Reply: Early plasticity versus early vulnerability: the problem of heterogeneous lesion mechanism

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Sir, Thank you for the opportunity to comment on this submission. Lidzba and colleagues identify a number of concerns with respect to our paper recently published in Brain (Lidzba et al., 2009). In particular, they question the validity and interpretation of our results, arguing that two factors—presence of epilepsy and bilaterality of lesions—have not been sufficiently considered in the study design.

We agree with the authors regarding the importance of both of these factors in the outcome for children with brain disease or insult. As Lidzba et al. note, there is considerable literature to point to the impact of each of these factors. However, we would argue that, in fact, each of these factors has been carefully considered and incorporated into the design of our study and the interpretation of our findings.

First, with respect to epilepsy, information on seizures was collected and is reported in Table 1 of our paper (Anderson et al., 2009), as is information on developmental delay and academic difficulties. As discussed in our paper, we conceptualized seizures as a secondary consequence of brain insult in the same manner as a hemiparesis or a developmental delay. We believe that, given our study design, which is based on timing of insult and brain pathology (based on MRI), this is a defensible approach. On the basis of this approach, we can say that brain pathology sustained before the age of 2 years is associated with the poorest outcome, with these children being at higher risk of a number of consequences, including seizures, developmental delay, cognitive impairment and educational difficulties.

Second is the issue of bilaterality of lesions. While some past literature has identified bilateral lesions as being linked to particularly poor outcomes following early brain insult, this finding has not been universal (Jacobs and Anderson, 2002; Anderson et al., 2005). There are a number of possible explanations for these inconsistencies: (i) many studies identifying poor outcomes following bilateral lesions were published over a decade ago, as noted by Lidzba et al., and thus did not have access to the sophisticated imaging tools that are currently available; (ii) few of these studies incorporate quantitative image analysis in their data; and (iii) most reports have not confined their samples to children with focal lesions, with the result that bilateral lesions often refer to larger lesions than unilateral lesions. In our study, we were able to employ state-of-the-art imaging, quantitative analysis of lesions and only recruited children who had sustained focal pathology. Of note, using similar methods in a different sample of children with focal pre-frontal lesions (Jacobs and Anderson, 2002; Anderson et al., 2005), we identified similar patterns to those described in the study under discussion when comparing unilateral and bilateral focal lesions. Given these factors, we suggest that previous results of poorer outcome associated with bilateral lesions may reflect inclusion of children with larger lesions or generalized pathology, which leave limited brain regions undamaged and
available for recruitment. As we recruited only children with focal pathologies, with considerable healthy brain remaining, such recruitment might be argued to be more likely, leading to better outcomes.

In conclusion, we agree with the importance of factors such as seizures and lesion size in influencing outcome from early brain insult. We also argue that age at insult is a factor that, while difficult to study, needs to be taken into consideration. It is likely that early brain insult will disrupt normal developmental processes in an ongoing way, both at the level of brain and behaviour. We believe that our study requires replication and extension. However, it also provides a challenge for the field to consider more innovative approaches to solving the mystery of seemingly inexplicable variability in outcome from early brain insult.

References