Back to the future: rehabilitation of children after brain injury

Rob J Forsyth

Arch Dis Child 2010 95: 554-559
doi: 10.1136/adc.2009.161083

Updated information and services can be found at:
http://adc.bmj.com/content/95/7/554.full.html

These include:

References
This article cites 58 articles, 18 of which can be accessed free at:
http://adc.bmj.com/content/95/7/554.full.html#ref-list-1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:
http://adc.bmj.com/cgi/reprintform

To subscribe to Archives of Disease in Childhood go to:
http://adc.bmj.com/subscriptions
Back to the future: rehabilitation of children after brain injury

Rob J Forsyth

ABSTRACT

A mistaken optimism persists that outcomes for childhood acquired brain injury (ABI) are in general superior to those for similar injuries in adults, a misconception based on naive concepts of greater ‘plasticity’ in the immature brain. The challenges of rehabilitation after ABI, of bringing children ‘back’ to face the ‘future’ of completing childhood development with an injured brain, are reviewed in the context of the science of brain recovery from injury. Unrealistic expectations of recovery may cause subsequent events to be perceived as academic or employment ‘failure’. The challenges of supporting children and families after ABI are reviewed.

In one of his more cynical moments Voltaire claimed the role of the doctor to be ‘entertaining the patient while nature takes its course’. While most branches of medicine have long since thrown off such slurs, there may be a lurking doubt in many minds that in relation to rehabilitation medicine he may not have been too far off the mark. In this review I hope to lay such doubts to rest and illustrate that neurorehabilitation is a medical specialty whose time has come, propelled by progress in understanding the neuroscience of injury and recovery.

FAILURE OF THE NEUROPROTECTION PARADIGM

We begin with a salutary recent tale of misplaced optimism. The 1990s were designated ‘The decade of the brain’ by George Bush Sr in recognition of the huge strides that were occurring in understanding the pathophysiology of brain injury. For the first time it was recognised that injury led not only to direct damage but also to secondary injury due to a cascade of downstream processes. These events occurring in the hours and days after stroke, traumatic brain injury (TBI) or asphyxia, and their obvious potential as therapeutic targets aroused great interest. Particular attention was paid to the extracellular accumulation of neurotransmitters, especially glutamate, due to diminished reuptake (in turn the result of partial energy failure and reduced ATP supply).1 These excessive levels of extracellular glutamate, an excitatory neurotransmitter, triggered a cascade of events leading to apoptotic cell death, a process termed excitotoxicity.2 Sadly, however, with some notable exceptions,3 4 the impact of neuroprotective interventions in TBI has been extremely disappointing5 and the principles of neurointensive care of the injured brain in the paediatric intensive care unit (PICU) of the early 21st century are depressingly similar to those of the 1980s.6 7

Why did these agents that were so effective in animal and in vitro models fail to deliver on their clinical promise? The answer is undoubtedly multifactorial: we certainly need to pay more attention to the heterogeneity of injury mechanisms (asphyxia, inflammation, trauma)8 that combine in these situations and their relative importance in individual cases.9 But it is also important to recall that excitatory neurotransmission has important adaptive functions and is not primarily there just to cause havoc at times of injury: it is central to learning.10 Persistent changes in the brain in response to external stimuli – changes that outlast the stimulus and provide a record, an engram, of its occurrence – are the basis of memory and learning. Hebb long ago captured the central neurobiological hypothesis of learning: coincident activity in adjacent neurons tends to strengthen mutual synaptic connectivity: ‘cells that fire together, wire together’.11 At a molecular level excitatory neurotransmission is thought to be central to ‘coincidence detection’.10 It is also thought that the biology of recovery after injury (which is essentially a process of re-learning) is the same as that of developmental learning.11 Drugs blocking excitotoxicity if given too late after injury may be starting to interfere with the re-learning recovery process.

THE NEUROBIOLOGY OF RECOVERY

It is clear that we require an understanding of the neurobiology of recovery after injury at least as sophisticated as that of excitotoxic injury.12 Watching a child progress from coma through low-level states to more complete recovery is unceasingly fascinating. The process tends to follow a fairly characteristic sequence13 and there is a temptation to envisage an intrinsic programme of functional restoration akin to a computer ‘booting up’, but there is no evidence for this. Three processes underlie recovery: the healing of reversibly injured tissue, restoration and compensation.14 The first is undoubtedly very important but arguably already fully exploited. The second and third comprise the twin aims of rehabilitative therapy. The optimal balance between a focus on restoration (eg, continued physiotherapy efforts to re-establish walking) and compensation (eg, providing a wheelchair) in an individual case is a constant practical challenge of great importance. In other contexts it is assisted by longitudinal prognostic frameworks such as the Gross Motor Function Classification System.15 Further consideration in the context of acquired brain injury (ABI) is, however, beyond the scope of this review.

Early after injury the neurochemical, neurohumoral and neurogenetic milieu of the recovering
central nervous system (CNS) is comparable to that of the immature brain. The CNS is plastic, or malleable, but plasticity alone is not enough to ensure recovery. Plasticity can be maladaptive, leading for example to the establishment of post-traumatic epilepsy. Adaptive plasticity requires ‘shaping’, and the driving force behind recovery is attempted action (figure 1).

The existence of cortical maps indicating representations of body areas in sensory and motor cortex is readily revealed by brain stimulation and functional MRI (fMRI) techniques. Our ideas of the permanence of these maps has been revolutionised by basic neuroscience insights of the last decade. Hubel and Wiesel’s seminal work on the establishment of binocular vision in the 1960s16 and the ‘amblyopia paradigm’ emphasised the critical period concept: windows of opportunity for change confined to the immature nervous system. In recent years, however, the view that these cortical mappings were ‘hard-wired’ once these windows had closed have been dramatically revised.17–19 Many cortical representations are the results of dynamic equilibria between competing neuronal projections that continuously update to reflect input and usage. If a cortical area loses a previous input, alternative competitor populations begin to invade. These changes are mediated by processes operating on at least three different timescales: loss of inhibition of pre-existing, suppressed projections (which can occur within minutes); processes in the dendritic tree of changes in synaptic connectivity driven by Hebbian learning (see above) occurring over hours to days; and axonal processes of sprouting and reinnervation occurring over weeks to months.14

WHAT WE KNOW ABOUT WHAT WORKS

There is a wealth of animal data about recovery from various forms of ABI, but translating this to clinical practice is very challenging and raises many questions that reflect the complexities of real world rehabilitation. It is abundantly clear from rodent work, for example, that environmental richness has a profound effect on recovery although this is more straightforward in the converse: environmental deprivation clearly worsens recovery (with a clear relevance to the Romanian orphanage literature20).

There is a complex interaction between age at injury, time since injury and development. Ultimately, these arise from a term first coined by Taub et al.23 24 The term is best understood in the context of (adult) hemiplegic stroke, where it is often used to refer to a process at a behavioural level: the consequences of a person’s acquiescent acceptance of the reduced function of the impaired arm.25 Given the dynamic nature of cortical maps (above), however, it is evident that this acquiescence will have direct consequences at a neuroanatomical level too: ‘use it or lose it’. The logical response to learnt non-use is forced use of the impaired arm (sometimes referred to as constraint therapy): the compelling of attempted action with the impaired arm by impeding function in the good arm with a large mitt, sling or even temporary plaster cast.26 The effects of forced use are again readily demonstrable in animal models, although it is clear that it is a powerful, unpredictable process. Extreme forced use, where a hemiplegic rat’s good side is totally immobilised in plaster for prolonged periods, appears capable of worsening outcome: apparently the massive demand on the paretic side for action causes an excitotoxic ‘burning out’ of penumbral tissue extending the injury.27 28 While this degree of extreme forced use is not clinically relevant, and the benefits of constraint therapy have been demonstrated at least in the short term,29 controversy about the emotional impact, particularly for children, of being repeatedly ‘made to do the one thing I can’t do’ persists.30

Another important and complex issue is learnt non-use, a term that finds from adult clinical research can be directly translated to children. Figure 2 shows schematically the importance of considering time of injury relative to developmental milestones.

ADULT HUMANS, OUR BEST ANIMAL MODEL

It should be evident that there are very real limits to the extent that findings from adult clinical research can be directly translated to children. Figure 2 shows schematically the potential for pharmacological manipulation of plasticity (what might be termed neuroreconstructive therapy in distinction to neuroprotective treatments) is of understandable interest. A number of drugs have been shown to modulate recovery after acquired injury in animal models.31–34 Although some (particularly growth factors) would be very difficult to deliver across the blood–brain barrier, many are drugs already in clinical use for other indications. Stimulant drugs (dexamfetamine, methylphenidate) have received particular attention.31 35–38 They have been shown to improve motor function in animal models of focal brain injury, but it is important to understand that the drug alone is ineffective. This is an effect mediated via rehabilitation. The drug increases ‘learning efficiency’, allowing greater gains from rehabilitation.36 38 39 Positive effects on use-dependent plasticity have also been shown in healthy human volunteers.40 41 These actions are distinct from ‘attention deficit’ effects42 and are more than a matter of helping someone concentrate during a rehabilitation session. The addictive potential of these drugs highlights their intrinsic neuroplastic actions. Animal data highlight a complex timing-dependent interaction between stimulant drug exposure and environmental exposure.43–47
The biology of the glutamatergic system (and particularly the properties of glutamate receptors) shows developmental changes analogous to the switch from fetal to adult haemoglobin and given the centrality of excitatory neurotransmission to both injury and recovery, the applicability of any findings from adult neuroplasticity research to paediatric practice will require specific study.

**ACQUIRED BRAIN INJURY**

Just as the usefulness of ‘cerebral palsy’ as a disease concept is regularly challenged in an age of advanced neurogenetics and imaging, it is worth asking whether ABI is too broad a term to be useful. It certainly covers a very heterogeneous group of conditions. As with cerebral palsy, however, the main justification may relate to service provision and planning. Services for children with additional needs, within health and education, are largely designed for the much larger numbers of children with developmental disabilities (including cerebral palsy) than for its later function’.

Age-at-injury effects have been a subject of much controversy, simplistic thinking and confusion over many years. A belief that ‘younger was better’ is often erroneously attributed as the ‘Kennard principle’ in reference to seminal works on recovery in immature and adult monkeys by Margaret Kennard in the 1950s. Although such beliefs remain widespread, this simplistic notion misrepresents her work. The benefits of greater plasticity in the immature brain need to be balanced against the unfinished work of completing development – to ‘make a year’s progress every year’ – with an injured brain. The result of the trade-off differs by domain of function (figure 3).

The biology of the glutamatergic system (and particularly the properties of glutamate receptors) shows developmental changes analogous to the switch from fetal to adult haemoglobin and given the centrality of excitatory neurotransmission to both injury and recovery, the applicability of any findings from adult neuroplasticity research to paediatric practice will require specific study.

**Figure 2** Schematic representation of the differing effects of injury to primary motor cortex at different ages. Rows represent from top to bottom: intact, prenatal, early postnatal and late postnatal injury. The final, adult architecture (far right in each row) differs in each case because of interaction between the injury and developmental milestones, in this case the physiological regression and loss of ipsilateral corticospinal projections (blue) that occurs in normal early postnatal life due to competitive inhibition from the contralateral corticospinal tract (green).
The epidemiology of ABI is awkward from both a research and service delivery perspective. Annual paediatric admissions to intensive care units (ICU) for TBI (the commonest type of ABI) have recently been confirmed as 5.6 per 100 000 population with a post-ICU admission mortality of 9.2%. We previously estimated the incidence of non-traumatic coma (defined as a Glasgow Coma Scale score<12 for >6 h) as 30.8 per 100 000 with a post-admission mortality of 24%. Not all survivors of ABI have significant morbidity, but every health service district sees single-digit numbers of new cases every year, not quite prevalent enough to ensure robust and universal district level provision, but frequent enough to regularly highlight deficiencies.

**SERVICE PROVISION**

The characteristics of a successful rehabilitation programme lie less in team composition or facilities (although clearly both are important) than in philosophy. A defining feature of rehabilitation as a medical philosophy is goal focused working: in ICF (International Classification of Functioning, Disability and Health) parlance, a focus on participation over impairment. Flexible interpretation of professional role boundaries is also key to a continuity of input across the rehabilitation process allowing the family to work with a single team throughout. If co-location allows it, it is highly beneficial for the rehabilitation team to become involved during the ICU phase: not only does this allow early preventive intervention (such as splinting to prevent contractures) but also eases what is often a very difficult transition for families from PICU to the rehabilitation phase of care. Medical contributions in the early phase may include management of agitation (primarily environmental modification to reduce over-stimulation: propranolol in severe cases and paradoxically stimulants to aid orientation in less severe cases) and control of severe dysautonomia, seizures and spasticity. As with other groups with ‘vulnerable’ nervous systems such as the elderly, unwanted behavioural, confusional and sedative effects of drug treatment are very common. Intrathecal baclofen pumps are invaluable in the thankfully rare situation of severe total-body spasticity. It is, however, important not to assume ‘all stiffness is spasticity’ and to be alert to other movement disorder states including dystonia and parkinsonism.

**OUTCOMES**

Prospects for improvement are understandably a major focus of early interaction with families. Aetiology is a crucial factor: the outlook for early motor gains is much better in TBI (which is often predominantly a micro-multifocal pathology) than more pan-neuronal insults such as hypoxic ischaemia or hypoglycaemia. Where physical disabilities persist, swallowing and feeding issues are managed in manners familiar from care of children with cerebral palsy. However, as stressed above, acquired injuries should always be assumed to be patchy. A child sustaining major physical disability after 10 or more years of normal development is likely to have some preserved comprehension of spoken language, insight into their situation, and a desire and right to skilful augmentative and alternative communication (AAC) assessments to access expressive communication. Providing appropriate educational provision for such children can be very problematic. While this group’s needs are undoubtedly severe, they are at least visible. The greater challenge lies in advocating for the much larger group (particularly of TBI survivors) who make...
often misleadingly good motor recoveries yet have very significant residual cognitive deficits that if unaddressed rapidly lead to educational, emotional and behavioural deterioration. It is important to understand the complexities of the processes that determine outcome after injury. It is not possible to state simply whether someone has ‘fully recovered’ from ABI until the impact on final adult function can be inferred. Although acquired injuries are heterogeneous, infero-medial temporal and inferior frontal lobe structures are characteristically vulnerable (particularly in traumatic injury) due to their proximity to the floors of the middle and anterior cranial fossae. As an oversimplification: skills gained prior to injury tend to remain more-or-less intact, but hippocampal injury reduces the efficiency of new learning so children gradually fall behind. Another important concept is that of ‘latent’ injury. Frontal lobe injury in preadolescence may be relatively inapparent as the frontal lobe is still developmentally silent – it manifests several years later when the expected ‘maturity’ of later adolescence fails to emerge.

These children pose great challenges to teachers who may struggle to understand what it is they are seeing. Relying on a child’s ability to recognise commonalities between multiple examples and to generalise these to new settings, is a fundamental pedagogical approach. Unfortunately, it is a frontal skill that may be specifically impaired and having to explicitly teach this is an unfamiliar challenge to most teachers. Failure to appreciate the ways in which problems can emerge with time late after injury results in under-recognition. Regrettably it is still all too common for the fact that an injury occurred while the child was at primary school to not even be conveyed to high school staff on the basis that the child was thought to have ‘recovered’ and the incident is erroneously presumed closed. A great deal of information is available to inform the educational remediation of ABI: the challenge is recognising what is being seen and to make this information available at the right time.57

Education as rehabilitation

The renewed awareness of the plasticity of motor cortex even of adult brains re-opens the restoration–compensation debate again in relation to cognitive function. There is much debate in the psychological literature about the relative value of attempts to retrain cognitive skills on an individual basis (restoration) versus environmental optimisation (an important form of compensation). The evidence base in relation to cognitive restoration is currently limited (an authoritative database of evidence, largely confined to adult practice, is maintained at http://www.psycbite.com). Trials in children have shown definite but modest effects58 and the extent to which these benefits generalise to daily function beyond the specific trait practiced is still to be established. What is clear is that effective rehabilitation needs to be ecologically valid (delivered in meaningful contexts, such as school).59 60 Appropriate peer contact is very effective in modelling and providing feedback in emotional and social competence (http://www.bianys.org/learnet/). It is also clear that the family environment (including family ‘coping style’) is a hugely powerful mediator of late outcome.61–63

THE FUTURE

Many challenges remain in rehabilitation research. Our understanding of the many processes that occur in a rehabilitation encounter remains far from complete.64 A pharmacologist would say that we neither know the active ingredients nor how to specify dose for many of the interventions we wish to study. Even basic tasks, such as the identification of a child as making a better-than-expected recovery, which are fundamental to pilot studies require complex solutions.65 Nevertheless, the challenge is fascinating, and the motivation to improve the lot of survivors of ABI and their families a powerful one.

Dedicated to the memory of Mark Yvissaker.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES


