Biological developmental principles relevant to the practice of child and adolescent psychiatry

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Section A

Embryological development involves a sequence of distinct processes that overlap spatially and temporally:

1. Genetic patterning and neural induction
2. Neurulation
3. Neural crest separation and migration
4. Neuroepithelial cell proliferation and differentiation
5. Apoptosis
6. Neuroblast migration
7. Axonal pathfinding
8. Membrane excitability
9. Dendritic sprouting and synaptogenesis
10. Biosynthesis of neurotransmitters
11. Myelination

1. *in situ hybridisation*: method of histological identification of individual cells with a precise nucleic acid sequence and/or an expressed product of that sequence

neural induction: the process of maturation of central nervous system structures in response to signaling chemicals released by ectodermal or mesodermal tissues

4. *radial glial cells (21-30 weeks gestation*): one of the earliest neuroepithelial cells to differentiate; provide the bulk of the astrocyte population in the deep cortical laminae and the subcortical white matter at maturity, compared to the astrocytes of the superficial cortical layers that form from subventricular glioblasts from 20-40 weeks gestation

5. 30-70% of foetal neurones are surplus to the requirement of the mature central nervous system; apoptosis is a 'spontaneous' cascade of degenerative changes leading to cell death involving shrinkage of the nucleus, condensation of the chromatin, increased electron opacity of the cell, loss of the golgi apparatus, endoplastic reticulum, disaggregation of the polyribosomes, and nuclear membrane breakdown (Hamburger & Levi-Montalcini, 1949); biphasic process; accelerated or retarded by metabolic factors, eg thyroxine level (direct proportional relationship), glutamate/aspartate (direct proportional relationship), lactic acidosis, ammonia, electrolyte and calcium imbalances (direct proportional relationship), other environmental factors, eg synaptic relationships (inverse proportional relationship)

6. specialised foetal glial cells with long processes that serve as guides are associated with the precise and orderly process of neuroblast migration

7. cell-cell interactions, cell-substrate interactions and chemotactic interactions guide the process of axonal outgrowth projection which must occur prior to dendritic proliferation

11. myelination increases the speed of electrical conduction between mature neurones and other cells, mature neurones requiring (1) an electrically polarised and excitable membrane and (2) a secretory function

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Section B

Benes et al. (1994) has noted that ongoing myelination occurs in different areas of the hippocampus throughout childhood, adolescence and adult life. She concludes that as myelination represents one of the final stages in neuronal maturation, growth and development of different regions of the central nervous system (CNS) occur throughout the life cycle. This maybe particularly relevant for CNS areas involved in key relay functions.

Heteromodal association cortices:

1. Prefrontal Cortex
2. Inferior Temporal Cortex
3. Posterior Parietal Cortex

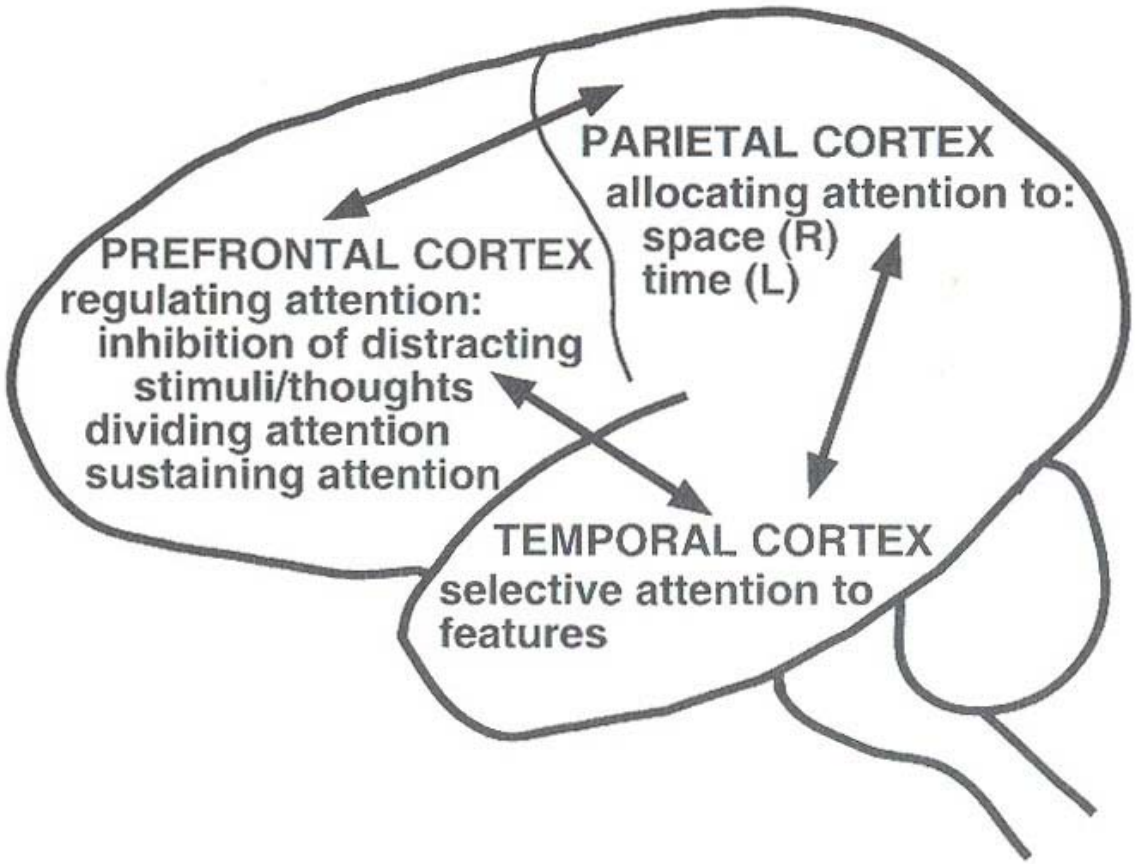

FIGURE 8.1 The prefrontal, parietal, and temporal association cortices form interconnected networks that play complementary roles in attentional processing.

Reference:
Pediatric Psychopharmacology – Pg 100.

Alexander, DeLong and Strick (1986) propose five functionally and anatomically distinct parallel neuronal circuits that involve the frontal cortex, striatum, globus pallidus/substantia nigra, and the thalamus:

1. DLPFC- novelty, new strategies, goal directed behaviour
2. lateral OFC-internal inhibition, inhibition of inappropriate responses
3. AC- inhibition of inappropriate responses, attention for action, inhibition of external stimuli
4. premotor SMA- internal generation of motor programmes, external inhibition
5. FEF- conjugate gaze

neuropsychological models of network specific versus component specific tasks (Pantelis et al., 1996)

Executive functions of cognition are key neuropsychological constructs that have been systematically investigated in childhood and adolescence: Examples include verbal and spatial working memory and (motor) response inhibition. Baddeley (1986) has defined working memory as the ability to hold information 'on-line' in order to strategically plan, organise and prioritise to achieve future goals.

Luciana & Nelson (1998) have noted that normal executive functions of cognition appear to develop sequentially throughout early, middle and late childhood (and into adolescence).

Section C

Normal Developmental Milestones

Intra-individual and inter-individual variation is wide

Girls develop earlier than boys and have a more rapid rate of maturation (Rutter, 1980). For both, identifiable periods of relatively greater rates of development occur. Differences in the Preschool years are relatively small (Prior et al. ,1993). Boys are better at visuospatial tasks and girls at speech, language and social tasks. Interestingly, Gillberg et al. (1983) have noted lower levels of HVA in CSF of girls which concords with the well-established finding of decreased HVA with age in the central nervous system.

Key Developmental Milestones

Gaze contact	1-2 hours
Smile	0-4 weeks
Vocalise	2-8 weeks
Head prone	2-3 months
Responds name	7-10 months
Pincer grip	9-12 months
Walks	10-16 months
First intended word	9-14 months
Pretend play	10-14 months
Complex play (toys)	18-24 months
I/Me/You	2-3 years
Mutual play	2-3 years
Sentences	2-3 years
Speech intelligible	2-5 years
Toilet trained	2-5 years
Time of day known	3-6 years

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Section D

Interestingly, investigations in disruptive behaviour disorders, anxiety disorders, depressive disorders and psychotic disorders suggest that generally the executive functions of cognition are delayed by a few (usually 2-3) years in these conditions.
In addition, different profiles and severity of executive functions of cognition deficits are described in different disorders.

Attempts to correlate neuroimaging data with such deficits of the executive functions of cognition have not led to replicated results, as yet.

The developmental principles of developmental delay and developmental deviation have been affirmed by data in psychiatric disorders affecting children and adolescents. For example…

Kagan et al.(1988) have noted from data obtained from longitudinal studies that childhood shyness and later social phobia can be associated with an inherited lower threshold to arousal and a decreased ability to habituate to arousal-provoking stimuli.

Pine et al. (1998) have noted that abnormalities of respiratory control, including room-air hyperventilation and increased variable breathing patterns, are evident in children and adolescents with anxiety disorders, primarily separation anxiety disorder and generalised anxiety disorder.

Kempton S, Vance A et al.(1999) have noted that the executive function deficits in Attention Deficit Hyperactivity Disorder (ADHD) are similar to the level of executive function performance in children 2-3 years younger (Luciana & Nelson, 1998).

Arnsten A & Goldman-Rakic PS (1998) have noted that acute stress induced through the exposure of adult rhesus monkeys to 105 db noise for 30 minutes prior to the test procedure led to a decreased spatial working memory test performance. These stress induced responses were ameliorated by pretreatment with haloperidol, clonidine, and naloxone. The former agent blocks dopamine receptors, while the latter agents decrease dopamine turnover.

Arnsten et al. (1998) have also proposed that different components of the dopaminergic and noradrenergic functional neurotransmitter systems are involved in changing prefrontal cortical activity associated with maximising/minimising executive function performance through changing levels of arousal. An inverted 'U' shaped curve has been described with both hypo- and hyper-arousal being associated with a minimised executive function performance.

A question: As models of neuropsychological constructs and clinical phenomena develop, how much can we actually attribute to

(a) an underlying central nervous system abnormality,
(b) a maladaptive internalised set of coping styles, and
(c) an environment that overwhelms the child with cues/stimuli?

Goodman (1994) outlines six principles that can be used to facilitate this process of attribution:

1. A standard neurological assessment identifies the majority of CNS lesions: seizure history, spasticity, EEG, CT, MRI abnormalities
2. Subtle neurological signs, abnormal neuropsychological/ neurophysiological profiles are risk factors rather than identifiers
3. A history of known risk factors for CNS injury: ABI, Encephalitis, CNS irradiation can be risk factors/identifiers
4. Genetic factors versus family history: a question of definition
5. Absence of psychosocial risk factors: false
6. Specific behavioural/clinical syndrome: false

The role of psychopharmacology in the treatment of child and adolescent psychiatric disorders **Section E**

-increasing use of medication in the treatment of disruptive behaviour disorders, obsessive compulsive disorder, and depressive disorders
-increasing use of medication in the longer-term
-safer medications with better risk-benefit ratios (SSRIs, atypical antipsychotic medication)

-impact of development on pharmacokinetics includes:
1. increased liver-total body ratio and greater renal clearance

-impact of development on pharmacodynamics include:
1. unique sensitivity to particular medications at particular developmental phases associated with particular beneficial and/or adverse-effects: aspirin-Reye's syndrome, tetracycline deposition in teeth and bone (Vitiello, 1998)
2. host of unknown factors affecting both -kinetics and -dynamics

Key changes in the central nervous system in childhood and adolescence

-synaptic density highest first 3 years with synaptic 'pruning' leading to adult levels at approximately 10 years of age
-CNS metabolic rate increases exponentially in first 3-4 years, remains high until approximately 9 years then gradually decreases to adult levels in middle to late adolescence
-striatal dopamine receptors increase from birth through to 3-4 years and then decrease
-a rodent model of critical developmental periods:
stimulation of 5-HT_{1A} receptors before puberty only accelerates physical and behavioural maturation while depletion of serotonin before puberty leads to a permanent decrease in synaptic density and life-long learning difficulties; NB haloperidol and morphine effects
-findings consistent with the general guidance-mechanism hypothesis

-in human beings the primary area of research has been possible effects secondary to in utero exposure to different classes of psychotropic medication: for example, peri-natal syndromes: phenothiazines-hypertonicity, restlessness, dystonias, parkinsonism; tricyclic agents-irritability

-longer-term valid and reliable data has not been collected

The possible role of medication in minimising the developmental vulnerabilities of cognition and mood and arousal regulation

-psychostimulant medication aids executive function performance both verbal and visuospatial

-clonidine (a central α_2-agonist) at a low (1.5 μg/kg) and high dose increases the rate of response initiation to difficult visuospatial working memory problems while a high dose (2.5 μg/kg) improves visuospatial working memory problems

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-medication is used as a facilitating agent within an existing psychological treatment programme
-medication is used to address specific goals rather than to treat a specific psychiatric disorder
-medication is used short-term with ongoing monitoring and thorough review
-ongoing monitoring involves an active treatment record being kept by the young person and/or their parent(s) that involves the specific goals for medication treatment being assessed on a daily basis with respect to the preceding day using a –2/-1/0/+1/+2 scale; regular treatment review by the treating clinician and a crisis plan are mandatory
-thorough review every six months of the diagnostic and multi-domain formulation (bio-psycho-social-cultural) is necessary to determine the specific goals for treatment, given a developmental trajectory that should be charted