Contributions of non-human primate research to understanding the consequences of human brain injury during development

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Abstract

In this introductory review, we first present a theoretical framework as well as a clinical perspective regarding the effects of early brain injury on the development of cognitive and behavioural functions in humans. Next, we highlight the contributions that nonhuman primate research make towards identifying some of the variables that influence long term cognitive outcome after developmental disease, or damage. We start our review by arguing that in contrast to adult-onset injury, developmental brain insults alter the ontogenetic pattern of brain organization and circuit specialisation depending on the variables of age at injury, the focality of the lesion, and the potential for reorganization. We then introduce the two nonhuman primate studies in this section (Kiorpes on vision; Bachevalier on cognitive memory), and highlight the relevance of their findings to our understanding of developmental conditions or injuries in humans, with the ultimate goal of improving the health and development of the young.

Introduction

This paper aims to provide a broad overview of basic principles of neurocognitive development that have been uncovered through the combination of clinical and basic research in pediatric populations and nonhuman animal models.

We will begin by outlining the peculiarities brought about by the dynamic and interactive nature characteristic of developmental processes and detail how we have come to learn that developing brains are fundamentally different from miniature adult brains. We will then discuss how interactions between spatially and functionally distinct brain regions, neural plasticity, and developmental timing are key to brain maturation, and how these properties of brain development result in unique vulnerabilities and responses to insult early in life. The

study of brain development, and especially its response to insult, is fraught with difficulties due to its multifactorial and time-sensitive nature, and therein lies the value of research on animal models alongside research in clinical and healthy children populations. The use of animal models to understand brain development provides unique opportunities by enabling prospective longitudinal studies, controlled loss-of-function manipulations, and direct access to developing neural circuits. Animal research therefore contributes critically to our understanding of how age at injury, plasticity, reorganization of function, and other factors all interact to contribute to cognitive outcome after childhood brain insult.

Differences in outcome after Adult vs. Child Brain Injury

The neuropsychology literature on the effects of brain insult in adults provides ample evidence of single, double, and even triple dissociations between cognitive domains (e.g., verbal vs. nonverbal and implicit vs. xplicit) and between specific aspects within each domain. Brain damage acquired in adulthood often results in severe, yet selective, dissociations in high-level cognitive impairments, such as amnesia, aphasia, agnosia, acalculia, or alexia. This evidence, alongside that gathered via experimentally induced loss of function (via, e.g., lesion or inactivation) in nonhuman primates (NHPs) and other animal models, has given rise to the view that the adult brain is composed of a complex set of specialized circuits, each dedicated to specific functions, and each implementing different algorithms to solve unique challenges (1). Current trends in both systems neuroscience and cognitive psychology recognize, however, that this modular view of the adult brain belies staggering circuit complexity, and there is widespread recognition that, even in the adult brain, specialization of function is balanced by dynamic interactions between spatially segregated circuit nodes.

The study of developing brains poses its own unique challenges. Indeed, when compared to that in adults, the literature on cognitive dissociations following brain insult in children is surprisingly limited, and mostly includes single dissociations [e.g., impaired language or perceptual function (2–5)].

Moreover, the cognitive impairments that have been reported extensively in children are of a more general type, including autism and learning disability. Studies that report deficits in selective cognitive domains almost invariably describe less-severe phenotypes than those observed in adults (e.g., dysphasia, dyscalculia, and dyslexia).

A particularly poignant exception to this rule is the case reported by Vargha-Khadem et al. (6), of an adolescent boy (Neil), who, following a metastasizing pineal tumor, presented with 3 severe and selective high-order deficits: global anterograde amnesia, visual agnosia, and alexia (not accompanied by agraphia), in the context of normal verbal intelligence. These dissociations are all the more striking as Neil was able to report postmorbid memories through the medium of writing, memories that remained consciously inaccessible to him.

This exception notwithstanding, the pattern of cognitive impairment following brain insult during development is radically different from that observed after brain damage acquired in adulthood. The reasons for these differences could be due to lower incidence (focal brain damage due to, for instance, stroke or head injury, may be rarer in children than in adults) and/or be the result of underreporting (neuropsychological research in pediatric populations may still be lagging behind that in adult populations).

Another plausible explanation for the adult–child difference in outcome is that focal lesions early in life have a widespread effect compared to equivalent lesions in adults because the learning potential of intact regions in the developing brain is reduced after damage to other regions with which they are associated during maturation. This results in the stunting of overall cognitive ability. Paradoxically, the effects of focal lesions in early life are less selective than those sustained in adults because the relative plasticity of the intact regions of the immature brain can to an extent compensate for the functions of the damaged regions. The pattern of cognitive deficits after childhood-acquired brain damage thus appears more generalized and less specialized than that resulting from adult-onset brain disease and trauma (7).

Although each of these factors may play a role, they are unlikely to be sufficient to account for the prevalent observation that brain damage during development affects the brain in a qualitatively different manner than in adulthood. An alternative hypothesis must be considered to account for these discrepancies, namely, that these differences may arise due to the timing of the initial injury and its effects on the trajectory of progressive hemispheric specialization.

Age at Injury, Equipotentiality and Specialization

Early theories of the ontogeny underpinning brain organization have swayed between the extremes of early specialization (8, 9) and equipotentiality/age-dependent plasticity (10), with both positions surviving the test of time with help from the application of neuroimaging

techniques (e.g., refs. 11–13). Recognizing the undeniable fact that in the absence of early brain damage the vast majority of adult individuals exhibit hemispheric specialization, most notably for speech and language, and cognizant of the need for compatibility between neuronal plasticity and early hemispheric equipotentiality, a number of researchers have argued for a middle ground between the 2 extremes (14), with the view that "constrained plasticity" (15), or "ontogenetic specialization" (16) progressively unfolds during brain maturation.

Ontogenetic specialization posits a genetically driven anatomical basis for the development of hemispheric specialization, with the functional manifestation of this genetic predisposition emerging in interaction with the environment during normal development until maturity is reached and Hebbian circuits are established with corresponding diminution in neuronal plasticity and compensation. Thus, if focal brain injury occurs at a late stage of development (viz during adolescence), the result is one of selective and chronic deficits resembling those reported in adults. An illustrative case is that of Nicola, who at the age of 13 y was diagnosed with Rasmussen's encephalitis and epilepsy partialis continua affecting the anterior region of her left hemisphere, necessitating an anatomical left hemispherectomy at the age of 15 y to arrest her seizures. In long-term follow-up, Nicola presented with a persistent Broca's aphasia and the rare, adult-reported syndrome of "deep dyslexia" which is attributed to the inability of the right hemisphere to subserve phonological decoding, a specialized function of the left hemisphere (17).

A very different scenario emerges if brain injury occurs early in life, during infancy or childhood. Here, the genetic predisposition for the development of hemispheric specialization is sacrificed to facilitate plasticity and compensatory mechanisms to rescue cognitive and behavioral functions, specifically high-priority functions such as speech and communication skills. The price for this reorganization, however, is the stunting of overall ability depending on the level of development achieved prior to the onset of the brain injury. An illustrative case is that of Alex, a young boy diagnosed during infancy with Sturge–Weber syndrome accompanied by epilepsy, hemiplegia, and hemianopia. As a young child, Alex was hyperactive, with limited cognitive ability (viz in the profoundly impaired range), and speechless until the age of 9.5 y, when after a total left hemispherectomy he began to speak for the first time, well beyond the "critical period" for the development of speech and language (18). In the first few months after speech onset, the rapid emergence of speech sounds and early words had the quality of a "release from inhibition," suggesting that the isolated right

hemisphere had already reorganized to accommodate the basic requirements of verbal praxis and orovocal expression. In long-term follow-up between the ages of 11 and 15 y, however, Alex's speech and language abilities increased incrementally, such that as an adolescent he spoke in well-articulated grammatical sentences with appropriate intonation and social communication skills. Alongside this increase, Alex's verbal intelligence quotient (IQ) also increased by an SD relative to his baseline, although his performance on other components of the IQ test (viz nonverbal IQ, working memory, and processing speed) showed more limited gains, thus reducing his composite full-scale IQ score. This case report suggests that, consistent with the original hypothesis of Lenneberg (10), the "critical period" for the trajectory of speech and language development extends from birth to puberty, and possibly beyond.

As stated above, ontogenetic specialization applies to normal development of brain organization. It follows the Hebbian principles of synaptic plasticity enabling the emergence of neuronal circuits for learning. However, in the presence of early brain injury, this progressive process of specialization is disrupted in favor of Lashley's principle of equipotentiality (19), where immature or not-yet-dedicated brain regions reorganize to subserve the putative lost functions. Compensatory mechanisms are competitive with respect to those of specialization, with the degree to which the former overrides the latter being determined by factors such as age and stage of brain maturity at onset of injury, locus and extent of brain damage, and stage of hemispheric specialization attained at the time of injury. As a general rule, early lesions reduce learning potential but facilitate the rescue of high-priority functions, while late lesions preserve the products of past learning but yield selective deficits similar to those reported in adults.

Limits of Reorganization

Whereas age at onset of unilateral lesions can be a good predictor of the extent of reorganization possible by the immature brain, bilateral homologous lesions can set the limit to such reorganization. This is the case in both children and juvenile monkeys, where, for example, neonatal bilateral lesions of the hippocampus will result in the emergence of a hippocampaldependent memory disorder later during development (20–23). As such, using monkey and/or rodent models of anatomical disruption of entire circuits, or parts thereof, can inform medical practice, for example in surgical decision making for childhood epilepsy surgery where bilateral pathology of the medial temporal lobe is suspected and consequences

of gaining seizure freedom needs to be weighed against the functional memory deficits that might ensue.

Early Focal Lesions and Their Widespread Effects during Development

Early focal lesions of either hemisphere accompanied by seizures, and sustained before the development of the building blocks serving cognitive function, can lead to deficits in learning and intellectual ability in the long term. Importantly, static lesions unaccompanied by seizures do not produce similar deficits, thus highlighting the deleterious consequences of earlyonset seizures on cognitive development (24, 25). The adverse consequences of temporal lobe lesional epilepsy before the age of 1 y is testimony to the widespread effects that such focal lesions can have on the wider cognitive network (26). Contrary to the widely held view that early lesions can rescue cognitive functions through plastic changes and reorganization, it is now recognized that some early lesions, even those that are unilateral, can have widespread effects by not only impeding circuit structure but additionally by interfering with the structure of other circuits with which they interact. This pattern of widespread structural and functional disruption is reported in both humans and NHPs (26, 27).

Growing into Functional Deficits

Insult to the developing brain has the potential to cascade from one brain circuit to another, across both space and time. Indeed, the cognitive effects of brain damage early in life often become apparent only much later during development. This phenomenon has been referred to as “growing into the deficits” (see ref. 28 for an example from the declarative memory domain) and is thought to reflect the differential maturation schedule of specific perceptual and cognitive domains. In the perceptual realm, for instance, it is known that the sequence of development of sensory systems is identical among vertebrates (29) (proceeding from somatosensation and olfaction to vestibular, auditory, and finally visual). In the cognitive domain, it is well documented that functions relying on prefrontal circuitry (most notably executive functions) exhibit a protracted developmental maturation, with gradual emergence in late childhood and completion well into adolescence and young adulthood. Thus, damage to frontal brain areas is often “silent” until adolescence and its severity manifests fully only later in life.

Early Life Adversity/Negative Caregiving and Their Widespread Effects during Development

Negative caregiving (maltreatment or neglect) during early life often translates into long-lasting and pervasive deficits in cognitive, affective, memory, social functioning, and stress reactivity later in life. It is the brain areas that display the more protracted maturational schedule that seem to be selectively vulnerable to early-life adversity: hippocampus, amygdala, and prefrontal cortex. Importantly, observational studies have documented how maltreatment and neglect are observed, in the wild, in both primate and nonprimate species (30). Animal models have been instrumental in charting the neurobiological mechanisms through which maternal responsiveness alters and regulates the infant's brain and establishes the infant–mother bond. Research from Sullivan's laboratory (for a review see ref. 31), in particular, has demonstrated that the first 10 d of life in the rat represent a sensitive period during which infant–mother attachment is established, via enhanced noradrenergic and concurrent suppression of amygdala activity (which dampens aversive learning). At around postnatal day 10, an important switch occurs, whereby amygdala function is disinhibited, thus allowing aversive learning to take place. The mother's presence, during this developmental period, is still an important regulator of aversive learning, via its modulation of corticosterone release (rodent equivalent of cortisol in humans). The presence of a caring mother thus regulates negative experiences in the rat pup, providing "social buffering" [a phenomenon also observed in humans and NHPs (32)]. When negative caregiving is experimentally induced in rat dams (by restricting access to bedding material), corticosterone levels in the pups increase, the attachment window closes early, and fear learning onset is also advanced. This, in turn, is thought to lead to long-lasting alterations in amygdala–prefrontal cortex interactions and stress reactivity (reviewed in ref. 33). Studies in animal models have demonstrated how limbic and hypothalamic circuits undergo critical functional changes early in life, and how these changes are modulated via mother–infant interactions, providing neurobiological explanations of why these circuits are highly vulnerable to adverse caregiving, especially at a time when infants are most dependent on maternal care.

The development of an NHP model of negative caregiving which results in infant maltreatment illustrates how this results in adverse outcomes on social behavior, stress, and emotional regulation, mediated via alterations in the developmental trajectory of prefrontal, amygdala, ventral striatum, and serotoninergic circuits (32). Using this experimental design, Sanchez et al. further demonstrate that early adversity results in acceleration of cellular aging (tracked via telomere length shortening) and that this, in turn, predicts elevated activity of the hypothalamic/pituitary axis later in life. NHP models of maltreatment and neglect, thus, carry

a strong translational value, as any of the above alterations can be studied prospectively and longitudinally; moreover, the introduction of a cross-fostering procedure (32) allows dissociation between the effects of postnatal experience and heritable factors, confounds that render interpretation of human findings extremely challenging.

Notwithstanding this challenge, studies of children exposed to severe psychological neglect/deprivation have documented long lasting aberrations in a range of psychological and biological processes (e.g., disruptions in the stress response system and the autonomic nervous system, disordered attention regulation, impoverished attachment), with reports of children raised in institutions revealing a plethora of adverse consequences on socialemotional functioning, psychiatric status, and neural integrity (e.g., reduced grey and white matter brain volumes) (see ref. 34 for a review).

The Contribution of Research in Animal Models to Our Understanding of Brain Pathology during Development

It is abundantly clear that development is dynamic, and therefore age at injury is a fundamental variable that we need to control in order to predict cognitive outcome after developmental brain injury. The use of experimental animal models is particularly critical, as these allow the design of prospective and longitudinal studies, which are of paramount importance to disentangle the effects of timing of injury from other variables affecting subsequent brain development.

Visual Development

Maturation of different brain circuits occurs in stages reflecting the hierarchical organization of functional systems. For instance, visual cortical system development follows a specific timeline, with brain areas synaptically close to the sensory periphery maturing earlier than those more distant to it. The work of Kiorpes (27) exemplifies the role of carefully developed NHP models of developmental diseases of vision in children (amblyopia) in understanding the complexity of outcomes following abnormal visual experience during development. Kiorpes and colleagues have demonstrated that the scope of the deficits following altered visual experience is not limited to primary visual cortical function but extends to higher-order perceptual abilities like binocular vision, form and motion perception, and perceptual organization. In particular, access to direct readout of neuronal population activity in this NHP model allows mechanistic understanding of how these deficits come about, with this

potentially informing the design of new therapeutic strategies. Work by Kiorpes and collaborators has already been instrumental in identifying how current therapeutic strategies may exacerbate, rather than ameliorate, outcome of visual function (binocular vision) and will therefore be critical for therapeutic strategy improvement.

Memory Development

Research on the development of memory has also benefited from work in animal models (both rodents and NHPs). The protracted postnatal maturation of hippocampal circuitry is thought to underlie the delayed emergence of long-lasting episodic memories in early childhood in humans (35, 36).

In rodents, memory development in the healthy brain has been studied both at the behavioral level (using spatial memory as a proxy for episodic memory; for a review see ref. 37) and at the circuit level (via single-neuron recording). Recording of neural activity in developing rodents has mainly focused, thus far, on when the different spatial responses characteristic of hippocampal neurons emerge (38–42) and has only recently started to uncover the potential mechanisms underlying the delayed emergence of spatial memory in rodents (43).

Work on NHP models has been instrumental in defining how the declarative memory system may respond to early insult. Bachevalier (44) and others (45) have made extensive use of developmental lesion studies, coupled with careful neuropsychological assessments, to define the time course of emergence of hippocampaldependent cognitive functions and the effects of early insult on their subsequent maturation.

In particular, in a series of studies Bachevalier and coworkers discovered that neonatal hippocampal lesions result in visual object recognition memory deficits (tested via a visual pairedcomparison task) that are delay-dependent only in 18-mo-old animals. This is an example of "growing into deficits": Monkeys with experimentally induced hippocampal lesions in the neonatal period demonstrated levels of object recognition memory indistinguishable from control animals at 1.5 and 6 mo of age, possibly because this cognitive function is supported by extrahippocampal structures at these ages. It is only when hippocampal function matures (between 6 and 18 mo in macaques) that the recognition memory deficits become apparent in the lesioned cohort (28). Interestingly, this deficit is

chronic and does not appear to be compensated for in adult monkeys (46). A striking similarity to the infant-lesioned monkey data is seen in humans who suffer perinatal damage to the hippocampus bilaterally as a result of hypoxic–ischemic events. In patients with developmental amnesia, hippocampal-dependent episodic memory deficits first emerge around the age of 5 to 6 y, equivalent to age 18 mo to 2 y in the monkey (23), and they prove chronic throughout childhood, adolescence, and adulthood. Thus, it appears that both humans and monkeys "grow into deficits" after bilateral damage to the hippocampus of sufficient severity (47), with this type of early injury setting the limit of compensation for specific aspects of cognitive memory (48).

The team led by Bachevalier (44) reports that neonatal hippocampal lesions result in facilitation of object discrimination (tested via paired and concurrent object discrimination tasks), a cognitive function thought to rely on the procedural memory system. There is a large literature (e.g., refs. 49–51) documenting that, in adults, the declarative and procedural memory systems compete for cognitive control. Bachevalier's work (44, 52) extends these findings to the developmental period.

It would be critical to understand whether this facilitation also occurs in clinical pediatric populations, and if this could be leveraged to ameliorate the otherwise devastating memory deficits caused by early hippocampal damage in humans.

Summary and Conclusions

We began this review by summarizing the fundamental differences between neurocognitive function during development vs. adulthood, with particular emphasis on how these differences translate into specific patterns of deficits after brain injury. While focal adult-onset injury often results in profound deficits, largely restricted to one or more cognitive domains, developmentalonset injuries effectively alter the developmental trajectory and give rise to constellations of deficits which are less specific but also generally less profound (when damage is restricted to a single hemisphere). As development is characterized by enhanced plasticity and relies on widespread interactions across brain circuits, timing of injury is a critical factor that will determine outcome. Moreover, diaschisis (functional alteration of structures distant to brain tissue directly affected by the primary injury) following developmental brain injury is the norm rather than the exception. Thus, NHP models are an excellent guide for studying

developing circuits and their response to brain injury, as they allow us to directly and causally probe the mapping between circuits and their functional correlates and facilitate this across multiple developmental time points.

Lesion studies in NHPs and neuropsychological studies in children have uncovered an important distinction between outcomes following unilateral vs. bilateral injury: Unilateral brain lesions alter the ontogenetic developmental trajectory, with their outcome critically dependent on age at injury. This is due to the progressive nature of specialization of function during development and to neuronal plasticity, which facilitates reorganizational potential in the developing injured brain. In contrast, bilateral
lesions, even when acquired early in life, test the extent and limits of such plasticity and reorganizational potential, often resulting in chronic and more profound deficits than their unilateral counterparts (over and above what would be expected by a simple "mass" effect). Experimental work in NHP models has been, and will continue to be, instrumental in enhancing our understanding of the limits of developmental plasticity and reorganization of function and in aiding the design/testing of the efficacy of therapeutic interventions that may harness these compensatory mechanisms to promote more favorable outcomes.

The study of brain development in animal models is particularly valuable as it affords the design of prospective and longitudinal
designs, which are best suited to chart the "growing into deficits" phenomenon, whereby injury that occurred at a given developmental period will not become functionally apparent until later in life, when the cognitive function of the damaged brain area would have "come online." For example, the consequences of damage to frontal circuits early in life often manifest themselves behaviorally only around puberty; similarly, the effects of bilateral damage to the hippocampus at birth becomes evident only when the child reaches the age of 5 to 6 y, when healthy hippocampal circuits begin to support long-lasting episodic memories during typical development.

This review has emphasized the value of NHP developmental research, drawing examples from 2 distinct domains: sensory (Kiorpes' work on visual circuits), and cognitive (Bachevalier's work on memory circuits). Each of these lines of research directly translates to clinical conditions in children and adolescents and highlights the brain mechanisms that ultimately contribute to functional outcome.

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