Paediatric epilepsy surgery: making the best of a tough situation

This scientific commentary refers to 'Temporal lobe surgery in childhood and neuroanatomical predictors of long-term declarative memory outcome' by Skirrow *et al.* (10.1093/brain/awu313).

Interest in resective surgery as a therapeutic option for uncontrolled paediatric epilepsy is increasing (Cross *et al.*, 2006). Seizures that are left unchecked can have deleterious and largely irreversible effects on cognitive development, particularly if they occur during critical periods of neurodevelopment in the very young. However, surgery itself can lead to cognitive deficits if it entails resection of an area that had been supporting key functions. In adults, there is a large literature on the neuropsychological consequences of surgery and on the careful planning and extensive testing that is performed to guide the resection or sometimes the decision not to perform surgery if removal of eloquent cortex would result in unacceptable deficits (Langfitt and Wiebe, 2008). In this issue of *Brain*, Skirrow *et al.* (2014) expand the corresponding literature in paediatric populations by presenting an elegant analysis of the impact of surgery on memory functions in patients who underwent temporal lobe resections for childhood-onset epilepsy at Great Ormond Street Hospital (GOSH).

The GOSH study is remarkable for several reasons: the sophistication of its analysis of neuropsychological outcomes, the duration of time over which the patients were followed (on average, 9 years post-surgery), and the gains in function that were detected years after surgery. In striking contrast to adults in whom memory is often negatively affected by surgery—in one large series, a third of adult patients who had temporal lobectomies experienced significant ($\geqslant$1 standard deviation) declines in verbal memory (Langfitt *et al.*, 2007)—no postoperative memory deficits were detected in the GOSH series. Instead, and as previously reported, full-scale IQ improved in the paediatric patients by ~10 points, although this took several years to occur (Skirrow *et al.*, 2011). Memory improved as well, but the patterns of improvement were complex. Most strikingly, improvements were seen in memory functions usually subserved by the non-resected hemisphere: verbal memory gains following right resections and visual memory following left. While at first glance counterintuitive, this is consistent with evidence that there can be substantial reorganization and re-lateralization of function in the developing brain (Tivarus *et al.*, 2012). The results of Skirrow *et al.* suggest that the healthy temporal lobe had been recruited to help maintain the functions of the seizure-occupied lobe, and that after surgery it was 'released' and allowed to return to its preferred tasks as function re-established itself in the operated hemisphere. Furthermore, larger memory gains were seen in association with greater residual hippocampal volumes and smaller resection of the temporal pole, depending on the type of memory tested. In children, recent efforts have focused so intently on stopping seizures before they do irreversible damage and on allowing the time window for developmental plasticity to be as large as possible that rather less attention has been paid to the extent of surgery and how it might interact with developmental plasticity. The findings of Skirrow *et al.* are novel and have important implications for planning resections so as to spare cognitive function in younger patients.

Perhaps equally important, earlier surgery and shorter duration of epilepsy were also associated with greater post-surgical gains. This is consistent with other studies of early life epilepsies that have focused upon more global measures of development and have demonstrated that the earlier surgery is performed, the better the overall post-surgical cognitive-developmental outcomes (Freitag and Tuxhorn, 2005).

Several further points raised by the Skirrow *et al.* study need to be considered. The average delay to surgery in the GOSH series was ~10 years (average age at onset was ~3 years and at surgery ~13 years). By the time the children were evaluated for surgery, overall cognition was substantially impaired with presurgical IQ in the low 80s, a good standard deviation below population norms. Almost 20% of the children had abnormal language lateralization indices. Whether these deficits and abnormalities were present for reasons other than seizures and treatment is unknown; however, cognition has been shown to decline over the course of pharmacoresistant epilepsy both in children (Berg *et al.*, 2004) and adults (Hermann *et al.*, 2006). This suggests that damage was occurring in the years before surgery.

This 10-year delay is probably typical of the period in which these surgeries were performed (1992–2002) and typical of what occurs in many places without good access to a surgical centre. Surgery is generally viewed as a last resort therapy when all else has failed; in fact, the delay may be as much, if not more, due to attitudes about surgery than it is about access to surgical therapies. However, delays have consequences. How much does cognition deteriorate during the average 10-year delay? What if surgery were performed early enough for cognitive functions not to have had chance to reorganize/re-lateralize? Would that mean better cognitive outcomes? Better social outcomes? Could it have an impact on seizure outcomes post-surgery? Notably, studies in children and adults who underwent resective frontal lobe procedures suggest that a prolonged delay ($>$5 years) to surgery is associated with relapse many years

later after patients have been seizure-free for extended periods of time (Simasathien *et al.*, 2013).

The complexity of the findings, as well as the implications for planning resection in younger brains, are considerable. While all brains are capable of plasticity to some degree, we generally think of the greatest potential for plasticity as being in the first few years of life, with plasticity dropping off steeply in adolescence and early adulthood. Given that the average age at surgery was 13, this raises questions about whether the findings might have implications for older surgical patients, many of whom also have epilepsy of early childhood onset.

Perhaps most importantly, the findings of Skirrow and colleagues highlight the urgent need for earlier intervention and the importance of considering developmental plasticity and reorganization as part of efforts to spare and maximize post-surgical cognitive function.

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A mouse model of autoimmune encephalitis

This scientific commentary refers to 'Human *N*-methyl D-aspartate receptor antibodies alter memory and behaviour in mice' by Planagumà *et al.* (doi: 10.1093/brain/awu310).

Anti-*N*-methyl D-aspartate receptor (NMDAR) encephalitis is a severe autoimmune neuropsychiatric disorder accompanied by prominent memory and behavioural deficits (Titulaer *et al.*, 2013). The disorder is characterized by circulating anti-NMDAR autoantibodies (NMDAR-Abs), which cause a selective and reversible internalization of cell-surface NMDARs in cultured neurons (Mikasova *et al.*, 2012). This suggests an antibody-mediated pathogenesis, as does the frequent response of patients to immunotherapy (Titulaer *et al.*, 2013), but to date there has been no animal model available to test this. In the current issue of *Brain*, Josep Dalmau and colleagues present robust evidence that continuous ventricular infusion of NMDAR-Abs induces memory and behavioural deficits in mice (Planagumà *et al.*, 2014).

Experiments revealed that infusion of CSF from patients with anti-NMDAR encephalitis, but not from controls, causes mice to develop progressive memory impairments (Fig. 1) as well as anhedonic and depressive-like behaviours, while leaving their performance on other behavioural and locomotor tasks unchanged. Immunoblot and confocal microscopy revealed a progressive decrease in total hippocampal NMDAR protein, as well as total and synaptic receptor clustering, further implicating the NMDAR in the observed symptoms.

NMDARs are heterotetrameric calcium-permeable ion channels that are essential for brain plasticity and for the long-term synaptic modifications thought to underlie cognitive functions. NMDARs are composed of two constitutive NR1 subunits and two variable subunits from among GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B (Paoletti *et al.*, 2013). Animal models based on genetically modified NMDARs have already confirmed the critical role of NMDARs in memory and learning (Cui *et al.*, 2004), but with their mouse model, Planagumà *et al.* not only reveal a direct pathogenicity of NMDAR-Abs, but also validate a method for investigating mechanisms of synaptic dysfunction. A number of other neuropsychiatric diseases featuring altered NMDAR-mediated synaptic plasticity will benefit from this innovative approach of using antibodies from patients with autoimmune synaptopathies.

The demonstration that NMDAR-Abs affect learning and memory