

Visual Memory and Learning in Extremely Low-Birth-Weight/ Extremely Preterm Adolescents Compared With Controls: A Geographic Study

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Background Contemporary data on visual memory and learning in survivors born extremely preterm
(EP; <28 weeks gestation) or with extremely low birth weight (ELBW; <1,000 g) are lacking.

Methods Geographically determined cohort study of 298 consecutive EP/ELBW survivors born in 1991
and 1992, and 262 randomly selected normal-birth-weight controls. **Results** Visual learning and memory
data were available for 221 (74.2%) EP/ELBW subjects and 159 (60.7%) controls. EP/ELBW adolescents ex-
hibited significantly poorer performance across visual memory and learning variables compared with controls.
Visual learning and delayed visual memory were particularly problematic and remained so after controlling
for visual-motor integration and visual perception and excluding adolescents with neurosensory disability,
and/or IQ <70. Male EP/ELBW adolescents or those treated with corticosteroids had poorer
outcomes. **Conclusion** EP/ELBW adolescents have poorer visual memory and learning outcomes com-
pared with controls, which cannot be entirely explained by poor visual perceptual or visual constructional
skills or intellectual impairment.

Key words low birth weight; preterm; visual learning; visual memory.

Introduction

Children born extremely preterm (EP; <28 weeks gestation)
or with extremely low birth weight (ELBW; <1,000 g) are at
increased risk for long-term neurobehavioral impairment
compared with children born at term (Hutchinson et al.,
2013; Johnson, 2007). For example, in a regional cohort
of children born EP/ELBW followed up at 8 years of age,
55% were found to have some form of neurobehavioral im-
pairment, ranging from mild academic and behavioral diffi-
culties to severe intellectual impairment and cerebral palsy
(Anderson & Doyle, 2003). A high proportion of EP/ELBW

children (50–60%) require educational remedial assistance
and numerous studies have documented difficulties acquir-
ing basic educational skills such as reading, spelling, and
arithmetic (Anderson & Doyle, 2003; Lefebvre, Mazurier, &
Tessier, 2005; McGrath & Sullivan, 2002; O'Brien et al.,
2004; Zhang, Mahoney, & Pinto-Martin, 2013).

Visual memory and learning are of fundamental im-
portance for normal classroom learning (Aylward, 2002;
Bull, Espy, & Wiebe, 2008; Klin & Jones, 2006;
Mitchell, 2006; Packiam, Banner, & Smith, 2010;
Rourke, 1988, 1993, 1995), and may contribute to the

academic difficulties of EP/ELBW children. While most specific learning problems in the general population have been linked to language, visual deficits have also been clearly linked to specific subtypes of reading difficulty (Laycock & Crewther, 2008; Leat & Woo, 1997), maths problems (Clayton & Dodd, 2005; Forrest, 2004; Strang & Rourke, 1985), and more general learning difficulty, such as nonverbal learning disability (Rourke, 1988, 1995).

There are at least two reasons for expecting poorer visual memory and learning in EP/ELBW children compared with term born peers. Sensory visual difficulties, such as refractive errors, strabismus, amblyopia, and impaired stereopsis, are reported at relatively high rates in EP/ELBW children (Cooke, Foulder-Hughes, Newsham, & Clarke, 2004; Darlow, Clemett, Horwood, & Mogridge, 1997; O'Connor & Fielder, 2007; Stephenson et al., 2007), which may affect higher-order visuocognitive skills such as visual memory and learning. EP/ELBW infants are exposed to sensory stimulation at a time when ophthalmological and neurological systems are developing rapidly, potentially altering normal developmental processes. Furthermore, EP/ELBW infants are at risk for a range of perinatal complications and treatments, some of which are strongly linked to poor visual outcome such as severe retinopathy of prematurity (ROP), white matter brain injury, and postnatal corticosteroids (Bassi et al., 2008; Bassler et al., 2009; Bohn & Friedrich, 1982; Cioni et al., 1997; Dunlop, Archer, Quinlivan, Beazley, & Newnham, 1997; Palmer et al., 2005; Ricci et al., 2011; Schmidt et al., 2003; Yeh et al., 2004). ROP refers to the pathologic vasoproliferation in the immature retina and is estimated to account for 6–18% of childhood blindness in developed countries (Gilbert, Rahi, Eckstein, O'Sullivan, & Foster, 1997), while focal or diffuse white matter pathology (Huppi, 2004; Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Volpe, 2003) can disrupt neural networks involved in processing visual information (Lein, Finney, McQuillen, & Shatz, 1999). Postnatal corticosteroids used to treat/prevent chronic lung disease may have adverse effects on the development of neural structure and function, including regions important for visual processing (Halliday, 2004; Murphy et al., 2001). Indeed, treatment with postnatal corticosteroids has been implicated in long-term visual difficulties (Yeh et al., 2004).

Altered growth of the hippocampus is another reason to speculate visual memory and learning deficits in the EP population. The hippocampus is well known to be important for memory and learning (Nadel, Samsonovich, Ryan, & Moscovitch, 2000; Winocur & Moscovitch, 1990), and research has demonstrated reduced hippocampal volume in very preterm (VP) infants (Beauchamp et al., 2008), children (de Kieviet, Zoetebier, van Elburg, Vermeulen, &

Oosterlaan, 2012; Omizzolo et al., 2013), and adolescents (Abernethy, Palaniappan, & Cooke, 2002). Furthermore, we have shown that the hippocampi of VP infants are less curved and infolded than term infants, and that these shape differences are associated with white matter pathology and postnatal corticosteroid exposure (Thompson et al., 2013). The functional consequences of these shape alterations are not yet clear.

Despite high rates of visual sensory impairment and reports of altered hippocampal development in preterm children, as well as evidence that acquisition of basic educational skills is dependent on effective visual spatial encoding, storage, and retrieval (Forrest, 2004; Strang & Rourke, 1985), there is a paucity of research that has examined visual memory and learning in this group. Studies that have been published tend to focus on very young children and with cohorts born before 1990 (Hack et al., 1992; Rose, 1980; Rose & Feldman, 1996; Rose, Gottfried, & Bridger, 1979; Sigman & Parmelee, 1974). The relevance of these findings to contemporary cohorts of EP/ELBW children is questionable, given the introduction of important perinatal intensive care interventions in the early 1990s such as exogenous surfactant therapy, administration of antenatal corticosteroids, and improved ventilation and monitoring techniques, which substantially improved survival rates (Doyle et al., 1999; O'Shea & Doyle, 2001; Wilson-Costello, Friedman, Minich, Fanaroff, & Hack, 2005), particularly of those born EP (Victorian Infant Collaborative Study, 1997b) or with ELBW (Victorian Infant Collaborative Study, 1997a). As EP/ELBW children are at the greatest risk for long-term morbidity, including visual impairments, it is essential to examine visual memory and learning outcomes for these children born in the 1990s, the post surfactant era. Further, long-term follow-up into adolescence and adulthood is required to differentiate impairment from developmental delay, which is conspicuously limited in the preterm literature particularly within the visual modality.

The aims of this study were to compare visual memory and learning ability between EP/ELBW and normal-birth-weight (NBW; >2,499 g birth weight) control adolescents and explore the relationship between perinatal (severe ROP, brain injury, and postnatal corticosteroids) and demographic (gender, birth weight *z* score, social risk, and corrected age) factors and visual memory and learning functioning. It was hypothesized that EP/ELBW adolescents would have higher rates of visual memory and learning abnormalities in all areas assessed than NBW controls. We also hypothesized that severe ROP, brain injury, and postnatal corticosteroids would significantly predict poorer visual memory and learning performance.

Methods

Participants

The subjects were derived from a geographical cohort of all 298 surviving EP/ELBW children born between January 1991 and December 1992, inclusive, in the state of Victoria. A control cohort, enrolled at birth, comprised 262 randomly selected infants who had birth weights >2,499 g. Children in the control group were matched to infants in the EP/ELBW group on the basis of expected due date, gender, mother's country of birth (English speaking or not), and health insurance status (private health insurance or not). These children have had extensive evaluations of their growth and development at 2 (Doyle et al., 1997a; Doyle et al., 1997b), 5 (Doyle & the Victorian Infant Collaborative Study Group, 2001), and 8 (Doyle & Anderson, 2005) years of age; none of these included formal assessments of visual memory and learning. Previous follow-up of this cohort has reported improved survival rates (Doyle et al., 1999), but higher rates of sensorineural disability (Doyle et al., 2000), cognitive, educational, and behavioral impairments (Anderson & Doyle, 2003) in EP survivors in comparison with NBW peers. A follow-up study in adolescence was approved by the Human Research Ethics Committees of the participating sites: The the Royal Women's Hospital, Mercy Hospital for Women, Monash Medical Centre, and the Royal Children's Hospital. Participants were aged 14–20 years for the present study, and 221 (74.2%) EP/ELBW and 159 (60.7%) NBW control adolescents provided data for the measures of interest. Written informed consent was obtained from parents and the participants themselves, if they were able to provide consent.

Outcome Measures

Subjects were assessed by trained examiners, unaware of previous history or group status. Visual memory and learning were assessed using the Rey Visual Design Learning Task (RVDLT) (Rey, 1964; Spreen & Strauss, 1991). The

RVDLT provides a measure of immediate visual memory, visual learning, delayed visual memory, and visual recognition (see Table I for a description of variables). The RVDLT consists of 15 simple geometric forms, which in this study were presented individually on a computer screen at a rate of 2 s per design. Following the presentation of all 15 designs, the participants are asked to draw as many of the designs that they can recall. Another four trials were administered following the initial trial. The participants are given 60 s to draw as many as they can in the first trial and 90 s for trials 2–5. After a 30-min delay, participants were asked to recall as many of the geometric forms as they could (delayed recall), followed by a recognition task that required identification of the 15 designs embedded within a chart of 15 distracters. Although norms are available based on Swiss school children collected in 1964, these were considered outdated and unlikely to be representative of Australian children in 2008, as such continuous data were examined using raw scores and discrete comparisons (abnormal vs. normal) were conservatively determined by scores below the 10th percentile of the control group. This equated to <3 for immediate visual memory, <32 for visual learning, <9 for delayed visual memory, and <13 for visual recognition. Error scores were determined by commission errors and design mistakes such as an incorrect shape, two elements incorrectly placed with regard to each other, triangles having clearly faulty orientations, reversal or rotation of the two elements with respect to each other, and confabulations, unrecognizable or incomplete elements. Slight distortions that do not affect recognizability, designs reproduced on a larger or smaller scale but respect the proportions between the two elements, and spontaneous corrections were not considered errors.

The RVDLT has satisfactory reliability and validity properties (Wilhelm, 2004; Wilhelm & Van Klink, 2007). In contrast to other measures of visual learning and memory (e.g., Rey Complex Figure [Rey, 1941; Spreen & Strauss, 1991], Benton Visual Retention Test

Table I. Description of Variables From the Rey Visual Design Learning Task

Variable	Range	Cognitive demand/description
Total number of correct designs trial 1	0–15	Immediate visual memory
Total number of correct designs recalled trial 1–5	0–75	Visual learning (consolidation)
Delayed recall	0–15	Delayed visual memory
Delayed recognition	0–15	Visual recognition
Visual learning total errors		Total number of design and commission errors over five learning trials
Delayed visual memory errors		Number of design and commission errors
Visual recognition errors		Number of commission errors

[Benton, 1974], and the Wechsler Memory scale-revised [Wechsler, 1987]), the RVDLT has short stimulus presentation durations, it has a large array of test items, the test procedure is repeated five times allowing learning with repetition to be evaluated, and participants are unlikely to adopt a verbalization strategy (Wilhelm, 2004) likely owing to the complexity and ambiguity of test items. Further, a study examining the relative contributions of several cognitive domains found that visual constructive skills and attention, concentration, and speed of information processing did not contribute to the total score (visual learning) or delayed recall score after accounting for visual spatial reasoning (Wilhelm, 2004). This is also supported by research by McCoy, Conrad, Richman, Nopoulos, and Bell, (2013), who found that preterm birth per se rather than neuropsychological profile, attention deficit hyperactivity disorder status, or learning disability subtype predicts memory impairment.

Descriptive Measures

General Intellectual Function

The Wechsler Abbreviated Scale of Intelligence was used as an estimate of general intellectual function (Wechsler, 1999).

Visual Acuity

Visual acuity was assessed monocularly (the left and right eyes were assessed separately) using the 3 m Early Treatment Diabetic Retinopathy Study logMAR chart test, as detailed by Taylor (1977). As is commonly used, a score better than 6/9 (logMAR equivalent <0.20) was considered normal (i.e., lower scores represented better acuity) (Cooke et al., 2004; Jongmans et al., 1996; McGinnity & Bryars, 1992; Pows, Botting, Cooke, Stephenson, & Marlow, 1997), and participants with logMAR ≥ 0.2 were determined to be visually impaired.

Visual Perception

Five subtests from the Test of Visual Perceptual Skills 3rd Edition (TVPS-3) were administered (Davis, Burns, Wilkerson, & Steichen, 2005; Martin, 2006).

1. Visual discrimination: Assessed ability to distinguish one object from another.
2. Visual-spatial relationships: Assessed ability to identify one item that was different from remaining items in terms of direction/orientation.
3. Form constancy: Participants selected the item that included the same shape as the reference item; size and/or spatial orientation varies.

4. Visual figure-ground: Participants selected the item in which the reference item was imbedded within another object.
5. Visual closure: Participants selected the item that would match the reference item if all lines on the picture were connected.

Each scale is age standardized with a normative mean of 10 (SD 3), with higher scores indicative of better performance; the upper age band of 18 years 11 months was used for all subjects aged >19 years.

The scaled scores of these five subtests were added to form an overall visual perceptual score. To classify visual perceptual impairment we used a cutoff equivalent to the 10th percentile of the control group (scores ≤ 28).

Visual-Motor Integration

The Developmental Test of Visual-Motor Integration (VMI), 5th Edition (Beery, Buktenica, & Beery, 2004), was used to assess the coordination of visual perception and finger-hand movements. The norms were based on a well-defined sample and the test is reported to have good psychometric properties, with sufficient levels of reliability and validity (Beery et al., 2004). The VMI is age standardized with a normative mean of 10 (SD 3), with higher scores indicative of better performance. Impairment was recorded as those with scaled scores below the 10th percentile in this task, as defined by test norms (Beery et al., 2004).

Perinatal Risk Factors

Detailed perinatal data had been collected during the infants' stay in hospital; however, only the variables of interest to the current study are described here. Although there are a number of perinatal factors that may negatively affect visual memory and learning, many of them are interrelated. Consequently, we selected variables based on what we previously reported to be associated with adverse neurological outcome at 5 years in this cohort (Doyle & the Victorian Infant Collaborative Study Group, 2001), or on theoretical underpinnings that suggest an association (Bassi et al., 2008; Bassler et al., 2009; Bohn & Friedrich, 1982; Cioni et al., 1997; Dunlop et al., 1997; Palmer et al., 2005; Ricci et al., 2011; Schmidt et al., 2003). Information was collected from medical histories by a neonatal research nurse:

- i. Birth weight z score (i.e., 0 = expected birth weight for gestational age and gender; positive values are birth weights above expectations for gestational age and gender; negative values are birth

- weights below expectation for gestational age and gender),
- ii. ROP; a pediatric ophthalmologist examined the eyes at intervals in the nursery, starting at 30–32 weeks' postmenstrual age and reassessed at intervals until the resolution of ROP or retinal maturation. The international classification of ROP was used to determine severity (i.e., stages 1–5), and severe ROP was defined as stage 3 or greater in either eye,
 - iii. Presence of significant severe white matter injury (grade 3 or 4 intraventricular hemorrhage or cystic periventricular leukomalacia) was diagnosed by serial cranial ultrasound examination,
 - iv. Postnatal corticosteroids (usually dexamethasone) administered 3–4 weeks after delivery for the treatment or prevention of bronchopulmonary dysplasia, for high oxygen need, or inability to wean the preterm infant from respiratory support (Doyle, 2000).

Maternal Education

Maternal education when EP/ELBW children were 8 years of age was used as a proxy for social risk. Higher social risk was classified as <12 years of formal education. Maternal education when the children were 8 years of age was used because the data set was most complete at this age.

Statistical Analysis

Data were analyzed using SPSS version 20. Participant characteristics were compared between EP/ELBW and control groups using *t*-tests for continuous data or chi-squared for categorical data. Given the broad age range, we first undertook a one-way analysis of variance to determine if there were any mean differences in visual memory and learning between each major age band (i.e., 14 years–14 years 11 months, 15 years–15 years 11 months, 16 years–16 years 11 months, 17 years–17 years 11 months, 18 years and over). Because these analyses revealed no significant differences or linear patterns, age was not used as a covariate in our primary analyses comparing mean scores between groups. Between-group differences (EP/ELBW vs. NBW) for visual memory and learning continuous data were analyzed by *t* tests and were adjusted for unequal variance as determined by Levene's Test for Equality of Variances. Effect size was noted using eta square and Cohen's guidelines for interpreting this value were used (0.01, small effect; 0.06, moderate effect; and 0.14, large effect) (Cohen, 1988).

Recognizing visual perceptual and visual construction skills as potentially important confounders for the

task demands, we reexamined group differences including the VMI scaled score and TVPS total score as covariates in a one-way analysis of covariance, as well as excluded participants with intellectual impairment and/or neurosensory impairment (EP/ELBW, $n = 17$; controls, $n = 2$).

The prevalence of impairment (dichotomous data) in the several domains of visual memory and learning in the EP/ELBW and control groups was compared using χ^2 analysis. A small proportion of participants who attempted the neuropsychological assessment were unable to complete or adequately comprehend the task demands and so were allocated a score that was equivalent to the lowest achieved by a participant who was able to complete the task and were scored as impaired on the task. Analyses of group differences of impairment (dichotomous data) were repeated excluding children with intellectual impairment ($IQ < 70$; $n = 14$), impaired visual acuity (≥ 0.2 after habitual correction; $n = 69$), impaired visual perception (total score on TVPS ≤ 28 ; $n = 70$), impaired visual-motor integration (scaled score < 7 ; $n = 162$), and/or neurosensory impairment ($n = 13$). This equated to excluding $n = 141$ EP/ELBW adolescents and $n = 64$ controls, with some participants impaired on more than one outcome.

The relationships between perinatal factors (birth weight z score, postnatal corticosteroids, severe white matter injury, and severe ROP) on visual memory and learning outcomes were explored adjusting for corrected age (i.e., age calculated from an infant's expected date of birth), sex, and higher social risk, without exclusions. Each perinatal variable was assessed univariably, with significant variables included in a multivariate model (perinatal variables were assessed for multicollinearity but none were found to correlate significantly). It was not expected that any of the variables would be better predictors over any other, thus all variables were entered simultaneously in the multivariate models.

Results

Two hundred twenty-one (74.2%) EP/ELBW and 159 (60.7%) control adolescents provided data for this study. The mean age at follow-up was 17.0 years (SD, 1.5; range, 14.3–20.0 years) for the EP/ELBW group and 17.4 years (SD, 1.6; range, 14.4–20.2) for the control group. Reasons for nonparticipation were refusal (EP/ELBW, $n = 38$; control, $n = 54$), loss to follow-up (EP/ELBW, $n = 15$; control, $n = 21$), living in other states or countries (EP/ELBW, $n = 3$; NBW, $n = 5$), or other reasons (EP/ELBW, $n = 14$; control, $n = 15$). A further seven EP/ELBW adolescents participated in some parts of the follow-up study (i.e.,

questionnaires) but did not attempt the neuropsychological assessment.

Of the 221 EP/ELBW adolescents who attempted the neuropsychological assessment, 12 (5.4%) had a neurosensory disability and were too impaired to complete the RVDLT. One control was also too impaired to complete this task. In addition, five EP/ELBW adolescents and two controls did not complete the RVDLT primarily owing to computer unavailability ($n = 5$) or the participant refused ($n = 2$).

The representative nature of the follow-up sample was explored to determine any biases (Table II). There were no significant differences between EP/ELBW participants and nonparticipants for perinatal variables, except that nonparticipating EP/ELBW adolescents had higher rates of cystic periventricular leukomalacia and a higher proportion of males. When assessed at 8 years, nonparticipants were more likely to be legally blind or deaf. There were no differences between NBW participants and nonparticipants, except there were more female participants. Mean

differences between EP/ELBW and controls in IQ, VMI, and total visual perception score were also statistically significant.

In regards to the continuous outcome data, the EP/ELBW group performed significantly worse on each variable assessed (Table III). The magnitude of the differences in means for visual learning and delayed visual memory showed a moderate to high effect (eta squared: 0.09), whereas for immediate visual memory and visual recognition, the effect was small (eta squared: 0.02–0.04). Only visual learning, delayed visual memory, and total number of errors remained statistically significant after covarying for visual perception and visual construction and excluding adolescents with intellectual impairment and/or neurosensory disability.

Consistent with the continuous data, the EP/ELBW cohort exhibited significantly more impairments in immediate visual memory, visual learning, delayed visual memory, and visual recognition (Table IV). After excluding participants with intellectual impairment, impaired visual

Table II. Demographic and Perinatal Characteristics of EP/ELBW Adolescents Who Participated Versus Nonparticipants and the Control Group

Variable	EP/ELBW		Controls $n = 159$
	Participants $n = 221$	Nonparticipants $n = 77$	
Neonatal characteristics			
Male: n (%)	94 (42.5)	44 (57.1)*	64 (40.3)
Gestational age at birth (weeks): M (SD)	26.6 (2.0)	26.91 (1.7)	39.2 (1.4)**
Birth weight: (g): M (SD)	883 (161)	900 (160)	3394 (454)**
Birth weight < -2 SD: n (%)	35 (15.8)	11 (14.3)	1 (0.6)**
Multiple birth: n (%)	73 (33.0)	18 (23.3)	2 (1.2)**
Grade III or IV IVH: n (%)	15 (6.8)	3 (3.9)	0 (0)**
Cystic PVL: n (%)	9 (4.1)	9 (11.7)*	0 (0)**
Postnatal corticosteroids: n (%)	69 (31.2)	29 (37.7)	0 (0)**
Bronchopulmonary dysplasia: n (%)	77 (34.8)	34 (44.2)	0 (0)**
ROP stage ≥ 3 either eye: n (%)	28/215 (13.0)	8/76 (10.5)	0 (0)**
Neurosensory disability at age 8 years			
Cerebral palsy: n (%)	20 (9.2)	9 (15.5)	0 (0)**
Blind ^a : n (%)	0 (0)	3 (3.9)*	0 (0)
Deaf ^b : n (%)	0 (0)	2 (2.6)*	0 (0)
IQ < 70 : n (%)	13 (6.1)	1 (2.2)	2 (1.3)**
Higher social risk at 8 years			
Higher social risk: n (%)	107/214 (50.0)	33/55 (60.0)	50/154 (32.5)**
Neuropsychology outcomes at age 18			
WASI	95.18 (16.33)		106.46 (13.72)**
TVPS	41.19 (17.25)		50.67 (15.81)
VMI	5.69 (3.02)		7.68 (2.43)**

Note. EP/ELBW = extremely preterm/extremely low birth weight; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity; WASI = Wechsler Abbreviated Scale of Intelligence; TVPS = Test of Visual Perceptual Skills; VMI = The Developmental Test of Visual–Motor Integration.

^aVisual acuity worse than 6/60 in the better eye.

^bRequiring hearing aids or worse.

* $p < .05$ participant versus nonparticipants within EP/ELBW group.

** $p < .05$ EP/ELBW participants versus controls.

Table III. Visual Learning and Memory Outcomes Contrasted Between EP/ELBW and Control Groups—Continuous Raw Scores

Test variable	Unadjusted			Adjusted ^a			
	Mean (SD)		Mean difference (95% CI)	Eta Sq.	Adjusted mean (95% CI)		P.Eta Sq.
	EP/ELBW n = 221	Controls n = 159			EP/ELBW n = 199	Controls n = 156	
Immediate visual memory	3.93 (1.93)	4.45 (1.73)	-0.52 (-0.90, -0.14)*	0.02	4.36 (4.13, 4.59)	4.33 (4.07, 4.59)	<0.01
Visual learning	37.77 (13.97)	45.48 (11.08)	-7.71 (-10.24, -5.18)*	0.09	41.82 (40.51, 43.14)	43.92 (42.42, 45.42)**	0.01
Visual learning total errors	8.51 (5.35)	6.33 (5.02)	2.19 (1.10, 3.27)*	0.04	8.17 (7.48, 8.85)	6.71 (5.94, 7.49)*	0.02
Delayed visual memory	9.60 (3.81)	11.60 (2.79)	-2.02 (-2.68, -1.35)*	0.09	10.61 (10.26, 10.96)	11.18 (10.78, 11.58)**	0.01
Delayed visual memory errors	1.90 (1.76)	1.27 (1.50)	0.63 (0.29, 0.96)*	0.04	1.75 (1.54, 1.97)	1.43 (1.18, 1.67)	0.01
Visual recognition	13.25 (2.90)	14.15 (1.58)	-0.90 (-1.35, -0.44)*	0.04	14.02 (13.82, 14.23)	14.03 (13.80, 14.27)	<0.01
Visual recognition errors	1.0 (1.43)	0.60 (1.21)	0.39 (0.12, 0.68)*	0.02	0.87 (0.70, 1.04)	0.70 (0.49, 0.87)	0.01

Note. EP/ELBW = extremely preterm/extremely low birth weight; CI = confidence interval; Eta Sq = Eta squared; P.Eta Sq. = partial eta squared.

^aCovaried for VMI and TVPS and excluding cases with IQ <70 and/or neurosensory disability; n = 199 EP/ELBW and n = 156 controls remaining.

*p < .01.

**p < .05.

Table IV. Rates of Impairment in Visual Learning and Memory Outcomes Contrasted Between EP/ELBW and Control Groups

Test variable	EP/ELBW n = 221	Controls n = 159	Odds ratio (95% CI)	
			Inclusive	With exclusions ^a
Immediate visual memory impairment: n (%)	45 (20.4)	20 (12.6)	1.78 (1.00, 3.15)**	1.88 (0.64, 5.53)
Visual learning impairment: n (%)	65 (29.7)	16 (10.1)	3.77 (2.09, 6.82)*	5.17 (1.06, 25.08)**
Delayed visual memory impairment: n (%)	77 (35.2)	21 (13.2)	3.56 (2.08, 6.09)*	3.42 (1.26, 9.30)**
Visual recognition impairment: n (%)	42 (19.2)	18 (11.4)	1.85 (1.02, 3.35)**	1.41 (0.45, 4.37)

Note. EP/ELBW = extremely preterm/extremely low birth weight; CI = confidence interval.

^aExcluding cases with IQ <70, neurosensory disability, impaired visual acuity, impaired visual perception, or impaired visual-motor integration; n = 80 EP/ELBW and n = 95 NBW remaining.

*p < .01.

**p < .05.

acuity, impaired visual perception, impaired visual-motor integration, and/or neurosensory impairment, only the differences in rates of impairment for visual learning and delayed visual memory remained statistically significant.

Within the EP/ELBW group, immediate visual memory was not substantially associated with the perinatal variables, suggesting that these factors poorly predict clinical impairments in immediate visual memory (Table V). In contrast, increasing corrected age was associated with a reduced odds of impairment, and male sex and postnatal corticosteroids were associated with an increased odds of impairment, in visual learning and delayed visual memory, both univariably and adjusted for each other (multivariably). Only postnatal corticosteroid therapy was related to impaired recognition memory. Of note, severe white matter injury and severe ROP were not associated with any visual processing outcomes.

None of the perinatal or demographic factors significantly contributed to 18-year outcomes of the control group.

Discussion

The current study, which reports on a large regional cohort in the post surfactant era, confirms that EP/ELBW birth is associated with poorer performance in visual memory and learning in comparison with controls. Of concern is the high proportion of EP/ELBW survivors exhibiting impairments in short-term memory retrieval over learning trials (visual learning consolidation) as well as long-term retrieval after a delay. This is of concern, as these skills are important for other cognitive functions and academic achievement and cannot be entirely explained by poor visual perception or visual constructional skills, or intellectual impairment.

Contrary to expectation, this study found that perinatal risk factors, including severe white matter injury diagnosed by cranial ultrasound and severe ROP, were only weak predictors of adverse outcome in visual memory and learning. Administration of postnatal corticosteroids had the greatest impact on poor outcomes, predicting

Table V. Associations of Impaired Visual Processing Outcomes at 18 Years With Perinatal and Demographic Variables, Within EP/ELBW and Control Groups, Separately

Test Variable	EP/ELBW		Controls Odds ratio (95% CI); <i>p</i> (<i>n</i> = 159) Univariable
	Odds ratio (95% CI); <i>p</i> (<i>n</i> = 221)		
	Univariable	Multivariable	
Immediate visual memory			
Male sex	1.54 (0.80, 3.03); .20		1.25 (0.49, 3.23); .64
Birth weight <i>z</i> score	1.16 (0.88, 1.54); .30		0.69 (0.40, 1.18); .18
High social risk	0.62 (0.32, 1.20); .16		1.07 (0.41, 2.79); .88
Corrected age	0.98 (0.78, 1.22); .85		1.19 (0.86, 1.64); .29
Postnatal corticosteroids	1.84 (0.94, 3.62); .08		
Severe white matter injury	2.13 (0.81, 5.64); .13		
ROP \geq Stage 3	1.07 (0.41, 2.82); .89		
Visual learning			
Male sex	2.38 (1.33, 4.35); .004	2.04 (1.11, 3.70); .02	1.56 (0.55, 4.35); .41
Birth weight <i>z</i> score	1.14 (0.89, 1.46); .29		0.66 (0.36, 1.20); .17
High social risk	1.14 (0.64, 2.02); .67		0.90 (0.32, 2.56); .85
Corrected age	0.77 (0.63, 0.94); .009	0.79 (0.64, 0.97); .02	1.03 (0.73, 1.44); .88
Postnatal corticosteroids	3.00 (1.64, 5.51); < .001	2.48 (1.32, 4.65); .005	
Severe white matter injury	2.34 (0.94, 5.81); .07		
ROP \geq Stage 3	1.33 (0.58, 3.07); .50		
Delayed visual memory			
Male sex	2.38 (1.35, 4.17); .003	2.00 (1.10, 3.70); .02	1.75 (0.70, 4.35); .23
Birth weight <i>z</i> score	1.20 (0.95, 1.52); .13		0.75 (0.44, 1.27); .28
High social risk	1.19 (0.68, 2.07); .54		0.94 (0.37, 2.37); .89
Corrected age	0.72 (0.59, 0.87); .001	0.73 (0.60, 0.90); .003	1.17 (0.86, 1.60); .33
Postnatal corticosteroids	3.23 (1.78, 5.87); < .001	2.63 (1.41, 4.92); .002	
Severe white matter injury	2.17 (0.88, 5.36); .09		
ROP \geq Stage 3	1.95 (0.88, 4.35); .10		
Recognition memory			
Male sex	1.72 (0.88, 3.33); .11		2.63 (0.97, 7.14); .06
Birth weight <i>z</i> score	1.34 (0.99, 1.81); .06		0.99 (0.57, 1.72); .98
High social risk	1.11 (0.57, 2.18); .75		1.11 (0.41, 3.04); .84
Corrected age	0.94 (0.75, 1.18); .60		1.09 (0.78, 1.50); .62
Postnatal corticosteroids	3.38 (1.70, 6.71); .001		
Severe white matter injury	1.75 (0.64, 4.82); .28		
ROP \geq Stage 3	2.20 (0.91, 5.28); .08		

Note. CI = confidence interval; ROP = retinopathy of prematurity.

impairment in visual learning, delayed visual memory, and visual recognition. Demographic factors were also poor predictors of the outcomes of interest, especially within the controls. Male sex and decreasing corrected age had a small negative impact on some aspects of memory, but only for the EP/ELBW adolescents.

While research examining the visual domain is limited, difficulties have been noted in preterm children aged between 3 and 8 years in tasks such as remembering spatial locations, spatial span, and spatial working memory (Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004).

Research during adolescence, in contrast, has shown that preterm children demonstrate less difficulty (Curtis, Zhuang, Townsend, Hu, & Nelson, 2006; Saavalainen et al., 2007). However, some studies have had small samples, so statistical power may have been inadequate to ascertain group differences (i.e., <750 g) (Taylor, Klein, Drotar, Schluchter, & Hack, 2006; Taylor, Minich, Bangert, Filipek, & Hack, 2004). It is speculated that being born preterm may affect working memory generally, including remembering locations and positions, but with time the deficit is characterized only on more complex memory tasks (Saavalainen et al., 2007). Notwithstanding the

differences in task demands of the aforementioned studies, our results appear to be consistent with this premise in that EP/ELBW adolescents appeared to have greater difficulty with the more cognitively demanding aspects of visual memory (visual learning and delayed visual memory). Importantly, group differences in less demanding tasks (immediate visual memory and visual recognition) were negligible after controlling for visual perception and visual construction. It is also possible that tasks specifically designed to distinguish impairments in immediate visual memory may be more sensitive than the RVDLT and thus difficulties may be understated here.

Consistent with previous research, visual perception and visual construction were related to visual memory and learning outcomes, as demonstrated by reduced mean differences and smaller effect sizes after controlling for these variables. Despite the importance of the visual system for classroom learning (Chen, Bleything, & Lim, 2011; Peiser, 1972), the majority of studies tend to focus on phonological and linguistic components of learning difficulty, based on the assumption that basic visual processes are complete by ~7 years (Dobson, Mayer, & Lee, 1980). This view seems limited and dismissive of ongoing maturation of the visual system such as in accommodation speed, contrast sensitivity, and visual perception (Laycock & Crewther, 2008; Leat & Woo, 1997; Parrish, Giaschi, Boden, & Dougherty, 2005). There are several lines of evidence that implicate visual sensory and perceptual abilities as a factor in reading and math acquisition. For example, the magnocellular layers in the lateral geniculate nucleus are involved in visuospatial analysis, spatial attention, stereopsis, visual search, eye movement control, the perception of self- and object-motion, and the visual guidance of movements of the eyes and limbs (Milner, 1995). It is therefore argued that problems with processing within the magnocellular pathway could cause learning difficulties in a range of domains (Boets, Wouters, van Wieringen, De Smedt, & Ghesquiere, 2008; Fischer & Hartnegg, 2000; Stein, 2001). Several authors have documented a relative weakness involving magnocellular-based tasks for ELBW children (Atkinson & Braddick, 2007; Laycock & Crewther, 2008; Leat & Woo, 1997). This study supports the idea that visual perception and visual construction affect visual memory and learning outcomes, particularly lower-level skills.

The relatively high proportion of EP/ELBW adolescents with visual memory and learning problems is likely to have a significant effect on academic achievement, social cognition, and other functional outcomes. These results suggest that the nature of intervention for EP/ELBW children needs to be tailored carefully to take account of visual

processing difficulties including visual perceptual and visual construction weaknesses in this population. In contrast to repetitive learning and delayed memory, visual recognition appears to be relatively spared, suggesting that memory retrieval is the area of most vulnerability. This insight warrants consideration by educators/clinicians of EP/ELBW children who may be able to alter classroom activities or assessments to capitalize on this profile of difficulties. The dissemination of this information to families and educators is vital because school-based interventions predominantly focus on auditory and verbal difficulties, clearly inappropriate for children with visual-based difficulties. Visual-based learning problems are typically more difficult to detect, indicating that children born preterm at risk of learning difficulties would benefit from detailed neuropsychological examinations to appreciate more fully where core deficits lie.

Conceptually visual memory encapsulates distinct functional components that are subsumed by distinct neural networks. For example, immediate visual memory has a limited capacity to store visual information and functional imaging paradigms indicate that the posterior parietal cortex is correlated with this limited visual capacity (Todd & Marois, 2004). On the other hand, visual learning, or consolidation and maintenance of visual information, is subsumed primarily by the frontal and prefrontal cortex (Kennedy, Rodrigue, Head, Gunning-Dixon, & Raz, 2009; Suchan, 2008). Although several brain regions such as the visual ventral stream, medial temporal lobe structures, frontal lobe, and parietal cortices along with the hippocampus have been implicated in visual recognition memory (Kim & Cabeza, 2009; Neufang, Heinze, & Duzel, 2006; Yonelinas, Otten, Shaw, & Rugg, 2005), a consensus understanding is lacking. Consistent with the functional and anatomical differences of the components of visual memory and learning, the EP/ELBW group performed significantly more poorly than controls in visual learning, consolidation, and maintenance, suggesting that diffuse white matter differences detected in preterm infants and the potential for such injuries to derail neural networks underpinning visual processing and memory skills (Hagberg, Peebles, & Mallard, 2002; Huppi, 2004) may have the most significant effect on more complex aspects of cognition. It is also clear that lower-order visual perceptual skills have a significant effect on visual memory and learning outcomes but do not fully account for ongoing difficulties in more complex visuocognitive skills. From a developmental perspective, the implication of these findings is significant and highlights the persistence of cognitive difficulties, at least in the visual domain, over time for EP/ELBW survivors.

Given the importance of visual memory and learning to school success, it would be valuable to ascertain relevant and reliable risk factors, which may also guide research toward appropriate intervention strategies. As expected, postnatal corticosteroid therapy was an independent predictor of visual learning, delayed visual memory, and visual recognition. Previous research has noted that treatment with postnatal corticosteroids used to treat/prevent bronchopulmonary dysplasia resulted in significantly poorer motor performance, visual perception, motor coordination, and visual-motor integration (Yeh et al., 2004), which is broadly consistent with the current study. The likely mechanism disrupting visual development due to postnatal corticosteroid therapy has been speculated to be due to a reduction of myelin in the optic nerve, accompanied by a decrease in the number of myelinated axons, and a reduction in the myelin/axon area ratio of those axons that were myelinated (Bohn & Friedrich, 1982). Early disruption to the optic nerve could have detrimental effects on the information that is transmitted from that point as well as possibly affecting the normal development of the visual pathways.

Demographic variables were poor predictors of visual memory and learning impairment in both groups. Male sex, age at assessment, and postnatal corticosteroids had small impacts on some aspects of impaired visual memory, but only for the EP/ELBW adolescents. This is in contrast to a recent study reporting that at age 7 years, males born moderately preterm (32–36 weeks gestation) had caught up to their NBW peers on measures of intelligence, attention, visuospatial reasoning, and executive functioning, whereas females were still lagging behind (Cserjesi et al., 2012). However, it is consistent with others who have reported that EP males have higher mortality and neonatal morbidity (Costeloe, Hennessy, Gibson, Marlow, & Wilkinson, 2000), perform less well over the first 30 months (Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000), and have more disability and poorer cognitive scores than females (Marlow, Hennessy, Bracewell, & Wolke, 2007; Marlow, Wolke, Bracewell, & Samara, 2005).

This study has notable strengths. Data are from the oldest survivors born in the 1990s, providing important contemporary information about outcomes after extreme preterm birth in the surfactant era. Being a large regional cohort, the findings have important generalizability and provide invaluable information on long-term outcomes for parents and staff caring for the tiniest and most preterm infants. The current study has made significant advances toward understanding memory and learning in the visual domain in EP/ELBW adolescents; however, it is important to note the limitations. As with many neuropsychological

tests, the RVDLT is multifactorial and therefore taps more cognitive domains than visual memory. It is possible that other cognitive difficulties, such as fine motor skills and processing speed, often present in preterm children could be contributing to the visual learning and memory problems reported here. Importantly, visual memory and learning difficulties were still more prevalent in EP/ELBW adolescents after excluding those with visual processing difficulties and impaired visual-motor integration, albeit that the effect sizes were small; as such it seems difficulties in visual construction are not likely to entirely explain these group differences. Further to which, a study examining the relative contributions of several cognitive domains to performance on the RVDLT found that visual constructive skills and attention, concentration, and speed of information processing did not contribute to the total score (visual learning) or delayed recall score after accounting for visual spatial reasoning (Wilhelm, 2004). This is also supported by more recent research, which found that preterm birth per se rather than neuropsychological profile, attention deficit hyperactivity disorder status, or learning disability subtype predicts memory impairment (McCoy et al., 2013). It may have been beneficial to investigate the differences in types of errors to further elucidate this relationship. As is common in clinical research, the number of people with impairment, as well as the proportion with specific perinatal risk factors, was small by statistical standards. Larger groups may have provided an opportunity to investigate more detailed relationships with greater power. Although statistically significant differences remained between EP/ELBW and NBW adolescents in complex tasks of visual memory and learning, the magnitude of these differences was small and thus may not translate into clinically significant findings. Future research may focus on the clinical significance of visual memory and learning difficulties; for example, it would be useful to explicitly explore the relationship between visual memory and learning difficulties with other functional outcomes, such as academic achievement and social information processing.

In summary, the results of the current study reveal that a high proportion of EP/ELBW adolescents exhibit difficulties in tasks assessing visual memory and learning. Visual perception and visual construction skills were particularly influential on immediate visual memory and recognition memory outcomes; however, they did not entirely account for difficulties in more complex tasks of visual learning and memory. Given the importance of visually based tasks to other functional and adaptive outcomes, deficits in this domain likely have significant clinical relevance in terms of acquisition of other cognitive, motor, and

social skills. The finding that postnatal corticosteroid therapy has a detrimental effect on visual memory and learning provides important insight into the brain's capacity to recover after early brain disruption. Specifically these findings lend support to the notion that early disruption likely places limits on the brain's capacity to recover. This is in contrast to traditional modes of viewing young brain injury as more capable of recovery than adult brain injury (Kennard, 1936, 1940) but is consistent with more recent research, which argues that the immature brain may be particularly vulnerable during critical periods of growth (Anderson et al., 2009). Future research may endeavor to elucidate early indicators of visual learning difficulties, such as subtle forms of lower-order visual problems, as well as determine how early disruption may affect underlying neural circuitry involved in visual memory and learning.

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