Does Early Age at Brain Insult Predict Worse Outcome? Neuropsychological Implications

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Objective Traditionally early brain insult (EBI) has been argued to have better outcome than later injury, consistent with the notion that the young brain is flexible and able to reorganize. This view was investigated by comparing neurobehavioral outcomes of children sustaining EBI at different developmental stages (gestation to late childhood). **Methods** One hundred and sixty four children who had sustained focal brain insult (confirmed by MRI) formed six groups, based on age at EBI, (a) *Congenital*; (b) *Peri-natal*; (c) *Infancy*; (d) *Preschool*; (e) *Middle Childhood*; (f) *Late Childhood*, and were compared on a range of standardized neurobehavioral measures. Groups were matched for lesion characteristics and demographics. **Results** Children sustaining EBI before age 2 recorded global deficits, while children with later EBI performed closer to average. **Conclusion** These results question the advantages of early brain plasticity, demonstrating poorer outcome from very early insults, and increasingly better function with lesions later in childhood.

Key words brain injury; language; executive function; memory; outcome; plasticity.

Introduction

Recovery from early brain insult (EBI) is variable and unpredictable. Children with focal left-hemisphere insult, for example, may demonstrate age appropriate language abilities, free from the symptoms of aphasia observed following similar lesions in adulthood (Ballantyne, Spilkin, Hesselink, & Trauner, 2008; Ballantyne, Spilkin, & Trauner, 2007; Heywood & Canavan, 1987; Taylor & Alden, 1997). In contrast, generalized cerebral insult may result in poorer outcome in children than in adults suffering similar insults (Duval et al., 2009; Glosser, Cole, French, Saykin, & Sperling, 1997; Hessen, Anderson, & Nestvold, 2007; Mosch, Max, & Tranel, 2005; Strauss et al., 1995), with greatest deficits seen in ''fluid'' skills such as attention, information processing and executive skills.

Recent research has explored a range of factors that might influence recovery, and thus predict either ''good'' or ''poor'' outcomes. Apart from the well-established relationship between insult severity and outcome, and presence of epilepsy and poor prognosis, studies have failed to identify consistent links between underlying brain pathology and recovery within the pediatric domain (e.g., location, extent, laterality, neurological signs) (Ballantyne et al., 2007; Bates et al., 2001; Chilosi et al., 2005; Hertz-Pannier et al., 2002; Stiles et al., 2008). There is emerging evidence regarding the impact of pre-insult child function and environmental parameters (e.g., socio-demographics, access to interventions, parent/family function) (Anderson et al., 2006; Breslau, 1990; Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2008; Taylor et al., 2002). However, it remains unclear whether these factors are specific to particular outcome domains or have greater influence at particular developmental stages or times post insult (Catroppa & Anderson, 2008; Giza & Prins, 2006).

The developmental stage of the child at time of insult also influences outcome, although the direction of this influence is hotly debated. It is generally agreed that the young brain possesses greater plasticity and is less functionally committed than the adult brain, however the relative advantage that this provides is unclear (Giza & Prins, 2006; Johnston, 2009). *Early plasticity* theorists argue that the flexibility of young brain renders it more able to

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reorganize in response to injury (Ballantyne et al, 2007; 2008; Huttenlocher & Dabholkar, 1997; Kennard, 1936, 1940). In contrast, *early vulnerability* proponents postulate that the young brain is uniquely sensitive to insult, and that, if a cerebral region is damaged at a critical stage of cognitive development, functions dependent on that region will be irreversibly impaired (Hebb, 1942, 1949; Kolb, 1995; Luciana, 2003).

The young brain does have some capacity for neural restitution, via either neural regrowth or anatomical reorganization, although the time frame for this ''window of opportunity'' appears limited, probably to the preschool years (Giza & Prins, 2006; Johnson, 2005; Kolb, Pellis, & Robinson, 2004; Lenneberg, 1967). Even when such processes occur, full recovery may be limited by either: (1) establishment of inappropriate connections (Giza & Prins, 2006; Kolb et al., 2004; Stein & Hoffman, 2003) resulting in dysfunctional behavioral recovery; or (2) a ''crowding effect'' (Aram & Eisele, 1994; Vargha-Khadem, Isaacs, van der Werf, Robb, & Wilson, 1992), where functions normally subsumed by damaged tissue are crowded into remaining healthy brain areas, with a general depression of all abilities (Anderson et al., 1997; Duchowny et al., 1996; Ewing-Cobbs et al., 1997; Jacobs, Harvey, & Anderson, 2007; Leventer et al., 1999; Riva & Cazzaniga, 1986).

While there is growing consensus that developmental factors play a central role in outcome from EBI, the challenge remains to describe the nature of this relationship. To date, most research has focussed on specific conditions (e.g., stroke, traumatic brain injury), with varied findings (Anderson et al., 1997, 2005; Ballantyne et al., 2008; Duchowny et al., 1996; Vargha-Khadem et al., 1992). The picture is now consistent with respect to insults causing diffuse pathology, where there is limited healthy brain tissue to support plasticity processes, and where outcomes from early insults are usually poor (Anderson et al, 2005; Ewing-Cobbs, Barnes, & Fletcher, 2003). In contrast, findings from studies of children with focal lesions, where there may be healthy tissue available for reorganization, are conflicting (Ballantyne et al, 2007; 2008; Stiles, 2008). While this ''condition-specific'' approach has contributed to our understanding of developmental influences, it is unable to address age at insult effects across gestation and childhood, as very few conditions occur across the developmental spectrum. To comprehensively examine the impact of insult to the developing brain, it is necessary to explore conditions occurring both pre- and post-natally. Further, studies incorporating both neural and behavioral domains and their developmental processes will be of particular value.

Both brain maturation and cognitive development occur in the step-wise manner, where critical periods of rapid progress occur (Casey, Giedd, & Thomas, 2000; Flavell, 1992; Gogtay et al., 2004; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Piaget, 1963), separated by more stable periods. Disruption during these critical periods may cause ''flow on'' effects, as the establishment of other, later emerging, neural connections and functional skills is thrown off course (Mosch, Max, & Tranel, 2005; Thomas & Johnson, 2008). Animal research supports this view, describing different outcomes depending on the neural processes underway at the time of insult (Kolb et al., 2004). Similarly, cognitive theorists argue that skills in a rapid phase of development will be most vulnerable to the impact of central nervous system (CNS) insult (Catroppa et al., 2008; Dennis, 1989).

This study examines outcomes from EBI sustained across gestation and childhood. We constructed six ''age at lesion'' (AL) groups, defined according to developmental timetables for key neurological processes in the CNS as well as developmental timetables for cognitive processes (Anderson, 1998; Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Anderson & Lajoie, 1996; Dennis, 1989; Kolb et al., 2004; Pavlovic et al., 2006; Smidt, Jacobs, & Anderson, 2004). These studies suggest that both neurologic and cognitive developmental processes occurring at the time of brain insult are central to outcome. Of note, AL groups were necessarily heterogeneous for cause of insult as many CNS insults occur only at specific stages of development (e.g., penetrating head injury, developmental malformations). To minimize any confounding effects caused by this heterogeneity: (1) only children identified as having focal abnormalities on MRI scan were included in the sample; and (2) AL groups were compared with respect to lesion characteristics (size, location, laterality).

We addressed the early plasticity-early vulnerability debate by posing the following two hypotheses: (1) When compared to population expectations, children with EBI would display global neurobehavioral deficits impacting language, visuo-spatial skills, attention, memory, EF and processing speed; and (2) age at brain insult would have long-term implications for neurobehavioral outcome: (a) for language and visuospatial domains, which are established early in childhood, we expected children with lesions before or at age 2 years would perform worse than those with insults after age 2; (b) for attention and EF, skills with major growth spurts around 12 months and 5 years, we predicted that children with lesion $\leq$age 2 years would perform poorest, followed by those with lesions between 3 and 6 years, with older age at

lesion best; and (c) for memory and processing speed, which show incremental development throughout childhood, we expected an overall effect of age at lesion, with differences across specific groups not sufficient to reach significance.

Methods

Participants

The sample comprised 164 children, including 92 (56.1%) males, aged between 10 and 16 years at recruitment ($M = 13.07$, $SD = 1.88$), with a history of EBI. Participants were ascertained between 2005 and 2007, through the Royal Children's Hospital, Melbourne. Eligible children were identified via hospital records and consecutive referrals to neuroscience outpatient clinics.

Inclusion criteria were: (a) aged 10–16 years at assessment; (b) evidence of focal brain pathology on MRI scan; and (c) brain insult at least 12 months prior to assessment, to allow for stabilization of recovery processes. Exclusion criteria were: (i) evidence of diffuse pathology (e.g., traumatic brain injury, cranial irradiation, hypoxia) on MRI scan; and (ii) non-English speaking. Eleven children were excluded based on study criteria. Approaches were made to 215 families, with 51 declining to participate (77% participation rate) due to time burden ($n = 18$), lack of interest ($n = 29$), or distance ($n = 3$). Table I provides demographic information on the sample.

The sample was divided into six ''age at lesion'' (AL) groups: (a) *Congenital (CON) ($n = 38$)*: EBI during 1st and 2nd trimester; (b) *Perinatal (PERI) ($n = 33$)*, EBI within the third trimester to 1 month postnatal; (c) *Infancy (INF) ($n = 23$)*: EBI 2 months to 2 years postbirth; (d) *Preschool (PRE) ($n = 19$)*: EBI 3–6 years of age; (e) *Middle Childhood (MC) ($n = 31$)*: EBI 7–9 years of age; and (f) *Late Childhood (LC) ($n = 19$)*: EBI after age 10.

Diagnoses were diverse, in order to ascertain children sustaining EBI across the developmental span of interest, and included focal pathologies stroke, contusions, penetrating head injury, tumor, dysplasia, cyst, and abscess. Details of the mechanism of insult and extent, laterality and region of lesion across the groups are provided in Table II.

Materials

Demographic Information

Parents provided information on their child's medical and developmental history, parental occupation, and educational level. Socio-economic status (SES) was determined using Daniel's Scale of Occupational Prestige (Daniel, 1983), which rates parent occupation on a seven-point scale, where a high score reflects low SES.

MRI Scans

(a) *Acquisition:* MRI scans were conducted, via standard protocol, as part of routine clinical practice prior to recruitment. For those who had not undergone scanning, or whose scans were unavailable, scans were conducted simultaneously with neurobehavioral evaluation. All scans were conducted on a 1.5 Tesla scanner, and axial and coronal slices were obtained. (b) *Coding protocol:* A coding protocol developed by Leventer and colleagues (1999) was employed to describe brain insult characteristics including: brain regions affected (lobes, subcortical structures), laterality (left, right, bilateral), extent of insult (focal, multifocal), and volume of brain affected (number of regions). Scans were coded simultaneously by an experienced pediatric neuroradiologist (LC) and neuropsychologist (MSS) who were blind to group membership. A randomly selected subset of 10 scans was re-coded independently by LC and MSS, with inter-rater reliability of .97.

Table I. Demographics of Sample

	Congenital	Perinatal	Infancy	Preschool	Middle Childhood	Late Childhood	Total group
n	38	33	23	19	31	20	164
Gender *n* (%) males	19 (50.0)	23 (69.7)	13 (56.5)	12 (63.2)	16 (51.6)	9 (45.0)	92 (56.1)
SES *M* (*SD*)	4.40 (1.4)	4.07 (0.84)	4.04 (1.06)	4.09 (1.13)	4.21 (1.29)	4.25 (1.11)	4.20 (1.06)
Age at testing (years) *M* (*SD*)	12.97 (1.86)	13.24 (1.98)	12.48 (1.97)	12.57 (1.72)	12.90 (1.72)	14.45 (1.46)	13.07 (1.86)
Age at insult (years) *M* (*SD*)	N/A	N/A	1.35 (0.93)	4.80 (1.07)	8.30 (0.80)	11.85 (1.60)	N/A
Time since insult (years) *M* (*SD*)	N/A	N/A	11.10 (2.19)	7.78 (1.98)	4.59 (2.10)	2.50 (1.30)	N/A
Age at diagnosis (years) *M* (*SD*)**	3.56 (3.91)	1.96 (2.19)	1.60 (1.23)	4.95 (1.03)	8.47 (1.05)	11.91 (1.59)	5.20 (4.27)
Time from diagnosis *M* (*SD*)**	9.40 (3.68)	10.97 (3.68)	10.79 (1.85)	7.68 (1.99)	4.30 (2.05)	2.54 (1.28)	7.79 (4.14)
Handedness (Right) *n* (%)	19 (50.0)	23 (69.7)	13 (56.5)	12 (63.2)	16 (51.6)	9 (45.0)	92 (56.1)
Full Scale IQ** *M* (*SD*)	79.05 (16.10)	81.00 (18.40)	79.91 (17.53)	93.79 (13.67)	94.41 (19.99)	94.53 (17.08)	87.93 (20.10)

**$p < .001$

Table II. Lesion Characteristics across Age at Lesion Groups

	Congenital	Perinatal	Infancy	Preschool	Middle Childhood	Late Childhood	Total group
Pathology mechanism**							
Developmental *n* (%)	30 (78.9)	5 (15.2)	0 (0)	0 (0)	0 (0)	0 (0)	35 (21.3)
Infective *n* (%)	0 (0)	0 (0)	1 (4.3)	1 (5.3)	1 (3.2)	1 (5.0)	4 (2.4)
Ischemic *n* (%)	2 (5.3)	25 (75.8)	6 (26.1)	6 (31.6)	12 (38.7)	6 (30.0)	57 (34.8)
Neuroplasm *n* (%)	5 (13.2)	3 (9.1)	14 (60.9)	8 (42.1)	10 (32.3)	6 (30.0)	46 (28.0)
Trauma *n* (%)	0 (0)	0 (0)	2 (8.7)	4 (21.1)	8 (25.8)	7 (35.0)	21 (12.8)
Region[a]							
Frontal *n* (%)	21 (55.3)	23 (69.7)	8 (24.8)	9 (47.2)	14 (45.2)	11 (55.0)	86 (52.4)
Extrafrontal *n* (%)	21 (55.3)	23 (69.7)	8 (24.8)	9 (47.2)	14 (45.2)	11 (55.0)	105 (64.0)
Subcortical *n* (%)	29 (76.3)	23 (69.7)	17 (73.9)	11 (57.9)	14 (45.2)	11 (55.0)	91 (55.5)
Laterality							
Left *n* (%)	8 (21.1)	11 (33.3)	9 (39.1)	8 (42.1)	14 (45.2)	4 (20.0)	54 (32.9)
Right *n* (%)	9 (23.7)	6 (18.2)	8 (34.8)	5 (26.3)	7 (22.6)	9 (45.0)	44 (26.8)
Bilateral *n* (%)	21 (55.3)	16 (48.5)	6 (26.1)	6 (31.6)	10 (32.3)	7 (35.0)	66 (40.2)
Extent							
Focal *n* (%)	18 (47.4)	18 (54.5)	16 (69.6)	14 (73.7)	18 (58.1)	13 (65.0)	97 (59.1)
Multifocal *n* (%)	20 (52.6)	15 (45.5)	7 (30.4)	5 (26.3)	13 (41.9)	7 (35.0)	67 (40.9)
Seizures* *n* (%)	24 (63.1)	16 (48.5)	14 (60.9)	5 (26.3)	11 (35.5)	5 (25.0)	75 (46.9)

[a]There is some overlap across categories for this variable.
*$p < .01$; **$p < .001$.

Brain Insult

Timing of brain insult was determined from a combination of MRI, brain biopsy, and medical record (clinical history, medical investigations). For pre- and perinatal insults this information was reviewed by an experienced paediatric neurologist (R.L.) and a neuropsychologist (M.S.S.), and rated according to the coding established by Leventer et al. (1999). Ten random cases were double-rated, with 100% consistency. *Mechanism of insult* was coded as: developmental, infective, ischemic, neuroplastic, or traumatic. Presence of seizure history and neurological abnormalities were recorded.

Neurobehavioral Measures

Measures were selected to tap major neurobehavioral domains. This broad ranging approach was chosen in order to compare outcomes across domains, which are documented to emerge at different stages through childhood (e.g., language emerges in infancy, while executive skills emerge in later childhood). Criteria for test selection included: (a) robust normative data and psychometric properties; (b) appropriate across the age range under study. Unless otherwise specified, variables employed in analyses were scaled scores ($M = 10$, $SD = 3$).

(i) *Intelligence*: The four-subtest version of the Wechsler Abbreviated Intelligence Scale (WASI; Wechsler, 1999) was administered. Scores derived were Verbal (VIQ), Performance (PIQ) and Full Scale Intelligence Quotients (FSIQ) ($M = 100$, $SD = 15$).

(ii) *Language:* (a) Vocabulary (VOC) and Similarities (SIM) subtests from WASI (Wechsler, 1999): *T*-scores ($M = 50$, $SD = 10$); (b) Peabody Picture Vocabulary Test – III (PPVT-III; Dunn & Dunn, 1997): stanine score ($M = 5$, $SD = 2$); and (c) Rapid Automatized Naming completion time (RAN: Clinical Evaluation of Language Function – 4: CELF 4; Semel, Wiig, & Secord, 2003): raw scores.

(iii) *Visuospatial skills:* (a) Block Design (BD) and Matrix Reasoning (MR) subtests from WASI (Wechsler, 1999): *T*-scores ($M = 50$, $SD = 10$); (b) Rey Figure (REY; Rey, 1941); Copy Accuracy (REYACC): raw scores; and (c) Trail Making Test: Visual Scanning (TMT:VS): [Delis–Kaplan Executive Function System (D-KEFS); Delis, Kaplan, & Kramer, 2001].

(iv) *Attention:* (a) Letter Number Sequencing [LNS: Wechsler Intelligence Scale for Children-IV (WISC-IV); Wechsler, 2003]; (b) Sky Search: time per target (SS:TPT; TEA-Ch; Manly et al., 1999): (c) Score: total correct (SCORE:TOT; TEA-Ch; Manly et al., 1999): (d) Sky Search Dual Task: decrement (SSDT:DEC; TEA-Ch; Manly et al., 1999): and (e) Creature Counting: total correct (CC:TOT; TEA-Ch; Manly et al., 1999).

(v) *Memory*: (a) California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1991): List A, Trials 1–5 (CVLT:TOT): T-score ($M = 50$, $SD = 10$), Long delay free (CVLT:DFR) and cued recall (CVLT:DCR): ($M = 0$, $SD = 1$); (b) Faces [Children's Memory Scale (CMS)] (Cohen, 1997), immediate (FACE:IMM) and delayed, (FACE:DEL) recall; and (c) Rey Complex Figure: (Rey, 1941): Recall (REYREC) and recall savings (REYSAV): raw scores.

(vi) *Executive function:* (a) Verbal Fluency: Total correct (FAS:TOT: D-KEFS; Delis et al., 2001); (b) Tower Test: Total Achievement (TT:TA; D-KEFS; Delis et al., 2001); (c) CWI: Inhibition/Switching (CWI:I/S; D-KEFS; Delis et al., 2001); and (d) TMT: Number-letter switching versus combined number sequencing and letter sequencing (TMT:COM; D-KEFS; Delis et al., 2001).

(vii) *Processing speed:* (a) SS Motor Control (SSM: TEA-Ch; Manly et al., 1999): time taken: raw score; (b) Color Word Interference: Naming + reading time (CWI:NRT: (D-KEFS); Delis et al., 2001); and (c) TMT motor speed [TMT:PS: (D-KEFS); Delis et al., 2001].

Procedure

This study was approved by the Human Research Ethics Committee, Royal Children's Hospital, Melbourne, Australia. Eligible children were identified via medical records, neuroradiology meetings or outpatient clinics. Families were contacted to ascertain their willingness to participate in the study and then mailed details of the study. Participating families were seen as outpatients, with a small number of children assessed at home or school. Informed consent was obtained from each child's parent/guardian at the time of assessment. Children were assessed individually, by a trained psychologist. Tests were administered in fixed order. Testers were blind to group membership. Assessments lasted ~2 hrs.

Statistical Analysis

Quantitative analyses were conducted using SPSS (version 14.0).

Initial analyses (ANOVA, Chi-squared) focused on determining presence of any group differences on descriptive demographic (SES, age at test, handedness) and lesion variables (age at diagnosis, time since diagnosis, seizures, mechanism, region, and extent of insult) which might contribute to group differences on neurobehavioral measures.

To address our first prediction, that children with EBI would perform more poorly than expected across all neurobehavioral domains, the total sample was compared to published test norms, using single sample *t*-tests. Alpha levels were adjusted using Holm's sequentially rejective Bonferroni procedure (Holm, 1977). For hypothesis 2, that age at brain insult would have long-term implications for neurobehavioral outcomes, multivariate planned contrasts were conducted for the language, visuo-spatial, attention and executive function domains, and MANOVA was used as for the information processing and memory domains. Specifically, a single contrast was conducted in both the language and visuo-spatial domains, comparing children with EBI before or at age 2 to those with EBI after age 2. For the attention and executive function domains, three contrasts were conducted: (a) children with EBI before or at age 2 versus children with EBI at age 3–6 years; (b) children with EBI before or at age 2 versus children with EBI at or after age 7; and (c) children with EBI at age 3–6 years versus children with EBI at or after age 7 years. Where domains included measures that employed raw scores, age at testing was included as a covariate. Similarly, the presence of seizures was included as a covariate where appropriate. Univariate analyses for both the planned contrast and MANOVA analyses employed Holm's procedure for adjusting alpha levels, and effect size was determined by η^2.

For neurobehavioral measures, some children were unable to complete some measures due to low functioning. In these instances, if test means and standard deviations were available, missing data were recoded conservatively to 2 *SD* below the test mean. Where raw scores were used and means were not available, data were not recoded. Data missing for other reasons (e.g., failure to return a questionnaire) were not recoded.

Results

Sample Demographics

No group differences were identified for gender, SES, or handedness. A significant age at test difference was identified, $F(5, 158) = 3.21$, $p = .009$, $\eta^2 = .09$, revealing that the LC group was older than the CON ($p = .04$), INF ($p = .007$), PRE ($p = .02$), and MC ($p = .037$) groups. To account for the possible effect of age, MANCOVA was conducted for measures where raw scores were employed. Group differences were also present for age at diagnosis, $F(5, 149) = 64.25$, $p < .001$, $\eta^2 = .68$, time since diagnosis, $F(5, 149) = 39.95$, $p < .001$, $\eta^2 = .57$ and presence of seizures, $\chi^2(5, N = 158) = 17.44$, $p = .004$, $V = .332$, with a large proportion of children in the CON group with

epilepsy/seizures (SR = 1.7) and a small proportion in the PRE group.

Analysis of mechanisms of insult detected significant group differences, $\chi^2(20, N = 163) = 150.10$, $p < .001$, $V = .48$ (Table II). There were no group differences for region [frontal, $\chi^2(5, N = 164) = 7.84$, $p = .17$, $V = .22$; extra-frontal, $\chi^2(5, N = 164) = 9.74$, $p = .08$, $V = .24$; sub-cortical, $\chi^2(5, N = 164) = 5.08$, $p = .41$, $V = .18$], or extent of insult (unifocal/multifocal), $\chi^2(5, N = 164) = 5.46$, $p = .36$, $V = .18$.

Comparing EBI to Normative Expectations

As illustrated in Table III, using total group data, children with EBI achieved poorer scores than the normal population ($p < .001$) on all measures, thereby supporting our first hypothesis. All *p*-values were below the strictest adjusted alpha level calculated using Holm's sequentially rejective Bonferroni procedure, where $\alpha = .002$. For the majority of variables (17/22), and across all domains, effect sizes (ES) were large (>.75). For 6/22 measures, ES were very large (>1.0). These deviations from normal were observed across a range of domains: language (VOC), attention (SS:TPT, SSDT:DEC), executive function (CWI:I/S, TMT:COM), and visuo-spatial skills (TMT:VS).

Comparisons Across AL Groups

Analysis across all domains included either presence of seizures and/or age at testing as covariates. Tests of the homogeneity of slopes for each domain revealed no violations of this assumption (all $p > .05$).

Language

Seizures covaried significantly with the language domain, Wilks's = .93, $F(4, 129) = 2.61$, $p = .039$, as did age at testing, Wilks's = .89, $F(4, 129) = 3.93$, $p = .005$. After partialling out the variance associated with these variables, the multivariate contrast for AL group remained significant, Wilks's = .84, $F(4, 129) = 6.17$, $p < .001$, $\eta^2 = .16$. Univariate contrasts identified expected group differences, demonstrating that the CON, PERI and INF groups combined scored significantly more poorly than the PRE, MC, and LC groups combined on all measures. Significant differences remained after corrective adjustments were made to alpha levels (Table IV), providing support for hypothesis 2a.

Visuo-spatial Skills

Seizures covaried significantly with the visuo-spatial domain, Wilks's = .89, $F(4, 131) = 3.89$, $p = .005$, as did age at testing, Wilks's = .83, $F(4, 131) = 6.64$, $p < .001$.

Table III. Differences between Clinical Sample and Test Means for Functional Domains

Measure	Variable	Test *M*	Sample *M*	SD	*t*	df	*p*	Cohen's *d*
WASI	VOC	50	38.53	13.06	−25.00	159	<.001	***−1.15***
	SIM	50	41.91	13.00	−7.88	159	<.001	*−0.81*
	BD	50	45.27	14.30	−4.17	159	<.001	−0.47
	MR	50	42.51	13.57	−6.99	159	<.001	*−0.75*
PPVT	TOT	5	4.22	2.13	−4.47	148	<.001	−0.39
CVLT	TOT	50	41.83	14.23	−7.29	159	<.001	*−0.82*
	DCR	0	−0.73	1.41	−6.54	158	<.001	*−0.73*
	DFR	0	−0.72	1.38	−6.58	157	<.001	*−0.72*
CMS	FACES:IMM	10	7.46	3.56	−9.08	161	<.001	*−0.85*
	FACES:DEL	10	7.02	3.42	−11.06	161	<.001	*−0.99*
WISC-IV	LNS	10	7.65	3.89	−7.71	162	<.001	*−0.78*
TEA-Ch	SS:TPT	10	5.86	3.42	−15.46	161	<.001	***−1.38***
	SCORE:TOT	10	7.59	3.56	−8.59	160	<.001	*−0.80*
	SSDT:DEC	10	6.40	3.45	−13.14	158	<.001	***−1.20***
	CC:TOT	10	8.30	3.70	−5.85	161	<.001	−0.57
D-KEFS	FAS:TOT	10	7.69	4.14	−7.13	162	.001	*−0.77*
	TT:TA	10	8.20	3.40	−6.63	155	.001	−0.60
	CWI:I/S	10	6.02	3.55	−14.21	160	.001	***−1.33***
	CWI:NRT	10	8.98	3.57	−3.59	157	.001	−0.34
	TMT:VS	10	6.03	3.84	−13.07	159	.001	***−1.32***
	TMT:COM	10	6.91	3.64	−10.75	160	.001	***−1.03***
	TMT:PS	10	7.56	3.96	−7.76	158	.001	*−0.81*

*ES: >.6 = moderate; (italicized); >1.0 = large (bolded and italicized).

Table IV. Functional Outcomes across Age at Lesion Groups

	Congenital *M* (*SD*)	Peri-natal *M* (*SD*)	Infancy *M* (*SD*)	Preschool *M* (*SD*)	Middle Childhood *M* (*SD*)	Late Childhood *M* (*SD*)	*F*-values	η^2	*p*-value	Adjusted α-level[a]
Language[b,c,d]: Planned comparisons: CON, PERI, INF < PRE, MC, LC										
SIM	36.29 (11.16)	38.45 (12.74)	36.55 (12.98)	48.47 (9.69)	48.62 (12.02)	48.58 (11.86)	21.17	.14	**<.001**	.013
PPVT	3.45 (2.23)	3.74 (2.24)	3.52 (1.94)	5.16 (1.83)	4.70 (1.95)	5.26 (1.76)	15.98	.11	**<.001**	.017
VOC	34.97 (11.92)	34.79 (13.63)	35.52 (12.48)	42.79 (10.28)	42.83 (13.96)	45.00 (11.65)	8.44	.06	**.004**	.025
RAN:TIME	94.87 (41.70)	90.97 (47.09)	97.55 (61.45)	76.95 (29.98)	63.18 (19.07)	65.06 (35.56)	4.00	.03	**.048**	.050
Visuo-spatial[b,c]: Planned comparisons: CON, PERI, INF < PRE, MC, LC										
REY:ACC	18.41 (9.22)	18.92 (10.96)	20.52 (9.35)	23.68 (4.89)	26.27 (7.60)	28.08 (6.14)	11.45	.08	**.001**	.013
TMT:VS	4.66 (2.80)	4.88 (4.40)	5.18 (3.75)	7.42 (3.56)	7.17 (3.42)	8.67 (3.85)	12.00	.08	**.001**	.017
BD	38.63 (12.18)	41.09 (13.35)	42.50 (13.55)	52.47 (14.17)	52.62 (11.31)	50.37 (16.28)	12.20	.08	**.001**	.025
MR	37.42 (11.85)	40.39 (14.03)	39.00 (14.12)	47.58 (12.70)	49.34 (11.74)	44.89 (13.88)	6.76	.05	**.010**	.050
Attention[b,c] Planned comparisons: a. CON, PERI, INF < PRE; b. CON, PERI, INF < MC, LC; c. PRE< MC, LC										
CC:TOT	6.39 (3.23)	7.42 (3.44)	7.32 (3.56)	9.00 (3.83)	10.10 (3.24)	11.10 (2.81)	a. 4.31	.03	**.040**	
							b. 22.38	.13	**<.001**	.010
SS:TPT	4.84 (2.73)	5.12 (3.90)	4.73 (3.04)	6.26 (3.43)	6.73 (2.91)	8.45 (3.44)	b. 10.10	.07	**.002**	.013
SSDT:DEC	5.13 (3.27)	5.18 (2.89)	7.62 (3.79)	7.58 (4.38)	7.03 (2.74)	7.61 (3.11)	–	–	–	.017
LNS	6.45 (3.78)	6.91 (4.27)	6.50 (4.26)	8.74 (2.31)	9.42 (2.83)	8.65 (4.49)	b. 10.72	.07	**.001**	.025
SCORE:TOT	7.08 (3.75)	6.33 (3.02)	7.59 (4.00)	8.42 (2.87)	8.83 (3.71)	8.00 (3.38)	–	–	–	.050
Memory[c,d]: Planned comparisons: no differences predicted										
FACE:IMM	6.24 (3.36)	5.88 (3.55)	7.17 (3.59)	8.63 (3.18)	8.90 (2.90)	9.60 (3.27)	–	–	.013	.007
FACE:DEL	5.81 (2.94)	5.73 (3.26)	6.61 (3.76)	8.37 (3.20)	8.30 (2.94)	8.70 (3.60)	–	–	.025	.008
REY:REC	8.25 (6.60)	9.13 (6.72)	10.55 (7.05)	10.45 (5.87)	12.92 (7.16)	15.68 (8.99)	–	–	.430	.010
CVLT:TOT	41.05 (14.99)	39.42 (12.32)	40.77 (15.27)	45.63 (13.30)	42.60 (14.92)	43.74 (15.13)	–	–	.540	.013
REY:SAV	42.63 (29.05)	46.72 (22.22)	45.07 (24.02)	44.22 (20.85)	48.60 (21.79)	53.23 (28.52)	–	–	.950	.017
CVLT:DFR	−1.12 (1.28)	−0.77 (1.40)	−.84 (1.85)	−.50 (1.05)	−.42 (1.23)	−.47 (1.59)	–	–	.970	.025
CVLT:DCR	−1.08 (1.29)	−0.88 (1.09)	−.77 (1.59)	−.32 (1.15)	−.45 (1.45)	−.53 (1.74)	–	–	.970	.050
Executive function[b,c]: Planned comparisons: a. CON, PERI, INF < PRE; b. CON, PERI, INF < MC, LC; c. PRE < MC, LC										
CWI:I/S	4.05 (2.50)	5.73 (3.77)	6.50 (2.92)	5.74 (4.01)	7.35 (3.64)	8.10 (3.21)	b. 8.12	.05	**.005**	.013
TT:TA	6.92 (3.09)	7.29 (4.12)	7.23 (3.07)	9.22 (2.44)	10.20 (2.53)	9.39 (3.22)	b. 16.02	.10	**<.001**	.017
FAS:TOT	5.95 (3.24)	6.78 (4.04)	7.91 (4.80)	8.32 (3.51)	8.39 (3.62)	10.50 (4.80)	b. 5.97	.04	**.016**	.025
TMT:COM	8.08 (3.82)	8.09 (3.21)	8.32 (3.33)	10.37 (3.10)	10.21 (3.86)	9.83 (3.07)	a. 4.67	.03	**.032**	.050
							b. 7.24	.05	**.008**	
Processing speed[b,c,d]: Planned comparisons: no differences predicted										
CWI:NRT	5.71 (2.72)	5.60 (4.32)	6.27 (3.04)	7.26 (3.16)	9.10 (3.43)	8.55 (3.52)	3.65	.12	**.004**	.017
SSM	31.38 (16.11)	30.71 (17.36)	23.75 (11.03)	22.79 (9.34)	26.27 (14.45)	19.00 (15.74)	2.80	.09	**.019**	.025
TMT:PS	6.29 (3.58)	7.06 (4.39)	8.05 (3.88)	7.47 (3.88)	8.00 (3.96)	9.94 (3.28)	–	–	.140	.050

Bold represents significant univariate differences.

[a]Alpha adjustment using Holm's sequentially rejective Bonferroni procedure.

[b]Significant multivariate effect.

[c]Significant effect of seizures.

[d]Significant effect of age at testing.

After partialling out these effects, the multivariate contrast for AL group remained, Wilks's = .87, $F(4, 131) = 4.73$, $p = .001$, $\eta^2 = .13$. Univariate contrasts identified expected group differences, demonstrating that the CON, PERI, and INF groups combined recorded significantly lower results than the PRE, MC, and LC groups combined on all measures. Significant differences remained after corrective adjustments were made to alpha levels (see Table 4), also supporting hypothesis 2a.

Attention

Again, seizures covaried significantly with the attention domain, Wilks's = .88, $F(5, 142) = 3.94$, $p = .002$, as did age at testing, Wilks's = .92, $F(5, 142) = 2.40$, $p = .040$. The first contrast, comparing the CON, PERI, and INF groups combined to the PRE group identified no significant multivariate effect ($p > .05$) and only one significant univariate difference: CC:TOT (Table IV). The second contrast, comparing the CON, PERI and INF groups combined

to the MC and LC groups combined identified a significant multivariate effect of AL group, Wilks's = .84, $F(5, 142) = 5.30$, $p < .001$. Univariate contrasts identified expected group differences, with the CON, PERI, and INF groups combined recording significantly lower scores than the MC and LC groups combined on 3/5 measures: CC;TOT, SS:TPT and LNS. The third contrast, comparing the PRE group to the MC and LC groups combined identified no significant multivariate effect or univariate differences (all $p > .05$). These results provided partial support to hypothesis 2b.

Executive Function

Seizures covaried significantly with the executive domain, Wilks's = .90, $F(4, 140) = 3.73$, $p = .006$, but age at testing did not, $p > .05$. The first contrast, comparing the CON, PERI, and INF groups combined to the PRE group identified no significant multivariate effect ($p > .05$) and only one significant univariate difference: TMT:COM (Table IV). The second contrast, comparing the CON, PERI, and INF groups combined to the MC and LC groups combined identified a significant multivariate effect of AL group, Wilks's = .87, $F(4, 140) = 5.23$, $p = .001$. Univariate contrasts identified expected group differences, with the CON, PERI and INF groups combined recording significantly lower scores than the MC and LC groups combined on all four measures. The third contrast, comparing the PRE group to the MC and LC groups combined identified no significant multivariate effect or univariate differences (all $p > .05$). This again provided only partial support to hypothesis 2b.

Memory Skills

No group differences were identified for memory measures. Seizures, Wilks's = .882, $F(7, 124) = 2.37$, $p = .026$, and age at testing, Wilks's = .891, $F(7, 124) = 3.40$, $p = .002$, co-varied significantly with the memory domain, and no significant multivariate effect for group remained after accounting for these two variables, Wilks's = .743, $F(35, 524.1) = 1.10$, $p = .33$, $\eta^2 = .06$. Univariate analyses showed no group differences for any of the memory measures (Table IV), which does not support hypothesis 2c.

Processing Speed

Seizures did not covary significantly with information processing, Wilks's = .950, $F(3, 131) = 2.31$, $p = .079$, but age at testing did, Wilks's = .917, $F(3, 136) = 4.11$, $p = .008$. After partialling out the variance associated with age at testing, a significant multivariate effect remained, Wilks's = .798, $F(15, 375.84) = 2.13$, $p = .008$, $\eta^2 = .07$. After adjusting alpha levels, univariate analyses showed a significant group difference on CWI:NRT and SSM remained. Post hoc analyses revealed significant findings only for CWI:NRT, with the MC group recording significantly higher scores than both the CON ($p = .04$) and PERI ($p = .01$) groups. This provides partial support to hypothesis 2c.

Discussion

With the aim of progressing the plasticity-early vulnerability debate this study explored neurobehavioral skills after EBI in children sustaining focal EBI during six different developmental periods, from gestation to late childhood. Comparisons between the total EBI sample and normative expectations supported our first prediction, that children with EBI are at increased risk of neurobehavioral impairment compared to healthy children. Significantly reduced skills were evident across all domains under study—language, visuo-spatial skills, memory, attention, executive skills, and processing speed. As predicted by our second hypothesis, outcomes differed significantly depending on age at insult, with preliminary evidence of some variation across domains, suggesting that different stages of brain development may be critical for the establishment of specific cognitive functions. Further, presence of seizures was associated with poorer performance across AL groups for language, visuo-spatial skills, memory, attention, and EF.

Do Children with EBI Differ from Population Expectations?

Children with EBI, as a group, performed significantly below population expectations for all domains studied, consistent with much previous research (Ewing-Cobbs et al., 1997; Jacobs et al., 2007). It is of interest to note that, despite these highly significant group differences, mean scores for the EBI group generally fell less than one standard deviation below expectations, representing performances hovering at the lower end of average. On 6/22 measures group means were greater than 1 *SD* from the mean, and for these measures, scores for >50% of the total sample fell below the normal range.

Does Age at Insult Influence Long-term Outcome?

Age at insult does affect long-term neurobehavioral outcome, although the relationship is complex. Initial examination of the data indicates that a linear relationship might explain age at insult and neurobehavioral outcome, at odds with animal model predictions (Kolb et al., 2004).

Such an interpretation appears to be supported for memory and processing speed. However, the remainder of our findings (language, visuo-spatial, attention and EF domains) suggest that there is a significant discrepancy in skills between children with insults before age 2 years and those with insults sustained at 7 years or older, with EBI sustained before age 2 resulting in poorest results. In contrast, children with lesions after age 7 recorded better outcomes. This pattern is consistent with Dennis's (1989) prediction that disruption to neurobehavioral processes during the early stages of skill development will have maximal impact on outcome, while later insults, when skills are better established, will be less harmful.

These results support an early vulnerability perspective, with children sustaining serious focal brain insults prior to and around the time of birth and up to age 2 being most at risk for neurobehavioral deficits. Despite the documented focal nature of brain pathology, there was little evidence that this group had increased potential for reorganization of function, or recruitment of healthy brain regions to support recovery of function. Rather, findings suggested that it was children with insults in the second decade who were more likely to escape relatively unscathed.

When interpreting study findings, a number of potential limitations should be considered. First, this study recruited children based on AL rather than the traditional ''diagnosis-based'' approach. In doing so, the resultant sample included children for whom mechanism of insult varied, increasing the risk that findings might reflect differences in brain pathology rather than AL. To minimize this risk, we restricted participation to children with MRI documented focal lesions and collected detailed information regarding the location, laterality, and size of lesion. We believe that this approach has provided important data to assist in understanding the impact of EBI from an empirical perspective. Second, we employed a categorical approach to quantifying developmental stage. While these categories reflect CNS growth spurts, they are necessarily inexact and may mask specific critical developmental periods. Third, due to current privacy laws restricting researchers from accessing information on nonparticipating children we are unable to compare participating and non-participating children, and so we cannot be certain that our sample is representative of either children within each age at insult group or of all children with significant brain insult. Fourth, the cross-sectional nature of the study limited conclusions as to whether deficits identified represented a permanent deficit or a delay in skill development. To extend these findings, research with larger samples and including longitudinal follow-up is required. Finally, use of age standardized, normative data (and in a few instances raw scores or stanines), rather than an appropriately constructed healthy comparison group is a study limitation. Of importance, our results are consistent with previous research documenting the detrimental effects of brain insult sustained early in life (Anderson et al., 1997, 2005; Anderson & Moore, 1995; Chilosi et al., 2005; Ewing-Cobbs et al., 1997; Jacobs et al., 2007; Pavlovic et al., 2006), and provide little evidence to corroborate early plasticity notions, which argue for good outcome from EBI. Use of normative data does have an advantage over use of small, unrepresentative control samples (e.g., with inflated IQ scores) commonly reported in this field, which increase the risk of inaccurate characterization of the study results (Ballantyne et al, 2008).

In conclusion, our study supports the ''early vulnerability model'' for EBI. Results showed that, in comparison to population expectations, children with EBI were at increased risk for functional impairment across all domains assessed. Further, age at insult had a significant impact on outcome. While our findings were not entirely consistent with a linear relationship between age at insult and neurobehavioral outcomes, children sustaining EBI before age 2 years recorded more global and severe deficits, while children with later EBI, sustained at or after age 7, performed closer to normal expectations. Our results support the need for better access to diagnostic and early intervention services for children sustaining EBI, who have often been considered to have a low risk of long-term impairments. They also emphasize the importance of co-morbid seizures in children with EBI for long term neurobehavioral outcome.

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