Typical and Atypical Brain Development

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Objectives

Learn about main events involved in neural development

Learn about how these events contribute the development of cognitive processes

To learn about contributions from experience and genetics to these developmental events

Learn about anomalies in brain development

‘R’ and ‘L’ Sounds in Japanese

- Japanese people have difficulty differentiating between R and L sounds
- Japanese babies are however able to differentiate between these two sounds, but only before age 9 months
- The Japanese language does not contain R and L sounds and so they are not exposed to those sounds

The Brain is Highly Specialized

The brain comprises specialized regions

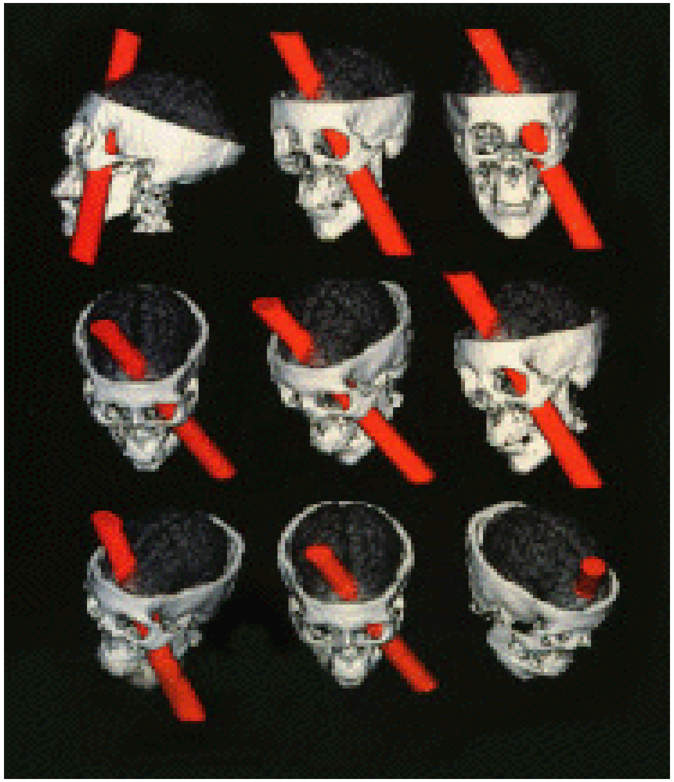
Brain functions can therefore be localized

In acquired or congenital disorders specific brain regions are found to be atypical

Atypical brain regions are associated with selective cognitive impairments

The Brain is Highly Specialized

Damage to specific regions in the adult brain is known to produce specific syndromes



How is a specialized brain sculpted

Interactions between specific genes and environment

New research shows that epigenetics also plays a key role in brain development

FOXP2 Gene and Language

FOXP2 gene has undergone rapid evolution since the human lineage separated from the ape lineage

It has been speculated that these rapid changes have allowed alteration of the motor circuitry making speech possible

Genes play a Critical Role in Brain Development

Brain development is guided by genetic codes

Anomalies in genes lead to neurogenetic disorders (e.g. FragileX syndrome, Turner syndrome, Williams syndrome, Prader Willi syndrome, Down syndrome etc.)

Dutch Famine

Children who were conceived during the Hunger Winter of 1944-45 in Western Netherlands have been found to show a different molecular setting for a gene that is involved in growth

The alteration was not in the genetic code, but was in the setting for the code indicating whether gene is on or off (Heijmans et al. 2008)

Epigenetics

In another study (Pembry et al. 2005) found that paternal smoking was associated with the body mass index at age 9 in their sons

Sins of parents and grand parents can influence health outcomes and brain development through epigenetics

Epigenetics allows adaptation to the changes in the environment

Experience Plays a Critical Role in the Development the of the Brain

Children can relearn the ability that was lost

Rehabilitation studies show evidence of training-induced plasticity

Objective 1

Learn about primary events during brain development

Milestones

The brain development occurs in an orderly manner

The main milestones of brain development include:

Gastrulation

Neural Induction and Neurulation

Neurogenesis

Cell Migration

Development of Axons and Dendrites

Synaptogenesis and Pruning

Myelination

- Formation of neural circuitries

Embryonic Period

By the beginning of second week after conception, the embryo is a two-layered structure

The upper layer contains epiblast cells and the lower layer, hypoblast cells

Gastrulation

By the beginning of third week, the epiblast cells differentiate into three stem cell lines: endoderm, mesoderm, and ectoderm

This process is known as gastrulation

Gastrulation [21]

Endoderm (inner layer) eventually develops into liver, thyroid, pancreas etc.

Mesoderm (middle layer) will develop into bone, heart, blood etc.

Ectoderm (outer layer) will go on to develop the central (brain and the spinal cord) and peripheral nervous systems

Neurulation

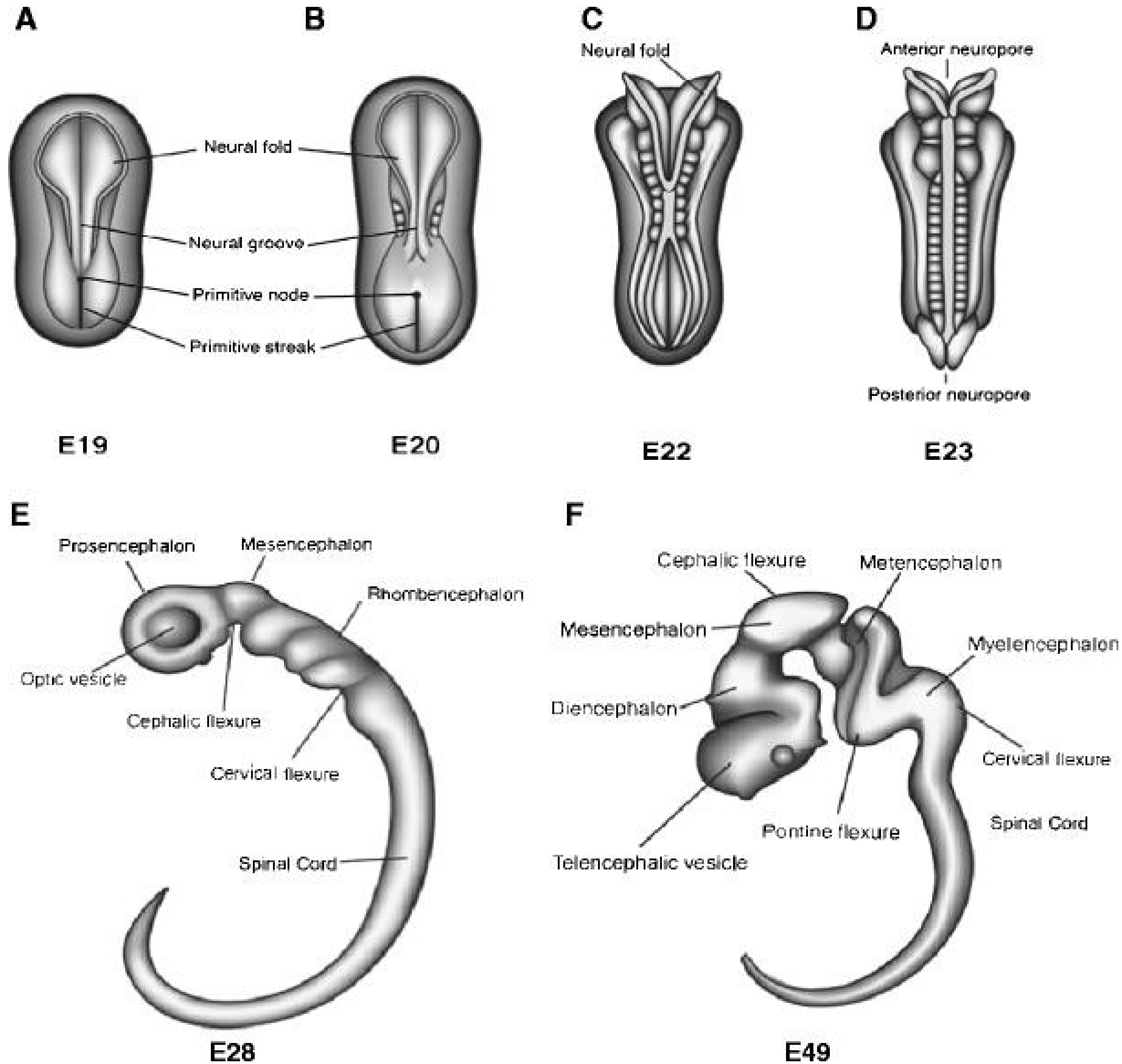
The next step is the formation of the neural plate and the generation of primitive central nervous system structure called neural tube

The neural tube is formed by folding the neural plate:

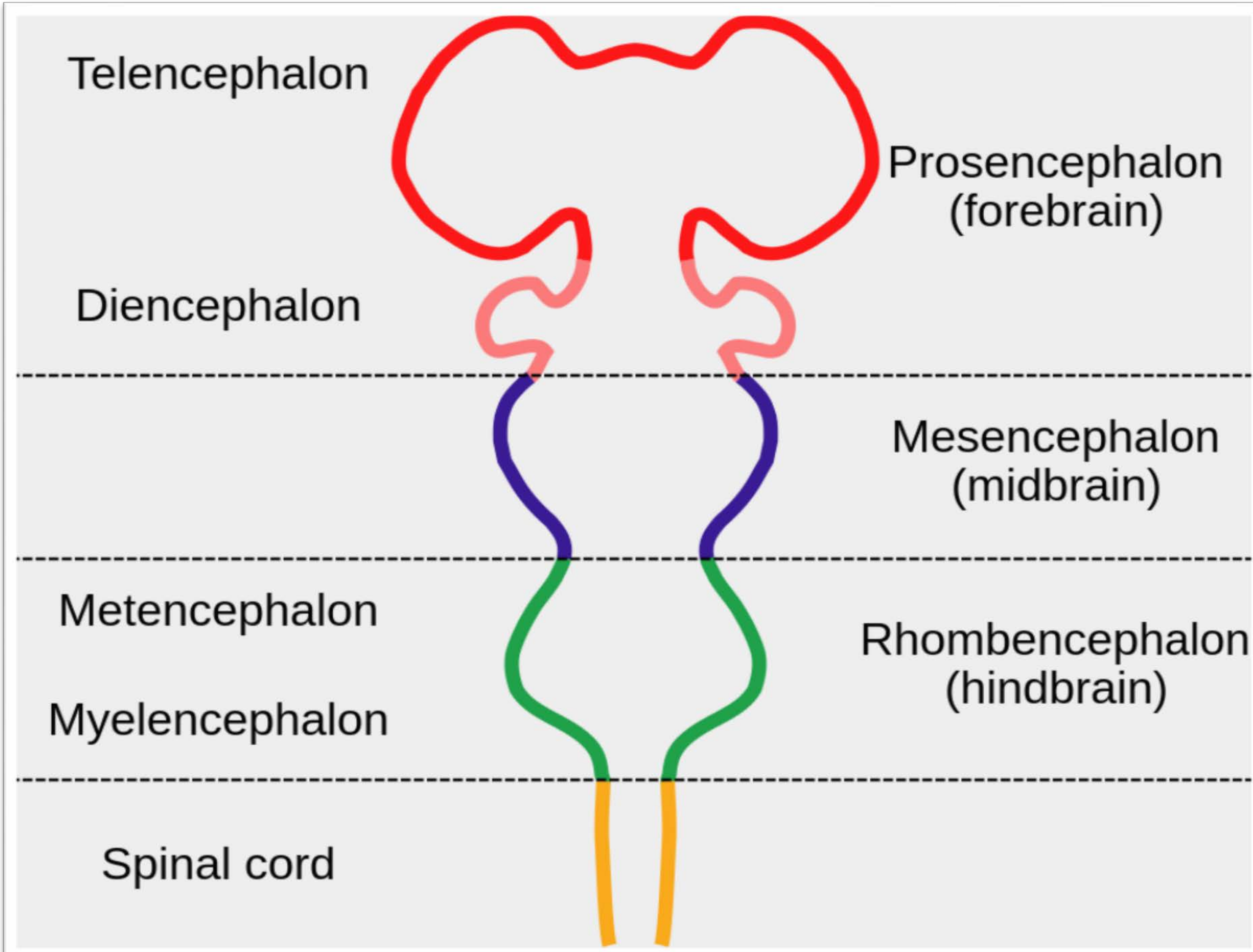
By embryonic day 21 (E21) the ridges are formed along the two sides of the neural plate with neural progenitor cells lying in between these ridges

Over the next few days the two ridges rise, fold inward and then fuse to form a hollow tube

The fusion takes place at the middle first and then progresses in both directions (rostral and caudal)



A
B
C
D
Neural fold
Neural groove
Primitive node
Primitive streak
Neural fold
Anterior neuropore
Posterior neuropore
E19
E20
E22
E23
E
F
Prosencephalon
Mesencephalon
Rhombencephalon
Optic vesicle
Cephalic flexure
Cervical flexure
Spinal Cord
Cephalic flexure
Metencephalon
Mesencephalon
Myelencephalon
Diencephalon
Cervical flexure
Spinal Cord
Pontine flexure
Telencephalic vesicle
E28
E49


Telencephalon
Diencephalon
Metencephalon
Myelencephalon
Spinal cord
Prosencephalon
(forebrain)
Mesencephalon
(midbrain)
Rhombencephalon
(hindbrain)

Neural Tube

The lining of the neural tube is called neuroepithelium, which is made of the epithelial cells that generate all neurons and glial cells

The focus of the next section is on how neurons are made and how they migrate

Neurogenesis and Migration

Progenitor or precursor cells give rise to neuroblasts and glioblasts

Neuroblasts become specialized neurons and glioblasts become glial cells

Neurogenesis begins around prenatal week 5 and peak between 3rd and 4th prenatal month

Neurogenesis and Migration [27]

Neurogenesis begins in the innermost region of the neural tube called the ventricular zone

The genesis of neural cells occurs through a process called *interkinetic nuclear migration*

That is the newly formed cells travel between the inner and outer zones of the ventricular zones

Neurogenesis and Migration [28]

Throughout the period of neurogenesis, the progenitor cells divide repeatedly

In the early phase of proliferation, cell division is symmetrical in that each daughter cell produced is identical with other daughter and parent cells

This will guarantee a rapid production of large number of cells

Cell Division (mitosis)

Asymmetrical cell division produces two daughter cells that differ in their properties

One daughter cell reenters the proliferative cycle and the other exists the cycle and migrates away from the ventricular zone

Cell Migration

Cells migrate from the VZ to their final destination through an intermediate zone

There are two types of migration patterns: radial and tangential

Pyramidal neurons- projection neurons- use radial glial cells to migrate

They move in an inside-out direction

Cell Migration [32]

How do cells know where to go?

The cortex is made of the layers of cells

Cells migrate to the inner layer first, then to the next layer and so on

At approximately 20 weeks of gestation, the cortical plate consists of 3 layers. By 7 months, all the six layers are visible

Neural Patterning

Even in the embryonic period (up to gestational week 8), there is a clear map of the brain (neural patterning)

It turned out that two molecules, Emx2 and Pax6, play a critical role in determining the different regions of the brain

High concentration of Pax6 together with low concentrations of Emx2 induces the production of motor neurons

Axons and Dendrites

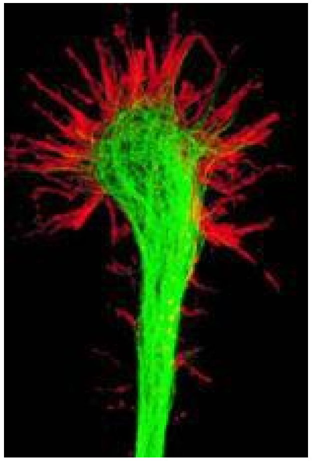
Like early settlers, migrated neurons have two options: develop axons and dendrites, and make connections with neighbors or face programmed cell death (apoptosis)

About 40 to 60 percent of all neurons may die

There is evidence to suggest that the growth corn at the top of an axon plays a critical role in its development

Axons and Dendrites [37]

There is also evidence that microspikes called filopodia and lamellipodia play a role in axon guidance



Dendrites develop in conjunction with
axons

Dendrites and axons continue to develop
postnatally reaching a peak around age 2

Neural Maturation

Two main events happen in the development of dendrites: arborization and formation of dendritic spines

Dendrites start as simple processes growing from the cell body, but they become increasingly complex

Dendrites develop at a slow rate (a few micrometers a day)

Synaptogenesis

A synapse is a junction that allows passing an electrical or chemical signals from one neuron to another

The first synapses can be observed around the 23 week of gestation

There is a massive overproduction of synapses followed by a gradual reduction

Synaptogenesis [41]

The peak production of synapses varies by the region

Visual cortex- between 4th and 8th postnatal month

Prefrontal cortex- 15 months

The Hebbian principle applies to the survival of synapses

Myelination

Myelin is the lipid-protein cover that insulates axons

It is a two-layered structure that contains large proteins and myelin basic proteins

These proteins are important for forming the membrane

The outer membrane contains cholesterol and glycolipids

Myelination [43]

Myelination begins around the third trimester

Although myelination is practically complete by the end of second postnatal year, it continues into the 6th decade of life

Myelination progresses from back to the front

Development of the Cortex

In the early stages of development, the rostral portion of the neural tube forms 3 primary vesicles

Proencephalon or forebrain

mesencephalon or midbrain

rhombencephalon or hindbrain

Development of the Cortex[45]

Two secondary vesicles develop from the proencephalon: the telencephalon (cerebral hemispheres) and the diencephalon (thalamus and hypothalamus)

From the rhombencephalon emerge two divisions: the metencephalon (pons) and the mylencephalon (medulla)

The mesencephalon remains undivided

These 5 brain vesicles are identifiable by the sixth week of fetal life

Objective 2:

How does brain development support typical development?

Memory development

How many memories from your infancy and preschool years do you have?

Infantile amnesia

Immaturity of the inferotemporal system

Infants are capable of recognition memory for short durations- Visual Paired Comparison procedure

Memory development[48]

After 12 months infants are able to tolerate longer delays between the presentation of a stimuli and recognition memory test

Deferred imitation task- showing a sequence of actions and performing it following a delay

Beyond preschool years, the maturation of the prefrontal cortex contributes to retrieval of information (metacognitive skills)

Development of Implicit Memory

Newborn infants are capable of acquiring conditioned responses

For example, eyeblink conditioning has been done with infants 10, 20 or 30 day infants

Eyeblink conditioning relies on the integrity of the cerebellum

Development of Language

Neuroanatomy of Language

To produce a verbal response, sound images must be transmitted to the Broca's area

Wernicke hypothesized that a bundle of fiber called the arcuate fasciculus transmitted sound images to the Broca's area

Wernicke anticipated that damage to the arcuate fasciculus also would produce impairments of language

Neuroanatomy of Language[53]

Wernicke observed a pattern of language impairments resulting from damage to a specific region of the temporal cortex (Broadman area 22)

These patients showed fluent speech, but displayed marked deficits in comprehension

Unlike patients with Broca’s aphasia, fluent aphasics also did not show right hempiparesis

Neuroanatomy of Language [54]

Wernicke's hypothesis was later elaborated by Norman Geschwind of the Harvard Medical School, who is considered the father of behavioral neurology in the US

Geschwind's major contribution was the demonstration that damage to connecting fibers in the brain caused disconnection syndromes

The syndrome resulting from damage to the arcuate fasciculus is called conduction aphasia

Neuroanatomy of Language [55]

Reading involves a neural network including the primary visual cortex (17), visual association cortex (areas 18 and 19), the angular gyrus (area 39) and the Wernicke's area (area 22)

Disconnection between the visual cortex and the Wernicke's area results in a loss of reading ability (alexia)

Neuroanatomy of Language[56]

Speech requires complex planning and coordination of mouth and tongue movements

A deficit in planning and coordination of movements is called apraxia of speech

Donkers (1996) reported that damage in a specific region of the insula was associated with apraxia of speech

Hidden under the opercula (lips) of the frontal and temporal lobes, the insula is a part of the paralimbic cortex

Neuroanatomy of Language [58]

Lesion studies also show that some subcortical structures are involved in language

There is evidence that damage to the thalamus and the basal ganglia produces aphasia

Neuroanatomy of Language [60]

Recent developments in neuroimaging have allowed directly probing the neural network subserving language

Neuroimaging methods also allow the study of individuals without pathological conditions such as vascular problems

Two main methodologies that have produced interesting results are functional magnetic resonance imaging and transcranial magnetic stimulation

Language development

At birth infants can discriminate about 200 phonemes

Until about 9 months, the infant is able to discriminate sounds, native or non-native

Babbling is followed by a marked increase in imitation of words

Then, an exponential increase in words and phrase length in the second year

Language development[62]

The amount of words heard is an important factor in the development of vocabulary

The capacity for production of sequence of words requires the maturation of frontal cortex (phonological loop)

Therefore, language development depends on the maturation of a circuitry including the auditory cortex, the motor cortex, the premotor cortex and the prefrontal cortex

Executive Functions

Executive function is an umbrella term that refers to a range of abilities involved in goal directed behavior

These include planning, attentional set shifting, regulation of goal directed behavior, flexible generation of responses, and error correction

Executive Functions [64]

It is known that the maturation of the prefrontal cortex is critical for the emergence of executive skills

These include planning, attentional set shifting, regulation of goal directed behavior, flexible generation of responses, and error correction

Underlying these skills are two primary competencies: working memory and response inhibition

Executive Functions 66

The development of working memory has been investigated in children using delayed response tasks

The paradigm involves hiding an object of interest, within the full view of an infant, in one of two location. After a brief delay, the infant is allowed to retrieve it.

Seven to 8 month old infant can perform the task when delays are between 1 to 3 seconds

By 12 to 13 months, the infant can do the task at 10 second delays

Executive Functions- Early to Middle Childhood

Dimensional Set Shifting (Zelazo et al., 1996) Three year old children perseverate on the previously correct rule, although they can repeat the rule

Day Night Task (Levin, 1991) Difficult for

- 3 year olds, but too easy for 6 to 7 year olds

Atypical Development

Atypical Neurulation: Neural tube defects result from atypical neurulation

- anencephaly- when the rostral end of the tube failed to close
- holoproencephaly- when there is a single undifferentiated forebrain
- spina bifida – posterior region of the neural tube failed to close

Atypical Development [70]

Atypical neurogenesis:

- microcephaly- prenatal exposure to alcohol, HIV virus
- Macrocephaly – genetic; autism

Atypical Development [71]

Atypical neural migration:

- X-linked lissencephaly; the exterior of the cerebral cortex is smooth
- Schizencephaly- cleft in the frontal cortex
- Disorders of axons and dendrites
- Fragile X syndrome
- autism

Williams Syndrome

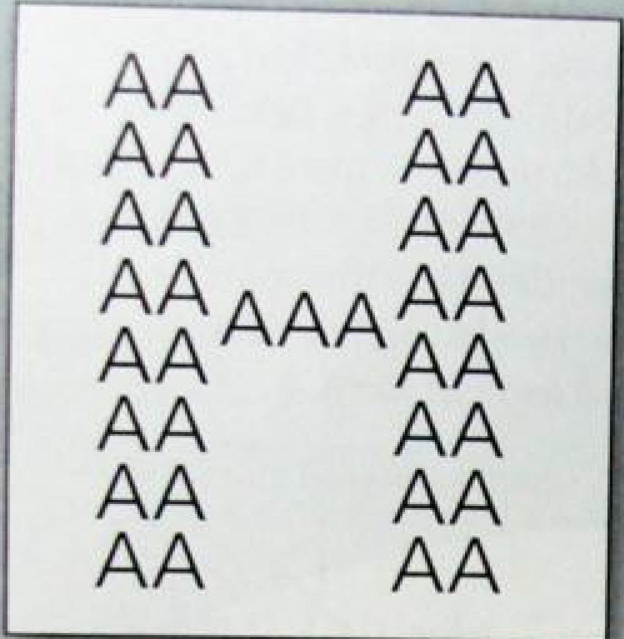
A rare genetic disorder caused by deletion of about 25 genes on one copy of chromosome 7

- facial phenotype
- congenital heart disease
- connective tissue problems
- behavioral phenotype

Williams Syndrome [73]

Intellectual profile

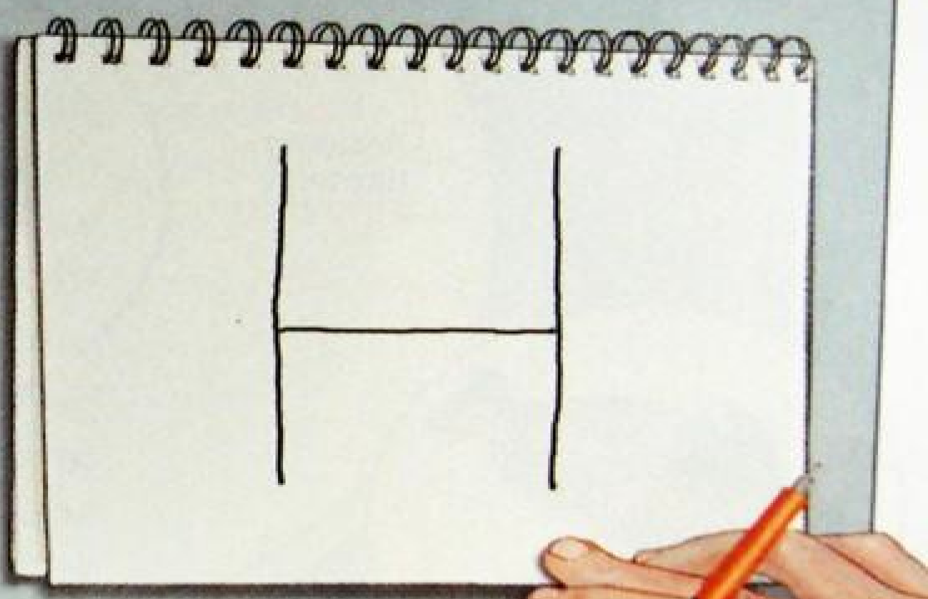
- Better performance on verbal than on visual constructional tasks
- Nonverbal reasoning is not as impaired as visual constructional abilities
- Intact concrete vocabulary, yet impaired vocabulary for relational terms (conjunctions and disjunctions) e.g. ‘either or’, ‘neither nor’
- On perceptual tasks, a bias toward local processing



▲ Original picture

In a classic experiment, Dean C. Delis of the University of California, San Diego, and his colleagues asked brain-damaged patients to study a picture of a large capital **H** made up of little **A**'s (*left*) and then redraw it from memory. The patients with damage to the right hemisphere (thus dependent solely on the left hemisphere) often simply scattered **A**'s over the page (*below left*). Patients with damage to the left hemisphere often just drew a large capital **H** with no **A**'s (*below right*). Thus, the human left brain characterizes stimuli according to one or a few details, whereas the right brain specializes in synthesizing global patterns.

Patients with



Patients with damage

Williams Syndrome [75]

Behavioral

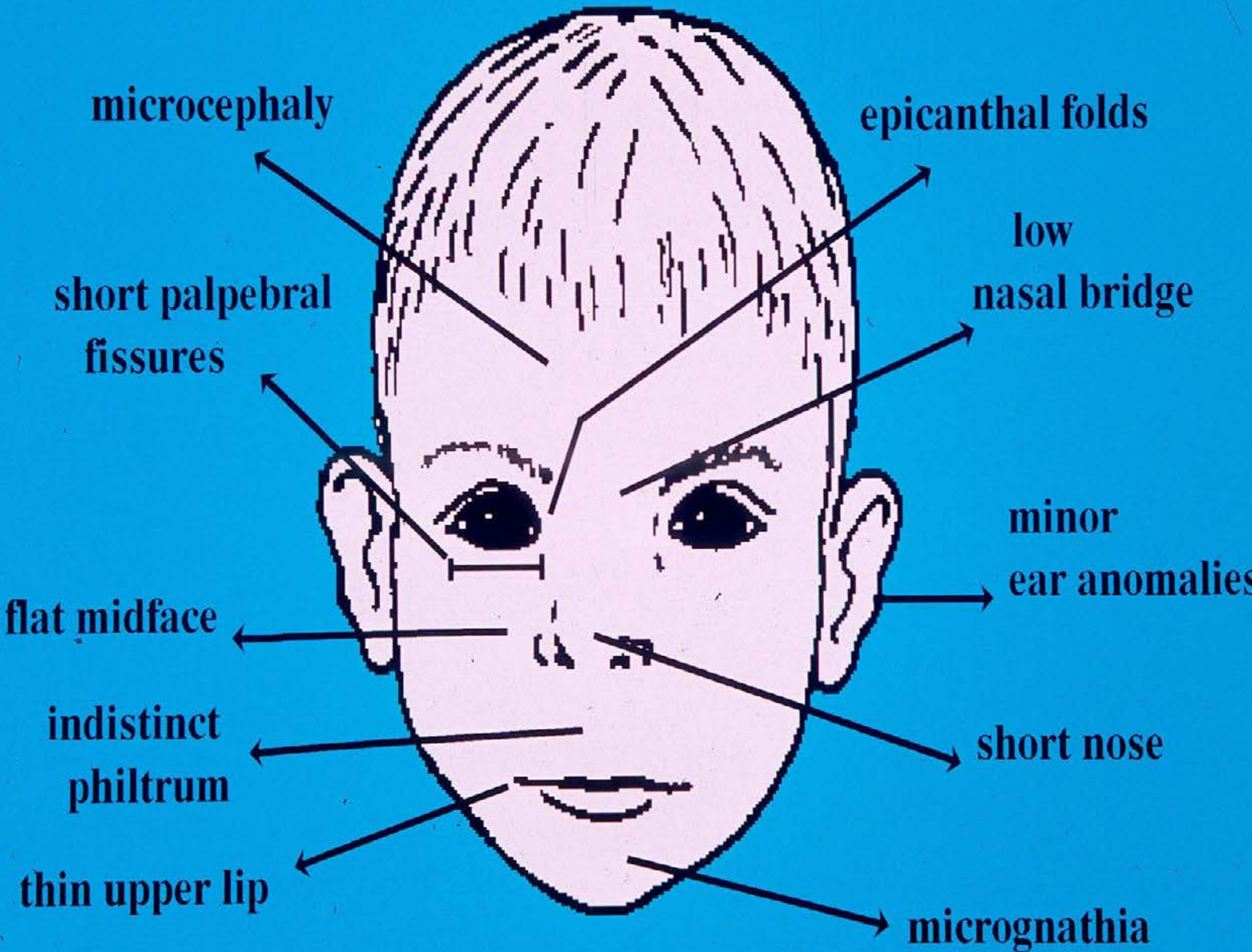
- social: able to express emotions using pedantic words
- disinhibited and overly friendly
- hyperactive
- anxious

Fetal Alcohol Spectrum Disorders

Exposure to substantial amounts of alcohol during pregnancy produces a range of morphological and behavioral outcomes

On one end of the spectrum are those with fetal alcohol syndrome, which characterized by prenatal/postnatal growth restrictions, facial dysmorphia, and central nervous system damage (microcephaly)

FACIES IN FETAL ALCOHOL SYNDROME



Smooth Philtrum and Thin Upper Lip