Healthy and abnormal development of the prefrontal cortex

MEGAN SPENCER-SMITH¹,² & VICKI ANDERSON¹,²,³

¹Murdoch Childrens Research Institute, Melbourne, Australia, ²University of Melbourne, Melbourne, Australia, and ³Royal Children’s Hospital, Melbourne, Australia

(Received 8 October 2008; accepted 3 June 2009)

Abstract

Background: While many children with brain conditions present with cognitive, behavioural, emotional, academic and social impairments, other children recover with seemingly few impairments. Animal studies and preliminary child studies have identified timing of brain lesion as a key predictor in determining functional outcome following early brain lesions.

Review: This research suggests that knowledge of healthy developmental processes in brain structure and function is essential for better understanding functional recovery and outcome in children with brain lesions. This review paper aims to equip researchers with current knowledge of key principles of developmental processes in brain structure and function.

Timetables for development of the prefrontal cortex (PFC), a brain region particularly vulnerable to lesions due to its protracted developmental course, are examined. In addition, timetables for development of executive skills, which emerge in childhood and have a prolonged developmental course that parallels development of the PFC, are also discussed.

Conclusions: Equipped with this knowledge, researchers are now in a better position to understand functional recovery and outcome in children with brain conditions.

Keywords: Development, prefrontal cortex, executive functions, brain injury

Introduction

Many children with brain conditions present with cognitive, behavioural, emotional, academic and social impairments, often requiring lifetime intervention and support. Some children, however, demonstrate considerable recovery and seemingly few impairments. Research attempting to understand this variance has focused on identifying predictors of outcome in groups of children with specific brain conditions, such as traumatic brain injury [1,2], focal brain injury [3–6], cerebral toxicity and childhood cancers [7–10], stroke [11], cerebral infection [12,13], seizures [14–17], metabolic disturbance [18,19] and prematurity [20]. Together these studies are building a picture demonstrating the capacity of the immature brain to recover and develop after a brain lesion. These studies also suggest that outcome is related to identifiable brain lesion characteristics as well as developmental, environmental and constitutional factors. Individually these factors do not adequately explain the variance in outcome observed in children with brain conditions. Functional recovery and outcome are clearly determined by a complex and constantly changing relationship with all of these factors.

Timing of brain lesion has been identified as a central predictor of functional outcome in animal focal lesion studies [21–24] and preliminary child studies [4,11]. Key principles that have emerged from this research suggest that developmental processes occurring at the time of the brain lesion are particularly vulnerable to disruption. Further, these studies suggest that aetiology of the brain condition may be only one of many factors that shape functional outcomes. Based on systematic studies of focal frontal lesions in rats, Kolb et al. [25] propose critical periods in rat neurological development when brain lesions are associated with poor or better functional outcome and further suggest these critical periods may extrapolate to humans. While human research provides preliminary support for these critical periods, the model has not yet been systematically examined to determine whether it applies to humans. Based on child and adult studies examining language outcome after brain injury, Dennis [26] proposed stages in skill maturatio
when injury will be associated with poor or better outcome for that skill. This heuristic, however, has not yet been empirically tested to determine whether its principles extend to other cognitive skills.

Considerable research and theory has been directed towards better understanding the development of structural and functional specificity through childhood. Early studies argued strongly for innate specialization of the brain [27], however more contemporary studies are accumulating that suggest regions in the developing brain may not be as functionally specific as those in the mature brain [28,29]. Accordingly, damage to the developing brain, when brain networks are less established and therefore more brain regions are recruited to perform tasks, may result in more generalized dysfunction. Alternatively, reduced localization of function may allow for compensation or development of new networks in the context of brain lesion. In order to determine when greater or less potential for recovery might occur in children with brain conditions, knowledge of healthy brain development is essential.

This paper outlines healthy processes in development of brain structure and function that are essential for understanding functional outcomes in children with brain conditions. General principles of brain development that are helpful for understanding the mature brain are discussed. A review of time-tables for key neurological processes in development of the prefrontal cortex (PFC) is presented. This brain region is especially vulnerable to brain lesions due to its extended developmental trajectory. Research shows that, in adults, executive functions (EF) rely strongly on the integrity of the PFC, which plays an important role in efficient EF. Therefore, timetables for development of executive skills are also outlined and parallels in development of brain structure and function are examined. This review aims to provide an understanding of functional outcome in children with brain conditions.

**Healthy brain development**

While there is some understanding about healthy brain development, the impact of brain lesions on the expected course of development is unknown. Knowledge of how and when the brain becomes specialized, leading to its mature state, assists in understanding and investigation of functional and structural consequences of brain lesions.

**Theories of human functional brain development**

The healthy adult brain is highly specialized in structure and function, thought to reflect a modular organization. This approach attributes the processing of particular behavioural functions to distinct cortical regions, connected via specific neural circuits [30,31]. Lesion studies and functional imaging studies demonstrate that separate frontal regions support specific cognitive processes. For example, the medial prefrontal region has been shown to support attentional control processes including focused attention [32] and self-regulation [28]. Some evidence challenges this modular approach [33–35]. Stuss [35] has reported executive dysfunction in adults after extra-frontal brain damage and interpreted these findings as evidence that EF are associated with complex frontal and extra-frontal systems. While the PFC is critical for EF, it appears that integrity of the whole brain may be necessary for efficient EF [36–38]. This is especially the case in the developing brain, which has less established connectivity and structure.

How and when the brain becomes specialized is particularly relevant to understanding the neurobehavioural consequences of brain lesions. Early researchers suggested contradicting possibilities. Lenneberg [39] argued that the infant’s brain was ‘equipotential’ and that functional specialization emerged gradually through early childhood. In contrast, the ‘innate specialization’ model argues that key skills such as language are localized at birth [27]. More contemporary research examining human functional brain development highlights the importance of accounting for the influence of experience and genetics on the developing organisation of the brain. Johnson [30,40] acknowledges these influences and identifies three separate, but not necessarily incompatible, approaches to understanding progression of cognitive abilities in infants: (a) maturation; (b) interactive specialization; and (c) skill learning.

The maturational view proposes that the developmental sequence of specific neuroanatomical regions enables the hierarchical emergence of sensory, motor and cognitive processes. For example, the dorsolateral PFC (DL-PFC) supports successful performance on the object retrieval task, designed to assess working memory and inhibitory control in children [41]. Successful performance on the task involves activation of several brain regions, but the particularly protracted development of the DL-PFC is thought to be primarily responsible for change in behaviour, limiting the child’s efficiency until these brain regions are mature.

The interactive specialization view suggests that emergence of a new skill reflects refinement of connectivity between brain regions and not just activity in one or more region. For example, Anderson et al. [42] reported differential language activation over time in 8 year-old identical twins discordant for a left frontal tumour and seizures commencing at age 5. The affected twin initially
demonstrated typical left-sided brain activation on a language paradigm. Over time, activation became bilateral, thought to be associated with growth in the tumour. However, with emerging and increasing right hemisphere activation over time, deterioration in expressive language skills was documented in the affected twin but not the unaffected twin. The authors suggest that the emerging right activation might reflect pathophysiologic effects of the tumour in the prototypical language cortex rather than language transfer. Or, increasing right hemisphere activation might represent an unsuccessful attempt to reorganize language to the non-dominant hemisphere. In this case, disruption of left hemisphere language by the epileptogenic, progressive tumour might have limited or prevented its functional reintegration, instead provoking further recruitment of right hemisphere homologues. Alternatively, the right hemisphere activation might reflect the loss of active inhibition from the homologous left frontal region or loss of some other form of reciprocal interaction between frontal homologues.

The skill learning approach suggests that activation of brain regions changes during skill acquisition. For example, recent functional neuroimaging studies demonstrate more diffuse activation within prefrontal and extra-frontal regions in children performing executive tasks compared with adults. Further, increasingly focal activation is observed with age [28,29], reflecting an association between performance and emerging patterns of interactions between different regions.

Developmental progression of brain development

There are several developmental processes acting and interacting that contribute to brain development, including: (1) hierarchical progression; (2) regressive and additive processes; and (3) growth spurts in neurological processes.

Hierarchical progression. In general, there is a hierarchical progression in the development of the central nervous system (CNS), with the brainstem and cerebellar regions developing first, followed by posterior areas and anterior regions reaching maturity last [43–47]. This pattern of posterior to anterior maturation has been observed using many measures of brain development, including whole brain volume and white matter volume [48], electroencephalography (EEG) [45] and metabolic activity [49]. For example, increases in white matter volume (reflecting myelination progression) have been observed to occur in stages from primary and sensory areas, to association areas and finally frontal regions [48]. Further, the process appears to be site-specific, with DL-PFC maturing later than orbito-frontal cortex (OFC) regions [50], in keeping with the developmental timetables of executive skills which these brain regions underpin. Not all brain regions follow this pattern of development. Myelination of anterior regions of the corpus callosum is complete prior to posterior regions, which do not mature until adolescence [51,52].

Additive and regressive events. Additive and regressive developmental processes have been described as important in refining and increasing efficiency of cortical systems. Additive development is the ongoing accumulation of growth processes, such as progressive linear myelination from infancy through to adulthood [48,53]. Some neuronal processes exhibit periods of regression, a cycle characterized by an initial over-production and then selective elimination of redundant elements. For example, excess synapses are formed in infancy and through experience the obsolete connections are pruned [54]. There is also an initial over-production of dendrites followed by pruning to leave only the most functional branches [55,56]. Other measures of cortical maturation demonstrate an inverse association over time. O’Donnell et al. [57] reported cortical thickness in the frontal-polar region and DL-PFC to decrease linearly with age between 8–20 years. This is consistent with volumetric studies showing increases in frontal grey matter during pre-adolescence followed by a decrease during adolescence [44,58–60].

Growth spurts in development of the prefrontal cortex. Brain maturation is not linear, but is punctuated by a series of growth spurts (times associated with rapid development). Figure 1 illustrates the onset and conclusion of key neurological processes in the PFC, represented by the horizontal bars. Based on current understanding of timetables in typical development of the PFC, a number of major growth periods can be identified: (a) 6–18 weeks gestation, involves rapid proliferation [61,62]; (b) 3–5 months gestation, involves rapid migration [63,64]; (c) 6–9 months gestation, when significant

Figure 1. The onset and conclusion of neurological processes in the PFC during childhood (represented by horizontal bars).
The mature prefrontal cortex

The PFC is the largest region in the human brain, comprising a quarter to one third of the entire cerebral cortex [75–77]. In defining functions of the PFC, studies increasingly emphasize that cytoarchitectonic differences between cortical areas may not be as important as patterns of connectivity between and within the specific region [75]. Three sub-regions of the PFC have been distinguished by connections with different cerebral areas, which each subserve different executive processes: medial PFC, DL-PFC and OFC [78,79]. The DL-PFC has strongest connections with other cortical regions, supporting the view that this region is associated with higher order cognitive functions. In contrast, the orbital medial prefrontal regions have strongest links with subcortical regions, including limbic structures, suggesting a greater role for this circuit in social and emotional control. Sub-regions of the PFC are not independent and have strong connections with one another [79–81]. The PFC is the most highly interconnected area of the brain, receiving afferent fibres of visual, auditory and somatic origin [75]. The complex pattern of connectivity within the PFC and between the PFC and other brain regions suggests that, although PFC may orchestrate behaviour, they are heavily dependent on all other brain areas for input. Efficient functioning is therefore reliant upon the quality of information received from other regions. Highlighting this, Saint-Cyr et al. [82] identified five frontal-subcortical circuits that involve pathways connecting regions and integrating information influencing both behaviour and movements. These circuits include the motor, oculomotor, dorso-lateral prefrontal, orbito-frontal and anterior cingulate circuits. The refinement and establishment of these circuits is likely to be crucial for efficient neurological and cognitive functioning.

Developmental timetables of the prefrontal cortex

This study presents a review of developmental timetables for key neurological processes in the human PFC, demonstrating the prolonged and intricate orchestration of events that occur from gestation through to late childhood. Interruption to neurological development has different structural and functional consequences, which appear to vary based on timing of brain lesion.

Prenatal brain development

The prenatal period is the most rapid phase of development across the lifespan and is devoted to gross structural formation of the CNS [83]. During this phase the human CNS is transformed from a thin layer of unspecified tissue into a complex system that can process information and organize actions [84,85]. This transformation is largely genetically pre-determined, resulting from the intricate processes of neurulation, proliferation, migration, axonal extension, synaptogenesis, differentiation and apoptosis. These processes are further refined by experience, which may have advantageous or deleterious developmental consequences. Due to the complex choreography of events during prenatal development via intrinsic or extrinsic mechanisms, development of the PFC is vulnerable to interruption at this time.

Neural induction. At day 16 of gestation, neural induction begins [86], which involves the mesoderm layer of the embryo specifying the ectoderm to become the CNS [87]. The neural plate folds in on itself to form the neural tube and a small group of cells lateral to this form the neural crest, a process completed around the 5th week of gestation [88,89]. The neural tube later gives rise to all cells of the CNS.
(brain and spinal cord) and the neural crest cells produce most of the peripheral nervous system.

Interruption to development at this time can result in neural tube defects, which commonly lead to termination of the foetus or profound birth defects [84]. Spina bifida is a common and severely disabling neural tube defect which results in a range of physical and cognitive limitations, but not necessarily intellectual disability [90]. Anencephaly arises when the rostral end of the neural tube fails to fuse correctly [91,92], resulting in the absence of the major portion of the brain and the top part of the skull. Most infants with anencephaly will be stillborn and those born alive will generally live for a very short time.

**Proliferation.** Once the neural tube is fused, neurons intended to form the cerebral cortex are born as neuroblasts in the anterior periventricular region between ~6–18 weeks gestation [62]. These neuroblasts proliferate and differentiate before migrating towards the developing cortical plate [61]. The rapid growth spurt of radial glial fibres, which guide migrating neuroblasts to their final destination, commences early and is completed by ~20 weeks gestation [93,94]. Proliferation ceases at ~18 weeks gestation and the last neuroblasts formed within the neural tube move to their final destinations at this time. A growth spurt in glial cells also occurs, but later in gestation, between 20–40 weeks.

Interruptions to cell proliferation can result in microencephaly, a severe malformation associated with seizures and intellectual impairment [95]. Developmental microencephalies of a genetic origin arise from a reduced production of neurons or radial glial fibres during proliferation. Destructive microencephalies arise secondary to another process such as ischaemia, a toxic event or infection [96], which may be a consequence of mitotic inhibition, impaired neurite differentiation or destructive neuronal depletion, depending on the time of exposure [84,94,97]. Over-production of neurons may also occur, as seen in megalencephaly, a condition characterized by an abnormally large, heavy brain [97,98].

**Migration.** Once neuroblasts are born they migrate to their pre-destined brain region, a process which peaks between the 3rd and 5th months of gestation [63,64]. At this final destination neurons aggregate together with other cells of a similar type to form vertical columns and by 7 months the six cortical layers found in the adult brain have formed [94]. In most cortical and several subcortical areas, the distribution of neurons has an ‘inside-out’ spatial-temporal gradient [99]. Earliest born neurons are found closest to the proliferative zone, representing the first wave of migration and later born neurons guided by radial glial fibres travel greater distances from the germinal zone, representing the second wave of migration [99,100] occurring ~11–16 weeks gestation [101]. At this time the telencephalon expands and differentiates to form the cerebral cortex, basal ganglia, corpus callosum and other structures [91]. Recent data indicate that migration ceases ~30 weeks gestation [102], however this is still a matter of debate.

The destination of the migrating cell is determined by the pattern in which it migrates: radial or tangential. The majority (80–90%) of pyramidal neurons migrate in a radial pattern [99–101,103,104]. The activated receptor on the surface of the migrating neuron initiates a series of intracellular reactions that result in the neuron travelling along radial glial fibres to the outer areas of the developing cortex. Here it receives a signal to disassociate from the radial glial cell and become part of the cortex, where it will later be employed in the mature brain. The remaining cells migrate in a tangential pattern, which enable neurons to travel parallel to the surface of the developing brain, entering and exiting different brain regions guided by glial and axonal fibres [105]. It has been suggested that through this process of tangential migration, cell movement and thus cell morphology, as well as neurotransmitter phenotype, is to some extent plastic [84]. It is possible that this process might allow for the amelioration of errors in migration and other developmental processes. It might also have detrimental consequences, permitting environmental perturbations to adversely affect the developing CNS during the later part of foetal development.

Subsequently, minor aberrations to the expected course of migration may not manifest in clinical symptoms and some evidence suggests that such aberrations may reflect a variant of normal development [92]. Gross malformations, however, do occur. Arrest of neuronal migration occurring before 16 weeks gestation may result in Lissencephaly, a disorder affecting the entire brain that is depicted by a thickened cortex usually reduced to four layers. However, neuronal migration disorders may be restricted to focal cortical or subcortical areas. Subcortical band heterotopia is a relatively common brain condition that occurs when neurons fail to migrate to their intended destination, instead forming a band of heterotopic neurons, as illustrated in Figure 2. Periventricular nodular heterotopia is characterized by small clumps of neurons that have not migrated correctly, forming nodules on the walls of the lateral ventricles. The underlying cause for migratory disturbance is unclear, but there is some
evidence suggesting a genetic origin [97,106] and extrinsic influences such as vulnerability to a virus may also play a role [94].

Dendritic development and synaptogenesis. Once migrating neurons reach their final destination rapid extension of the axon (the transmitting element of a neuron) and arborization of dendrites commences at ~15 weeks gestation [56]. The first apical dendrites of immature neurons are present at 13.5 weeks gestation [65,107]. The outward growth of the axon is guided by the growth cone, located at the tip of growing neurites (axons and dendrites) [108]. Finger like projections, filopodia, seek out an appropriate environment by extending often several centimetres [109] into the surrounding environment and retracting when the encountered environment is unsuitable [110]. On reaching the target, axonal elongation ceases and the formation of a synapse is initiated, beginning at ~27 weeks gestation in the frontal cortex [53,56]. The synaptic density increases to a level that greatly exceeds adult levels.

The process of establishing and strengthening connections with other neurons, crucial to normal functioning [111], involves neurotrophic factors (signalling molecules that are necessary for neural survival) such as nerve growth factor [112]. These molecules are in short supply in the CNS, with only enough neurotrophic factors to permit half of the cells to live [113]. Axons that receive neurotrophic factors establish strong synapses, while axons that do not are forced to seek other synaptic connections or risk cell death (most likely apoptosis, a form of programmed cell death that eliminates cells with poor and perhaps unnecessary synaptic connections) [112]. Apoptosis is involved in the degeneration of nearly half of all neurons during development and is therefore imperative for normal development. Increased rates of apoptosis, however, may have negative consequences. Foetuses with Down syndrome have experienced high rates of apoptosis [114], which is thought to account for intellectual impairment associated with this syndrome.

As axons extend and dendrites arborize, the developing CNS becomes more densely packed and the surface of the brain acquires convolutions (sulci and gyri) to accommodate this increased cortical mass. Thus, through these processes of axonal outgrowth, dendritic development and synaptogenesis, the brain increases in size, connections are formed and the brain takes on a more mature appearance [84]. Toxic or ischemic events occurring after 20 weeks gestation are likely to affect neurotransmitter production and cell-to-cell interactions important in guiding the developing axon to its target. These CNS abnormalities are often difficult to detect using present techniques and the suggestion that environmental agents may disrupt development is derived from the observation that abnormalities are not apparent before 20 weeks gestation and therefore unlikely to be a result of a disruption in cell proliferation or migration. Inhibition of neuronal and glial growth and maturation may also manifest as late developmental microcephaly [98].

Differentiation. Following migration, differentiation of neurons occurs, the process of cells becoming more specialized over time [84]. Some cells undergo myelination and glial cells differentiate into oligodendrocytes and astrocytes. Radial glial fibres lose their attachments and relocate in the white matter.
and the lower part of the cerebral cortex where they transform into astrocytes. The differentiating neuron must acquire specific enzymes necessary for the production of neurotransmitters it will use [115].

Differentiation of the cortex follows an inside-out sequence of development, mimicking neuronal proliferation and migration [84]. Thus, neurons in the deeper regions of the cortex differentiate before neurons that migrated to the more superficial layers of the cortex. In the PFC, the first differentiated pyramidal neurons are apparent between 17–25 weeks gestation (80% of neurons found in the cortex are pyramidal, efferent neurons that provide callosal, association and subcortical projections) [99]. This differentiation is greatly accelerated between 26–35 weeks gestation, a time when inward growing thalamic fibres enter the cortical plate [65].

Differentiation represents a time of rapid brain growth associated with particular vulnerability to teratogenic agents which may impact on glial multiplication, myelination and overall brain growth. This vulnerability to teratogenic processes has been shown in animals following nutritional deprivation [116]. Excessive consumption of alcohol, as seen in foetal alcohol syndrome, may induce abnormally precocious transformation of the radial glial fibres resulting in superficial ectopias and groups of ectopic neurons in the plexiform zone [94].

**Post-natal development of the prefrontal cortex**

Post-natal development is concerned with elaboration of the CNS and is characterized by increased dendritic arborization, synaptogenesis and myelination. In particular, the processes of synapse formation and pruning have a rather different time course in the PFC. Although largely genetically regulated, neurological processes and the formation of neural circuits are more susceptible to environmental events [62,85]. Brain lesions occurring post-natally may interfere with ongoing CNS elaboration and the development of interconnections and functional systems within the CNS. Disruption to developmental processes during the post-natal period may be qualitatively different depending on when the brain lesion is sustained.

**Dendritic development.** Dendritic development continues into early adulthood [117]. Both regional and layer-specific differences in the time course of the development of dendrites have been demonstrated within the PFC. Koenderink et al. [117,118] investigated basilar dendritic development of pyramidal neurons in Layers III and IV of the PFC. Their findings indicate that neurons in Layer III of the DL-PFC undergo rapid dendritic growth in the first year of life, with increases in branching continuing until early adulthood [117]. The number of dendrites per neuron is at a constant level by 7.5 months and from this time to 12 months there is a marked increase in length of the dendritic field. Similarly, in Layer IV the number of dendrites per neuron stabilizes by 12 months, although progressive elongation of the dendritic field continues through to 5 years when they are morphologically mature. While caution should be taken when interpreting results of static samples used to examine dynamic processes, these findings emphasize the intricacy of cerebral development.

Accelerated dendritic outgrowth occurs during the first year of life [67], with growth continued at a reduced rate up to ~5 years, followed by a stable level up to at least age 27 [117,118]. Production of pyramidal neuron dendrites reaches a peak during the 2nd year of life, coinciding with a peak in synaptogenesis between 2–3 years [66]. During this same period, non-pyramidal neurons demonstrate a reduction in spine number [66]. Evidence indicates an initial over-production of dendrites followed by pruning to leave only the most functional branches [55,56].

The non-linear pattern of dendritic development is consistent with patterns in grey matter volume changes. Grey matter volume of the frontal cortex peaks ~10 and 12 years of age in girls and boys, respectively, and from this time, there is an apparent loss in volume until ~30 years of age [44,48,59]. The age-related changes in grey matter volume may also include the maturational processes of neuronal pruning and cell death [119] or a gain in white matter (myelination) [31,44]. An alternative explanation is that the decrease in grey matter reflects synaptic reorganization [54,120] and therefore might reflect a wave of synapse proliferation [121].

Dendritic development is argued to be an important indicator of CNS change and has been linked to functional ability. Herschkowitz et al. [122] found that during the 2nd year of life, dendrites in Layer III of the PFC elongate and form expansions deep into Layer IV, the target for axons from the limbic region. Paralleling this development (towards the end of the 2nd year) they document the emergence of self-awareness, a skill that has been linked to medial prefrontal and limbic function in adults [123].

Early brain lesions have been associated with interruption to dendritic development, resulting in reduced innervations due to tissue scarring or development of aberrant connections [56]. In children with intellectual disabilities, abnormalities in dendritic branching and spines have been found [54,124,125], e.g. dendrites may be thinner, have smaller numbers of spines or shorter branches. As the formation of dendrites is associated with
functional outcome, early PFC lesions are likely to be associated with deficits in EF.

Development of synapses. Synaptic development roughly parallels the timeline for dendritic development [21] and occurs concurrently with myelination. Synaptic density accelerates during the first few years of life, increasing to well over adult levels [53,54]. While some researchers report maximum density is reached at 15 months of age [53], there have also been observations of a peak in PFC synaptogenesis between 2–3 years [66], followed by a decline over the next 16 years. Specifically, synaptic density of pyramidal cells in layer III of the DL-PFC increases after birth and reaches a peak at ~1 year of age [54]. Synapse elimination has been reported to commence in the middle frontal gyrus at ~4 years of age and continue until mid-adolescence [54]. According to studies examining adolescent brain development, there is a subsequent elimination and reorganization of PFC synaptic connections after puberty [54,120,126].

Initial over-production of synapses may be related to the functional property of the immature brain to allow recovery and adaptation after a prenatal or post-natal brain lesion [25,127,128] and may represent a critical period in development associated with better capacity for recovery. Bertenthal and Campos [127] suggest that through the over-production of synapses, the CNS may be better able to incorporate environmental experiences whenever they occur. Rakic et al. [129] have postulated that reduction in both synapse number and density may reflect reorganization for greater efficiency. The maturation of cognitive and behavioural processes is thought to parallel this improved efficiency in synapse organization. Conversely, the over-production of synapses appears to correlate with the emergence of a cognitive process. Synaptic density in the frontal cortex dramatically increases at 8 months and peaks at 2 years [54], coinciding with increases in the length of delay infants can tolerate on the A-not-B test.

Myelination. Synaptogenesis occurs concurrently with myelination, a process of insulation that ensures rapid transmission of electrical signals [69,99]. In the PFC myelination commences around the 4th month of life and the most rapid period of myelination in this region occurs prior to 2 years of age [48,68,69]. Peaks in myelination have been documented at 7–9 years and 11–12 years [70,72], with some changes during adolescence and beyond this age.

Changes in the extent of white matter (myelinated axons) are of interest because they are presumed to reflect inter-regional communication in the developing brain. There is consensus in the literature of a continuous increase in white matter volume, both global and local, from early childhood through to late adolescence using magnetic resonance imaging (MRI) techniques such as diffusion-weighted imaging [48,68,130,131]. In a longitudinal MRI study, Giedd et al. [48] demonstrated that white matter volume increased linearly in the frontal cortex throughout the studied age-range of 4–20 years. However, precisely when mature levels of myelination in the frontal regions are obtained remains controversial. Some studies report that myelination is completed around late adolescence [48,68,69,132,133] and others suggest it is not completed until ~25 years [134]. More recent volumetric imaging studies indicate that it takes at least four decades before the myelination process ceases, with intracortical connections being amongst the last to become myelinated [59,134].

Increases in myelination results in improved processing of information within frontal-cortical circuits and between the frontal cortex and other cortical and subcortical regions [31]. Ultimately, this supports more efficient EF. Myelination, however, is not likely to be a primary causal factor in the development of specific cognitive processes [135]. While the association between myelination and cognitive processes remains controversial, some infant studies suggest a relationship between myelination delay and neurodevelopmental lag [136], while others propose that delayed myelination may be an indicator of global developmental delay, involving cortical immaturity that is not yet able to be demonstrated by current imaging techniques [53].

Disruption to myelination processes in the context of brain conditions such as cranial irritation, head injury and Acute Disseminated Encephalomyelitis (ADEM) is likely to contribute to decreased conduction velocity, increased refractory periods after synaptic firing, more frequent conduction failures, temporal dispersion of impulses and increased susceptibility to extraneous influences [137]. Possible origins of myelin deficiencies are amino or organic acid disturbances, congenital hypothyroidism, malnutrition and periventricular leukomalacia (PVL) [95]. Figure 3 shows cystic PVL on MRI in an extremely pre-term infant. The scan identifies significant white matter lesions in the periventricular region, enlarged ventricles and delayed gyration.

Development of executive functions

Research shows that in adults, EF rely strongly on the PFC, which relies upon input from most brain regions for efficient functioning. In the developing
brain cognitive functions are less localized than in the mature brain and therefore integrity of the whole brain, including the PFC, is important for efficient EF. This presents a challenge for understanding how brain lesions impact on the development of executive skills and subsequent localization of function in children. To better understand executive deficits in children with brain conditions, a developmental approach to understanding EF was examined. The prolonged, hierarchical pattern of maturation of these skills and anatomical underpinnings are discussed, illustrating the vulnerability of EF to early brain lesions.

Defining executive functions

Despite the growing literature on EF, there is little consensus on its exact definition. Lezak [138] described executive processes as those mental capacities necessary for formulating goals, planning how to achieve them and carrying out these plans effectively. She argued that executive processes are the basis of all socially useful, personally enhancing, constructive and creative activities. EF in adults has been conceptualized as taking a neurobehavioural ‘managerial role’, directing attention, monitoring activity, coordinating and integrating information and activity. Executive skills are thought to be essential for efficient day-to-day functioning, required to perform both simple and more complex tasks [78,139]. Impairment in these skills is therefore likely to have serious implications for a child, who is rapidly acquiring a range of new skills and abilities.

Developmental conceptualizations describe a number of distinct, yet integrated domains which underpin cognitive and behavioural aspects of EF: (a) attentional control; (b) cognitive flexibility; and (c) goal setting [139]. Each domain involves highly integrated cognitive skills and each receives and processes stimuli from various sources, including subcortical, motor and posterior brain regions. The domains are argued to have separate developmental trajectories: attentional control matures early and is essential for the development and efficient functioning of cognitive flexibility and goal setting, which are later developing domains. Attentional control involves component skills of selective attention, response inhibition, self-monitoring and self-regulation. These skills are key in development of other executive domains as well as efficient EF. Deficits in this area are likely to impact on the integrity of all other executive processes. Cognitive flexibility is concerned with the processes of working memory, shift attention and conceptual transfer. Goal setting is associated with initiating, planning, problem-solving and strategic behaviour. Cognitive flexibility is strongly associated with goal setting, reflecting the importance of these domains in adaptive behaviour.

Prolonged and hierarchical development of executive skills

Executive skills have a protracted developmental course, with studies showing that these skills emerge in infancy and continue to develop and refine well into early adulthood. Development of EF is thought to unfold in a staged and hierarchical manner [140]. Different executive skills emerge at different rates, with adult-level performance on many standardized measures attained at different ages during childhood and adolescence [141–143]. This pattern of maturation corresponds with developmental timetables of brain development. Waber et al. [143] recently commenced a longitudinal study to examine healthy brain development using both neuropsychological and neuroimaging measures. Baseline neuropsychological data of 385 children aged 6–18 years from the first assessment point demonstrated a steep increase in performance on a range of tasks /C24/6–10 years of age and plateau at /C24/10–12 years. The researchers suggest that children reach adult levels of performance on a range of neuropsychological tasks at around this age. On some tasks performance scores increased linearly throughout the age range studied (e.g. basic information processing tasks),

Figure 3. Cystic periventricular leukomalacia in an extremely preterm infant. The scan shows significant white matter damage in the periventricular region, enlarged ventricles and delayed gyration.
performance on some tasks demonstrated a dip in performance during adolescence (e.g. attentional shifting for girls at 10–15 years) and the pattern of performance on other tasks demonstrated an increase in performance followed by a plateau and then another period of acceleration in mid-adolescence (e.g. attentional shifting). Anderson et al. [144] demonstrate similar findings in their study of 138 children, showing a generally flat developmental trajectory for EF during late childhood and early adolescence. However, findings for attentional control development differed. Anderson et al. reported a cross-over effect at ~11–12 years, when girls performed better on these tasks. In addition, a late growth spurt in attentional control-processing speed was observed at ~15 years.

Due to the extended development of EF, consequences of early brain lesions for the development of these skills may not be immediately apparent. Kennard [23,24,145] documented long-term developmental implications of early focal frontal lesions in monkeys, noting that some subtle deficits emerged over time following early lesions. Evidence from a number of child studies supports this developmental model of emerging deficits. For example, Eslinger et al. [146] reviewed case studies of early PFC damage and concluded that immediate consequences of these lesions are usually less evident than consequences of comparable lesions in adults. Specifically, the pattern of skill impairment emerged only later in development, when the specific skills would normally be expected to emerge. Bates et al. [3] report similar findings for the developmental pattern of language skills in infants and preschool children after single unilateral focal brain lesion sustained before 6 months of age. Some deficits have been reported to change over time, some skills are initially delayed but have caught up by 5 years of age, while other skills may be functioning appropriately at the time the brain lesion occurs and shortly after but show delays and deficits over time [3,147,148]. Most children with early unilateral brain lesions, however, go on to achieve levels of language performance within the normal range [148].

Anatomical underpinnings of executive skills

During development cognitive skills emerge at different rates, determined largely by the maturation of particular brain structures that underpin specific processes and the improved interconnectivity of brain regions that form functional systems. Adult studies demonstrate that the execution of EF relies strongly on the integrity of frontal structures and systems and in particular the PFC [33,75,78,149,150]. This has been supported by functional neuroimaging studies which demonstrate significant activation of PFC whilst performing EF tasks [29,76,151,152]. In addition, child and adult studies examining focal frontal lesions report striking deficits in specific executive processes [4,153,154], providing further evidence for the importance of frontal structures and systems in the execution of executive skills.

In children the contribution of extra-frontal and frontal brain regions to specific executive processes may be less clearly delineated, due to the immaturity of cerebral structures, particularly the PFC. This has been supported by functional MRI (fMRI) studies [29,155]. For example, Tamm et al. [29] studied the activation of frontal regions during performance of a Go/No-Go test (a widely used measure of impulse control) in 19 healthy participants aged 8–20 years. Findings showed that there was no difference in accuracy on the task with age, although reaction times to inhibit responses significantly decreased with age. However, fMRI data showed a negative age-related change in recruitment of specific regions of the PFC associated with performing the Go/No-Go test. Specifically, younger participants recruit greater regions of the left superior and middle frontal gyri than older participants, who demonstrated similar patterns of activation to adults. This study links development of the PFC and development of executive skills. The researchers speculated that younger children recruited more regions of the PFC due to inefficient strategies used to complete the task and relative immaturity of skills required for efficient response inhibition. An alternative explanation is that extensive activation of the PFC in children may be a compensatory strategy used while the brain is less efficient in integrating the range of executive skills required to perform the Go/No-Go test, such as working memory and inhibitory control [121,139]. This pattern of performance has also been suggested by focal lesion studies [4].

A recent study by Jacobs et al. [4] provides further evidence for the importance of whole brain integrity for efficient EF. They investigated localization of executive skills to the PFC by examining EF task performances in children aged 7–16 years of age with frontal pathology (n = 38), extra-frontal pathology (n = 20), generalized pathology (n = 21) and healthy children (n = 40). Findings demonstrated that there was very little differentiation in executive processes between frontal and extra-frontal pathology groups, contradicting the assumption that children’s EF are localized to frontal regions. In fact, children with focal lesions to any brain region were shown to be vulnerable to a range of executive deficits that would not normally be expected following similar pathology in adulthood. It is therefore argued that the integrity of PFC may be a necessary, but not sufficient,
Selective attention

Selective attention requires the individual to select among competing stimuli and preferentially process more relevant information [160]. This skill requires the ability to actively focus and maintain attention for a period of time. Observational and behavioural studies have shown that elements of attentional functions are formed in the first years of life. Lawson and Ruff [161] demonstrated that infants aged 7–10 months can focus attention on a novel object. Increases in selective attention have been reported to occur earlier in less structured situations compared with more structured situations [162]. Selective attention measured by free play and television viewing has been shown to develop considerably between 2.5–3.5 years. In contrast, on structured tasks such as reaction time tasks [162], auditory stimuli tasks requiring the child to listen to a specific story in a complex auditory environment [163] or visual search tasks [164], substantial changes in selective attention have been observed over the preschool years. Welsh et al. [164] describe considerable increases in performance in selective attention from 3–6 years of age, with ceiling effects attained at 6 years. This is consistent with general increases in attention at this age, as well as increases in aspects of inhibition and self-regulation.

Inhibition

Inhibition is conceptualized as the ability to intentionally suppress a dominant, automatic or potent response. This skill is required for withholding a response that, although prompted by current stimulation, might not be appropriate [167]. Studies of infants have shown that the ability to inhibit certain behaviours emerges as early as 7–8 months of age, but, at this age skills are not consistently employed, reflecting skill immaturity. Diamond [168] showed that at 7.5 months infants could correctly retrieve objects on a delayed response task when the delay was limited to 1 or 2 seconds. At 12 months a delay of 10 seconds was necessary to elicit perseverative errors, suggestive of a failure to maintain the current hiding place of an object in mind and inhibit a previously rewarded response.

Inhibitory capacity develops steadily between 1–4 years of age, with basic self-control functional by this time. A peak in performance is observed between 3–4 years on a number of inhibitory measures including object retrieval tasks [169,170] and Statue [140]. Tasks with greater situational demands (processing and memory demands) are difficult for younger children, with fluctuations in performance common. Vaughn et al. [171] examined self-control skills in 72 toddlers aged 18–30 months. Capacity to inhibit a response to a desired object was investigated using a task with hidden raisins, which required the infant to inhibit responding during a delay phase and then retrieve the raisin. Performance fluctuated according to the demands of the situation and time. However, the capacity and stability of the skill improved with increase in age.

Speed and accuracy on basic inhibition tasks improves up to ~6 years of age [170,172]. Over the next couple of years minor improvements in inhibitory control have been reported [173,174]. This time is then followed by a striking developmental advance at ~7–12 years of age, as reported by studies employing a range of inhibitory control tests.
such as the Go/No-Go test [175], stop-signal procedure [176], Matching Familiar Figures Test [164] and a study employing an inhibition cognitive dimension [177]. Some studies have observed an increase in performance from this time through to ~15 years [144,178], with little developmental change from 15–21 years [178].

Self-regulation and monitoring

Important skills associated with inhibition are those of self-regulation and monitoring, the capacity to manage one’s own thoughts, feelings and actions in adaptive and flexible ways across a variety of contexts [179]. Basic self-regulation skills have been reported to emerge prior to 2 years of age. Grazyna et al. [180] showed that children at 14 months demonstrate some compliance with caregivers’ request, described as self-regulation because it requires the capacity to initiate, cease or modulate behaviour in accord with parental standards [180,181]. They observed children and caregivers in naturalistic environments at 14, 22, 33 and 45 months and found an age-related increase in development of self-regulation from 14 months to 33 months, with greatest gains occurring from 14 months to 22 months (an increase in compliance from 27% to 50%). Similarly, Rothbart et al. [182] found that reaction times following an error on the Spatial Conflict task were 200 milliseconds longer than those following a correct trial at 2.5 years and over 500 milliseconds longer at 3 years. In contrast, no evidence of slowing was found at 2 years. While results may reflect a lapse in attention, the authors suggest that children were noticing their errors and using them to guide performance in the next trial.

Espy et al. [169] showed that efficiency in performance on the Shape School task (a colourful storybook designed to examine inhibition and switching processes) for children 3.5 years of age differed from older age groups broken down into 6-month segments (4, 4.5, 5 and 6 years). Studies of infants and young children suggest a rapid phase in development of self-regulation skills ~2.5 and 3.5 years of age, a time when basic inhibitory and attentional skills are functional, supporting the voluntary control of actions needed to regulate one’s own behaviour. These studies demonstrate the importance of parsing age into small units when examining skill development during the rapid developmental phase of childhood.

Self-regulation and monitoring skills are thought to be functioning more reliably at ~7 years of age [140]. Studies consistently report a period of rapid development from 8–10 years of age on a number of standardized tasks, including the Continuous Performance Test, Digit Cancellation Task [166], visual and verbal attention sub-tests from the NEPSY [140] and also on experimental tasks [183].

Although study findings report data that suggest self-regulation and monitoring behaviours become more efficient with age, a number of studies have observed a regression in these skills for a short period ~11 years [156,184]. Anderson et al. [156] examined children’s performance on the Tower of London and found that children aged 11 completed the task faster than children aged 15, although performing the task less accurately, with more failed attempts before successfully solving the problem. Some researchers suggest that the regression observed in performance may reflect a period of transition for the child, who now has a range of newly functional skills to coordinate and balance competing demands [139,185], which ultimately reflects executive control. A decline in performance around 11 years of age has been described for other executive skills. McGivern et al. [186] found that girls 10–11 years old and boys 11–12 years old required more time to assess emotionally related information on a match-to-sample task (participants were asked to decide if the face and word matched for the same emotion). The researchers linked the ‘dip’ in task performance to proliferation of synapses occurring around this time in frontal lobe development. They speculated that improved performance on the match-to-sample task in children from 13–14 years might be explained by the pruning of excess synapses into more specialized and efficient networks at this time in frontal lobe development.

Executive dysfunction

Impaired EF may present in a variety of ways, consistent with its multi-dimensional structure. Dysfunction may include inability to focus or maintain attention, impulsivity, disinhibition, reduced working memory, difficulties monitoring or regulating performance, inability to plan actions in advance, disorganization, poor reasoning ability, difficulties generating and/or implementing strategies, perseverative behaviour, a resistance to change activities, difficulties shifting between conflicting demands and failure to learn from mistakes [185]. Executive dysfunction may also present as problems in behavioural, social and emotional functioning, such as maladaptive affect, energy level, initiative and moral and social behaviour [146,153,187].

Executive dysfunction has been consistently reported in children with different developmental and acquired CNS conditions [188–190]. These include children with congenital brain disorders such as subcortical band heterotopia [191], acquired brain conditions such as traumatic brain injury [1,2], meningitis [12,13], phenylketonuria [192]
and low birth weight [20] and developmental disorders such as autism and Attention Deficit Hyperactivity Disorder [193]. In many instances impairments in function are described in children with comparatively intact intellectual abilities [194–197]. Anderson [185] points out that in a developmental context executive dysfunction may not be considered ‘deviant’, such as in an infant or child, highlighting the importance of understanding developmental expectations of cognitive processes.

**Parallels in development of brain structure and function**

Recent advances in neuroimaging techniques have enabled research into the parallels between the functional emergence of executive skills and the structural maturation of frontal brain regions in healthy individuals [28,29,198]. Prior to this technology researchers examined the relationship between the physical growth of the brain and the emergence of new behavioural abilities in non-human primates. Goldman-Rakic [21] linked synaptic patterns in development with the emergence and improvement of cognitive processes. In her work with monkeys she demonstrated that the capacity to perform simple delayed response tasks emerges around 4 months of age, coinciding with the end of the period of highest synaptic density in the principal sulcus (the region responsible for this skill in the adult monkey). She employed an autoradiographic method for studying prefrontal connections that enabled visualization of terminal fields and determination of the pathways by which the axons reach their targets. Specifically, radioactive isotopes are injected into the designated area, the radio-labelled amino acids are converted by the cell body into proteins and transported through to the terminal region. Goldman-Rakic concluded that a growth spurt in synapses in a specific brain region is important for the emergence of cognitive skills that recruit the specific brain region for efficient function. However, it is clear that skill development progresses long after maximum synaptic density has been reached. To this, she argued that mature capacity of a skill may depend upon the elimination of excess synapses that occurs during adolescence and young adulthood. This is consistent with the view that presence of numerous synaptic contacts is required to form functional neuronal circuits, with the elimination of synapses enabling shaping and refinement of systems, which ultimately has functional significance. Goldman-Rakic also emphasized the likely contribution of other neurobiological processes for the expression of skill progression, including continued myelination, further regulation of receptors and neurotransmitters and peptides and improved synaptic efficiency at the molecular level.

Recent human developmental imaging studies support previous animal studies, confirming the relationship between the physical growth of the brain and the emergence of new skills. Although this field is in its infancy, researchers have started to map maturational changes in brain-behaviour relationships across the lifespan. Marsh et al. [28] used fMRI in a cross-sectional study of 70 healthy individuals aged 7–57 years to examine the association between regional signal changes across the brain during performance of a Stroop task at different ages. Age-related improvements in performance were associated with the increasing activation of the inferolateral portion of the PFC, confined statistically to the right hemisphere. This parallel in development of brain structure and function is consistent with the fMRI studies using different measures of inhibitory control such as the Go/No-Go test [29,199]. These studies show that while both children and adults recruit prefrontal regions when performing inhibitory control tasks, a greater magnitude in signal of the lateral prefrontal region is observed in adults, a region known to underpin inhibitory control skills [28]. This result is particularly interesting as it implies different localization of inhibitory control in children and adults or may reflect increasing localization with age as children become more efficient in performing the task or perhaps children are using different strategies to adults and switch to more efficient strategies as neural circuits become more refined.

Neuroimaging studies suggest a more diffuse pattern of activation in prefrontal regions in children compared with adults when performing EF tasks [29,200,201]. However, evidence from group and individual activation maps of the PFC and other brain regions suggests that the location of activation in the PFC does not differ between children and adults, but that the overall volume of activation was greater for children relative to adults [28,155]. Casey et al. [155] suggested this pattern may reflect a gradual decrease in the brain tissue required to perform the task, which may parallel the loss rather than formation of new synapses observed in post-mortem studies. A later study by Casey et al. [202] demonstrated different developmental patterns of activity in the DL-PFC when completing the Go/No-Go test, leading them to conclude that the DL-PFC in children is less specific to type of information and less efficient in representing information relative to adults. Further, Tamm et al. [29] speculated that the pattern of PFC recruitment in younger children may reflect inefficient strategies for completing the task and relative immaturity of skills required for efficient response inhibition. Irrespective of the
reason for this differentiation, it is clear from these studies that the developing brain operates differently from the mature brain when undertaking complex cognitive activities.

Conclusions

This review highlights the complex choreography of developmental events that lead to the healthy mature brain. The PFC has a protracted and well-specified course of development, continuing at least until early adulthood and subsequently is particularly vulnerable to brain lesions. In the developing brain cognitive functions are less localized than in the mature brain and therefore integrity of the whole brain is important for efficient EF. This presents a challenge for understanding how brain lesions impact on the development of EF and subsequent localization of function in children.

Equipped with current knowledge of timetables for healthy development of specific brain regions and cognitive skills, researchers and clinicians are now in a good position to address gaps in understanding of functional recovery and outcome in children with brain conditions. The contribution of increasingly sophisticated neuroimaging techniques such as diffusion-weighted imaging and fMRI will be invaluable in this investigation. The importance of developmental processes has previously been postulated in animal models [25] and child models [26]. While child studies provide preliminary support for key principles of these theoretical models, hypotheses have not yet been systematically examined in children and subsequently the gap in knowledge regarding timing of brain lesion effects remains. It will be important for researchers to employ the current knowledge and imaging techniques to systematically examine the role of neurological developmental processes and level of skill maturation when the brain lesion occurs in determining functional recovery and outcome in children with brain conditions.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


178. Huizinga M, Dolan C, van der Molen M. Age-related change in executive function: Developmental trends and a