at term equivalent after germinal layer haemorrhage or IVH, but not requiring taps or shunts
	Neonatal focal punctate lesions
	Small haemorrhagic parenchymal infarction with normal basal ganglia and thalamus
	Isolated absent myelination in the PLIC at term equivalent
	Cerebellar atrophy
Severe (2)	Ventricular dilatation requiring intervention
	Cystic PVL, large haemorrhagic parenchymal infarction, or infarction in basal ganglia or thalamus, with involvement of the PLIC

DEHSI, diffuse excessive high signal intensity; IVH, intraventricular haemorrhage; PLIC, posterior limb of the internal capsule; PVL, periventricular leucomalacia.

and pulse oximetry; a paediatrician was in attendance throughout. Ear protection was used. The MRI scans included T1-weighted conventional spin echo (repetition time 600 ms; echo time 20 ms) and T2-weighted fast spin echo (repetition time 3500 ms; echo time 208 ms) scans in transverse and coronal planes. Infants recruited into the cohort study (n = 16) had the first scan as soon as possible after birth, and serial scanning during admission to the NICU. The remaining infants were scanned for clinical reasons (mainly abnormal cranial ultrasound findings). Scan timing depended on clinical stability. An MR image obtained at or soon after 36 weeks of postmenstrual age was defined as a term scan, as in previous publications.[11]

Both MRI and visual assessment procedures were approved by relevant NHS and university ethics committees.

Image analysis and classification

Two experienced observers performed independent qualitative analysis of the images and resolved any discrepancies through consensus. Neonatal images were reported as normal if they had age-appropriate white matter details and myelination, normal-sized ventricles and no diffuse or focal pathological findings.

Intraventricular haemorrhage was considered a significant finding if followed by ventricular dilatation at term.[11] T2-weighted term images were examined for diffuse excessive high signal intensity (DEHSI)[7 28] in white matter, which is associated with reduced developmental quotient (DQ) at 18–36 months of age.[11] DEHSI was visually rated "none/mild", "moderate" or "severe". Infants were then categorised into three groups (normal/mild (0); moderate (1); severe (2)) on a composite measure derived from the MRI data, on criteria in table 1.

Neurological follow-up evaluation

Follow-up assessments were performed at 16–25 months corrected age (mean (SD) 22.4 (3.4) months) by experienced paediatricians blind to the MRI findings. The Griffiths Mental Development Scales[29] provided an overall DQ. A neurological examination, at age 2 years, recorded any abnormalities of tone, posture and movement consistent with the criteria of Himmelmann *et al*[30] for cerebral palsy (CP). We took a DQ of 80 or below, and/or a diagnosis of CP, as a criterion of poor neurodevelopmental outcome, for comparison with the early visual measures.

Tests of visual cortical function in the first year

Our two tests of cortical visual function were an electrophysiological test of cortical pattern processing (the OR-VERP) and the "fixation shift" test of cortically controlled attention (FS).

OR-VERPs[16 17] were recorded from the scalp as the infant viewed high-contrast stripes alternating between opposite oblique orientations (45–135°). This method tests orientation-selective responses in the visual cortex, which normally develop after term. Procedures, displays and analysis were as described previously[24] and in the appendix. The "pass" criterion was a statistically reliable VERP on the circular-variance test[31] (appendix) with a stimulus frequency of 8 reversals/s, by 7 months after term.

For the FS test, a central schematic face was presented on a large cathode ray tube display; when the infant was fixating on this, a pair of alternating black/white stripes then appeared to either left or right. The latency for a gaze shift was tested in three conditions: "non-competition" (central target disappears at onset of peripheral target), "competition" (central target remains visible) and "confrontation" (peripheral targets appear both sides of centre). Displays and procedures are described in detail in the appendix and Atkinson *et al*[18] and Mercuri *et al*[22]. Typically developing infants up to 3 months after term show much longer latencies for competition than non-competition trials. This difference narrows with age, reflecting cortically controlled "disengage" mechanisms over-riding the subcortical reflex maintaining fixation on a central target.[18 19] The pass criterion was a difference between competition and non-competition mean latencies below 0.5 s by 7 months after term, with at least 3/4 initial fixations on the correct side in both conditions.

For visual assessment, at the VDU, children received an orthoptic examination (ocular movements, strabismus, corneal reflex, base-out prism and "cover" test) and "core vision tests" from the ABCDEFV battery[32] including preferential looking acuity, optokinetic nystagmus, visual fields and a photorefractive test of accommodation and refractive error.

RESULTS

Twenty-six children meeting the inclusion criterion were included in the study (mean (SD) gestational age at birth 28.1 (2.7) weeks). Median age at the first visit was 5.0 months after term, when normative data[16 17 20] show positive results in 85% or more healthy infants born at term.

Table 2 Details of individual children

No	GA at birth	Post-term age of OR-VERP tests (months)	Post-term age of FS tests (months)	MRI category	Neonatal MRI	Term MRI	"Core" vision on ABCDEFV	DQ on Griffiths Scale
1	29	3*	3	0	1 punctate lesion only	Minor DEHSI	Normal	100
2	28	3.5*	3.5†	0	Normal	–	Normal	n/a
3	24	7*	7	0	Normal	Normal	Normal	97
4	30	7	7†	0	Normal	–	Normal	100
5	26	3*	3	0	Normal	Normal	Normal	97
6	31	2.5*	2.5†	0	Normal	Minor DEHSI	Normal	106
7	31	2.5*	2.5†	0	Normal	Minor DEHSI	Field L narrow	113
8	31	2.5*	2.5†	0	Normal	Minor DEHSI	Field L narrow	105
9	30	6*	6	1	Punctate	Moderate DEHSI	Normal	95
10	31	5	5	1	Normal	Moderate DEHSI	Narrow fields	103
11	30	5	5†	1	Normal	Severe DEHSI	Normal	91
12	30	5	5†	1	Normal	Severe DEHSI	Normal	84
13	27	7		1	GLH	Wide ECS	Normal	93
14	27	4*	4†	1	IVH, GLH	HPI - small	Normal	102
15	24	7*	7†	1	IVH,GLH	Moderate DEHSI	Normal	86
16	24	3	3†	1	IVH,GLH	VD	Normal	91
17	28	5*	5†	2	Normal	VD, severe DEHSI	Normal	106
18	28	7*	7	2	Focal bilateral polymicrogyria	Moderate DEHSI	Normal	91
19	23	5*	5	2	GLH, IVH	VD	Normal	50‡
20	29	11	11	2	HPI, thalamic lesions	–	CS	75‡
21	25	10	10	2	IVH, HPI, bgl	VD	Hyperopic astigmatism	110
22	26	7,9	7,9	2	IVH, bgl	VD, porencephaly	CS	60‡
23	27	3,8	3,8	2	Multiple small fungal lesions, bgl	–	CS, narrow fields, poor accomm	47‡
24	32	9	9	2	PVL	–	CS, nystagmus, asymm OKN	44‡
25	30	7	7	2	PVL	PVL (post-term scan)	CS, narrow R field, asymm OKN	52‡
26	26	8,10*	8,10	2	PVL	–	Intermittent CS, narrow R field	80‡

MRI category: 0 = normal/mild; 1 = moderate; 2 = severe.
*OR-VERP is normal.
†FS is normal.
‡Cerebral palsy.
accomm, accommodation; asymm OKN, asymmetrical optokinetic nystagmus; bgl, basal ganglia lesion; CS, convergent strabismus; DEHSI, diffuse excessive high signal intensity in white matter; ECS, extracerebral space; FS, fixation shift test; GA, gestational age; GLH, germinal layer haemorrhage; HPI, haemorrhagic parenchymal infarction; IVH, intraventricular haemorrhage; L, left; OR-VERP, orientation-reversal visual event-related potential test; PVL, (cystic) periventricular leucomalacia; R, right; VD, ventricular dilatation.

At ophthalmological examination in the NICU, none of the group were found to have significant retinopathy of prematurity. On the MRI categorisation scheme, eight children fell into category 0, eight into category 1 (one did not complete both cortical tests), and 10 into category 2. For two children (both in category 0), DQ at 2 years of age was not available. For clinical reasons, four infants (all in the severe category) did not receive MRI scans at term, but findings on earlier and later scans indicated that these children would be classified as "severe" at term-equivalent age. Table 2 gives details of individual infants in the study group. Neurological follow-up results were available for 25 of the 26 children studied.

Thirteen of 25 children tested gave significant OR-VERP responses, and 11 out of 26 infants met the pass criterion for fixation shifts. Table 3 summarises the relationship between these measures and the Griffiths developmental assessment at 2 years. Table 4 shows sensitivity, specificity, positive and negative predictive values for a Griffiths DQ of 80 or below for failure on the OR-VERP and FS tests.

Table 5 shows numbers in each MRI category giving a positive response, appropriate for their post-term age, on each test, and fig 1 presents percentages. The number giving positive OR-VERP responses decreases systematically with the severity of the MRI findings ($p = 0.04$, Fisher exact probability test for a 3×2 table[33]).

Table 3 Relation between numbers of children passing/failing on infant cortical vision tests and Griffiths pass–fail at 2 years

	OR-VERP		FS	
	Pass	Fail	Pass	Fail
DQ >80	11	6	11	7
DQ ⩽80	1	6	0	7

DQ, developmental quotient; FS, fixation shift; OR-VERP, orientation-reversal visual event-related potential.

Table 4 Sensitivity, specificity and predictive values of infant cortical vision tests for developmental outcome (DQ⩽80 on Griffiths test at 2 years)

Vision test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
FS	100	61	50	100
OR-VERP	86	65	50	92

DQ, developmental quotient; FS, fixation shift; NPV, negative predictive value; PPV, positive predictive value; OR-VERP, orientation-reversal visual event-related potential.

Table 5 Results of cortical vision tests for infants in the three MRI categories

Group	0 (normal/mild)	1 (moderate)	2 (severe)
Tested on OR-VERP	8	7	10
Positive OR-VERP response	7 (88%)	3 (43%)	3 (30%)
Tested on FS	8	8	10
Met FS criterion	6 (75%)	5 (62%)	1 (10%)

Values are number or number (%).
FS, fixation shift; OR-VERP, orientation-reversal visual event-related potential.

Table 5 and fig 1 also break down the FS results between MRI categories. As with the OR-VERP, the proportion of children who met the FS criterion decreased significantly with MRI severity ($p = 0.008$; Fisher exact probability test). However, unlike the OR-VERP, even the "normal/mild" group fell well below age norms, close to the level of the "moderate" group.

As expected for a group with neurological impairments, core vision tests detected a number of problems, detailed in the appendix. Five children were strabismic, one had nystagmus, and eight had unilateral or bilateral narrowing of the visual fields. Fields are tested by confrontation with a Stycar ball appearing on one side, and so are related to the measurement made in the FS test. However, even children with detected vision problems all met age norms on preferential looking acuity testing.[34]

Visual assessments at 3–6 years are available on 24 of these infants (orthoptic check plus acuity measurement using the Cambridge Crowding Cards[35]). Table 6 shows that the OR-VERP test in particular is closely related to later visual performance, with sensitivity 89%, specificity 80% for predicting impaired acuity, and 100% and 87% for strabismus at 3–6 years.

Table 6 Results of visual assessment at 3–6 years in relation to cortical visual function in the first year

	OR-VERP		FS	
	Pass	Fail	Pass	Fail
Acuity >6/12 equivalent in both eyes	12	3	9	6
Acuity ⩽6/12 equivalent in either eye	1	8	1	8
Pass orthoptic test	13	2	8	7
Fail orthoptic test (strabismus)	0	9	2	7

FS, fixation shift; OR-VERP, orientation-reversal visual event-related potential.

DISCUSSION

The group who attended the VDU for this study were not necessarily representative of the very-preterm population. Compared with the consecutive series studied from the same hospital,[11] there is a similar or greater proportion in the "normal/mild" group, but the "severe" group are over-represented (although their lesions are those typically found in a preterm population). However, this weighted sample permits a better test of the consequences of perinatal brain damage.

Our results show that impaired orientation-specific VERP and fixation shifts were associated with the severity of MRI-detected abnormalities in preterm infants. This extends our finding that these visual cortical measures are related to significant cerebral insults in term infants with hypoxic–ischaemic encephalopathy.[22–24] The two measures appear to show different patterns of association. The OR-VERP test gives normal results in most of the "normal/mild" group, with markedly more failures in both "moderate" and "severe" groups. In comparison the FS test shows a similar suboptimal performance in both the "normal/mild" and "moderate" groups, with a sharp increase in the "severe" group. This is consistent with the idea that these two responses, although both cortically based, do not necessarily reflect the same neurological systems. Further longitudinal testing, currently underway, is needed to discover whether they have different longer-term correlates and, in particular, whether poor performance on the FS attention test in infancy is more associated with attention and other problems often encountered in preterm children at school age.[36]

These cortical visual deficits do not necessarily reflect sensory visual impairments. Although some children were strabismic, all had normal visual acuity (at least in one eye) on our early tests. The results confirm reports[37 38] that conventional early examination of vision does not necessarily identify significant developmental disorders, but show that central visual processing problems can be detected, associated with subsequent neurodevelopmental problems. However, it should be noted that children with major cerebral disorders also have an increased incidence of sensory visual loss.[39] Also, failure on our early cortical vision tests did relate to the more sensitive measures of visual acuity possible at 3–6 years.

Overall, this preterm group performs considerably worse on the cortical tests than expected in a normal term-born population. We have found[20 26] a significant OR-VERP in 80–85% of term infants at 12–17 weeks; most typically developing infants also achieve the FS criterion at these ages.[18] We previously tested OR-VERP in 24 low-birthweight infants born at 24–32 weeks' gestation.[26] MRI was not available, but nine infants had abnormal cranial ultrasound scans, including four whose severe abnormalities (cystic periventricular leucomalacia or large intraventricular haemorrhage) were in the present "severe" category. None of these showed significant OR-VERP by 4.5 months. Of those with normal ultrasound scans, 68%

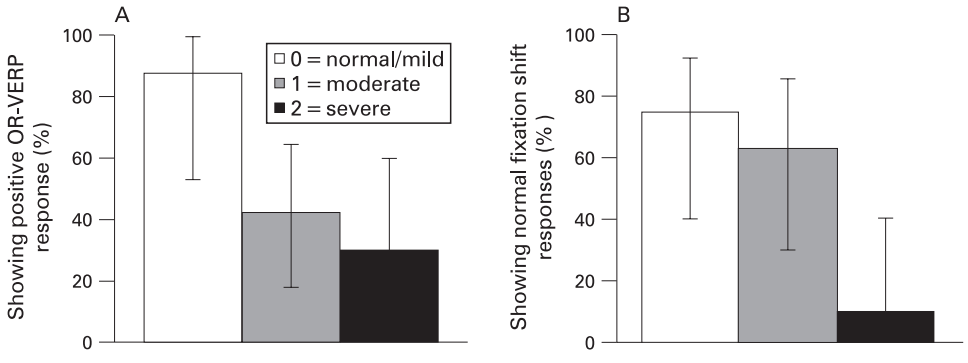

Figure 1 Proportion of infants passing the tests of cortical visual function in each of the three categories defined by neonatal and term MRI: (A) results of the orientation-reversal visual event-related potential (OR-VERP) test; (B) results of the test of fixation shifts under competition. Error bars show the 95% CI on each proportion.

What is already known on this topic

- Non-invasive electrophysiological and behavioural tests can assess the onset of function in visual cortex in the first months after term.
- In infants who have suffered potential perinatal brain insult at term, failure on these tests is related to brain damage detected by MRI and is predictive of a poor neurodevelopmental outcome.

What this study adds

- In the group of preterm infants studied, failures on tests of cortical visual processing are associated with brain damage as detected by MRI.
- Preterm infants who fail tests of cortical visual processing are at increased risk of neurodevelopmental delay at age 2 years.

showed significant OR-VERP, a value close to the combined 66% for the present "normal/mild" and "moderate" groups.

The sensitivity and specificity for predicting DQ from our visual tests are similar to those for full-term infants with hypoxic–ischaemic encephalopathy.[27] The high sensitivity implies that children with a poor developmental outcome have a very high probability of failing these tests. Conversely, the high negative predictive values mean that a pass strongly predicts relatively good developmental outcome. The lower specificity implies that a substantial proportion of children with a relatively good 2-year DQ nonetheless fail the cortical tests in infancy. It remains possible that the Griffiths test at this age is a relatively insensitive measure for some aspects of cognition (eg, attention)[40] and that deficits of early cortical function may relate better to later outcomes, when more sensitive cognitive measures are possible.

CONCLUSIONS

Visual cortical function in the first months of life can provide effective measures of the functional effect of perinatal brain damage. These may help to identify functionally significant cerebral impairment in very-preterm infants, and to gauge plasticity and recovery from perinatal brain damage in early life. They may provide early surrogate clinical outcome measures in trials of neuroprotective and other treatments for the at-risk preterm infant, and for evaluating the functional relevance of new measures by neonatal MRI. They have the advantage of being rapid, functional, non-invasive tests, which are acceptable for this vulnerable population. Neonatal or term MRI is an expensive procedure, requiring sedation and equipment and expertise that is not widely available in neonatal units. These visual measures are less invasive and could be installed relatively cheaply, albeit with a requirement for staff training. They therefore merit further exploration as predictors of neurological function in the first months of life.

However, prospective validation of these tests with confirmation on a larger sample is desirable to confirm their predictive value.

The scope for developmental assessment at 2 years is limited. The criterion of DQ$\leqslant$80 identifies only a particular group of seriously impaired children, particularly those with motor problems. At later ages, a broader range of more sensitive cognitive measures become possible. Studies that we are currently carrying out will determine how far visual cortical tests can predict specific cognitive outcomes, including whether infant fixation shifts predict later measures of attention. Such longer-term prediction is important in evaluating infant cortical function markers as surrogate outcome measures for trials of early interventions.

Acknowledgements: We thank the Medical Research Council, the Garfield Weston Foundation and Wellbeing for financial support, and the participating families without whose consent and cooperation this work would not be possible. We are also grateful for support from the NIHR Biomedical Research Centre funding scheme. We thank John Wattam-Bell for help with VERP techniques and other members of the VDU who contributed to visual assessments.

Competing interests: None.

REFERENCES

1. **Larsson HJ,** Eaton WW, Madsen KM, *et al*. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol* 2005;**161**:916–25.
2. **Jones PB,** Rantakallio P, Hartikainen A-L, *et al*. Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 North Finland general population birth cohort. *Am J Psychiatry* 1998;**155**:355–64.
3. **Wood NS,** Marlow N, Costeloe K, *et al*. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;**343**:378–84.
4. **Bhutta AT,** Cleves MA, Casey PH, *et al*. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002;**288**:728–37.
5. **Marlow N,** Wolke D, Bracewell MA, *et al*. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005;**352**:9–19.
6. **Stevenson RC,** McCabe, CJ, Pharoah, PO, *et al*. Cost of care for a geographically determined population of low birthweight infants to age 8–9 years. I. Children without disability. *Arch Dis Child Fetal Neonatal Ed* 1996;**74**:F114–17.
7. **Maalouf EF,** Duggan PJ, Rutherford MA, *et al*. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. *J Pediatr* 1999;**135**:351–7.
8. **Woodward LJ,** Anderson PJ, Austin NC, *et al*. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006;**355**:685–94.
9. **Roelants-van Rijn AM,** Groenendaal F, Beek FJ, *et al*. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. *Neuropediatrics* 2001;**32**:80–9.
10. **Rutherford MA.** *MRI of the neonatal brain*. London: WB Saunders, 2002.
11. **Dyet LE,** Kennea N, Counsell SJ, *et al*. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics* 2006;**118**:536–48.
12. **Atkinson J.** *The developing visual brain*. Oxford: Oxford University Press, 2000.
13. **San Giovanni JP,** Allred EN, Mayer DL, *et al*. Reduced visual resolution acuity and cerebral white matter damage in very-low-birthweight infants. *Dev Med Child Neurol* 2000;**42**:809–15.
14. **Cioni G,** Bertuccelli B, Boldrini A, *et al*. Correlation between visual function, neurodevelopmental outcome, and magnetic resonance imaging findings in infants with periventricular leucomalacia. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F134–40.
15. **Guzzetta A,** Cioni G, Cowan F, *et al*. Visual disorders in children with brain lesions: 1. Maturation of visual function in infants with neonatal brain lesions: correlation with neuroimaging. *Eur J Paediatr Neurol* 2001;**5**:107–14.
16. **Braddick OJ,** Wattam-Bell J, Atkinson J. Orientation-specific cortical responses develop in early infancy. *Nature* 1986;**320**:617–19.
17. **Braddick OJ.** Orientation- and motion-selective mechanisms in infants. In: Simons K, ed. *Early visual development: normal and abnormal*. New York: Oxford University Press, 1993:163–77.
18. **Atkinson J,** Hood B, Wattam-Bell J, *et al*. Changes in infants' ability to switch visual attention in the first three months of life. *Perception* 1992;**21**:643–53.
19. **Braddick O,** Atkinson J, Hood B, *et al*. Possible blindsight in babies lacking one cerebral hemisphere. *Nature* 1992;**360**:461–3.
20. **Braddick O,** Birtles D, Wattam-Bell J, *et al*. Motion- and orientation-specific cortical responses in infancy. *Vision Res* 2005;**45**:3169–79.
21. **Hood B,** Atkinson J. Sensory visual loss and cognitive deficits in the selective attentional system of normal infants and neurologically impaired children. *Dev Med Child Neurol* 1990;**32**:1067–77.
22. **Mercuri E,** Atkinson J, Braddick O, *et al*. Visual function and perinatal focal cerebral infarction. *Arch Dis Child Fetal Neonatal Ed* 1996;**75**:F76–81.
23. **Mercuri E,** Atkinson J, Braddick O, *et al*. Visual function in full term infants with hypoxic-ischaemic encephalopathy. *Neuropediatrics* 1997;**28**:155–61.
24. **Mercuri E,** Braddick O, Atkinson J, *et al*. Orientation-reversal and phase-reversal visual evoked potentials in full-term infants with brain lesions: a longitudinal study. *Neuropaediatrics* 1998;**29**:1–6.

25. **Mercuri E,** Atkinson J, Braddick O, *et al*. Basal ganglia damage in the newborn infant as a predictor of impaired visual function. *Arch Dis Child Fetal Neonatal Ed* 1997;**77**:F111–14.
26. **Atkinson J,** Anker S, Rae S, *et al*. Cortical visual evoked potentials in very low birthweight premature infants. *Arch Dis Child Fetal Neonatal Ed* 2002;**86**:F28–31.
27. **Mercuri E,** Haataja L, Guzzetta A, *et al*. Visual function in term infants with hypoxic-ischaemic insults: correlation with neurodevelopment at 2 years of age. *Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F99–104.
28. **Counsell SJ,** Allsop JM, Harrison MC, *et al*. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. *Pediatrics* 2003;**112**:1–7.
29. **Huntley M.** *The Griffiths Mental Development Scales: from birth to 2 years*. Association for Research in Infant and Child Development (ARICD), 1996.
30. **Himmelmann K,** Hagberg G, Beckung E, *et al*. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995–1998. *Acta Pædiatr* 2005;**94**:287–94.
31. **Wattam-Bell J.** Analysis of infant visual evoked potentials (VEPs) by a phase-sensitive statistic. *Perception* 1985;**14**:A33.
32. **Atkinson J,** Anker S, Rae S, *et al*. A test battery of child development for examining functional vision (ABCDEFV). *Strabismus* 2002;**10**:245–69.
33. **Simple Interactive Statistical Analysis**. http://www.quantitativeskills.com/sisa/statistics/five2hlp.htm (accessed 18 Apr 2008).
34. **Salomao SR,** Ventura DF. Large sample population age norms for visual acuities obtained with Vistech-Teller Acuity Cards. *Invest Ophthalmol Vis Sci* 1995;**36**:657–70.
35. **Atkinson J,** Anker S, Evans, *et al*. Visual acuity testing of young children with the Cambridge Crowding Cards at 3 and 6 metres. *Acta Ophthalmol* 1988;**66**:505–8.
36. **Bhutta AT,** Cleves MA, Casey PH, *et al*. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002;**288**:728–37.
37. **Weisglas-Kuperus N,** Heersema DJ, Baerts W, *et al*. Visual functions in relation with neonatal cerebral ultrasound, neurology and cognitive development in very-low-birthweight children. *Neuropediatrics* 1993;**24**:149–54.
38. **van den Hout BM,** Stiers P, Haers M, *et al*. Relation between visual perceptual impairment and neonatal ultrasound diagnosis of haemorrhagic-ischaemic brain lesions in 5-year-old children. *Dev Med Child Neurol* 2000;**42**:376–86.
39. **Atkinson J,** Van Hof-van-Duin J. Visual assessment during the first years of life. In: Fielder A, Bax M, eds. *Management of visual impairment in childhood*. London: MacKeith Press, 1993:9–29.
40. **Barnett AL,** Guzzetta A, Mercuri E, *et al*. Can the Griffith's scales predict neuro-motor and perceptual-motor impairment in full term infants with neonatal encephalopathy? *Arch Dis Child* 2004;**89**:637–43.

APPENDIX

Detailed procedure of cortical vision tests

(a) OR-VERP. The orientation reversal (OR) stimulus was a high contrast sine wave grating oriented at 45° or 135°, spatial frequency 0.3 c/degree, presented on a CRT screen at 40 cm viewing distance. The orientation alternated between 45° or 135° at a rate of 4 or 8 reversals/s. These orientation reversals were embedded in a sequence of random phase shifts at 24/s. VERP signals were averaged over sweeps each containing one complete stimulus cycle (ie, two ORs).

The VERPs were recorded with three gold cup electrodes: on the vertex, 1 cm above the inion, and a ground electrode positioned high on the forehead, using an Espion Electrophysiology system (Diagnosys LLC, Lowell, Massachusetts, USA). Impedance was measured with an applied voltage of 100 Hz, and electrodes were adjusted to achieve a balanced level below 10 kΩ. Signals were amplified (20 000×) and band pass filtered between 0.5 and 30 Hz. The infant's attention was kept focused on the screen as necessary by a small noisy toy that could be shaken in front of the screen throughout the recording. If the infant's attention shifted from the direction of the screen, the experimenter could interrupt the signal acquisition. Any sweeps containing voltage excursions greater than 200 μV from peak to peak were automatically rejected from the averaging as artefacts. Sampling continued until 200 sweeps had been recorded.

The responses to OR were separated from those to the phase shifts by Fourier analysis of the VEP signal; responses at the frequency of the reversal rate (the second harmonic of the sweep frequency) was taken as an indicator that the infant cortex included orientation-sensitive mechanisms. The presence of a significant ($p<0.05$) VERP signal at this frequency (the second harmonic of the sweep frequency) was assessed by the "circular-variance" test.[26]

(b) Fixation shift (FS). Infants were seated 40 cm away from a large, computer-controlled monitor (51×38 cm). In each trial, they initially fixated on a central face-like figure, which alternated between two formats at 3 Hz. When they were fixating, a target appeared 13.5 cm either left or right of centre. The target consisted of adjacent bright and dark stripes, each 2.9 cm wide by 14.7 cm high, reversing in contrast at 3 Hz. An observer, who was blinded to target location or condition, pressed a button to record the time and direction of the child's first fixation towards one or other target location. The target then disappeared, and the central face appeared so that the display was ready for the next trial. Each infant was tested in five blocks of five trials each. Each block contained in random order left-side and right-side "non-competition" trials (ie, central figure disappeared at target onset), left-side and right-side "competition" trials (central figure remained visible), and one trial where the central figure disappeared and bilateral targets appeared. Thus the complete run included 10 competition and 10 non-competition trials, each equally divided between left-field and right-field targets.