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Do children really recover better? Neurobehavioural plasticity after early brain insult

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Plasticity is an intrinsic property of the central nervous system, reflecting its capacity to respond in a dynamic manner to the environment and experience via modification of neural circuitry. In the context of healthy development, plasticity is considered beneficial, facilitating adaptive change in response to environmental stimuli and enrichment, with research documenting establishment of new neural connections and modification to the mapping between neural activity and behaviour. Less is known about the impact of this plasticity in the context of the young, injured brain. This review seeks to explore plasticity processes in the context of early brain insult, taking into account historical perspectives and building on recent advances in knowledge regarding ongoing development and recovery following early brain insult, with a major emphasis on neurobehavioural domains. We were particularly interested to explore the way in which plasticity processes respond to early brain insult, the implications for functional recovery and how this literature contributes to the debate between localization of brain function and neural network models. To this end we have provided an overview of normal brain development, followed by a description of the biological mechanisms associated with the most common childhood brain insults, in order to explore an evidence base for considering the competing theoretical perspectives of early plasticity and early vulnerability. We then detail these theories and the way in which they contribute to our understanding of the consequences of early brain insult. Finally, we examine evidence that considers key factors (e.g. insult severity, age at insult, environment) that may act, either independently or synergistically, to influence recovery processes and ultimate outcome. We conclude that neither plasticity nor vulnerability theories are able to explain the range of functional outcomes from early brain insult. Rather, they represent extremes along a 'recovery continuum'. Where a child's outcome falls along this continuum depends on injury factors (severity, nature, age) and environmental influences (family, sociodemographic factors, interventions).

Keywords: brain injury; child; neurobehaviour; plasticity; recovery

If the developing brain were completely "plastic" (a most unfortunate word) and any part capable of doing the part of any other, how are we to explain the tragedies of mental retardation resulting from biological problems occurring before birth (Isaacson, 1975, p. 1).

Introduction

Plasticity is an intrinsic property of the CNS, reflecting its capacity to respond in a dynamic manner to the environment and experience via modification of neural circuitry. This phenomenon is linked to processes of brain development and function across the lifespan (Mosch *et al.,* 2005; Duffau, 2006; Taupin, 2006; Kadis *et al.,* 2007). In the context of healthy development, plasticity is considered a beneficial property, facilitating adaptive change in response to environmental stimuli, such as routine learning or specific training and enrichment. In these circumstances, research has documented establishment of new neural connections as well as modifications to the mapping between neural activity and behaviour.

In the context of environmental deprivation and/or brain injury, and associated disruption to programmed developmental processes, the influence of plasticity is less clear cut, and the immature brain may not always benefit from plasticity processes. While there may be an opportunity to take advantage of the immature brain's lack of functional specificity, for example, via transfer of functions from damaged to undamaged areas, the brain's capacity for plasticity might also reflect 'vulnerability', with predetermined developmental processes being derailed, neural resources depleted and an absence of a developmental 'blueprint' to guide recovery (Hebb, 1949; Kolb, 1995; Pascual-Leone *et al.,* 2005). Recent progress in the neurosciences provides an exciting opportunity to investigate mechanisms underpinning plasticity and recovery and their behavioural correlates and to advance theoretical paradigms and clinical knowledge in this field.

Exploration of the consequences of brain insult sustained early in life has a long history, dating back to the 1800s, when Broca observed speech function in a patient with congenital absence of the left frontal lobe, and postulated that the right hemisphere could subsume speech functions (Broca, 1861, 1863). A few years later Barlow described a young boy with sequential lesions to left language cortex and later right language cortex, who demonstrated initial recovery and then loss of language after the second lesion, also supporting the notion of the right hemisphere's potential to subsume language (Barlow, 1877; Payne and Lomber, 2001). These reports were contrary to localizationist views of the time, and it was not until the 1930s and 1940s that interest in the unique consequences of early brain injury was renewed (Lashley, 1929; Kennard, 1938, 1942; Hebb, 1949), and the debate around plasticity versus vulnerability was rekindled. In the late 1960s, the seminal work of Hubel and Weisel (1965, 1970) demonstrated the plasticity of the visual system and its susceptibility to environmental input. Comprehensive reviews began to emerge (e.g. Isaacson, 1975; St James-Roberts, 1975; Finger and Stein, 1982), as both animal- and child-based research began to accumulate. In this literature, early insults were regarded as qualitatively and quantitatively distinct from those occurring in adulthood. Children with early left-hemisphere disease, for example, were reported to acquire age-appropriate language, free from the obvious symptoms of aphasia observed following similar lesions in adulthood (Bates *et al.,* 2001; Ricci *et al.,* 2008). Similarly, early vascular accidents need not preclude normal intellectual and academic achievement (Smith and Sugar, 1975; Ballantyne *et al.,* 2008). Even when an entire cerebral hemisphere was removed, an infant might develop relatively normal cognition (Dennis and Whitaker, 1976). In contrast, children sustaining generalized cerebral insult were noted to experience slower recovery and poorer outcomes than adults (Anderson and Moore, 1995; Hessen *et al.,* 2007).

Despite lively and continuing interest, recovery from early brain insult remains imperfectly understood. Relevant to the current state of knowledge, early brain insult is defined in various ways in the literature, usually depending upon the particular brain region, network or functional skills under consideration, and their developmental trajectories. For the purposes of this review, early brain insult will refer to brain insult in the preadolescent period, during which brain structures and/or their related neurobehavioural functions show rapid maturation. Clinical observations suggest great variability in outcome from early brain insult, highlighting that, while children may indeed have great capacity for plasticity, they can also experience poor recovery (Giza and Prins, 2006). From these inconsistencies two seemingly contradictory explanations have emerged: first, 'early plasticity', arguing for the greater flexibility of the immature brain, and associated good recovery and outcome; and secondly, 'early vulnerability' referring to the young brain's unique susceptibility and subsequent poor outcome. Both perspectives focus on the degree to which the developing brain, and the functions it subsumes, can recover and continue to develop, and the mechanisms and influences that might lead to specific outcomes. Both agree that infancy and childhood are developmental stages associated with unique responses to brain injury, and suggest a largely linear relationship between age at insult and functional outcome. However, they differ dramatically with respect to their interpretation of the direction of this relationship and the capacity of the immature brain for recovery. A crucial issue in the debate is whether specific cerebral functions (e.g. speech, memory) are 'innately specialized' to particular brain regions, with limited potential for reorganization or transfer, resulting in poor outcome, or if the immature brain is 'equipotential', with minimal functional localization early in development, enabling healthy brain to take up functions previously the responsibility of damaged areas (Aram, 1988; Oddy, 1993). Animal and human work has broadened the framework of this debate, extending the scope of inquiry from being brain specific to include environment (social context, parenting style, access to interventions) and pre-morbid characteristics (gender, age at insult, adaptive abilities, temperament) as potential mediators of recovery after early brain insult (Kolb, 1995; Yeates *et al.,* 1997; Catroppa and Anderson, 2008). Advances in the neurosciences (e.g. transcranial magnetic stimulation, functional MRI, tractography, deep electrodes) provide the necessary tools to consider these factors and their interactions with developmental processes.

In this review, we argue that, rather than representing contradictory perspectives, early plasticity and early vulnerability models reflect opposite extremes along a 'recovery continuum'. Where an individual child's recovery falls along this continuum will depend upon a number of influences including injury-related factors (e.g. nature, severity, timing of insult), constitutional factors (e.g. developmental stage, cognitive capacity, genetic make-up, gender) and environment (e.g. family function, social status, access to rehabilitation/intervention). While these influences may act in isolation, it is more likely that they will interact dynamically, in keeping with the wide spectrum of outcomes observed post-early brain insult. To this end we begin with an overview of normal brain development, to provide a backdrop for understanding the potential for brain insult to disrupt the developmental blueprint. Secondly, we describe the biological mechanisms associated with recovery from brain insult, with a focus on those relevant to early brain insult. Thirdly, we review the available literature examining behavioural recovery following early brain insult, with a major emphasis on neurobehavioural domains. Finally, we discuss the literature that has explored factors which may act, either independently or synergistically, to influence processes of recovery, ongoing development and ultimate outcome.

Normal development

Brain development is a complex and protracted process, commencing in the third gestational week and continuing well into early adulthood. Normal developmental processes are subject to a variety of exogenous and endogenous influences, from the molecular events of gene expression to environmental inputs (Stiles and Jernigan, 2010). At varying time points during gestation, neurons are generated and migrate to predetermined areas. Once they reach their destinations they begin connecting with specific neuron groups, thus forming neural networks that will subsume future functions (Uylings, 2006). Individual brain structures and cortical layers demonstrate different maturation timetables, based on a series of precise and genetically predetermined stages (Luna and Sweeney, 2001; Gogtay et al., 2004), involving a sequence of complicated and overlapping processes, the outcome of which is partially determined by the outcome of previous stages of development, but is also vulnerable to both intrinsic (e.g. trauma) and extrinsic (e.g. environment) influences. Below we provide a brief overview of key aspects of brain development relevant to this review. For more detailed discussion of these issues see recent reviews by Stiles and Jernigan (2010) and Spencer-Smith and Anderson (2009).

The prenatal period

The prenatal period is characterized by dynamic activity and is primarily concerned with gross structural formation (Orzhekhiovskaya, 1981; Casey et al., 2000). A series of intricate processes—neurulation, proliferation, migration, dendritic development, synaptogenesis, differentiation and apoptosis—enable the transformation of the primitive neural tube into a series of complex neural networks comprising the CNS. Interruptions to
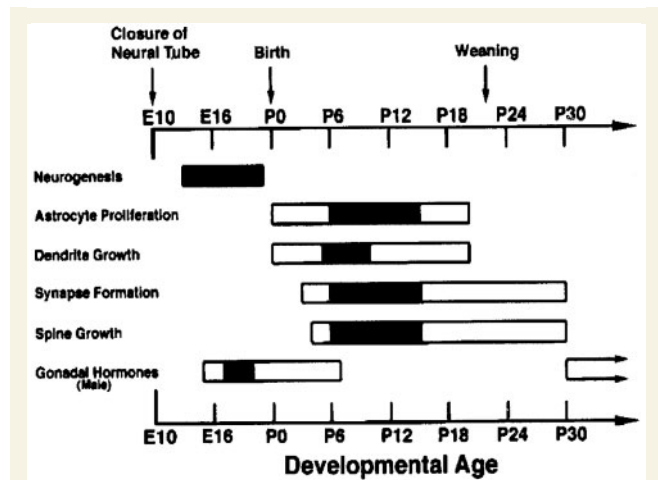
Figure 1 Timing and sequence of developmental processes of the CNS (adapted from Kolb, Gibb, Gorny, 2000b).

development during this period (e.g. genetic aberrations, intrauterine compromise, infection) are likely to have a significant impact on cerebral development, so that the brain's morphology appears abnormal even at a macroscopic level.

The early CNS is represented by a neural plate that folds in on itself to form the neural tube, within which neurulation occurs between gestational Months 1–5 (Altman and Bayer, 1993; Rakic, 1995; Spencer-Smith and Anderson, 2009). This process is precisely regulated so that appropriate numbers of cells are formed at predetermined times and in well-defined regions (Fig. 1) and interruption may cause neural tube defects and associated major structural abnormalities, such as spina bifida or anencephaly (Verity et al., 2003). Proliferation, the period in which neurons intended to form the cerebral cortex are born, takes place between 6 and 18 weeks of gestation. Specific cell populations emerge in particular regions of the neural tube and will develop into specific CNS structures (Rourke, 1989; Johnson, 1997). Overproduction of neurons may occur, as seen in megalencephaly (Verity et al., 2003). Between ∼5 and 7 months of gestation, neuroblasts migrate to their permanent locations (Evrard et al., 1992; Gupta et al, 2005). The majority of neurons migrate in a radial pattern (Rakic, 1971, 1978; Johnson, 1997; Nadarajah and Parnavelas, 2002), travelling along radial glial fibres via previously generated neurons. Arrest of neuronal migration may result in focal cortical or subcortical dysplasias (Verity et al., 2003; Spencer-Smith et al., 2009).

Dendritic development and synaptogenesis are critical for the establishment of cerebral connectivity. As axons extend and dendrites arborize, the developing CNS becomes densely packed and the brain surface begins to fold (sulci and gyri) to accommodate this increased cortical mass (Mrzljak et al., 1988, 1990; Kostovic and Rakic, 1990; Monk et al., 2001; Kostovic and Jovanov-Milosevic, 2006). Once neurons have migrated, differentiation begins, with cells becoming committed to specialized systems, relevant connections being established, and functional activity commencing. Cells not associated with these functional systems may be eliminated (Uylings, 2006). Apoptosis, a form of

programmed cell death that eliminates cells with poor or unnecessary synaptic connections (Henderson, 1996), results in degeneration of nearly half of all neurons during development. While necessary for healthy development, excessive rates of apoptosis have been linked to conditions such as Down syndrome (Busciglio and Yanker, 1995).

Prenatal and perinatal development are characterized by expanding cortical connectivity, linked to increases in the number and size of cortical regions (Rakic, 1988). The increase in cortico-cortical connections leads to the formation of distributed neural networks (Selemon and Goldman-Rakic, 1988), which underpin the complexity of human behaviour.

The post-natal period

Post-natal development is primarily associated with elaboration of the CNS, with differentiation and maturation progressing into adolescence and early adulthood. As with prenatal processes, post-natal development appears to follow a set sequence, with early development characterized by growth of short cortico-cortical connections, rapid synaptogenesis and dendritic development, myelination and development of local circuitry. All progress in a largely hierarchical manner, with anterior regions the last to reach maturity (Klinberg *et al.,* 1997; Gogtay *et al.,* 2004). Rapid dendritic growth and synaptogenesis occur from 8 months to 2 years, leading to levels higher than those seen in adulthood, and followed by selective elimination. This process of selective pruning provides an opportunity for CNS structures to be influenced by environment and experience (Luciana, 2003; Uylings, 2006).

From 16 months to 2.5 years, dendrites display growth spurts resulting in adult maturity. An initial overproduction of dendrites is followed by pruning, to leave only the most functional branches. Growth continues at a reduced rate to 5 years, followed by a stable period up to the age of at least 27 years (Koenderink *et al.,* 1994, 1995). Early brain lesions have been associated with interruption to dendritic development (Purpura, 1975, 1982; Webb *et al.,* 2001), for example, dendrites may be thinner, have smaller numbers of spines or shorter branches. Synaptogenesis parallels dendritic development (Goldman-Rakic, 1987). Research suggests maximum synaptic density between 15 months (Huttenlocher and Dabholkar, 1997), and 2–3 years (Mrzljak *et al.,* 1988), followed by a decline over the next 16 years (Huttenlocher, 1979; Zecevic and Rakic, 1991; Bourgeois *et al.,* 1994; Blakemore and Choudry, 2006). Initial overproduction of synapses may provide scope for recovery and adaptation after a prenatal or postnatal brain lesion (Huttenlocher, 1984; Berthenthal and Campos, 1987; Kolb *et al.,* 2000) and may underpin critical periods in development associated with better capacity for recovery. Berthenthal and Campos (1987) suggest that, through the overproduction of synapses, there is potential to select and refine active synapses, resulting in reorganization for greater efficiency (Rakic *et al.,* 1986).

Myelination is the process of insulation that ensures rapid transmission of electrical signals (Yakovlev and Lecours, 1967; Johnson, 1997) and transmission of information within and between neural circuits (Paus, 2005). Peaks in myelination have been documented around 2, 7–9 and 11–12 years (Thatcher, 1991, 1997), with some changes during adolescence and beyond (Giedd *et al.,* 1999; Paus *et al.,* 1999). Disruption to myelination has been reported in association with toxicities, inflammation, and cranial irritation, resulting in decreased conduction velocity, increased refractory periods after synaptic firing and more frequent conduction failures (Konner, 1991).

Critical periods in development

Brain maturation is not linear, but is punctuated by a series of developmental spurts, some additive and some regressive (Stuss, 1992; Kolb *et al.,* 2000). Linked with these stepwise processes is the concept of 'critical' or 'sensitive' periods. While not yet well understood, critical or sensitive periods are hallmarks of early development, which result in either particularly good, or conversely, particularly poor outcomes. They mark phases of increased plasticity, when specific brain circuits are maximally sensitive to acquiring certain kinds of information, or even need that information to be consolidated so that the system involved can establish interconnections with other systems (Anderson *et al.,* 2001; Stein and Hoffman, 2003; Hensch, 2004; Uylings, 2006; Thomas and Johnson, 2008). Within the context of healthy development, critical periods are times when neural networks are most sensitive to environmental influences, such as learning and instruction. Brain disruption or insult during a critical period is thought to be particularly detrimental, causing a cessation of development or altering its course. If this progression does not occur appropriately it may never occur, there may be delay in ongoing development of damaged brain regions, or asynchrony with respect to the sequential establishment of neural connections (Schneider and Koch, 2005; Kolb *et al.,* 2008b; Johnston, 2009). Each of these scenarios has functional consequences. Animal research suggests that insult during critical periods can result in optimal outcome, particularly if the developmental stage is associated with redundancy of neural elements such as synapses or dendrites (Kolb *et al.,* 1994a).

The concept of critical periods has been best established for the visual system. For example, impaired vision during early life, due to ocular disorders, causes disparate images to be transmitted for visual cortices, resulting in reorganization of visual pathways and permanent amblyopia. Similar conditions later in childhood, when the visual system is more mature, have no such consequences (Tagawa *et al.,* 2005; Majdan and Shatz, 2006; Johnson, 2009). Within the motor system a similar 'critical period' is described, with young children being more able to compensate for damage to the motor cortex. Several researchers report that, following large early unilateral lesion to motor cortex, neuronal representation of the primary motor region is reorganized to the ipsilateral region, so that motor representations are accommodated in the undamaged hemisphere (Carr *et al.,* 1993; Kuhnke *et al.,* 2008; Wilke *et al.,* 2009). These examples highlight the potential interactions between timing of injury and functional domain.

Critical periods for more complex neurobehavioural domains are less well understood (Fox *et al.,* 2010), although work from our research team has identified differentially poor outcomes for

children sustaining either focal or diffuse brain insult before the age of 2 years (Anderson *et al.,* 2005*a*, 2009*b*, *c*, 2010), for intellectual ability, language, memory, attention and executive function. However, many questions remain, for example: are there different critical periods for neurobehavioural domains? Do some skills have shorter critical periods? Are some functions less likely to be influenced by plasticity processes?

Mechanisms underpinning recovery

Basic science and animal studies have provided an increasing awareness of the physiological consequences of brain insult and the possible mechanisms underpinning recovery. There is, however, still much to learn, and ongoing dispute regarding the efficiency of these processes, as well as their impact on the immature brain. We do know that the processes that occur following brain injury are rather dynamic and can be progressively modified via both internal (e.g. activation) and external (e.g. environment, experience) factors. In the following discussion, we review mechanisms of recovery and consider whether these processes confer any advantage for early brain insult.

Brain insult, be it vascular, traumatic, aplastic, hypoxic or degenerative, results in a 'cascade' of events, some detrimental and some beneficial, with the balance depending, to some extent, on the type of insult incurred and the nature of the subsequent pathology. Insult results in destruction or disruption of neural networks, via death of neurons and glia, damage to axonal tracts, alterations to neurotransmitter systems and disruption to vasculature (Nieto-Samedro, 2004; Giza and Prins, 2006). Within the human CNS, destroyed neurons are not replaced and abnormal/damaged axons struggle to spontaneously regenerate, impacting neural circuitry and altering the cellular environment (Giza and Prins, 2006). Secondary processes, such as inhibitory influences of glial cells and associated scarring, hinder recovery processes and compete with neuroprotective responses, to determine the degree of recovery (Nieto-Samedro, 2004; Yiu and He, 2006). Consistent with these acute neuronal processes, adult studies demonstrate dramatic improvements in conscious state and neurological function in the days post-insult, followed by rapid gains in neurological and functional status over 3–6 months. After that, progress slows, with incremental gains reported for up to 2 years. Findings from our laboratory suggest that this recovery course may be somewhat longer in children, as illustrated in Fig. 2 (Anderson *et al.,* 2009*a*). While typical patterns and time course of functional recovery are increasingly well documented, their relationship to underlying neurophysiological processes remains unclear.

Recovery mechanisms can be grouped into two general classes—restitution and substitution (Rothi and Horner, 1983; Kolb and Gibb, 2001). Restitution suggests that, as the damaged brain heals, neural pathways are reactivated and functions are restored. Substitution theories refer to recovery via transfer/reorganization of functions from damaged brain tissue to healthy sites.
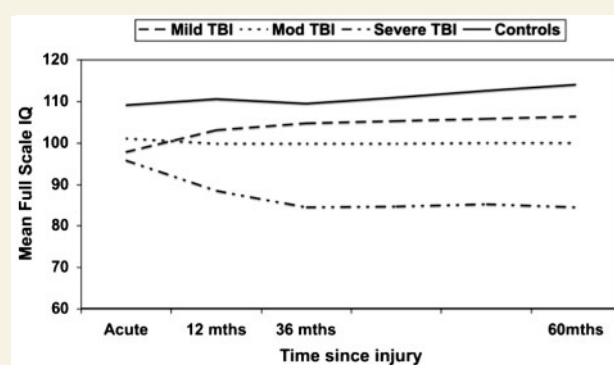
Figure 2 Recovery trajectories for intellectual ability over 5 years following childhood traumatic brain injury (TBI) (adapted from Anderson *et al.,* 2009*a*).

Restitution of function

Diaschisis

One of the best known and accepted restitution theories is that of diaschisis (Von Monokow, 1914; Stein and Hoffman, 2003), the period of rapid recovery of function immediately following brain insult, which reflects the generalized nature of impairment in the early stages post-insult and involves biochemical mechanisms (e.g. intracranial pressure, neurotransmitter release) and genomic alterations in protein synthesis, not just restricted to site of insult and necrotic tissue, but also involving distant brain regions (Pascual-Leone *et al.,* 2005). Von Monokow (1914) conceptualized injury triggering a form of long-lasting inhibition or inertia, which temporarily suppresses or weakens synaptic connectivity, as well as interactions between damaged and undamaged sites. Roberston and Murre (1999) argue that, with synaptic sites no longer firing together, there is a loss of function in distant, but disconnected sites, associated with the clinical symptoms that are observed post-insult. The patient's rapid improvement in conscious state and neurological function in the days and weeks after injury reflects physiological recovery, or stabilization, of undamaged sites within the CNS, the function of which had been interrupted but not destroyed.

Apoptotic cell death is slower to commence, extending from ∼6 h to 5 days post-insult, with more diffuse impact. This process is characterized by cytoplasmic and nuclear condensation, and cell shrinkage and fragmentation into apoptotic bodies that are engulfed by adjacent cells (Bittigau *et al.,* 1999). Apoptosis can impact recovery by disconnecting neural circuits, causing calcium accumulation in dying cells, triggering inflammation and altering the extracellular environment (Giza and Prins, 2006).

Animal research has provided insights into these acute neuronal processes. Work addressing the consequences of hypoxic–ischaemic insults in the perinatal period (common in prematurity and cerebral palsy) (Ivako *et al.,* 1996; Liu *et al.,* 2002; Ong *et al.,* 2005; Vannucci and Vannucci, 2005; Kumar *et al.,* 2008), as well as early traumatic insults (Giza and Prins, 2006), describes acute alterations to neurotransmission, with abnormalities identified in multiple neurotransmitter systems including glutamatergic,

cholinergic and aminergic. Bittigau and colleagues (2004) and Felderhoff-Mueser and Ikonomidou (2000) describe specific insult-related excitotoxic and apoptotic cell death responses, which reflect disruption to the normal action of these physiological mechanisms. Excitotoxic degeneration, most evident at site of insult, is characterized by rapid swelling of dendrites, cell bodies and intracytoplasmic organelles and nuclear flocculation and cell lysis, and peak at ~4 h post-insult before declining.

The sequence and time course of these processes differ somewhat according to the nature of insult. In the context of traumatic insult, age-specific discrepancies in degree of myelination and water content in the brain allow more diffuse transmission of traumatic forces, and may account for the differential susceptibility of the immature brain (Bittigau *et al.*, 1999, 2004; Giza *et al.*, 2007). Felderhoff-Mueser and Ikonomidou (2000) report that the immature brain is highly susceptible to these neurodegenerative processes, providing support for early vulnerability perspectives.

Regeneration

Following this initial period of neuronal suppression and cell death, several recovery processes have been described. Regeneration, the process by which damaged neurons, axons and terminals regrow and establish previous neuronal connections, has been demonstrated to be functionally advantageous in the peripheral nervous system, as well as in the CNS in animal studies (Dallison and Kolb, 2003; Dancause *et al.*, 2005; Ward, 2005). Animal studies have further found dendritic growth at both lesion site (Dallison and Kolb, 2003), and sites contralateral to the lesion (Dancause *et al.*, 2005; Ward, 2005; Monfils *et al.*, 2006). The possibilities for such regrowth in the human CNS remain unclear (Bjorkland and Stenevi, 1971; Boller, 2004; Delgado-Garcia and Gruart, 2004). While there is currently little evidence for cortical regeneration, the hippocampus, retina, cochlea and olfactory bulb can produce new neurons, at least in primates (Altman and Bayer, 1993; Lois and Alvarez-Buylla, 1994; Lopez-Garcia and Nacher, 2004; Taupin, 2006; Johansson, 2007). In reality, however, damaged cell bodies cannot be replaced, and damaged axons have been observed to show some slow and minimal regrowth (1–2 mm) (Kalet, 2009). Such neuronal regeneration is at best highly local and often hindered by scar tissue and blood clots, which prevent reconnection of severed or disrupted pathways. In the immature brain, where injury is likely to derail the normal 'developmental blueprint', the potential for regeneration processes to translate into functional recovery is as yet unclear.

Sprouting

While brain insult can result in widespread neuronal death, many neurons will be only partially damaged or even undamaged, with neural components such as axons having the potential for 'sprouting' or 'reinervation' by finding a new cell 'target', and reconnecting to functional systems (Kozlowski and Schallert, 1998; Delgado-Garcia and Gruart, 2004). Remaining nerve fibres develop branches that occupy sites left empty by damaged neurons, thus re-innervating unoccupied areas in the vicinity of the lesion, and facilitating synaptic contacts (Delgado-Garcia and Gruart, 2004), although the efficiency of this process is inhibited by the action of glial cells at the site of injury (Yiu and He, 2006).

Axons may regrow, but only a subset will reach their appropriate destination, resulting in incomplete or maladaptive recovery. Sprouting is reported to occur early post-insult, being complete in a matter of weeks, with some evidence of associated behavioural improvement (Voss *et al.*, 2006), although there is, again, no evidence for advantage to the immature brain.

Denervation supersensitivity

Denervation supersensitivity (Cannon and Rosenbleuth, 1949; Gonzalez-Forero *et al.*, 2004) provides another possible mechanism for restoration of function. This process suggests that post-synaptic cells, deprived of their characteristic synaptic inputs, will develop increased sensitivity to any neurotransmitter substance leaking from pre-lesion neurons, via the emergence of new receptors and a larger surface area (Salpeter *et al.*, 1986). Thus supersensitivity facilitates activation of post-lesion pathways and restitution of normal functioning. Of note, these processes are likely only possible in the context of small lesions, and no advantage has been identified for the developing brain. Further, negative consequences are also reported, as with increased sensitivity, there is the potential for increased pain.

Molecular genetic processes

Underpinning neural plasticity at all levels are two mechanisms that modulate the effects of neurotransmitters, protein phosphorylation and regulation of gene expression. These have been identified as potentially protective in the context of insult. Protein phosphorylation is the molecular mechanism by which neural activity is modulated via regulation of ion channels and neurotransmitter receptors, signal transduction pathways, and neurotransmitter synthesis and release to the expression of genes in the nucleus that underlie synaptic changes linked to learning and memory (Hyman and Nestler, 1993; Schulman, 1995; Cicchetti and Blender, 2006). Regulation of gene expression is also a key mechanism that produces quantitative and qualitative changes in the protein components of neurons, for example, modification of frequency and nature of ion channels and receptors on the cell membrane as well as levels of proteins that modulate neuronal structure and the number of synaptic connections that form. Neurotransmitters continually regulate neuronal gene expression, fine-tuning the functional state of neurons in response to varied synaptic inputs. Typically, changes to the CNS mediated by protein phosphorylation have a rapid onset, are more readily reversible, and have a shorter duration compared with neural plasticity mediated by gene expression (Hyman and Nestler, 1993). However, both processes mediate the long-term effects of experience on the brain. The changes induced through protein phosphorylation and gene expression result in alterations in the function and efficacy of synapses, in the transmission of information by individual neurons, and ultimately in communication within neural networks. To date, in the context of insult, no age effects have been documented.

Implications for intervention

Improved understanding of the mechanisms associated with brain insult and recovery provides the opportunity for designing effective interventions. Currently much research effort is focused on

pharmacological interventions (Delgado-Garcia and Graut, 2004). Based on the assumption that greater cortical excitability is linked to greater plasticity, then drugs that enhance inhibition, such as anaesthetics, anti-convulsants and benzodiazepines have been associated, experimentally, with impaired plasticity, while others have been noted to increase plasticity (Felderhoff-Mueser and Iconomidou, 2000; Giza et al., 2007; Kolb et al., 2008a; Johnston, 2009). Other approaches, for example, acute hypothermia treatment, have been applied successfully in animals and adults in an attempt to minimize secondary brain damage (e.g. brain swelling and vascular events) (Fink et al., 2005). However, results in infants and children are less consistent. While Shankaran and colleagues (2005) and others report good outcomes in the context of hypoxic–ischaemic encephalopathy in neonates, more equivocal findings have been reported following child traumatic brain injury (Hutchison et al., 2008).

Substitution of function

Substitution models of recovery argue for either anatomical reorganization or functional adaptation, and are largely derived from indirect evidence (e.g. behavioural data, functional imaging) of changes in the brain following insult.

Anatomical reorganization

The first group of substitution theories, purporting anatomical reorganization, suggests differential processes depending on age at insult. Early theorists, such as Munk (1881) and Lashley (1929), argued that large areas of the brain are 'unoccupied' or equipotential, with the capacity to subsume functions previously the responsibility of damaged tissue. The advantages of such mechanisms are thought to diminish with age, as brain regions become more 'committed' (Staudt et al., 2002). Recently, however, reorganization has been reported in adults (Kadis et al., 2007). Gonzalez-Forero and colleagues (2004) have described several potential mechanisms for such anatomical reorganization: (i) redundancy of pathways subsuming the same function; (ii) uptake of previously inactive or silent connections with a latent capacity to subsume lost functions (vicariation or multiplexing); and (iii) sprouting of fibres for surviving neurons to establish new functional connections. Evidence for these mechanisms comes from animal and neuroimaging research with functional activation described in areas both adjacent to and contralateral to lesion sites (Hertz-Pannier et al., 2002; Staudt et al., 2002; Bach-Y-Rita, 2003; Bennay et al., 2004; Dancause et al., 2005).

Extending this work, there are a number or possible scenarios for functional reorganization: (i) interhemispheric reorganization—functions transfer to the analogous site in the non-damaged hemisphere; (ii) intrahemispheric reorganization—reorganization of functions within the damaged hemisphere; and (iii) intrahemispheric maintenance—skills subsumed by damaged tissue are maintained within that tissue, resulting in maximum dysfunction (Table 1). The precise factors that govern which of these options occurs are not well understood, but appear to be dependent on factors including the nature (diffuse versus focal); size (small, large) and laterality of brain damage; distribution of the neural network underpinning the impaired skills (for example, memory has a relatively focal representation, while attention is subsumed by a distributed neural network); as well as timing of insult with respect to developmental stage of the child.

Interhemispheric transfer is probably the best researched of these scenarios and is based on the premise that the contralateral hemisphere has some capacity to subsume skills lost due to brain insult, and so is most likely to occur in the context of unilateral brain damage, and during infancy. Instances of such reorganization are well established in conditions such as infant hemispherectomy for intractable epilepsy (Dennis and Whitaker, 1976) and cerebral palsy, following unilateral lesions in the motor system (Carr et al., 1993; Eyre et al., 2000; Eyre, 2007). Within the neurobehavioural domain, interhemispheric transfer has been observed for language and some non-language functions (e.g. memory), particularly for children with early-onset epilepsy, where skills 'transfer' to the analogous site in the non-damaged hemisphere, or these areas are 'recruited' to assist with functions normally subsumed by damaged tissue (Hertz-Pannier et al., 2002; Staudt et al., 2002). These processes are not necessarily advantageous following early brain insult, due to the risk of 'crowding effects' that can result in depressed function (Lansdell, 1969; Satz et al., 1994; Anderson et al., 2002; Wilke et al., 2009; Beharelle et al., 2010).

Intrahemispheric transfer is more commonly described in the context of unilateral focal lesions, for example, developmental dysplasias, strokes or tumours, where there is adjacent healthy tissue to take up skills normally subsumed by damaged tissue (Anderson and Moore, 1995; Taylor and Alden, 1997; Anderson et al., 2002; Beharelle et al., 2010). Such reorganization is most commonly reported for insults sustained either during the prenatal period or early in childhood. Potential for intrahemispheric transfer is well illustrated by a recent functional MRI study of children born pre-term (Shafer et al., 2009) identified to have diffuse cerebral pathology. At 12 years of age, despite performing at normal levels on a lexical semantic retrieval task, these children demonstrated different patterns of functional connectivity within the left hemisphere to those of same-aged healthy peers, with discrepancies reflecting frontal and temporal pathology identified on structural scans.

Finally, intrahemispheric maintenance is generally associated with poorest outcome, and can be caused by brain insult at any

Table 1 Factors affecting cerebral organization of language following early brain insult

Mode of reorganization	Age at onset	Lesion characteristics
Interhemispheric transfer	Infancy	Small or large unilateral lesions, e.g. hemispherectomy
Intrahemispheric transfer	Prenatal—preschool	Unilateral, focal lesions, e.g. stroke, tumour, focal dysplasia
Intrahemispheric maintenance	Through childhood, although outcome worse at younger age	Bilateral, generalized/diffuse e.g. traumatic brain injury, hypoxic–ischaemic encephalopathy

time through childhood, including the prenatal period. It is most likely following bilateral or diffuse insults, such as cerebral infection or hypoxic–ischaemic encephalopathy, where little healthy brain tissue is available to support reorganization. As a consequence, the brain is unable to reorganize or recruit healthy brain regions and functional outcomes commonly include speech and language delay or global developmental delay (Aram and Enkelman, 1986; Devinsky *et al.*, 1993; DeVos *et al.*, 1995; Anderson *et al.*, 2004*a*; 2005*a*).

Research supporting the functional translation of these reorganization processes into recovery or enhanced performance is less commonly reported. Imaging research has shown that reorganization or 'recruitment' of additional brain areas post-insult may, in fact, be associated with poorer function (Anderson *et al.*, 2002; Hertz-Pannier *et al.*, 2002; Beharelle *et al.*, 2010). For example, we conducted serial functional MRI scans in an 8-year-old child who presented with epilepsy secondary to a focal left frontal tumour (Broca's area) and demonstrated both inter- and intrahemispheric transfer or 'recruitment', using a language-generation task. Soon after diagnosis, the child showed minimal activation on functional MRI and deficits in language function. Over several months, repeat functional MRIs initially showed activation in the region posterior to the tumour in the left hemisphere, and later in analogous regions in the contralateral hemisphere, suggesting that this area had 'taken up' language functions. Concurrent behavioural testing showed a corresponding decrease in language skills over this period (Anderson *et al.*, 2002), suggesting that neural reorganization/recruitment does not necessarily reflect improved function.

Modification of brain function after brain injury has also been achieved via transplantation or grafting, with these experimental methods widely reported in the animal literature, and now emerging in the human domain. Researchers have reported improved motor function following intrastriatal transplantation in Huntington's disease and metabolic and functional changes in the context of translation of specific neural cells in Parkinson's disease and following stroke. Stem cell graft research also shows promise, having the potential to guide axonal regrowth and block factors inhibiting regeneration, when utilized in combination with growth factors (Duffau, 2006). Transcranial magnetic stimulation also has positive functional outcomes in adult stroke, in association with rehabilitation (Berweck *et al.*, 2008; Kirton *et al.*, 2008; Johnston, 2009).

Behavioural compensation does not assume any neural recovery, but suggests that, post-insult, the individual develops new strategies or routes for functions that were previously dependent on damaged tissue. Behavioural compensation, then, underpins the philosophy for rehabilitation, referring to functional recovery through use of strategies, experience and environmental modifications. Such development may occur in several ways: (i) spontaneously, for example, in the right-handed patient who suffers right hemiplegia and needs to learn to use the left hand; (ii) it may involve 'substitution of function' or development of compensatory strategies. For example, a child with right parietal damage, resulting in spatial impairments, may be trained to implement verbal mediation strategies when performing spatial tasks; (iii) direct retraining approaches, for example where a patient with expressive aphasia is assisted by therapy to begin to speak again; and (iv) environmental modification, where external strategies are employed to minimize residual deficits. For example, a child with memory deficits may benefit from a diary or note system to compensate for poor learning.

There is a small body of research utilizing specific intervention methods, which provides evidence for a neural response to behavioural intervention. Functional imaging studies following constraint-induced movement therapy and approaches employing mental imagery of movements have reported re-expansion of motor areas, which then correlate with improved motor function (Hoare *et al.*, 2007; Kuhnke *et al.*, 2008; Sakzewski *et al.*, 2009). Similarly, language therapy has been reported to result in reshaping of the language map using functional MRI (Duffau, 2006). As with restitution theories, there is no indication that children will benefit more than adults (Anderson and Catroppa, 2006).

In summary, current research provides some limited evidence for restitution of neural substrates following brain insult in humans, although it is not clear that such recovery translates into functional recovery. Further, there is evidence for reorganization of brain function, but the consequences are unclear. Of particular relevance to early brain insult, there appears little reason to expect that the developing brain will be advantaged by these processes, and may in fact be at greater risk.

Early plasticity versus early vulnerability: theoretical principles and developmental considerations

With the emergence of the neurosciences providing the capacity to integrate genetic, imaging and behavioural findings, there is a growing opportunity to define the principles of brain plasticity. The following discussion aims to describe theoretical principles in the field, to provide a framework for interpreting current research. As an initial step, it is important to acknowledge the distinction between two separate, somewhat independent dimensions: neural and functional plasticity. Neural plasticity, the brain's response to the environment, refers to physiological processes, and can be observed at molecular, cellular, neurochemical and neuroanatomical levels, and at the level of brain systems or, in the context of insult, through neural recovery processes, such as regeneration and axonal sprouting. In contrast, functional plasticity refers to behavioural change or recovery occurring in response to environmental or injury-related events. Contrary to the parallel processes seen for normal neural and cognitive development, once the genetically predetermined sequence of brain maturation has been interrupted, neural recovery may not necessarily translate to functional recovery (Kozlowski and Schallert, 1998; Felderhoffen-Meuser and Ikonomidou, 2000).

Functional specialization and reorganization: underpinnings of plasticity?

Debate around the benefits of plasticity for the immature brain has been informed by work investigating whether functional organization in the normal brain is 'equipotential' or 'innately specialized'. These concepts are also explored in the adult literature, with some arguing for region-specific localization of function ('localizationists') and others proposing that the brain is structured into a series a neural networks, with functions dependent on multiple brain regions for their efficient execution ('system theorists'). Historically, these viewpoints have been characterized primarily through exploring language skills following brain injury.

Equipotentiality

At one extreme is the view that the young brain is 'equipotential' (Basser, 1962; Lenneberg, 1967; Smith, 1981, 1984), with both cerebral hemispheres capable of mediating a range of skills, especially language. This view is consistent with the early plasticity perspective and would predict that skills disrupted due to early brain insult are effectively managed by other brain regions, without loss of function. To support this model, Lenneberg (1967) cited the surprising lack of impairment of speech function in children who had undergone hemispherectomy for the treatment of intractable epilepsy, regardless of lateralization of initial injury or subsequent cortical removal (Basser, 1962). He claimed these results provided evidence that, early in development, spared brain regions can take on functions normally subsumed by damaged areas. Consistent with this suggestion, research following children from language-deprived backgrounds shows that the capacity to acquire language skills is best if intervention occurs within the preschool period, then declines markedly to the age of 10 years (Curtiss, 1981).

Innate specialization

Evidence gathered for this position has also focused on language outcomes. While there is little argument that language is lateralized to the left ('dominant') hemisphere in adults, the process and timing of lateralization is less clear. Taking a localizationist perspective, the innate specialization position argues that language is 'biologically special', and that there are predetermined cortical regions critical for its acquisition and representation. If areas pre-specified for language are damaged, language impairment would be expected, consistent with early studies (Woods and Teuber, 1973; Dennis and Whitaker, 1976; Zaidel, 1977; Day and Ulatowski, 1979; Dennis, 1980).

One of the greatest problems in evaluating the validity of innate specialization models has been the lack of direct evidence, with most studies employing indirect techniques (e.g. head-turning behaviour, dichotic listening). Post-mortem, sodium amytal ablation and functional imaging techniques (cortical activation, transcranial magnetic stimulation, PET, functional MRI, diffusion tensor imaging) provide more 'direct' evidence that the left hemisphere is innately specialized for language (Geschwind and Levitsky, 1968; Wada *et al.*, 1975; Dall'Oglio *et al.*, 1994).

Interactive specialization

Others (e.g. Johnson, 2001, 2005; Thomas and Johnson, 2008) have taken a compromise position, where brain development is characterized by increasing specialization, or fine tuning of response properties, with these properties specific to brain regions and changing as they interact and compete with each other to acquire their roles. Support for this notion is now emerging from the neuroimaging literature, with studies demonstrating increasing lateralization of language function with age (Szaflarski *et al.*, 2006). This position is also supported by studies which report that, in some instances of early brain insult (e.g. hemispherectomy), the non-dominant hemisphere can mediate language, albeit with high risk of delayed emergence and imperfect recovery (Vargha-Khadem *et al.*, 1994; Bates *et al.*, 1997, 2001; Reilly *et al.*, 1998; Bates, 1999; Herz-Pannier *et al.*, 2002).

Assessing plasticity and recovery from early brain insult: developmental and measurement considerations

Review of findings from child-based literature indicates that, following brain injury at any age, various recovery trajectories may be observed. At one extreme is full recovery and, at the other, severe and permanent impairment. Two other patterns are commonly reported: (i) absence of impairment, but emerging problems over time; and (ii) early slowed development, but catch up over time (Dennis, 1989; Anderson *et al.*, 2001; Luciana, 2003). These contradictory findings may be due to a failure to account for a number of important timing considerations (e.g. age at testing, time since insult) and measurement-based issues (e.g. neurobehavioural domain assessed) that are unique to the developmental context of early brain insult.

Timing issues

Age at insult and time since insult

A number of 'time'-related variables have been identified as critical to the reliable assessment of sequelae following early brain insult (Taylor and Alden, 1997). Age at insult is probably the best known, and will be discussed in detail in the following section. Briefly, however, it is generally agreed that the age at which a child sustains brain insult will influence their development and mastery of neurobehavioural skills, although the relationship is not a simple one (Anderson *et al.*, 2009b). Time since testing is also important, due to: (i) the rapid recovery that occurs post-insult; and (ii) the potential for children with early brain insult to struggle to keep pace with their peers developmentally, due to neurobehavioural impairments resulting from their insults (e.g. reduced attention, processing speed, executive skills). As a consequence, studies that report performance in the acute stages post-injury may reflect transient impairments that will recover with time (delayed development), or fail to identify impairments in skills that are yet to develop (emerging deficits), and so need to

be distinguished from those investigating children in the chronic stages of recovery. To illustrate how these two variables may interact, we conducted a longitudinal study documenting the recovery (to 30 months) of intellectual abilities of children sustaining traumatic brain injury between birth and 12 years of age (Anderson *et al.*, 2005). Our results showed that, while all children with serious insults demonstrated similar levels of impairment at 3 months post-injury, by 30 months, children injured prior to 7 years of age had made a slower recovery and performed significantly worse than older participants. These findings suggest that age at insult effects may become more evident with time since insult, with important implications for clinical practice and, in particular, long-term follow-up of children injured in infancy.

Age at testing is also of importance when assessing recovery and outcome from early brain insult, as it will determine the range of neurobehavioural skills that can be reliably measured. For example, within the language domain, impairments in simple language skills (e.g. picture naming, single word comprehension) may be apparent even in the preschool years, while deficits in higher-order language may not emerge until later in development. This concept is well illustrated in studies of children with early focal left hemisphere lesions whose language skills fell within the normal range when tested before 5 years of age (Aram, 1988; Vargha-Khadem *et al.*, 1991; Bates *et al.*, 1999), but within the impaired range when assessed after 5 years of age, at a time when developmentally appropriate language demands increase (Bates *et al.*, 1999). Similar age at testing effects have also been reported by others (Eslinger *et al*., 1999; Anderson *et al.*, 2004; Westmacottt *et al.*, 2009) across a range of different conditions. Of note, to date few studies have considered 'age at testing' effects into adolescence. Recent advances in our understanding of the significant brain growth occurring during this period indicate that future studies are needed to evaluate the impact of this development on long-term neurobehavioural consequences of early brain insult (Blakemore and Choudry, 2006).

Emerging deficits

While children may function normally immediately post-insult, over time, and with increasing environmental demands, they may fail to make age-appropriate developmental gains (Dennis, 1989), or 'grow into' seemingly new deficits. For example, a toddler with a severe early brain insult may initially present with normal abilities; however, by adolescence, when day to day demands have increased (e.g. managing homework tasks, planning daily activities), executive problems may 'emerge', giving the impression that he/she has 'grown into' their deficits (Dennis, 1989; Anderson and Moore, 1995; Eslinger *et al.*, 1999). A number of studies, both animal and child-based, provide support for this notion, documenting the presence of 'new' impairments over time with serial testing (Kennard, 1942; Kolb *et al*., 2000*a*, 2004; Puellella *et al.*, 2006; Westmacott *et al.*, 2009).

Delayed development

Others have described delayed skill acquisition, but gradual catch up following early brain insult (Vargha-Khadem *et al.*, 1994; Reilly *et al.*, 1998; Bates, 1999; Stiles *et al.*, 2009), with some evidence

of delayed onset of neuropathology (Fernandez-Bousaz *et al.*, 1992; Paakko *et al.*, 1992). In our laboratory, we followed children who contracted bacterial meningitis (median age at illness 18 months) to 10 years post-infection and administered a range of neurobehavioural measures. At 2 years post-illness, the group was characterized by specific expressive language deficits. By 6 years, these deficits were no longer evident, but specific reading difficulties were detected. At 10-year follow-up, reading skills were now age appropriate and high-level language deficits (pragmatic language, verbal learning) were the only symptom, suggesting that, while new problems may indeed emerge with time from insult, previous deficits may diminish as children 'catch up' with their peers (Anderson *et al.*, 2004*a*).

The impact of these timing issues for recovery processes is illustrated in the case of 'JB' who sustained a severe early brain insult as a result of a tractor accident at 3 years of age. Acute CT scan demonstrated extensive right frontal and subcortical pathology (Fig. 3A). MRI scans 8 years later shows the original damage (Fig. 3B and 3C), plus additional generalized atrophy in the right hemisphere, indicating delayed pathology. Consistent with this pattern of late-emerging neurodegeneration, JB demonstrated slowed skill acquisition (Fig. 4) post-insult. From 6 months to 2 years post-insult, when recovery processes were active, JB kept pace with peers. After that time, while there was no evidence of skill regression, the gap gradually widened between JB's abilities and developmental expectations. This lack of progress on formal testing was paralleled by equally poor development of other functional skills such as educational abilities and daily living skills.

Measurement issues and development

Skill-specific plasticity following early brain insult

One of the complexities of recovery and its relation to underlying plasticity is the inconsistency seen across neurobehavioural domains. Lower-order skills, such as simple language, visual and sensori-motor skills, which might be considered to be subsumed by less complex neural networks, often show evidence of good functional recovery (Bates *et al.*, 1999; Staudt *et al.*, 2002; Luciana, 2003; Stiles *et al.*, 2009; Wilke *et al.*, 2009), regardless of damage site or laterality. For these domains, functional neuroimaging studies have demonstrated that brain activation patterns are quite circumscribed, compared with the more diffuse activation seen for higher-order skills such as executive functions (Kuhunke *et al.*, 2008). Following insult, functional MRI paradigms have demonstrated reorganization or 'recruitment' of healthy brain regions in parallel with functional recovery (Duffau, 2006; Stiles *et al.*, 2009). Further, functional imaging pre- and post-intervention (e.g. constraint-induced movement therapy) has shown specific expansion of underlying systems in motor regions (Hoare *et al.*, 2007; Kuhnke *et al.*, 2008; Sakzewski *et al.*, 2009).

Recovery of more complex skills, such as attention, executive functions or social cognition, which are likely subsumed by complex and diffuse neural networks (Stuss *et al.*, 1995; Kolb *et al.*, 2000*b*; Adolphs, 2003; Power *et al*., 2007; Hanten *et al.*, 2010), appears less complete. For example, Heatherington and Dennis
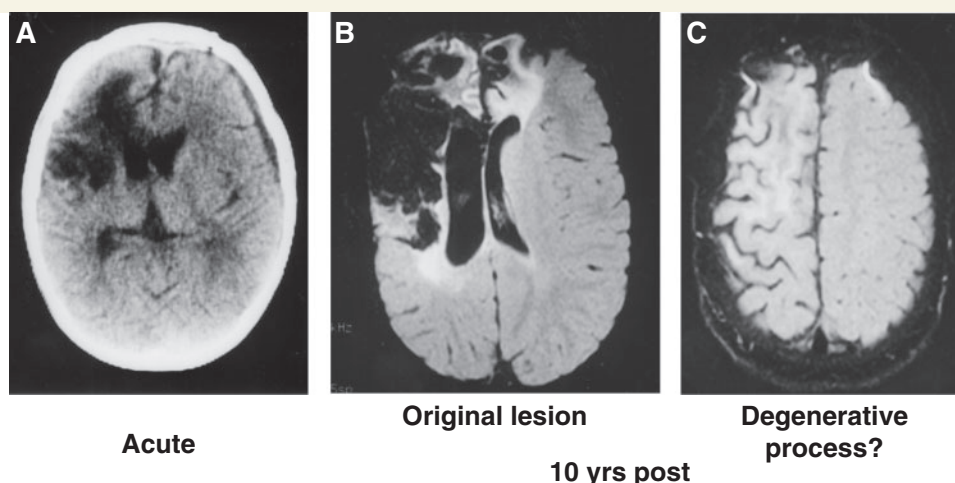
Figure 3 Brain pathology following brain insult in a 3-year old child (J.B.). (**A**) Acute CT scan, demonstrating extent of initial injury, which includes extensive right frontal and subcortical damage. (**B**) MRI scans 8 years post-injury, illustrating the residual pathology, as well as generalized right hemisphere atrophy (**C**).
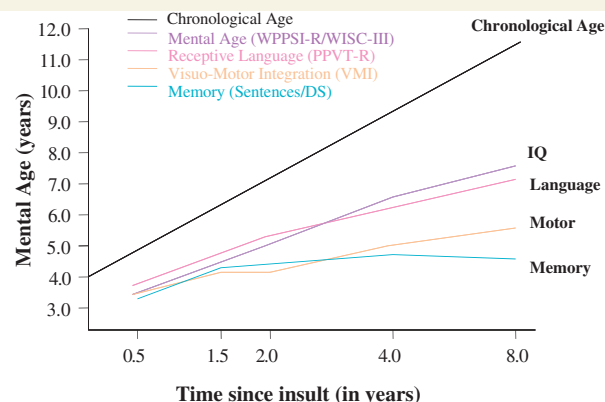
Figure 4 Neurobehavioural outcome to 8 years post-insult (J.B.).

(2004) report recovery of simple, but not complex, language skills after ischaemic stroke in a 7-year-old boy, and Eslinger and colleagues (1999, 2000) describe intact basic cognition alongside impaired moral reasoning and social cognition following early frontal lobe insult. While these differential findings help explain discrepancies in the literature, they also make intuitive sense, suggesting that functions subsumed by discrete, lateralized brain regions may have greater capacity for reorganization than those dependent on more diffuse neural networks.

Developmental stage and level of skill development

Based on studies of language in children with traumatic brain injury, Dennis (1989) has argued that the developmental stage of a specific skill at the time of insult needs to be considered when evaluating the consequences of early brain insult. At any time through the lifespan, outcome depends on an interaction between brain maturity, nature of skill (lower- or higher-order) and level of skill maturity (emerging, developing and established) at the time of insult. Insult during infancy, when skills are

emerging, has widespread implications for the developmental course of all skills, and may lead to anomalies in timing or order of skill acquisition. Brain insult when skills are developing may influence the rate, mastery and strategy of these skills, so that development might be slowed, ultimate levels achieved depressed, and children might need to implement compensatory strategies to achieve in the skill area. In Dennis' model, established skills are generally associated with best recovery. Dennis' model has gained partial support from empirical research, suggesting that patterns of improvement post-insult vary across skills depending on the level of development of the skill at time of insult (Bates *et al.*, 1988; Pentland *et al.*, 2000; Dennis and Barnes, 2002; Anderson *et al.*, 2009*b*),

Taken together, work addressing cognitive outcomes following early brain insult indicates that, in contrast to adult findings, the full extent of consequences of insult may not be apparent until many years post-insult. This finding supports the importance of long-term follow-up for children with early brain insult, in order to identify and treat such problems as they emerge and become functionally significant.

Neurobehavioural recovery from early brain insult—early plasticity or early vulnerability: what is the evidence?

Evidence of recovery of function derives from a variety of research methods. Animal research has been, and continues to be, particularly influential, having the advantage of being able to control for confounding factors including lesion size and location, age at lesion and environment. Animal work has also documented pathways for normal development and critical periods for good and poor outcomes after early brain insult; however, it is unclear

whether animal findings translate directly to humans. Human research, in contrast, has been more indirect, and has several strands. First, lab-based approaches, using normal samples and experimental paradigms, have contributed to our understanding of issues such as language lateralization and functional specialization. Secondly, individuals with brain injury have assisted in delineating brain–behaviour relationships, although it is only relatively recently that child-focused research has emerged. Advances in neuroimaging provide a unique opportunity to more directly address the issues of language laterality, brain reorganization and neural correlates of recovery.

Animal research

Margaret Kennard's animal work of the 1930s and 1940s is seminal to the plasticity debate. Kennard compared sparing and recovery of function in monkeys with pre-motor lesions in infancy, adolescence and adulthood, and reported that unilateral motor cortex injury in infancy resulted in better outcomes than those seen in adults (Kennard, 1938, 1940, 1942). Kennard interpreted her findings as evidence of reorganization of function to the contralateral hemisphere. Her work was later coined the 'Kennard principle' (Teuber, 1971, 1974), and purported to support the view that early lesions are associated with better outcomes than similar lesions in adulthood. Later animal work also demonstrated good recovery from early brain insult. Kolb and Gibb (1993) and Villablanca and colleagues (1993, 1998) found that frontal lesions in infancy in rats and cats led to better behavioural performances compared with similar lesions in adult animals. Goldman and Galkin (1978) reinforced these findings, identifying no deficits following lesions to the dorsolateral prefrontal cortex in monkeys during the migrational period. Further, dissection showed compensatory reorganization of the cortex and thalamic connections.

Follow-up work has painted a more complex picture than early findings predicted. For example, Kennard's subsequent work (1942) showed that, while plasticity of motor cortex was observed, infant monkeys demonstrated adult-like deficits following lesions to the frontal lobes. As a result of these findings she modified her view to suggest that, if a brain region is functionally established at the time of insult, outcome would be similar for both early and late lesions, emphasizing the important influence of timing of insult. Goldman and Rosvold (1972) documented similar effects in adult and infant monkeys following large caudate lesions, and while Goldman (1971) reported unimpaired behavioural function acutely following early prefrontal lesions, significant deficits were identified when these monkeys reached adolescence (Goldman *et al.*, 1970). Additionally, Kolb and Tomie (1988) and Burgess and Villablanca (1986) examined both anatomical and behavioural outcomes following hemidecortication, and found that each was better in neonatally lesioned animals, than in adult animals.

Over a number of years Kolb and his group have reported on a series of studies of young rats with focal lesions sustained at different developmental stages and in varying brain regions. Results have been mixed, further supporting the complex relationship between early brain insult and behavioural outcome, and the lack of

a direct association between neural and functional recovery. For example, Kolb and colleagues (1993) found that lesions during migration or early synaptogenesis led to behavioural impairment, but those sustained later in synaptogenesis were associated with better recovery. There was also a decline in spine density and atrophy of dendritic connections following lesions at birth, but not later in infancy (Kolb *et al.*, 1994a). Kolb concluded that functional recovery was closely related to age at lesion, with poorest recovery from lesions sustained around birth (in human terms), and a brief window for good recovery between 1 and 2 years of age (Kolb *et al.*, 2000a).

Most animal researchers employ focal lesion models, but such lesions are relatively uncommon in children. A few have explored diffuse insults, which are likely to have a more significant impact on the immature brain, due to lack of undamaged brain tissue remaining post-insult. Bittigau and colleagues (1999) employed a weight drop device with rats to inflict diffuse traumatic brain injury, and found greater neurodegeneration in animals injured at a younger age, with greater pathology in rats injured between post-natal Days 3 and 7. Sifringer and colleagues (2007) have replicated and extended these findings. Using a percussion injury model, again with rats, Giza and Prins (2006) demonstrated that early traumatic injury leads to disconnection of neural circuits, and accumulation of dying cells, triggering inflammatory processes, neuronal death and functional impairment.

In summary, while results of early animal research have been interpreted as evidence for the benefits of plasticity following early brain insult, recent findings highlight the complexities of the field, and provide support for the unique vulnerability of the immature brain. Age effects may not be linear, with windows of opportunity, or critical periods, identified in association with developmental processes, where better recovery is seen or when influences such as the environment can moderate recovery.

Human research

Early human studies, mostly with children with focal unilateral lesions or hemispherectomy for treatment of intractable epilepsy, reported good recovery following early brain insult (Basser, 1962; Alajouanine and Lhermitte, 1965; Lenneberg, 1967; Woods and Carey, 1979; Woods, 1980; Vargha-Khadem *et al.*, 1985; Aram and Enkelman, 1986; Riva and Cazzaniga, 1986; 1992; Bates *et al.*, 2001). Further evidence emerged from the epilepsy literature, via methods such as sodium amytal ablation, dichotic listening and implanted electrodes (Penfield and Roberts, 1959; Rasmussen and Milner, 1977; Everts *et al.*, 2010), demonstrating the capacity of the young brain to reorganize language following early seizure onset. For example, the Montreal series (Rasmussen and Milner, 1977) showed that left hemisphere language dominance was less frequent in patients whose damage occurred prior to 6 years of age. Some studies of childhood stroke (Pavlovic *et al.*, 2006; Ballantyne *et al.*, 2008) also report good recovery and normal development after unilateral perinatal and child stroke. Heatherington and Dennis (2004) describe a 13-year-old twin who sustained a left hemisphere ischaemic stroke at the age of 7 years, but recovered basic language skills supporting the possibility of transfer of language functions to

undamaged brain regions. However, the authors also identified impairments in complex language skills, suggesting that there are limitations to plasticity in the immature brain.

Functional imaging studies provide evidence that, following early brain insult, there is potential for relocation of language skills or at least 'recruitment' of the non-dominant hemisphere (Müller *et al.,* 1999a). Herz-Pannier and colleagues (2002) reported serial functional MRI pre- and post-left hemispherectomy, with initial post-surgery assessments identifying global language impairment, and then gradually recovering receptive, but not expressive skills. Ten months post-surgery, functional MRI showed a right shift in language-related networks, mirroring left hemisphere language areas. While the authors interpret these results to suggest the presence of a pre-existing bilateral language network, it may be that such networks are specifically activated in the context of complete left hemisphere resection. Indeed, other researchers report less dramatic effects, where undamaged areas are recruited to support, rather than take over, language function (Thulborn, 1998; Heiss *et al.,* 1999; Anderson *et al.,* 2002).

While neural plasticity may underpin good recovery following early brain insult, it fails to explain instances of poor outcomes. Children with prenatal lesions, those sustaining insults during the first year of life, and those with bilateral or diffuse pathology commonly experience severe and permanent neurobehavioural impairment (Rasmussen and Milner, 1977; Riva and Cassaniga, 1986; Leventer *et al.,* 1999; Anderson *et al.,* 2004b). Longitudinal research investigating outcomes from generalized early brain insult suggests significant deficits, with sequelae reducing as the age at insult, and thus the maturity of the brain, increases (Anderson *et al.,* 1995, 2005a; Anderson and Moore, 1997; Ewing-Cobbs *et al.,* 1997). Similarly, studies comparing outcomes across the lifespan have highlighted poorest results associated with early brain insult (Strauss *et al.,* 1995; Hessen *et al.,* 2007; Duval *et al.,* 2009). For example, Glosser and colleagues (1997) report that adults with early-onset focal epilepsy demonstrate abnormal brain structure and reduced cognitive skills, not seen following adult onset. Similarly, Duval *et al.* (2009) studied a large sample of 725 cases of brain insult occurring from 0 to 84 years and concluded that later insults were associated with better recovery and outcome.

Many studies supporting the early vulnerability model document impairments in abilities important to the acquisition of knowledge and skills (e.g. attention, learning, executive function) which may have a cumulative effect on ongoing development, with increasing deficits emerging through childhood as more functions are expected to mature and need to be subsumed within the undamaged tissue (Ewing-Cobbs *et al.,* 1997). Milner (1974, p. 87) originally articulated this possibility, describing the process of crowding and its implications as follows: '...there is always a price to pay for such plasticity...verbal skills tend to develop at the expense of non-verbal ones in this kind of hemispheric competition, but the fact remains. Both are low.'

In summary, human research investigating the relative advantages and disadvantages of early brain plasticity is plagued by methodological flaws, which likely explain some of the inconsistencies in findings. Many studies are based on selected case studies, or small samples. These samples are commonly heterogeneous with respect to critical variables including nature, timing, lesion location, presence of seizures, sample selection criteria and imaging methods, age at testing and domains assessed (Vicari *et al.,* 2000). Outcome measures are often insensitive, and follow-up periods are frequently too short to rule out the emergence of later dysfunction. A critical evaluation of the literature demonstrates that neither early plasticity nor early vulnerability perspectives are able to explain the range of outcomes following early brain insult, and that each represents an oversimplification of the multiple complexities in play (St James-Roberts, 1975; Taylor and Alden, 1997).

# Factors impacting recovery following early brain insult

In order to better understand outcome from early brain insult, it may be informative to consider instances associated with either uniformly poor or good outcomes. For example, diffuse insults, leading to observable pathology on neuroimaging (for example, due to hypoxic–ischaemic encephalopathy or traumatic brain injury), results in uniformly poor outcomes, regardless of timing of insult or environmental influences. The search for consistently good outcomes is more complex. For example, while early brain insult due to mild traumatic brain injury or uncomplicated cerebral infection have been reported to be mostly benign, when insult is sustained in infancy or where family dysfunction or pre-existing neurobehavioural problems are present, recovery may be incomplete. One potential explanation for the failure to move forward the debate regarding the magnitude and quality of recovery following early brain insult may be the lack of acknowledgement of the influences of factors that contribute to recovery and outcome—nature, size and site of insult/pathology and related complications (e.g. seizures), age at insult, gender and environment, despite the fact that such factors were recognized by Kennard as early as 1936 (Ward and Kennard, 1942; Dennis, 2009). The following discussion examines the literature relevant to these factors and considers the hypothesis that early plasticity and early vulnerability are not opposing views, but represent extremes along a 'recovery continuum'. Where an individual falls on that continuum is determined by a complex interplay between these various factors.

Injury factors: nature, extent, site of insult

Injury-related factors are by far the best investigated of all potential influences for recovery. A recent emphasis on such issues in the developmental literature has highlighted that adult-based findings cannot necessarily be extended to brain–behaviour relationships and recovery patterns following early brain insult.

Extent/severity of lesion

Early research, both animal and human, consistently reported that larger lesions produce greater impairment. Others hypothesize that
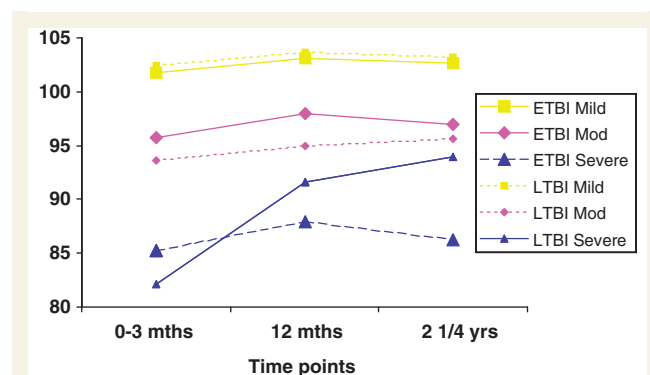
Figure 5 Impact of diffuse early brain injury (traumatic) and age at insult on intellectual function up to 2.25 years post-insult (ETBI = injury ⩽ 7 years; LTBI = injury ⩾ 8 years). Adapted from Anderson *et al.* (2005*a*).

extent of lesion and outcome are best represented by a U-shaped curve, with small and large lesions leading to better outcome than intermediate lesions (Thal and Bates, 1989; Bates, 1999), or that there might be no relationship at all (Vargha-Khadem *et al.,* 1985; Ballantyne *et al.,* 1992; Dall'Oglio *et al.,* 1994; Jacobs and Anderson, 2002). As expected, small, focal lesions appear the most 'plastic', with good recovery documented (Aram and Eisle, 1994; Ballantyne *et al.,* 2008). In humans, a similar result has been documented for large, unilateral lesions, with the proposition being that interhemispheric transfer of function may be forced, with minimal impact on functional abilities (Ballantyne *et al.,* 1992; Anderson *et al.,* 2006). Kolb and colleagues (1989, 1997) have also documented good outcome associated with massive re-organization of cortical circuitry in rats following total resection of one frontal cortex. The impact of 'crowding' remains uncertain, especially in the context of large lesions, where multiple functions need to be subsumed by less brain, potentially causing a general depression of neurobehavioural function.

Results appear to be more consistent when early brain insult is diffuse or bilateral, regardless of age at insult, with large lesion size or extent of pathology associated with greater impairment (Catroppa *et al.,* 1999; Stevens *et al.,* 1999). For example, as illustrated in Fig. 5, our group has reported on a prospective, longitudinal study of children with traumatic brain injury, demon-strating significant and sustained differences in intellectual ability up to 30 months post-insult, with children sustaining more severe insults showing lower ability (Anderson *et al.,* 2004*b*). We have identified similar 'severity' effects on intellectual measures for chil-dren sustaining complicated versus uncomplicated meningitis (Grimwood *et al.,* 1995), and for children treated with varying doses of cranial irradiation for the treatment of leukaemia (Anderson *et al.,* 1994, 2000). These results support the need for the presence of some healthy tissue for optimal recovery.

Site of lesion: laterality/location

The majority of studies addressing the impact of lesion site have examined children with perinatal stroke and early-onset epilepsy, and have failed to establish consistent laterality effects for all but

the simplest motor functions (Thal and Bates, 1989; Vargha-Khadem *et al.,* 1992; Cohen-Levine, 1993; Bates, 1999; Ballantyne *et al.,* 2007). These results are largely replicated in studies of other focal conditions, with the exception of a handful of studies, which report that right and left frontal lesions lead to somewhat different impairment profiles in the domains of atten-tion and executive function (Eslinger and Biddle, 2000; Anderson *et al.,* 2000, 2005*b*).

In stark contrast to adult findings, few studies examining the neurobehavioural consequences of early brain insult have identi-fied location-specific effects. In their early work, Rasmussen and Milner (1977) argued that lesion location was relevant for reorganization of function, with intact frontal and parietal regions necessary for this to occur. Work from our laboratory supported the importance of these areas for reorganization or 'recruitment' of additional cerebral regions, but with reorganization not neces-sarily linked to behavioural outcome (Anderson *et al.,* 2002, 2006). More recently, several publications have emerged describ-ing outcome from unilateral perinatal (Ballantyne *et al.,* 2007) and acquired child stroke (Pavlovic *et al.,* 2006), and focal lesions (Jacobs and Anderson, 2002; Anderson *et al.,* 2009*c*; Jacobs *et al.,* 2010), which provide little evidence for a relationship between lesion location and outcome. Even in the highly studied area of child traumatic brain injury, correlations between path-ology site and behavioural outcome are inconsistent (Power *et al.,* 2007). Rather, it appears that the extent of damaged tissue is the strongest predictor of outcome.

In summary, there is a complex relationship between injury fac-tors, recovery and outcome. While dose–response relationships between insult severity and outcome are well established in in-stances of diffuse pathology, this association is not easily extra-polated to more localized insults. Further, indices that are generally diagnostic in adults, location and laterality are less predictive of recovery following early brain insult, possibly due to incomplete functional localization in the immature brain during early child-hood. These findings imply that the integrity of the entire brain may be necessary for efficient function in the child, and provide little support for the innate specialization model or for localization-ist approaches.

Age/developmental level at the time of brain insult

Animal research describes a complex and non-linear relationship between age at insult and recovery, in keeping with previously discussed notions of critical or sensitive periods (Kolb *et al.,* 2000*a*; Johnson, 2005), and the neural processes underlying these. A capacity for neural restitution, either via neural regrowth or anatomical reorganization after early brain insult (Kolb *et al.,* 2004; Giza and Prins, 2006), is clearly established; however, win-dows of opportunity for good recovery appear quite limited. Kolb and his team have described precise embryonic ages in rats in relation to both neural and behavioural recovery and propose that these may extrapolate to humans, with poorest recovery from birth to post-natal Day 7 (equivalent to the human perinatal period up to 1 month of age) and better recovery after that. Kolb

Table 2 Developmental stage and associated neural and behavioural recovery after early brain injury

Developmental stage		
Rats/humans	Neural recovery	Behavioural recovery
E18/human 1–2 trimester	Abnormal cortical growth	Functional recovery
P1–P6/human—last trimester	Small brain, dendritic atrophy	Severe functional impairment
P7–12—1–8 months	Dendritic/spine growth, cortical regrowth	Functional recovery
P120 (5 years+)	Dendritic atrophy, then growth	Partial functional recovery

Adapted from Kolb *et al.*, 2000*b*. E = embryonic day; P = post-natal day.

also provides a time line, linking developmental stage (rat/human), brain growth and pattern of behavioural recovery following early brain insult, highlighting that neural and functional outcomes are not always consistent (Table 2). Providing a rough guide, Kolb suggests that children will demonstrate reasonable recovery from focal frontal insult in the first and second trimesters, and early after birth (1–8 months), with poorest outcomes following insult in the third trimester and only partial recovery following lesions after the age of 5 years. Support for these findings comes from Schneider and Koch (2005), who demonstrate disrupted structural brain development after excitotoxic lesions in prenatal rats tested at puberty, but not in adult animals.

Human research has addressed both brain and behaviour dimensions in the context of age at insult. The drastic effects of early age at insult are probably best illustrated by examples of disruption of early gestation. Verity and colleagues (2003) describe conditions resulting from very early prenatal insults, leading to neural tube defects and severe functional impairment, for example, anencephaly and spina bifida. Later occurring disorders of proliferation (e.g. microcephaly, megancephaly), migration (e.g. lissencephaly, subcortical band heterotopia), and differentiation may result in more subtle intellectual and neurobehavioural impairment. Recent studies support poor outcome after prenatal injury, with little evidence of transfer of function from lesion site to undamaged tissue, and increased risk of developmental disability (Leventer *et al.*, 1999; Liegeois *et al.*, 2004; Spencer-Smith *et al.*, 2009). Examining outcomes from early lesions of the motor cortex, using transcranial magnetic stimulation, Staudt and colleagues (2004) identified a progressive decrease in the capacity for reorganization through pregnancy in response to insult. Moving chronologically through childhood, there is a wealth of evidence that brain insult during the perinatal period, such as hypoxic–ischaemic encephalopathy, can have drastic consequences for development (Bava *et al*., 2005). Stiles and colleagues (2009) have described region-specific thinning, corresponding to site of injury in the corpus callosum after neonatal stroke, suggesting disrupted neural transmission to the undamaged hemisphere. Supporting these findings, Max and colleagues (2010) report differential risk of neurobehavioural impairment following early compared with late childhood stroke, while Tasker (2005) describes atrophic changes in brain structure after early traumatic brain injury, as illustrated in the case of JB (Figs 3 and 4). Using extra-operative cortical stimulation in frontal and temporal language cortex with children with early-onset focal epilepsy, Duchowny and colleagues (1996) investigated whether language reorganization was related to epilepsy onset, and found no

evidence for a shift in language localization for children with prenatal or late childhood onset. In contrast, children with epilepsy onset between these ages showed potential for partial reorganization. Similarly, functional MRI language activation studies with children with unilateral perinatal stroke and other developmental lesions have found no evidence for large-scale reorganization of language (Raja *et al.*, 2002; Anderson *et al.*, 2006; Saccuman *et al.*, 2006).

Investigating the effects of age at insult in isolation may be misleading, as this factor may interact with other influences, for example, nature, site and insult severity. For example, Woods and Carey (1979) reported that the first 12 months of life were optimal for neural and functional reorganization. In contrast, examining focal and diffuse lesions separately, recent research suggests that damage during this time may be particularly detrimental, and may lead to neurodegeneration (Bittigau *et al.*, 1999, 2004), global cognitive deficits and social dysfunction, regardless of whether pathology is focal (Pavlovic *et al.*, 2006; Westmacott *et al.*, 2009) or diffuse (Anderson *et al.*, 1997; 2005*a*). Vulnerability appears to continue through the first 5 or 6 years of life in the context of diffuse insults, with infants and preschoolers showing poorer outcomes than school-aged children (Jacobs *et al.*, 2004; Anderson *et al.*, 2005*a*; Keenan *et al.*, 2007). In a study from our laboratory (Anderson *et al.*, 2009*c*) we found non-linear relationships, with focal lesions before 2 years of age associated with significantly elevated risk of neurobehavioural impairment compared with focal lesions after the age of 2 years (Fig. 6). Children with focal lesions in middle childhood show relatively spared function compared with those with early or later damage across a range of domains.

Functional neuroimaging provides an opportunity to explore interactions between age at insult and lesion characteristics, and the potential for reorganization more directly than was possible with earlier paradigms. Using PET, and a sentence-listening paradigm, in patients with left focal lesions, Müller and colleagues (1999*b*) found more right-biased activation following early lesions (<5 years) compared with later-onset lesions (>20 years). While this appears to support age effects on lateralization, the latter group showed a bilateral pattern of blood flow changes, which differed from the typical picture of left-biased activity in controls. In another study, using a sentence-generation task, patients with lesions prior to 6 years showed weaker asymmetry than those with late-onset lesions (>10 years) (Müller *et al.*, 1999*b*). Interestingly, when left hemisphere language dominance is retained, there appears to be an increase in intrahemispheric reorganization (Devinsky *et al.*, 1993). Taken together, these data support the
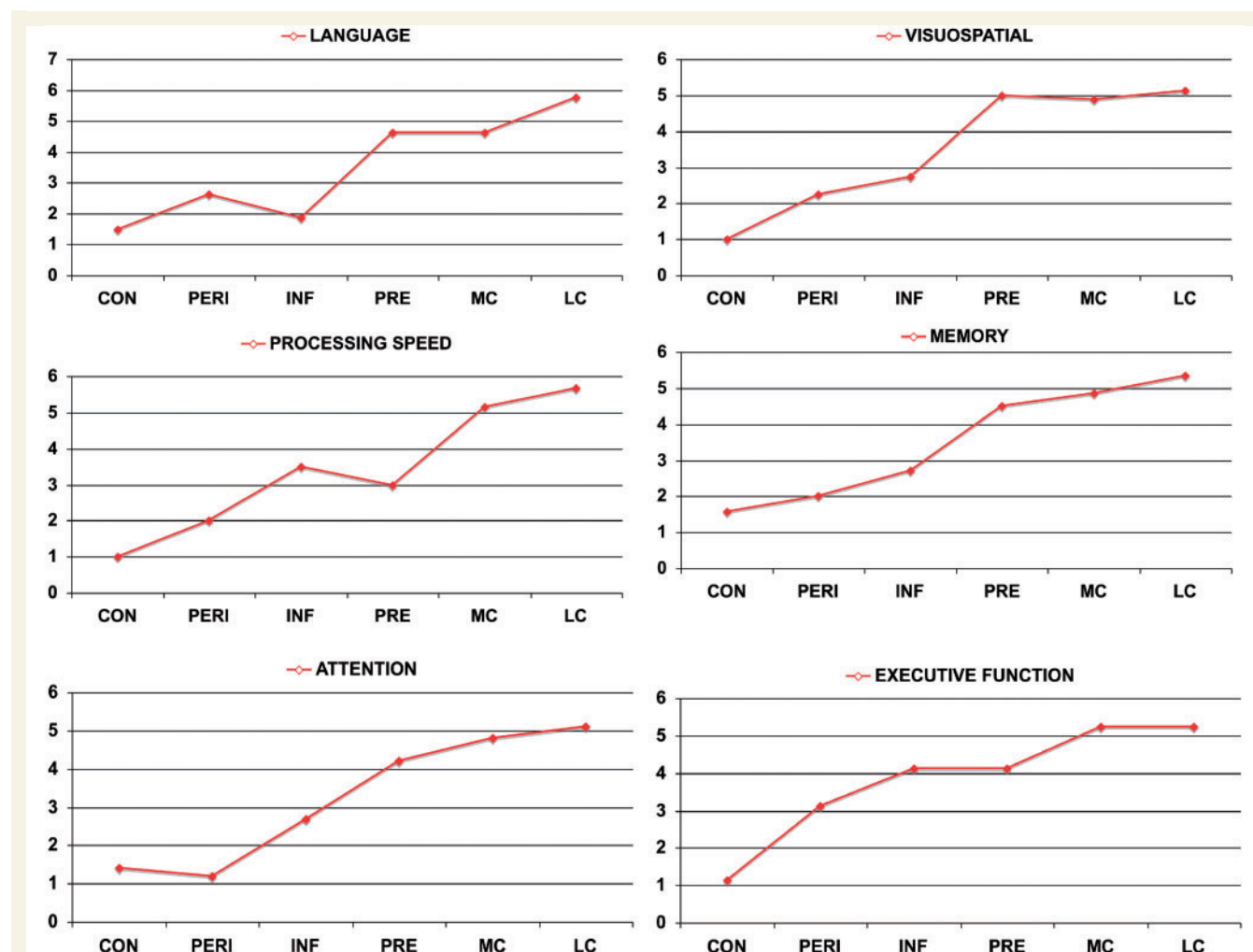
Figure 6 Early focal brain insult, age and neurobehavioural outcome. Adapted from Anderson *et al.*, 2009*b*. CON = congenital; INF = infancy; LC = late childhood; MC = middle childhood; PERI = perinatal; PRE = preschool.

notion that atypical lateralization is more frequently associated with early brain insult; however, some authors argue that the opportunity to reorganize may be graded in relation to age (Müller *et al.*, 1999*b*; Szaflarski *et al.*, 2006).

Lastly, it appears that there may be an interaction between age at insult and insult severity. A series of our studies, and those of others, have considered this possibility in children with acquired brain insult. Results are consistent across a range of CNS conditions and are in keeping with a 'double hazard' where more severe insult, earlier in development has the most devastating effects (Fig. 6). In contrast, less severe insult at early age and more severe insult at a later age are associated with better outcome. This pattern has now been demonstrated for traumatic brain injury (Anderson *et al.*, 2005*a*), meningitis (Anderson *et al.*, 2004*b*), cranial irradiation for the treatment of childhood cancer (Anderson *et al.*, 2000), and acute demyelinating encephalomyelitis (Jacobs *et al.*, 2004).

In summary, while there is evidence for a relationship between age at insult and recovery, this association is not entirely linear, particularly in early childhood where rapid changes are occurring within the CNS, and may not mimic patterns described in animal literature. Rather, recovery in these early years may be linked to underlying neural processes and related critical periods that provide 'windows of opportunity' for good outcome or, alternatively, periods in which plasticity is less functional.

Gender

Evidence supporting gender-specific effects of early brain insult is gradually emerging. Animal studies suggest that cortical development follows differential paths in males and females, largely due to hormonal factors, with the female brain developing more rapidly during early childhood (Kolb, 1995). These results are consistent with MRI studies of normal children, which show that grey matter volume peaks at around the age of 10 years in girls and not until the age of 12 years in boys (Giedd *et al.*, 1999; Sowell *et al.*, 2001; Gogtay *et al.*, 2004). Greater dendritic volumes have also been demonstrated in females (Jacobs and Scheibel, 1993; Kolb and Stewart, 1995), and functional MRI studies document gender-specific patterns of cerebral activation, with females exhibiting more bilateral activation (Shaywitz *et al.*, 1995). Further, Kolb (1995) reports earlier left hemisphere maturation in female

rats and suggests that this rapid development may leave fewer synapses free in language cortex, with a greater likelihood of transfer of function to the less specific right cortex. If female brains are more diffusely organized, and have a greater capacity for functional transfer, there may be greater potential for plasticity and reorganization of function (Strauss et al., 1992). Animal studies support this proposition, providing evidence that males and females demonstrate different plastic brain changes following early brain insult (Kolb and Stewart, 1995), despite relatively equivalent behavioural recovery. Gender effects are also identified in response to environmental influences, with young injured male animals showing a greater response to enriched environments than females, at both neural and functional levels (Kolb et al., 2000b).

Other research has considered the neuroprotective role of oestrogen in the female brain, with evidence that oestrogens are associated with enhanced cerebral reperfusion and antioxidant activity. Animal research supporting this possibility has documented a relative resistance to brain damage following stroke in female rats compared with males (Yager et al., 2005). Further, Strauss and colleagues (1992) argue that the male brain is less mature and so more vulnerable to insult, and Vargha-Khadem and colleagues (1992) report a similar finding in the context of perinatal insult.

Environment and experience

Stimulating, enriching environments are important for optimal development in healthy children, and may also play a role in maximizing recovery following early brain insult (Giza et al., 2005). Animal research shows that manipulation of post-injury environment influences both brain structure and subsequent learning capacities (Greenough et al., 1987; Kolb and Fantie, 1989; Neville, 1993; Fischer and Rose, 1994; Kolb, 1995; Ullen, 2009; Belsky and de Haan, 2011). Animal researchers have detected environmentally linked CNS changes in cortical thickness, size of dendrites and axons and number of synapses (Greenough et al., 1973; Rozenweig and Bennett, 1996). Enhanced brain connectivity, reorganization of functional cortical maps and associated cognitive benefits have also been reported in the context of complex housing (Kolb et al., 1994b), tactile stimulation (Kolb et al., 2000a), parent nurturing and specific training (Nudo and Milliken, 1996; Fineman et al., 2000; Liu et al., 2000; Williams et al., 2001). In young rats, even brief exposure to an enriched environment can decrease behavioural impairment and evidence of brain pathology (Kolb et al., 1994b), supporting the importance of intervention post-insult.

In keeping with broader principles of differential plasticity across the lifespan, it appears that the age at which the animal is exposed to these environmental influences plays a major role in their impact. Kolb and colleagues describe qualitatively different changes in distribution of synapses in young and old animals housed in complex environments and those provided with tactile stimulation, with these morphological responses paralleled by behavioural enhancement (Kolb and Gibb, 2001). Benefits were more robust for animals injured earlier (which were more severely impaired) than those injured later (which had better spontaneous recovery) (Kolb et al., 2000a). Timing of environmental

manipulation post-injury is critical, with little impact acutely, but better recovery associated with exposure to an enriched environment after the acute recovery period (Giza et al., 2005).

In children, environmental factors have also been identified as crucial for optimal development and recovery post early brain insult. Healthy babies given tactile stimulation grow faster and have earlier hospital discharge (Schanberg and Field, 1987; Field et al., 1996), while children from deprived backgrounds show accelerated growth when provided with enrichment experiences (Fox et al., 2010). Family function, socioeconomic status and response to disability also contribute to recovery following early brain insult (Breslau, 1990). Studies evaluating the impact of such factors in the context of insult severity suggest that environment and experience may become more important over time. With time since injury, children with severe cerebral insults, from disadvantaged social backgrounds and with limited access to support resources, exhibit significantly greater impairment and slower recovery than children with adequate social resources (Breslau, 1990; Taylor and Schatschneider, 1992; Taylor and Alden, 1997). Of note, recent research suggests that a focus on the child's environment, via parenting interventions, may enhance the injured child's recovery (Woods et al, in press).

Findings in this area have particular relevance to clinical practice, with environment and experience being unique in that they have the potential to be manipulated post-early brain insult in order to maximize recovery. To date, child-based research has generally failed to replicate findings from animal studies with respect to optimal timing for intervention (Fineman et al., 2000; Ip et al., 2002), and such research poses major ethical challenges.

Recovery from early brain insult: early plasticity, early vulnerability or a continuum?

Plasticity and recovery of function are concepts that have captured the interest of developmental neurobiologists, neurologists and neuropsychologists for several decades now, leading to a series of fundamental principles, and redefined ideas about neural and functional development and the repercussions of interruptions to these processes. The emerging picture depicts the young brain as dynamic, in constant interaction with the environment, and responding adaptively to learning and experience. In the context of injury, these predetermined processes continue, but appear to be vulnerable to disruption, particularly in the context on early brain insult. While the nature and extent of disruption due to early brain insult remains imperfectly defined, it is clear that recovery and outcome are underpinned by a range of complex neural processes that appear to be specific to the immature brain. These 'neural' processes interact with developmental, constitutional and environmental influences, which may act independently, but also in synergy. Thus, neither early plasticity nor early vulnerability perspectives in isolation are able to explain the range of consequences observed in the wake of early brain insult. Rather, as illustrated in Fig. 7, these two positions represent

Figure 7 Recovery from early brain insult: a continuum?
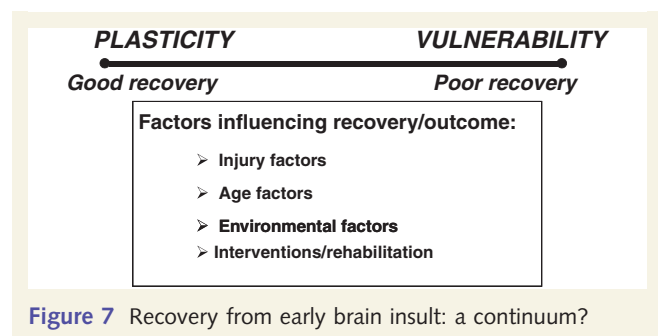
extremes along a recovery 'continuum', with biological, developmental and environmental agents making substantive contributions to where the individual's recovery trajectory will fall along the continuum.

Based on the evidence reviewed, and employing this continuum model, several key 'recovery' principles emerge:

  (i) plasticity processes respond differently within healthy and damaged brains;
 (ii) neural and functional plasticity are related, but not synonymous processes, with functional recovery not a necessary consequence of neural recovery;
(iii) insult to the immature brain derails subsequent development and impacts on the establishment of functional neural networks, causing abnormal functional systems and localization of function;
 (iv) critical periods in development are particularly sensitive to brain insult, with the potential for both best and worst outcomes during these growth spurts;
  (v) recovery mechanisms, including both restitution and substitution of function, offer little advantage to the developing brain over the mature brain;
 (vi) the full extent of consequences of early brain insult may not be evident until many years post-insult, when impairments become apparent in response to increasing environmental demands;
(vii) both injury and non-injury factors impact on recovery from early brain insult, and are likely to interact in a complex way which may vary according to severity of insult, age at insult and time since insult; and
(viii) the impact of early brain insult differs among functional domains, at least in part because of their varied neural representation and developmental trajectories.

Clinical implications

Evidence is building at multiple levels of investigation—basic science, clinical neurology and behavioural sciences—to highlight the increased risk of morbidity following early brain insult, as compared with similar later insult. This elevated risk is associated with the immaturity of the CNS, and the potential that disruption will lead not only to direct, injury-specific insult, but will also derail ongoing developmental processes. This work is still in its infancy. The challenge then is to identify acute interventions, tailored specifically to the developing brain, which will minimize secondary

effects of brain insult (e.g. pharmacological agents, hypothermia treatment) and reduce neurobehavioural morbidity.

Increases in our evidence base highlight specific risks associated with more severe insult, young age at insult, social disadvantage and, potentially, male gender. When any two (or more) of these factors occur together (e.g. severe injury/young age, severe injury/social disadvantage), a 'double hazard' effect may result where risk is greater than simply the additive effects of the individual dimensions. This pattern of findings has important clinical implications. First, long-term outcome studies are important to map the full extent of the neurobehavioural recovery after early brain insult and predictors of these outcomes, including studies following survivors of early brain insult into adolescence. Secondly, for 'high risk' children, where multiple risk factors are present, the need for intervention and follow-up is greatest. Thirdly, while injury and developmental factors are difficult to influence, the experience and environmental dimensions offer opportunities for intervention. Specifically, child-based rehabilitation, school-based assistance and parent support, each of which take advantage of the potential of the CNS to modify based on external input, may be critical to optimize recovery and outcome for the injured child. The empirical base for effective treatments for child brain injury is limited, and plagued by ethical challenges. Despite this, there is a small and growing body of literature that demonstrates enhanced recovery post-early brain insult in a range of domains including: motor function (e.g. constraint-induced movement therapy), cognitive skills (metacognitive training, use of compensatory aids), and social and behavioural function (individual psychotherapy, parent training). There is a need to expand these intervention options in order to maximize outcomes and future quality of life for survivors of early brain insult.

Future directions

Despite technological and scientific progress over recent decades, theoretical advances have been slower to emerge. More than 150 years ago, researchers grappled with the issues that continue to capture our interest, albeit without the sophisticated tools that we now have available. Today, we have made significant gains in our knowledge within individual disciplines. Basic scientists can now identify genetic mechanisms and age-specific recovery processes; psychologists have more sensitive tools with which to measure neurobehavioural impairment; and the clinical neuroscientist has developed methods to more directly picture neural and functional recovery. While progressing largely in parallel, the potential synergies across research focusing on neural and functional processes and outcomes are becoming evident as researchers in each area begin to drill down to consider the various potential influences on recovery processes.

The future challenge is to embark on translational research that brings together bench science, behavioural research, neuroimaging and clinical expertise, to share knowledge and concepts and direct new research paradigms appropriately and lead the way in developing effective treatments. Multi-centre, longitudinal research, employing such a cross-discipline approach is likely to be particularly effective in achieving these goals.

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