HUMAN DEVELOPMENT: BRAIN DEVELOPMENT, FUNCTIONAL CHANGE AND GENETIC INFLUENCES.

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Overview

- Brain Development
  - Early Development
  - Stages
  - Basic Embryology
- Neuroplasticity
- Genetic Influences
- Examples of Plasticity

Why study neurobiology of development?

- Understand variations and abnormal development

- Understand genetic and environmental influences on development

- Neurobiological substrate underpins function > psychopathology

  Is it that clear?

- Avenues for research

What is the Brain?

- Organ of Learning
- Diffuse network of millions of neurons work synchronously in service of behaviour
- Shaped by evolution

Brain Development

- “When is it Complete?” Mid 20’s ?

- Sequential Stages -
- “pre-programmed” operating “programs” or learning “stages”
- “Evolve” as child grows
  - Such as sitting, crawling, standing, walking, drawing and the order of consonants learnt, development of syntax

- How does it develop? Experience dependent and interactional
  - Molecular level — Action of genes
  - Physiological level — Growth/Action of synapses
  - Anatomical level — Specific functional areas

Early Brain Development - Stages

- Neuralation
- Regionalisation
- Proliferation
- Cell Migration
- Differentiation
- Synaptogenesis
- Myelination

Summary

Time	Migration	Differentiation	Synaptogenesis	Myelination
15 weeks		1st dendritic spines	X	X
20 weeks			X	Cranial Nerves
23 weeks			First synapse	
24 weeks	6 layers cortex			
25 weeks	Complete			
27 weeks	X	Increase dendritic spurs		
	X			
Birth				
1yr			Peak synapse formation	Cerebellum, brainstem
4yrs			Occipital cortex Adult number synapse	
Adolescence		Grey matter peaks		
20yrs				Complete

Brain Development and Neuroplasticity

- Brain development requires experience to be "normal" – checks and balances
- Environmental/genetic influences on CNS Development
- Critical and Sensitive periods -
- Impact of experience on brain is not constant throughout life. As brain develops its sensitivity to experience changes.
- The developing brain is more experience dependent than the adult brain.

Neuroplasticity

- “Reorganising structure, function or connections in response to extrinsic or intrinsic stimuli”

- Encompasses both synaptic plasticity and non-synaptic plasticity (potential for cells to change function)
- refers to changes in neural pathways and synapses due to
  - neural processes
  - injury
  - Environmental factors
  - thinking
  - emotions
  - changes in behaviour

Neuroplasticity

- Neuroplasticity has replaced the formerly-held position that the brain is a physiologically static organ
- Neuroplasticity occurs on a variety of levels, ranging from cellular changes due to learning, to large-scale changes involved in cortical remapping in response to injury.
- Has a role in healthy development, learning, memory, and recovery from brain injury.

Neuroplasticity

The ability to be moulded by experience

- Good experience = "good" brain ?
- Bad Experience = "bad" brain ?

Experience an interplay of

- Developmental status of brain at time of exposure
- Nature of exposure
- Degree of experience
- Organism's involvement with experience
- Genetic Background

Neuroplasticity –
Ex. Early Influences/Factors

Genetic	Metabolic	Toxins/ drugs	Infections	Experience
• Syndrome • Sex • (gonadal hormones)	• Amino Acid • Organic Acid • Fatty Acid • Peroxisomal • Lysosymal • Kernicterus	• Alcohol • Lead • Drugs- prescribed/ abuse	• TORCH • HIV	• IUGR • Sensory/ motor deprivation • Early adversity • Stress • Parent child interactions

Neuroplasticity – Time of exposure

	Infection	Toxins	Deprivation	Metabolic
Prenatal	CMV	Alcohol	Placental insufficiency leading to IUGR	
Perinatal	Encephalitis		Malnutrition	Kernicterus
Postnatal	Meningitis	Lead	Head Injury	

Brain Development – Neuroplasticity and examples of genetic influences

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- Post Natal Neurogenesis

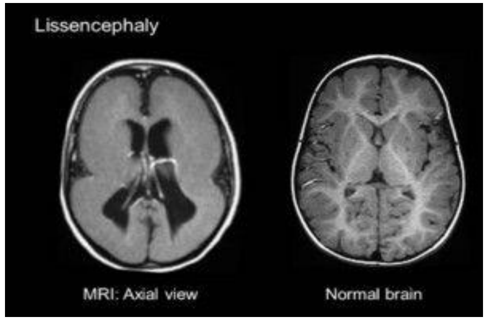
Migration and Differentiation

- Patterns
  - Radial - 70-80% migrating neurones
  - Tangential form Cortical interneurons and Brainstem nuclei
  - “Inside out” and “outside in”
- Migration complete by 25th Pre-natal week
- At 6 months post conception – 6 layers of cortex formed
- Once migrated – neurons can begin to differentiate.
- Two outcomes of migration:
  - Retraction by apoptosis (est 40-60%)
  - Develop processes – axons and dendrites

Migration

RELN gene - Reelin

- Regulates neuronal migration, positioning
- Modulates synaptic plasticity, synapatic function
- Stimulates dendrite development
- Regulate neuroblast migration in adult neurogenesis



- Total lack of expression of gene causes a form of lissencephaly
- Low expression in schizophrenia/psychotic bipolar disorders
- Role in Alzheimer's
- Candidate gene and some evidence of association with ASD

Differentiation

several classes of axon guidance molecules

- Slits aka Sli:
  - Secreted proteins
  - normally repel growth cones
  - Via Robo (Roundabout) class receptors.
  - Robo 1 – possible association with dyslexia
- Semaphorins
  - Mediate axonal path migration
  - Mutation in SEMA6A/6B assoc with abn neuro development in dentate nucleus in mice, assoc. with anxious phenotypic features

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Synaptogenesis

- First synapse – approx 23 weeks gestation
- Peak production – in first year of life

- Neuroligin - “post- synaptic glue”
  - Neuroligin3 mutations associated with ASD
- Neurexin - “Pre-synaptic glue”
  - Mutations associated
    - Schizophrenia
    - Tourettes
    - ASD

Synaptogenesis and pruning

Massive overproduction of synapses then reduction

	Peak number of synapses	Adult Numbers
Human Occipital Cortex	4-8 months	4-6yrs
Middle frontal Gyrus	1-1.5 years	Mid to late adolescence

Middle frontal gyrus – executive functions, attention, working memory

Neuroplasticity– Synaptogenesis and Pruning

- **Pruning -** Hebbian "Principle"
  - Increase in synaptic efficacy from pre-synaptic cell repeated and persistent stimulation of postsynaptic cell

- *"cells that fire together, wire together"*
  - Use synapse strengthened
  - Disuse weakened/eliminated
  - Quantitative – reduce overall number
  - Qualitative – refinement – silent or abnormal connections eliminated

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Myelination

MRI studies show

- Begins 5th fetal month

  (motor cortex)

- Throughout first 2 decades of life

Myelination

Prenatal	• motor roots • sensory roots • 1y visual and auditory cortex

Birth	• Brainstem
	  • tactile sensation
	  • proprioceptive sensation

Post natal, in 1st year	• Brainstem • Cerebellum • corpus callosum

Dysmyelination

- Defective structure and function of myelin sheaths
- Shiverer mouse represents one animal model of dysmyelination.
- Human diseases where dysmyelination has been implicated include leukodystrophies (Pelizaeus–Merzbacher disease, Canavan disease) phenylketonuria and schizophrenia.

Neuroplasticity- Post Natal- Myelination

- Neuroimaging shows:

- Linear increase in white matter until 20yrs age

- Grey matter - non linear
  - Frontal, parietal lobes – increase to age 12 then decrease
  - Temporal lobe – increase to age 16, then decrease

- Grey matter volume peaks age 12
- White matter volume peaks age 20

Examples of Plasticity:
Visual Processing/ Social Development

Quinn et al. demonstrated that the social environment also influences the tuning of face processing during the first months of life.

3-month-old infants prefer to look at female faces when paired with male faces.

This preference may reflect a gender bias of the face prototype toward the primary caregiver, which in most cases is female.

Identified a population of infants for whom the father was the primary caregiver; such infants demonstrate a bias for male faces when tested in the same manner.

Examples of Plasticity: Language Development

Experience plays a role in the development of language function.

Infants ability to discriminate between native speech sounds improves between 6-10 months and the ability to discriminate among foreign speech sounds declines.

Infants < 12 months given experience of speech sounds in non native language- ability is retained

Kuhl et al propose that exposure to native language during this 1st year of life leads to neural commitment of the native language.

This neural commitment interferes with foreign language processing during adult life.

(Kuhl et al, 2003)

Examples of Plasticity: Language Development

- Sowell et al 2004
  - 1) cortex thins by 0.3mm/yr in frontal and parietal regions, specifically related to language functions
  - 2) Cortical thinning in left dorsal frontal and parietal lobes correlates with improvements in performance of general IQ test

Examples of Plasticity:
Social & Emotional Development

Maternal behaviour to adolescent positive affect- associated with changes in adolescent neuroanatomy.

Mother /adolescent interaction observed during 2 tasks- event planning interaction & problem solving interaction.

Mothers who displayed more punishing response to adolescent + behaviour

- Changes in affective neural circuitry
- Larger left Ant cingulate gyrus & bilateral orbitofrontal cortex

113 healthy adolescents participated in this study. - Whittle et al (2009) Journal of Social Cognitive & affective Neuroscience

Implications ?

- Aggressive maternal response is related to changes in adolescent neural circuitry.
- Prefrontal & limbic cortex- plasticity in adolescence. Vulnerable to environmental influences.
- Orbitofrontal cortex, ant cingulate gyrus & amygdala associated with social, cognitive & affective functioning.
- ? Long term implications for adult functioning.

Examples of Plasticity: Anxiety Possible Aetiological Factors

Generalized biological vulnerability

- physical or chemical tendency towards anxiety
- hereditary
- sensitivity to stress stimuli

Generalized psychological vulnerability

- childhood learning
  - Experience of environmental stressors

Environmental “Triggers”

- Significant external stresses

Examples of Plasticity:Anxiety
Limbic Hypothalamic–Pituitary–Adrenal Axis

- Release of Corticotrophin-Releasing Hormone from the hypothalamus is influenced by stress
- Anatomical connections between brain areas such as the amygdala, hippocampus and hypothalamus facilitate activation of the HPA axis
- Dopamine, serotonin, norepinephrine involved in regulating LHPA
- Increased production of cortisol mediates alarm reactions to stress, facilitating adaption

Amygdala

Central processor for fear and anxiety

Sensory information enters via basal nuclei – basolateral amygdala

Processes sensory related fear memories

Communicates threat importance to memory and sensory processing areas such as medial prefrontal cortex

Amygdala activation (by stress/stress hormones)leads to dendritic arborisation and increase synaptic transmission

Amygdala - inhibition

(SK2) potassium channels mediate inhibitory influence on action potentials

Over expressing (SK2) in basolateral amygdala

Reduced anxiety and stress induced by corticosterone secretion

Reduced dendritic arborisation

R Mitra, D Ferguson, and RM Sapolsky 2009

Brain Development

- Organ of Learning

- Evidence of “Plasticity” – change due to intrinsic and extrinsic influences

“Self- Organization”

- Evidence the brain organizes itself in response to experience

  - Does this also apply to Learning?
  - Does this have a role in development of memory?

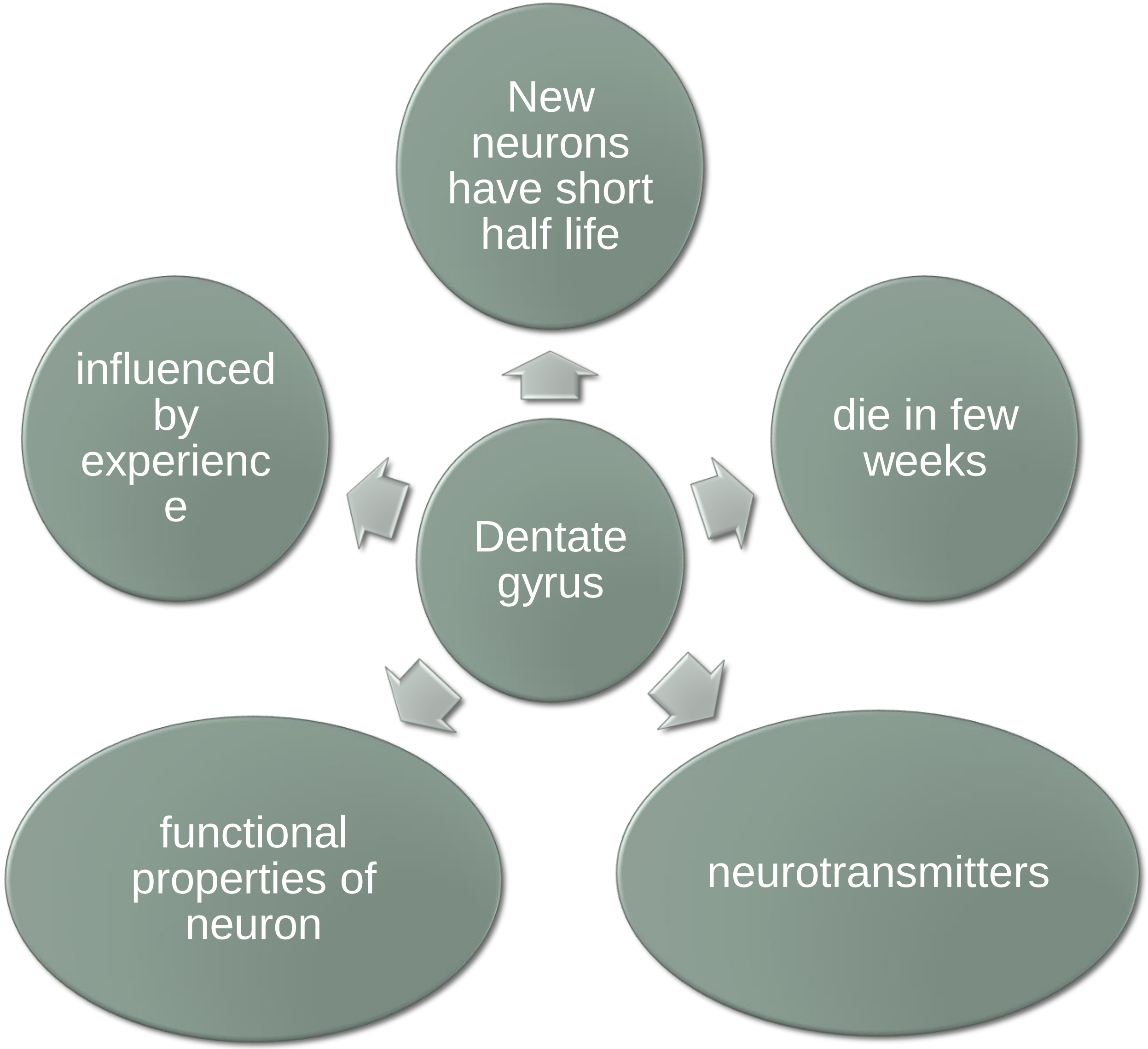
Post-Natal Neurogenesis

- Occurs in:-
- Subventricular zone (SVZ)
  - Lines lateral ventricles
  - Migrate to Olfactory Bulb

- Subgranular zone (SGZ)
  - hippocampus - Dentate gyrus
    - (Reelin and Notch1 interact in development of dentate gyrus)

- Cingulate gyrus
- Amygdala
- Piriform cortex
- Inferior temporal cortex

Post-Natal Neurogenesis



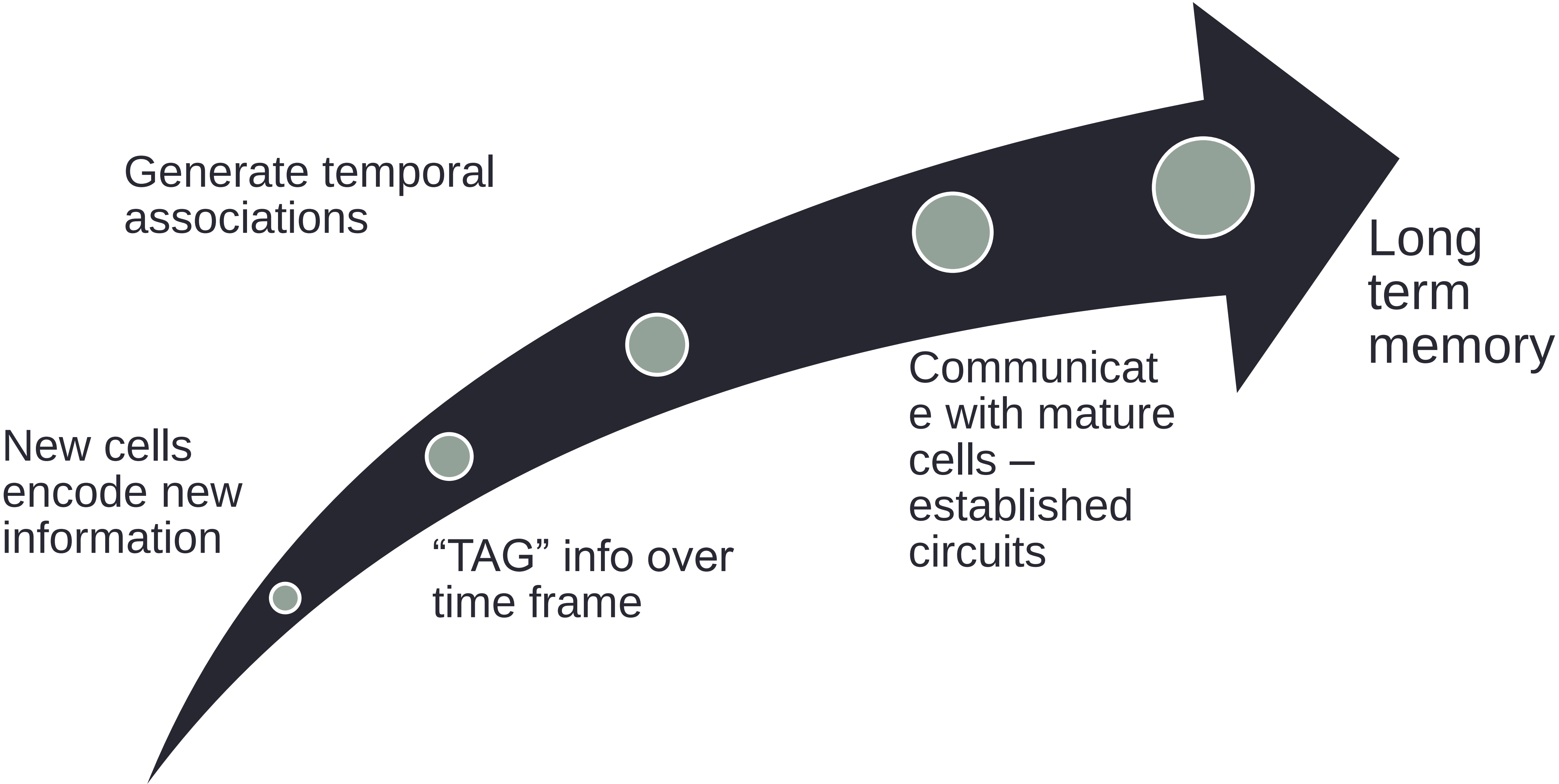
Post-Natal Neurogenesis

Mice – demands placed on learning/memory/exercise – enriched environment
Increases number of cells produced in dentate gyrus – whether old or young mice

Stress – decrease number derived.
Dominant animals produce more neurones than non-dom.

Move to enriched environment – increase number of neurons in both dom and non , but dom have advantage/fare better)

Post-Natal Neurogenesis



Summary

Architecture – Established fairly early

“Predictable” Developmental Course

Development subject to experience - Neuroplasticity

Continued development from infancy, through childhood to adolescence

Additional resources

- Suggested reading
  - Rutter – Child and Adolescent Psychiatry Fifth Edition, Ch. 12 Neurobiological perspective on Developmental Psychopathology p145-159
  - Gillberg – Clinical Child Neuropsychiatry
- On-line material
  - Brain atlas
    - http://www.med.harvard.edu/AANLIB/home.html
  - Embryology Tutorials
    - http://www.embryology.ch/indexen.html