Predicting neurocognitive and behavioural outcome after early brain insult

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This article is commented on by Forsyth on page 297 of this issue.

AIMS The aims of the study were to investigate (1) the impact of age at brain insult on functional outcome and (2) the influence of insult and environmental factors on cognitive and behavioural outcomes.

METHOD The study was a cross-sectional, retrospective observational study, involving 138 children (76 males, 62 females; mean age 13y 1mo, SD 1y 11mo, range 10–16y) with magnetic resonance imaging (MRI) evidence of focal brain insult sustained from the first trimester of pregnancy to adolescence. Children underwent MRI and intellectual, executive, behavioural, and social evaluation. Outcome predictors were insult (lesion location, laterality, trimester of pregnancy to adolescence. Children underwent MRI and intellectual, executive, behavioural, and social evaluation. Outcome predictors were insult (lesion location, laterality, and extent, history of seizures, age at insult) and environmental (social risk and family function) factors.

RESULTS Focal insult before the age of 3 years was associated with poorer outcomes than insult after the age of 3 years across all domains. For IQ outcomes, insult characteristics and seizures were highly predictive. For executive and behavioural domains, family function and social risk had the greatest impact. Earlier age at insult predicted poorer social competence.

INTERPRETATION Focal brain insult before age 3 years has devastating consequences for children’s development. Findings suggest that greater emphasis should be placed on providing early intervention for children who sustain early focal brain insults.

Advances in the neurosciences demonstrate that brain plasticity is a beneficial characteristic that facilitates changes in the brain in response to environment and experience. The young healthy brain possesses a high level of neural ‘plasticity’, however, the relative advantage that such plasticity confers on the young damaged brain is unclear, and risk and resilience factors for neural plasticity are not yet well established. Recently, research has described the young brain as uniquely vulnerable in the context of diffuse brain insult (e.g. traumatic brain injury, cerebral infection), arguing that, after such events, there is limited healthy brain to support reorganization. Traditionally, outcomes after localized or focal brain insult (e.g. stroke, tumour) have been thought to be positive, with the assumption that the remaining healthy brain tissue can assume the functions of the disrupted regions.

A comprehensive review of the literature highlights the inconsistencies in current empirical evidence and the potential for a multitude of factors to contribute independently and synergistically to outcomes from early brain insult. In addition to established predictors – nature and severity of brain insult, medical complications, age at insult, time since insult, child pre-insult status, family function, and access to intervention – there are other important considerations. In particular, the nature of neural underpinnings of specific outcome domains (e.g. focal or distributed networks), the level of development of those domains at the time of insult, and the potential for brain insult to impair skills important for later knowledge acquisition have been identified as critical influences on outcome. To date, no study has successfully incorporated this range of factors into its methodology. As noted below, most studies address only one or two of these predictors, and those that have included multiple factors have reported limited explanatory power.

Both animal studies and clinical reports have demonstrated that, in children, the extent and location of insult do not fully explain the severity of residual impairments as they do in adults. Emerging evidence indicates that developmental and environmental factors make a significant contribution to outcome and may interact with the timing of brain insult to determine functional recovery. For
example, skills established pre-insult may be relatively spared, as their underlying neural substrates are mature, whereas those emerging at or after insult are at greatest risk of disruption.6,26,27 This notion predicts that brain insult in infancy or early childhood would disrupt cell characteristics and neural network connections as well as functional organization,6,27,28 having a global and dramatic impact on functional development. Later childhood brain insult, sustained when the brain is more mature, would have more localized effects leading to specific impairments. Previous work from our team supports this position, demonstrating that brain insult before age 3 years is uniquely associated with an elevated risk of functional impairment.29–32

We aimed to contribute to the ‘functional plasticity–vulnerability’ debate by investigating potential predictors of functional outcome (intellectual ability, executive function, behaviour, and social skills) after focal brain insult sustained from gestation to late childhood. Adult research demonstrates that injury factors, in particular localization of pathology, make a substantial contribution to outcome after brain insult, with age at insult and environmental factors less relevant. However, we expected, given the immaturity of the young brain and the potential for disruption of developing neural networks, that the extent rather than the site of brain insult would best predict neuropsychological outcome, and, furthermore, that age at insult and environmental factors would also be important factors.

METHOD

Participants

Children with a focal brain insult were identified through hospital and neuroradiology records, and consecutive referrals to neuroscience services at the Royal Children’s Hospital, Melbourne, Australia, between 2005 and 2007. Inclusion criteria were (1) the participant was aged between 10 and 16 years at the time of assessment; (2) there was magnetic resonance imaging (MRI) evidence of focal brain pathology; and (3) the insult was sustained >12 months before assessment. Exclusion criteria were (1) diffuse pathology was identified on the MRI; (2) the participant had a history of closed head injury, radiotherapy, chemotherapy, or anoxia; and (3) the family was non-English speaking. Approaches were made to 215 families, with 51 declining to participate (77% participation) owing to time and/or distance (n=21), or lack of interest (n=30). A further 26 children were excluded from the study as their MRI was unavailable, resulting in a total of 138 children in the final sample. This total constitutes a subset of a larger sample that has been reported on previously.29

Based on current literature,21,26,33,34 six ‘age at insult’ groups were initially derived: (1) early prenatal, brain insult occurred in first to second trimester (n=33); (2) perinatal, brain insult occurred in third trimester to 1 month post birth (n=25); (3) infancy, brain insult occurred from 2 months to 2 years post birth (n=19); (4) preschool, brain insult occurred from 3 to 6 years (n=17); (5) middle childhood, brain insult occurred from 7 to 9 years (n=28); and (6) late childhood, brain insult occurred after age 10 (n=16). However, after preliminary statistical analyses, detailed below, the total group was divided into children sustaining insult before the age of 3 years (n=77) and those sustaining insults at 3 years of age or older (n=61). Tables I and II provide demographic and insult information for these two groups.

What this paper adds

- The vulnerability of the young brain (age <3y) to focal insult is highlighted by poor outcomes at a later age, across a wide range of functional domains.
- Insult factors contribute to cognition outcomes, while environment factors contribute to social and behavioural outcomes.
- The presence of seizures is a strong predictor of poorer cognitive outcome.

Materials

Predictors of outcomes: insult factors

MRI was conducted on a 1.5-tesla scanner, as part of routine clinical practice, before recruitment, or at the same time as neuropsychological evaluation. Axial and coronal slices were imaged.

Images were reviewed using a coding protocol modified from Leventer et al.,33 which rated extent of brain pathology from 0 to 10, with a higher score reflecting more brain regions involved. The protocol described lesion location (lobes involved, depth of lesion, involvement of cortical/ subcortical regions, ventricles), laterality (left hemisphere, right hemisphere, or bilateral lesion), and volume of brain affected (number of regions) as we have previously described.29 Images were reviewed by a paediatric neuroradiologist and a neuropsychologist, blind to age at insult. Ten scans were coded independently, with an interrater reliability of 0.97. The mechanism of focal brain insult was classified as developmental (cortical dysplasia, focal malformations, cyst), ischaemic (stroke), neoplastic (tumour), traumatic (penetrating injury, focal contusion), or infective (abscess). For further details on coding methods, refer to our previous publication.29

The timing of the brain insult was determined via MRI findings, neuropathology results (where available), and medical record review (clinical history, medical investigations). Where timing was imprecise, consensus was reached through discussion between the neurologist and neuroradiologist. Ten cases were double-rated, with 100% consistency.

Background information

Medical, developmental, and seizure histories were collected during parent interviews and were confirmed via medical record review.

Predictors of outcomes: environmental factors

Socio-economic status was determined using the Social Risk Index35 based on family structure, education of the primary income earner, language at home, and maternal age at birth of the child. Higher scores indicate greater social risk.

Family function was measured using the General Family Functioning scale from the Family Assessment Device36...
completed by the parents. Lower scores indicate better family functioning.

Neuropsychological outcome measures
The four-subtest version of the Wechsler Abbreviated Scale of Intelligence was administered to measure IQ. The scores derived from this were Verbal, Performance, and Full-scale IQ (mean 100, SD 15).

The Behavior Rating Inventory of Executive Function (parent version) provided an index of the child’s executive function abilities. The Behavior Rating Inventory of Executive Function Global Executive Composite score was calculated (mean 50, SD 10), where a higher score represents greater impairment.

Using the Strengths and Difficulties Questionnaire, parents rated their child’s behaviour on 25 items using a Likert scale. The total difficulties score from this questionnaire was used in analyses.

Social skills were measured by the Walker–McConnell Scale of Social Competence and School Adjustment: Adolescent Version, which was completed by the parents. It consists of 53 items which combine to provide a total score (mean 100, SD 15), with lower scores indicating poorer social skills.

Procedure
This study was approved by the human research ethics committee of the Royal Children’s Hospital, Melbourne. Informed consent was obtained from parents or guardians at the time of assessment. Trained examiners completed assessment protocols and were blind to age at insult. Assessments lasted 2 hours, with a fixed test order.

Statistical analysis
Missing scores were recoded to 2SD below the test mean for children unable to complete measures owing to low

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**Table I: Demographic and brain insult characteristics of the sample**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Age at brain insult &lt;3y (mean, SD)</th>
<th>Age at brain insult ≥3y (mean, SD)</th>
<th>Differences in means (95% confidence interval)</th>
<th>p value for group comparison</th>
</tr>
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<tbody>
<tr>
<td><strong>IQ</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>WASI: Full-scale IQ</td>
<td>81.7 (18.1)</td>
<td>95.4 (19.5)</td>
<td>−13.7 (−20.1 to −7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WASI: Verbal IQ</td>
<td>79.4 (16.8)</td>
<td>93.3 (18.2)</td>
<td>−13.9 (−19.8 to −7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WASI: Performance IQ</td>
<td>85.0 (18.0)</td>
<td>99.7 (19.8)</td>
<td>−14.7 (−21.2 to −8.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
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<tr>
<td>BRIEF: Global Executive Composite</td>
<td>64.6 (14.5)</td>
<td>58.9 (13.7)</td>
<td>5.7 (0.8 to 10.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Behaviour</td>
<td></td>
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<tr>
<td>SDQ: total difficulties score</td>
<td>15.0 (7.4)</td>
<td>12.3 (6.8)</td>
<td>2.7 (0.2 to 5.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Social Skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS: total score</td>
<td>97.8 (14.8)</td>
<td>100.2 (15.7)</td>
<td>−5.7 (−11.3, −0.1)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

For Behavior Rating Inventory of Executive Function (BRIEF) and Strengths and Difficulties Questionnaire (SDQ) results, higher scores indicate poorer outcomes. For all other variables lower scores denote lower outcomes. WASI, Wechsler Abbreviated Scale of Intelligence; WMS, William-McConnell Scale of Social Competence and School Adjustment.
functioning. Data missing for other reasons (e.g. failure to return questionnaire) were excluded.

Analyses were conducted using Stata, version 11.0 (Stata Corp, College Station, TX, USA). Initially age at insult was categorized into six groups (described above). However, preliminary results exploring the four outcomes of interest consistently found a dichotomous effect of age at insult (<3y and ≥3y), as can be seen in Figure 1; hence analysis was collapsed into two age at insult groups: early brain insult at less than 3 years of age (n=77) and late brain insult at 3 years of age or older (n=61). Multivariable models were therefore presented with age at insult as a dichotomous variable.

Early brain insult and late brain insult groups were compared on characteristics identified as potential predictors of outcome using t-tests or χ² tests. The characteristics were divided into brain insult factors (nature, volume, and laterality of brain lesion, frontal lobe involvement, and history of seizures (yes/no) and environmental factors (social risk, family function). Next, linear regression models were used to assess the predictive value of these characteristics to outcome. Initially, separate univariable models were used to explore the effect of each predictor on each outcome domain fitted separately for children with early brain insult and children with late brain insult. Factors identified as important predictors in either group were then entered into a single multivariable model, one for each outcome variable, along with any other factors that became significant in the combined model, to assess independent contributions.

Interactions were employed to explore whether the effect of each factor varied across the age at insult groups. Lesion volume, nature, and laterality were highly correlated (χ², p<0.001), making it difficult to evaluate the independent contribution of these variables simultaneously. Results are presented as regression estimates (REs) and their 95% confidence intervals (CIs).

RESULTS
Sample demographics
One hundred and thirty-eight participants were included in the study (76 males, 62 females; mean age 13y 1mo, SD 1y 11mo, range 10–16y). Initial analyses indicated no significant differences across the six age-at-insult groups for demographic variables, with the expected exceptions of age at insult and time since insult. For medical variables, younger age at insult was associated with the presence of seizures and developmental delay. Exploration of differences between early brain insult and late brain insult identified a similar pattern, with no significant group differences for sex, social risk, family function, or frontal lobe involvement (Table I). In the early brain insult group, seizures were more common (p=0.002), and it was more likely that the brain insult mechanism was developmental and less likely that the mechanism was traumatic (p<0.001). On average, the late brain insult group had smaller lesions than the early brain insult group (early brain insult vs late brain insult: 3.9g vs 2.36g; p=0.04), although results indicated, as expected for focal lesions, that overall lesions affected fewer brain regions.

Figure 1: Mean outcomes and confidence intervals across functional domains for six age-at-insult groups. WASI, Wechsler Abbreviated Scale of Intelligence; FSIQ, Full-scale IQ; BRIEF, Behavior Rating Inventory of Executive Function; WMS, Walker–McConnell Scale of Social Competence and School Adjustment: Adolescent Version; SDQ, Strengths and Difficulties Questionnaire.
Predictors of outcome
The early brain insult group performed more poorly than the late brain insult group across outcome domains (Table III).

Intellectual ability
Wechsler abbreviated scale of intelligence Full-scale IQ. Age at insult had a dichotomous effect on outcome, with late brain insult predicting higher Full-scale IQ (RE=13.69; 95% CI 7.31–20.08; p = 0.001). Lesion volume, laterality, and seizure history were also predictive of Full-scale IQ in univariable analysis, with larger lesion volume (RE=–3.17; 95% CI –4.44 to –1.90; p < 0.001), right hemisphere (RE=2.70; 95% CI –5.98 to 11.39; p = 0.001) or bilateral pathology (RE=–10.95; 95% CI –18.72 to –3.18; p = 0.001), and history of seizures (RE=–11.99; 95% CI –18.74 to –5.51; p < 0.001) all predictive of lower Full-scale IQ. From the multivariable model, age at insult, lesion volume, and seizure history were independent predictors, with the effect of laterality being explained by the other factors in the model. Environmental factors did not contribute significantly to Full-scale IQ.

Wechsler abbreviated scale of intelligence Verbal IQ. The results for Verbal IQ were similar to those for Full-scale IQ, with age at insult having a dichotomous effect on Verbal IQ and late brain insult associated with higher Verbal IQ in both univariable (RE=13.85; 95% CI 7.86–19.84; p < 0.001) and multivariable models. Additionally, in the univariable model, larger lesion volume (RE=–2.39; 95% CI –3.62 to –1.15; p < 0.001), right hemisphere (RE=2.68; 95% CI –5.64 to 11.01; p = 0.01) or bilateral lesion pathology (RE=–7.9; 95% CI –15.46 to –0.52; p = 0.01), and history of seizures (RE=–13.10; 95% CI –19.11 to –7.08; p < 0.001) were predictive of lower Verbal IQ. In the multivariable model, the impact of lesion volume disappeared owing to a strong correlation with lesion laterality. In this model, age at lesion, lesion laterality, and a history of seizure were all independently predictive of verbal abilities.

WMS: total score

Predicting Outcome from Early Brain Insult

Executive functions
Behavior rating inventory of executive function global executive composite score. When age at insult was treated as a dichotomous variable, as described previously, there was evidence of greater executive difficulties for the early brain insult group in both univariable (RE=–6.4; 95% CI –10.96 to –2.01; p = 0.005) and multivariable analyses. Larger lesions (RE=1.44; 95% CI 0.51–2.37; p = 0.003), seizure history (RE=5.47; 95% CI –0.93 to 10.00; p = 0.02), and greater family dysfunction (RE=12.14; 95% CI 6.87–17.40; p < 0.001) were important univariable predictors, with some suggestion that frontal lobe involvement may also be predictive (RE=4.33; 95% CI –0.21 to 8.87; p = 0.06). In the multivariable model, only younger age at insult and poorer family function remained significant contributors.
**Child behaviour and social skills**

*Strengths and difficulties questionnaire total difficulties score.* Late brain insult was associated with fewer behavioural problems in both univariable (RE = −2.70; 95% CI = −5.16 to −0.24; \( p = 0.03 \)) and multivariable models. Poorer family function and higher social risk were also predictive of behaviour difficulties in both univariable (Family Assessment Device: RE = 4.79; 95% CI = 1.84–7.75; \( p = 0.002 \); Social Risk Index: RE = 0.83; CI = −0.24 to 1.42, \( p = 0.006 \)) and multivariable models.

*Walker–McConnell scale of social competence and school adjustment total score.* For children’s social skills, the only significant predictor was age at insult, with early brain insult predictive of poorer social function in both univariable (RE = 5.68, CI = 0.09–11.72 points; \( p = 0.05 \)) and multivariable models, with no definitive evidence for a contribution from other lesion or environmental factors.

**DISCUSSION**

This study aimed to contribute to the ‘functional plasticity–vulnerability’ debate by exploring developmental, insult, and environmental predictors of outcome from focal brain insult. Children sustaining focal brain insult from gestation to late childhood were assessed during late childhood/adolescence, when brain and cognitive maturational processes are considered to be largely complete. Age at insult groups were derived based on current evidence,26 to correspond with periods of brain maturation and critical periods of development. Interestingly, preliminary findings identified very similar outcomes for all children with insults sustained before age 3 years (early brain insult groups) and a similar homogeneity of results for those with insults after age 3 years (late brain insult groups).

Consequently initial groups were collapsed into two groups – insult before age the age of 3 years and insult at 3 years and older. Neuroimaging results were coded to provide details for lesion location, laterality, and volume, and the presence of frontal lobe involvement and the child’s history of seizure was documented. Standard data regarding family function and social risk were also collected. Analyses demonstrated that age at insult was the strongest and most consistent predictor of outcome, with children who sustained insult before age 3 years recording poorer results across all domains. Insult-related variables and seizure history contributed to cognitive outcome, and social and family factors were more closely linked to behaviour and social skills.

These results provide support for an early vulnerability perspective, at least with respect to functional outcomes requiring involvement of complex neural networks known to develop in the early stages of childhood. For cognitive domains, children with early brain insult recorded mean scores more than 1SD below expectations on all measures, compared with results within the average range for those with late brain insult. Behavioural and social skills were also significantly lower in the early brain insult group. These findings are consistent with a growing body of research which emphasizes the elevated risk associated with early brain insult.14,15,18 Of note, most previous research has focused on children with diffuse brain insult. This study extends these findings to focal brain insult, suggesting that age at insult is important regardless of whether brain pathology is focal or diffuse. The brain is in a state of rapid development prenatally and in the first few years of life. Processes such as synaptogenesis, dendritic arborization, apoptosis, and myelination, critical for the establishment of healthy brain connectivity and functional networks, are all highly active.12,42 Brain insult during this period may derail future maturation, potentially resulting in abnormal connectivity and/or disruption to the establishment of mature functional networks.

Findings also highlight that different factors are predictive of outcomes in different domains. Lesion-related factors (volume, laterality, and history of seizure), were associated with cognitive outcomes, including verbal and non-verbal skills and executive functions. Larger lesions, right-sided and bilateral lesions, and positive seizure history all predicted poorer outcomes. Although not a universal finding, similar results have been reported in other studies.7,14,43–46 In contrast to adult studies, but consistent with recent child-based work, lesion location (in this case, frontal involvement) was only relevant for executive functions, and then only marginally so.33,47,48 These results might be taken to support the early views of Lenneberg1 and others, that the young brain is a blank slate, with no preordained functional organization. Alternatively, and as noted above, we would suggest that larger lesion volumes lead to more widespread disruption of diffuse neural networks beyond the immediate perilesional area underpinning many cognitive skills, resulting in disconnections within networks and a picture of global impairment.

There was little evidence that environmental factors contributed to cognitive outcomes, with the exception of executive skills, which were poorer in children from more dysfunctional families. The reason for this link is not clear, but similar findings have been reported by other groups49 and may relate to literature on early deprivation,50 in which there is evidence of alterations to brain architecture combined with high-level cognitive difficulties in children whose early development has been disrupted by drastically impoverished environments.51

For behavioural outcomes, there was little evidence of the influence of insult factors, but social risk and family function did play a role. Children from dysfunctional families with high social risk were rated as having more behavioural problems. With the exception of age at insult, none of the predictors employed was able to determine factors underpinning social impairments.

Several study limitations need to be considered. In contrast to previous literature, which employs a diagnosis-specific approach, our sample necessarily included children with a range of insult mechanisms, which might be argued to confound results, and should be considered when interpreting study findings. Of note, to study brain insult onset
using a single diagnosis is not practical as many childhood focal brain insults are confined to specific developmental periods (e.g., dysplasia occurs prenatally). In addition, use of specific diagnostic groups may confer the impression of group homogeneity, despite wide variations in extent and location of insult and subsequent complications. For example, research often considers traumatic brain injury as a single entity, while, in fact, pathology patterns may vary dramatically. By confining our sample to those with focal insults and carefully documenting and quantifying the anatomical features of a spectrum of brain pathologies, we were able to explore potential confounding factors (lesion volume, laterality, location), which are present but not acknowledged in diagnosis-specific work. However, our focus was on lesion location and volume, and future work, using more sophisticated tractography techniques will be able to examine disruptions to neural networks more closely, which are likely to be key to long-term outcome.

Using age at insult as a categorical variable may decrease study sensitivity and mask specific critical developmental periods. Unfortunately, it is not possible to obtain accurate age at insult indices for children with pre- and perinatal insults and carefully documenting and quantifying the developmental stage, and an index of level of acquisition of skills and knowledge. Thus, interpretation of age-related effects needs to acknowledge the complexity of these processes and their potential interactions.

CONCLUSIONS

The results from this study lend support to the ‘early vulnerability model’ of childhood brain insult. Compared with children sustaining brain insult after age 3 years, those sustaining insult before age 3 years demonstrated increased risk of impairment across verbal and non-verbal abilities, executive function, behaviour, and social skills, confirming the significance of age at insult for functional outcomes after focal brain insult in children. Larger lesion volume, right hemisphere and bilateral lesions, and positive seizure history contributed to cognitive outcomes, while social risk and family function were linked with psychosocial outcomes. These findings highlight the complex interplay between developmental, insult, and environmental factors for determining outcome after early focal brain insult. From a clinical perspective these findings provide guidance to assist in targeting children at high risk of poor outcome for more intense and long-term follow-up.

ACKNOWLEDGEMENTS

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