NEURODEVELOPMENTAL DISORDERS-Etiology

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Agenda

- Brain development and organization
- Factor affecting CNS devlopment:

Two models

-Infections /inflamation and brain development

-Prematurity and brain development

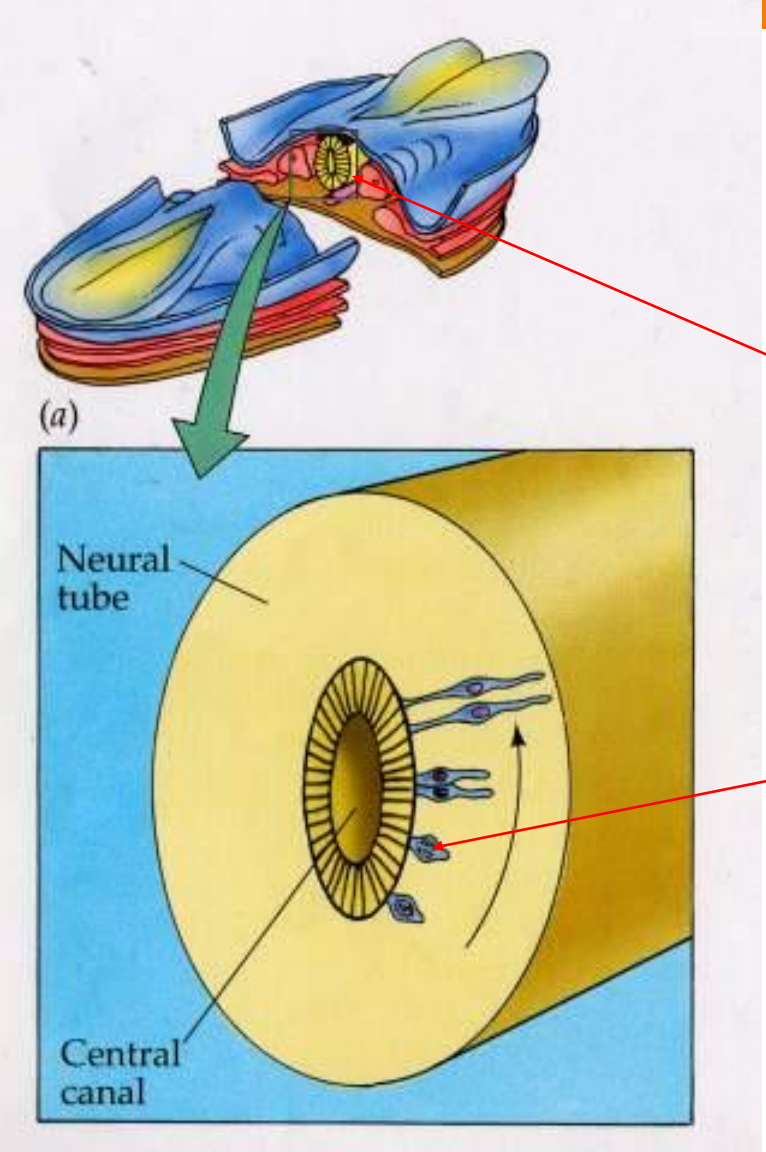
Brain development

- a complex organization of processes under *genetic, environmental,* and *immune regulation*
- vulnerable to a variety of insults

Phases of brain development

- Neural plate induction
- Neural proliferation
- Migration & aggregation
- *Axon growth & synapse formation*
- *Cell death & synapse rearrangement*

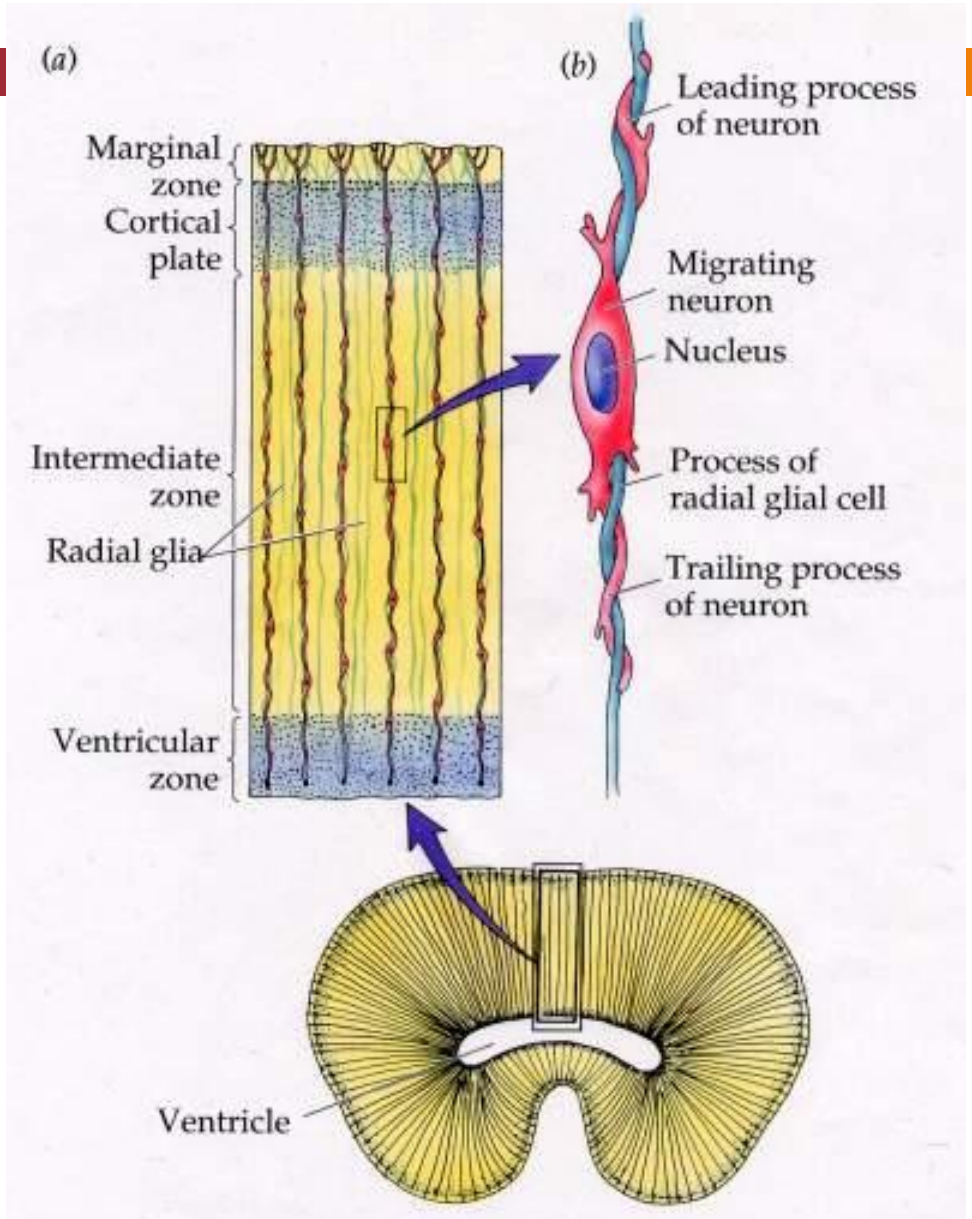
Mitosis/Proliferation



- **Proliferation –**
  - Generation of new cells
- 3 swellings at the anterior end in humans will become the forebrain, midbrain, and hindbrain

- **Occurs in ventricular zone**
- **Rate can be 250,000/min**
- **After mitosis "daughter" cells become "fixed" post mitotic**

Migration



Radial glial cells act as guide wires for the migration of neurons

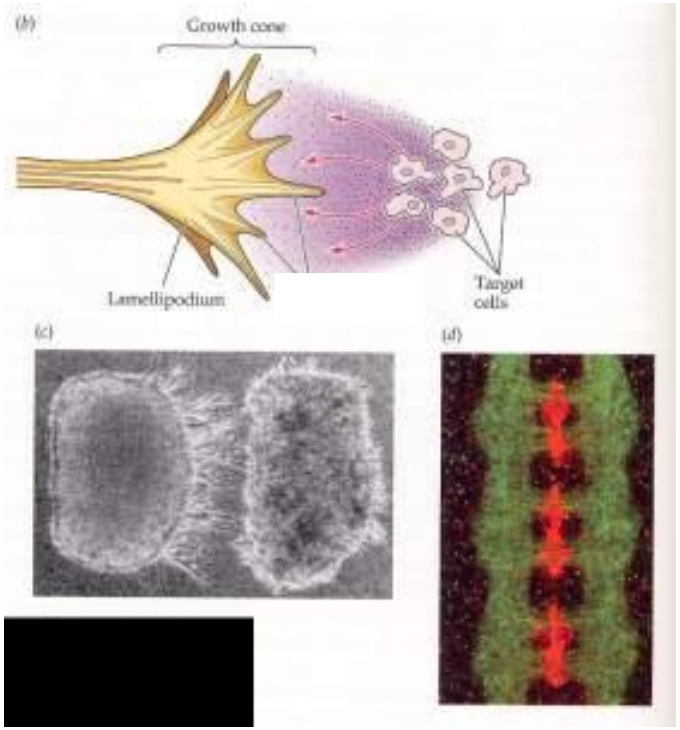
Migrating cells are immature, lacking dendrites

Cells that are done migrating align themselves with others cells and form structures

Axon Growth/Synaptogenesis

- Once migration is complete, axons and dendrites begin to grow to their "mature" size/shape.

- Axons and dendrites form a synapse with other neurons or tissue (e.g. muscle)



Postnatal Cerebral Development

- Overproduction of synapses may underlie the greater "plasticity" of the young brain

- Young brain more able to recover function after injury, as compared to older brain

Models for Brain Functions

- Old hypothesis: Specific brain regions are responsible from brain disorders

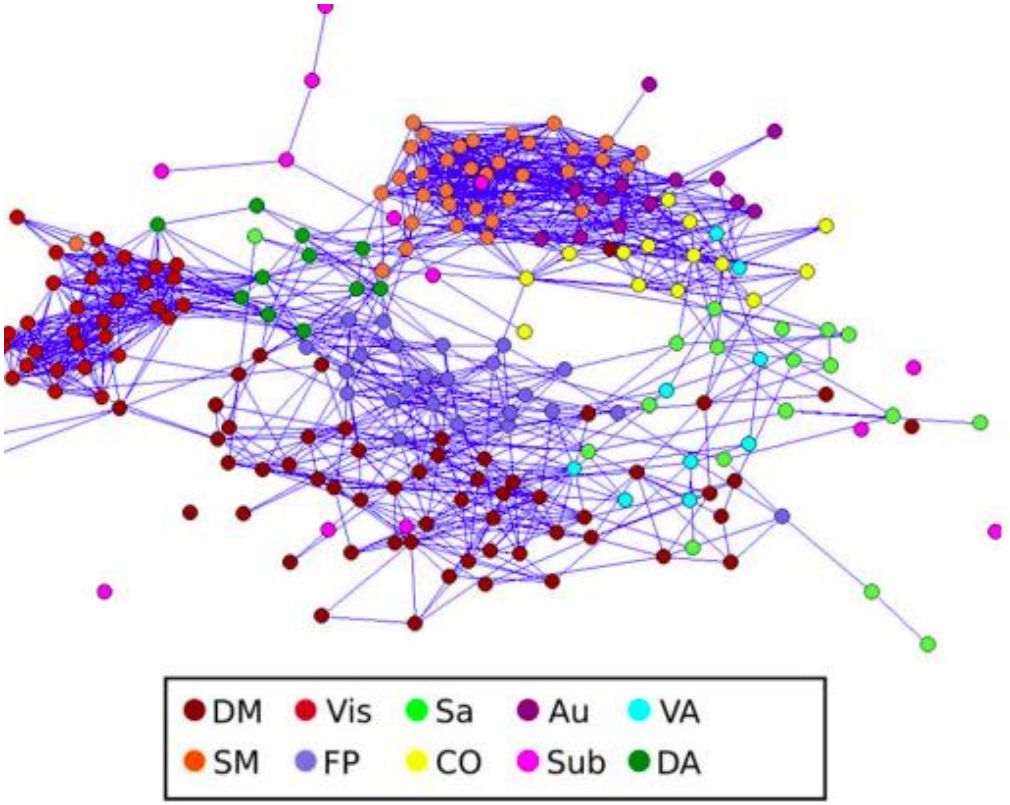
- New hypothesis: Disturbances of interconnected neural systems: *Connectivity*

Connectivity and Connectomes

- Human neurodevelopment requires the organization of neural elements into complex structural and functional networks called the *connectome*

Anatomical -Functional Connectivity

Anatomically separated brain regions are functionally connected with each other



Definition of Neurodevelopmental disorders (NDD)

- behavioural and cognitive disorders that
- arise during the developmental period
- involve significant difficulties in the acquisition and execution of *specific intellectual, motor, or social functions*

(ICD-11)

Etiology

- Most neurodevelopmental disorders have complex and multiple contributors rather than any one clear cause

- A combination of genetic, biological, psychosocial and environmental risk factors, as well as behavioral risk factors such as alcohol, tobacco, or illicit drug use

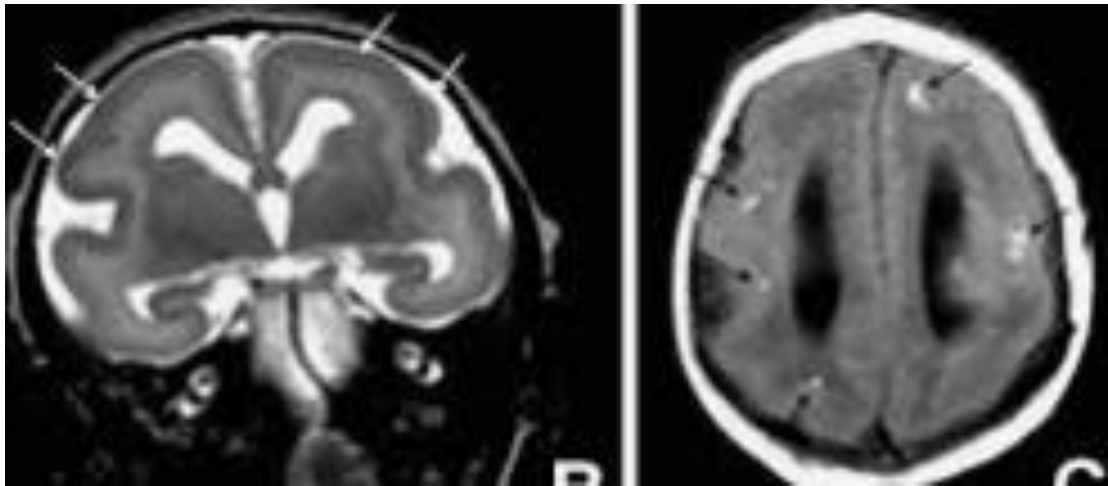
Etiology

- **Genetic causes:** genetic mutations and metabolic conditions at conception.
- **Prenatal causes:** nutritional deficiencies, toxic insults or maternal infections during pregnancy,
- **Perinatal causes:** hypoxia, vascular accidents
- **Postnatal causes:** traumatic brain injury, infections like meningitis or exposure to environmental toxins after birth.

Infections/inflamation and brain development

Zika virus (ZIKV) and NDD

- 2015 Brazil
- Severe microcephaly, significant cranio-facial disproportion, cortical malformations, intracranial calcifications, opthalmological abnormalities



ZIKV and NDD

- Loss of fetal noncortical brain volume, injury to the ependymal epithelium, and loss of late fetal neuronal progenitor cells
- Long-lasting effects of ZIKV infection on behavior, brain structure and functions

NeuroImmunoModulation

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Zika Virus as a Possible Risk Factor for Autism Spectrum Disorder: Neuroimmunological Aspects

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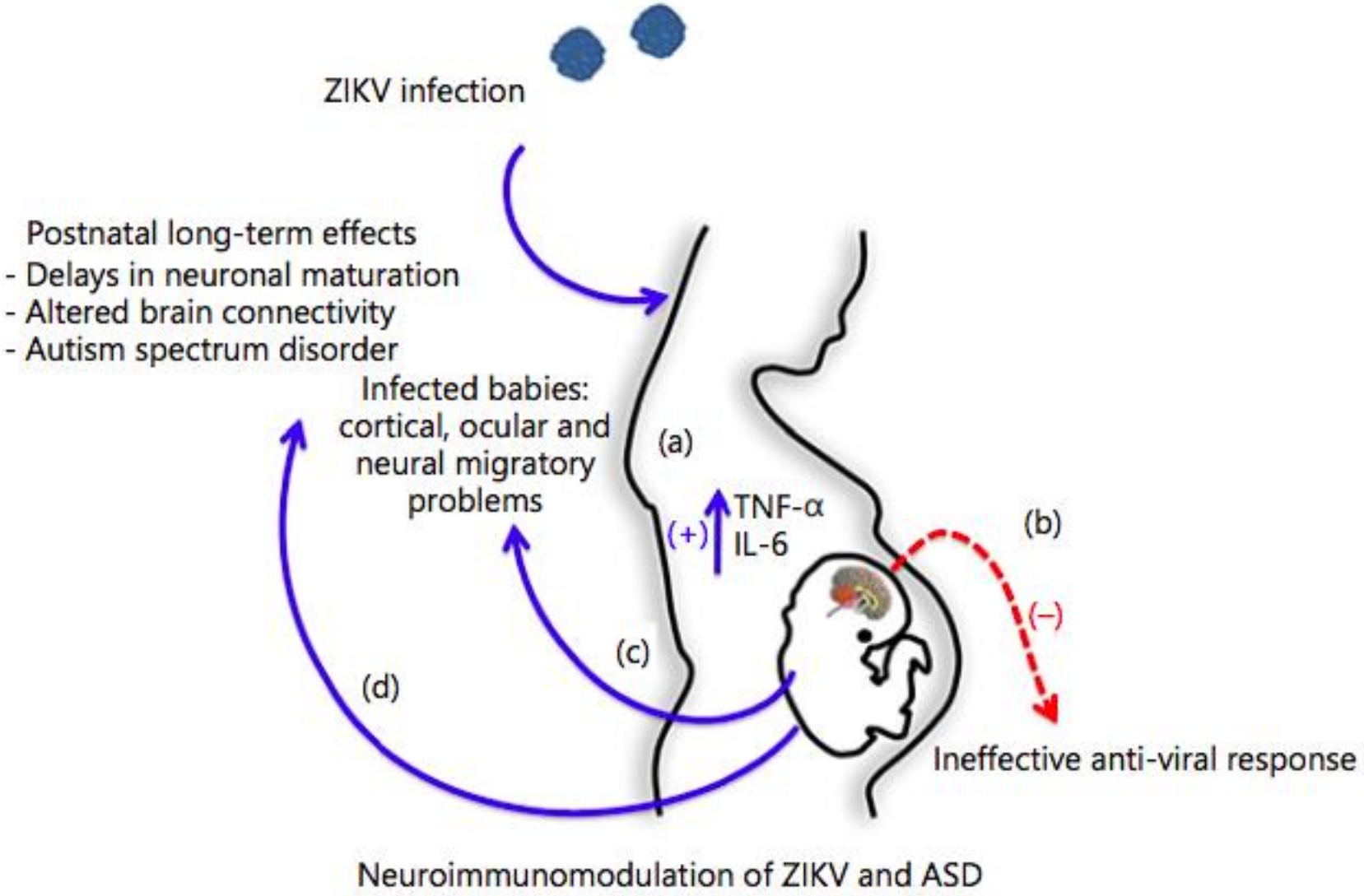
Neuromodulation of ZIKV



Neural→←Immune cross-talk

- CNS can regulate the immune system through neuronal and hormonal pathways,
- Immune system can modulate brain function and influence the neurogenesis process and connectivity
- Multiple cytokines and MHCI molecules are normally produced in the healthy brain

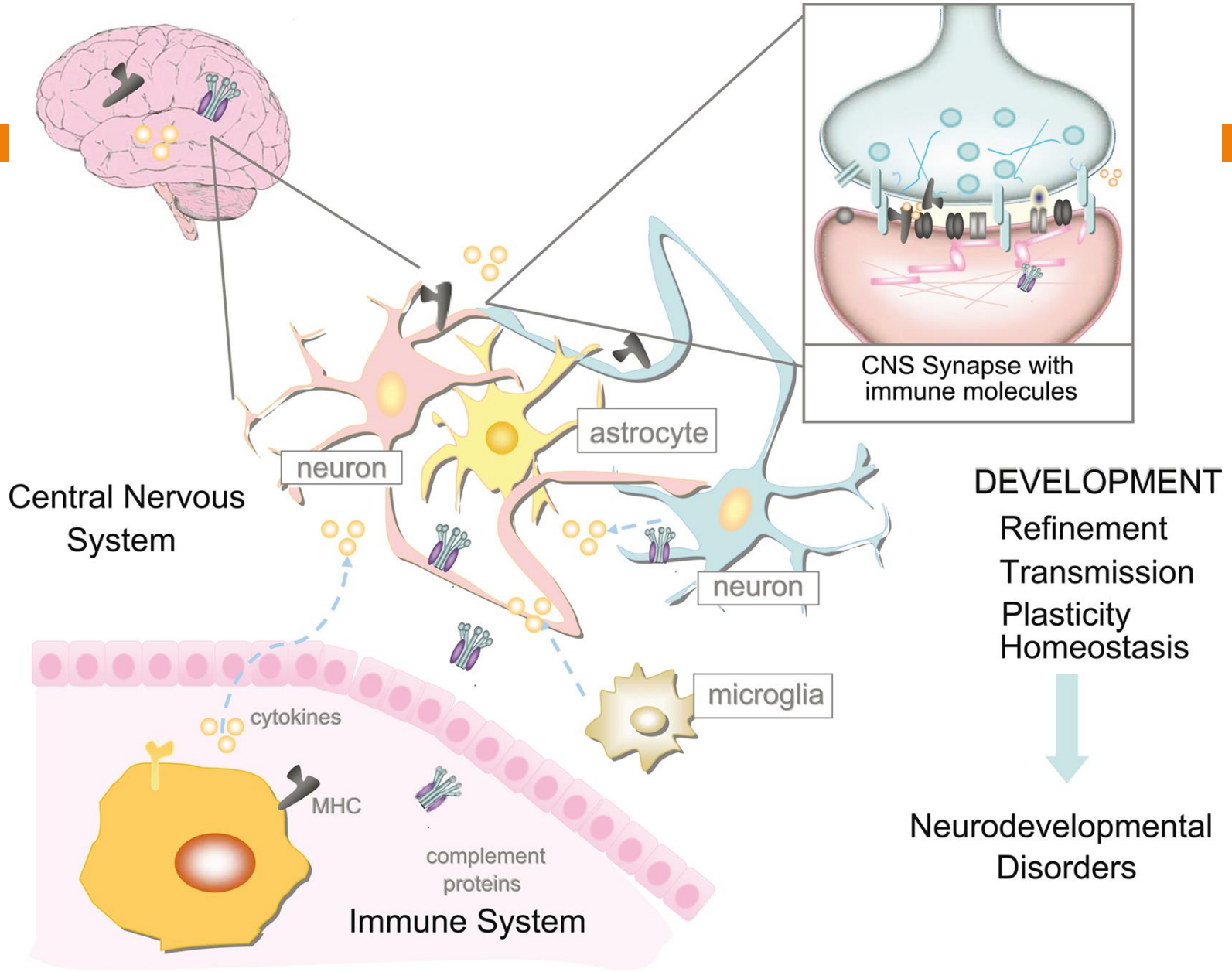
Cytokines and chemokines in brain

- Critical roles in almost every aspect of neural development, including neurogenesis, migration, differentiation, synapse formation, plasticity, and responses to injury

Immune genes and enviromental effects

Expression and signalling of genes in cytokines, cytokine receptors, and MHCI are affected by many environmental influences;

- stress,
- infection,
- hormones
- brain activity


CNS Synapse with immune molecules
astrocyte
neuron
neuron
Central Nervous System
microglia
cytokines
MHC
complement proteins
Immune System
DEVELOPMENT
Refinement
Transmission
Plasticity
Homeostasis
Neurodevelopmental Disorders

Prenatal immune environment- Early Effects

Immediate disturbance of the neuronal development

Influences on *the earliest stages* of brain ontogeny, possibly promoting the later development of disorders across *multiple scales*

(Boulanger, 2009; Coulthard, 2018)

Prenatal immune environment- Late Effects

Epigenetic alterations: Susceptibility to a "second hit"

Correlations between higher concentrations of inflammatory markers and cognitive and behavioral development of children between 12 and 24 months of age

(Estes, 2016)

Abnormal cytokine levels and connectivity of CNS

- Elevated levels of *the pro-inflammatory cytokines* IL-6, TNF-α and IL-1β have been found in the cerebrospinal fluid , blood, and post-mortem brain tissue of people with autism

(Vargas, 2005)

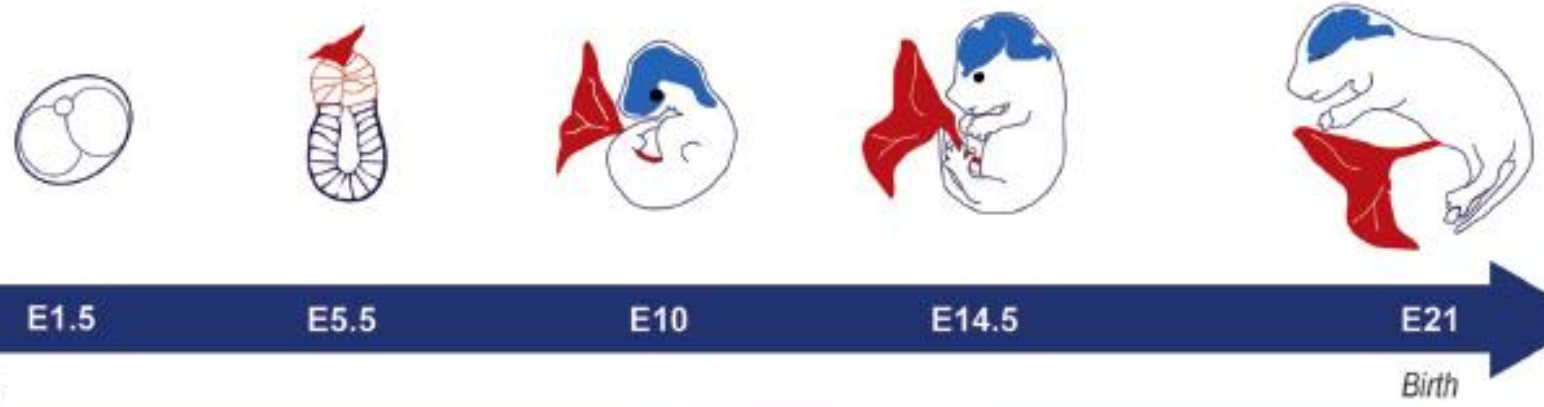
Immune system and ASD

- High levels of IL-6 in the anterior cingulated gyrus, in the frontal cortices and cerebellum of ASD patients and could mediate autistic-like behaviors

Immune system and NDD

- CNS inflammation, due to cytokine production by the mother and/or child may modify the activity of brain regions, such as the hippocampus

- TNF-α may regulate the dopaminergic differentiation as well as the apoptosis of neurons, leading to impaired fetal brain function



E1.5
E5.5
E10
E14.5
E21
Mating
Birth
Brain development events
NEUROGENESIS
MACROGLIOGENESIS
AXONAL GROWTH
INTERNEURONS MIGRATION
SYNAPTOGENESIS
Models of neuropsychiatric disorders following immune challenge
POSITIVE SYMPTOMS OF SCHIZOPHRENIA
AUTISM SPECTRUM DISORDER
NEGATIVE SYMPTOMS OF SCHIZOPHRENIA
CEREBRAL PALSY

Prematurity and Disconnectivity

- The wide spectrum of disability associated with preterm birth is consistent with pervasive abnormalities in brain *growth and connectivity*

(Back, 2015, Volpe, 2009)

3. Trimester of Fetal Brain

High activity of

- Neuronal connectivity,
- Brain growth and
- Cortical maturation

Prematurity and NDD

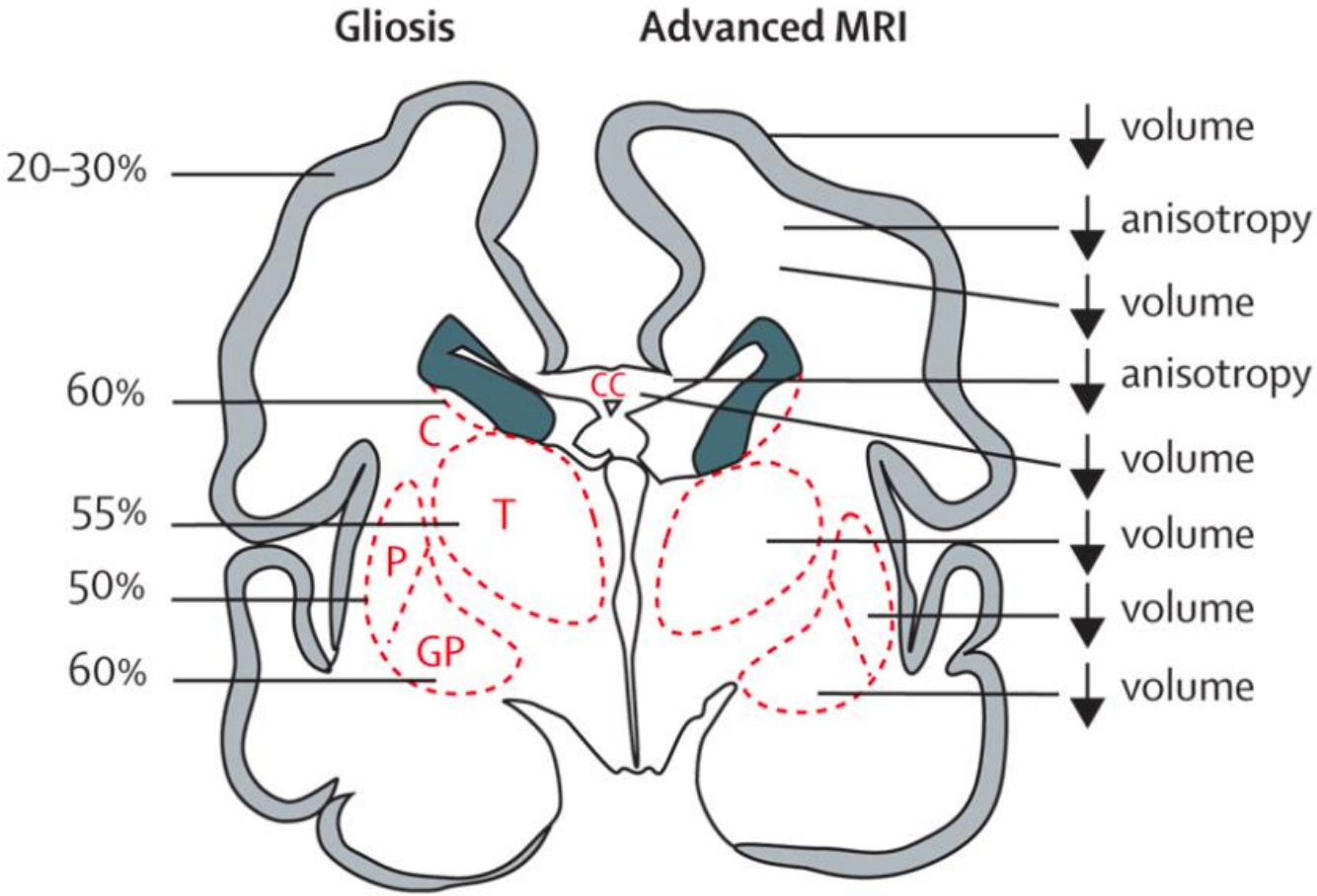
- High prevalence of motor, cognitive, language, and social-emotional deficits in childhood
- Increased risk of developing psychiatric disorders in adulthood

VLBW Babies and Cognitive Functions

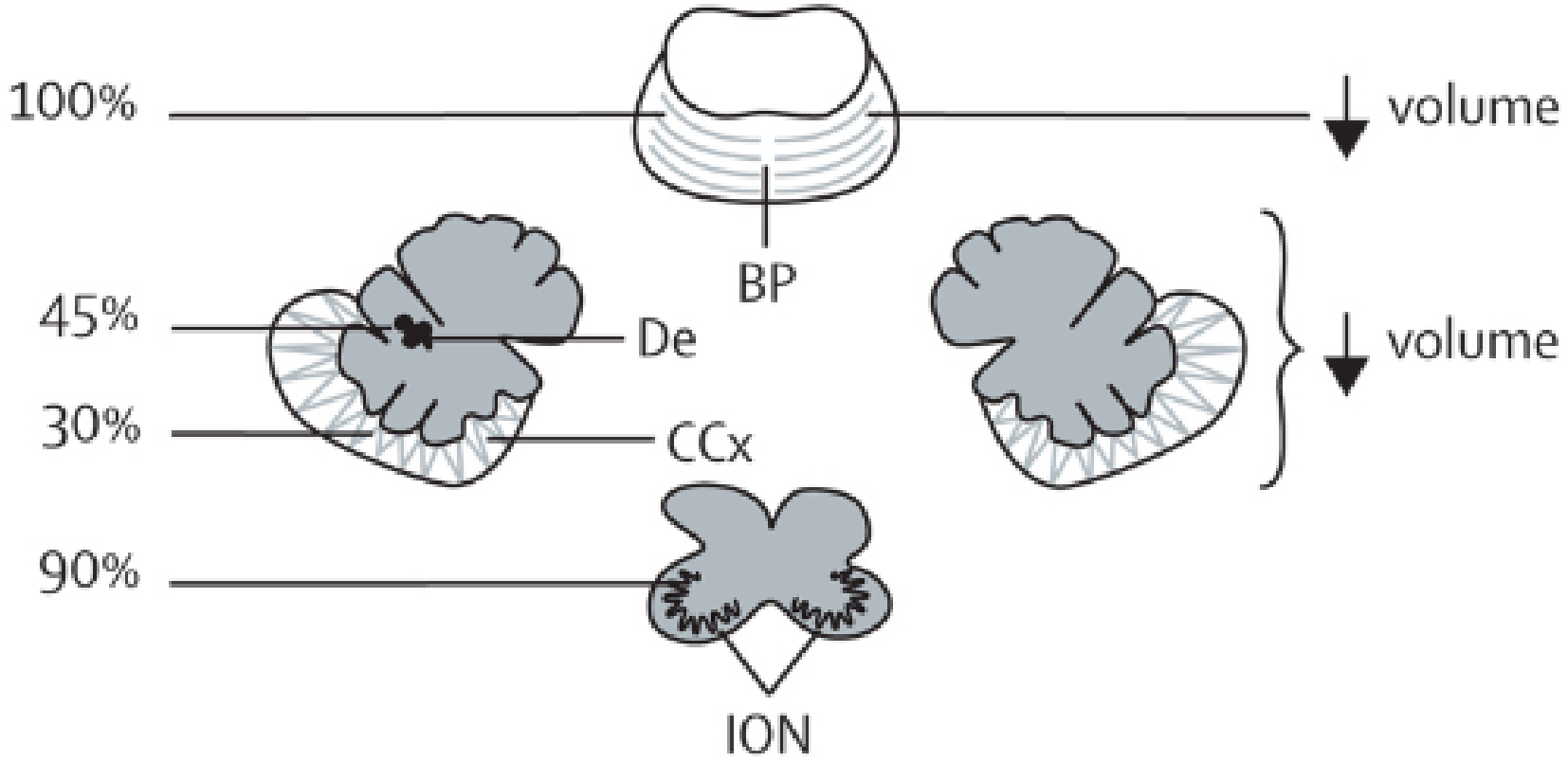
- Mild to moderate motor impairment : 40%
- Intellectual disabilities: 15–20%
- Specific learning disorders: 10–15%

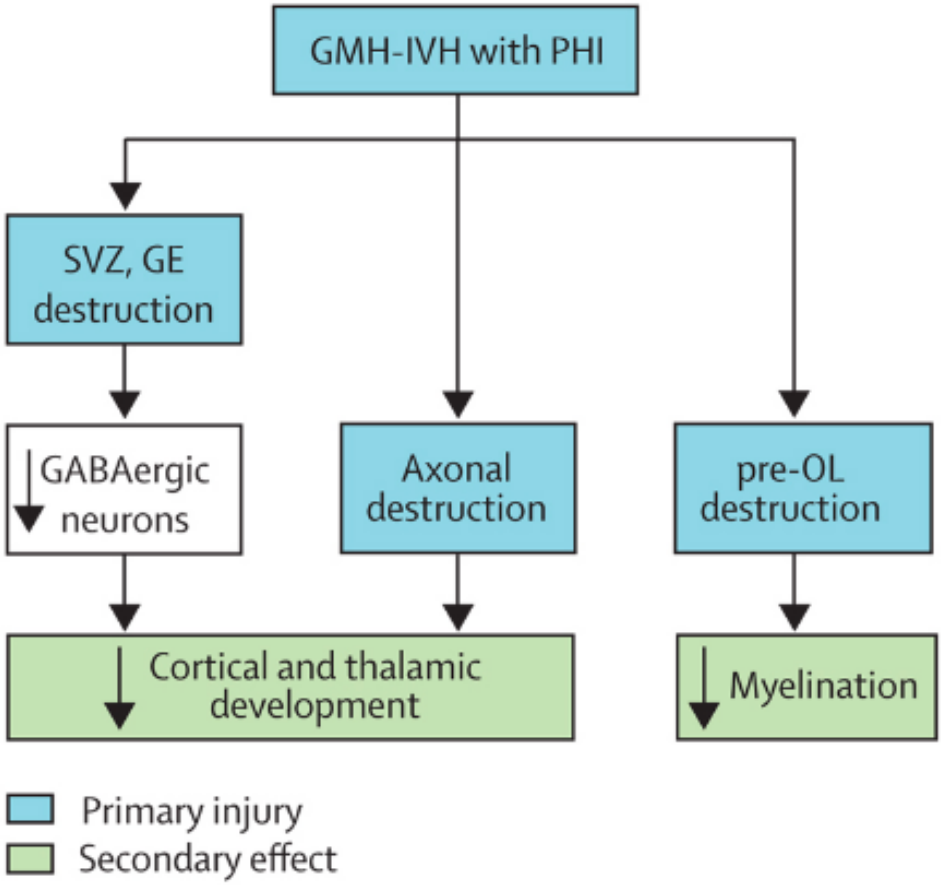
Full Scale Intelligence Quotient (IQ) scores up to 10 points lower than term children

Main neuronal/axonal structures affected by PVL-1



Main neuronal/axonal structures affected by PVL-2



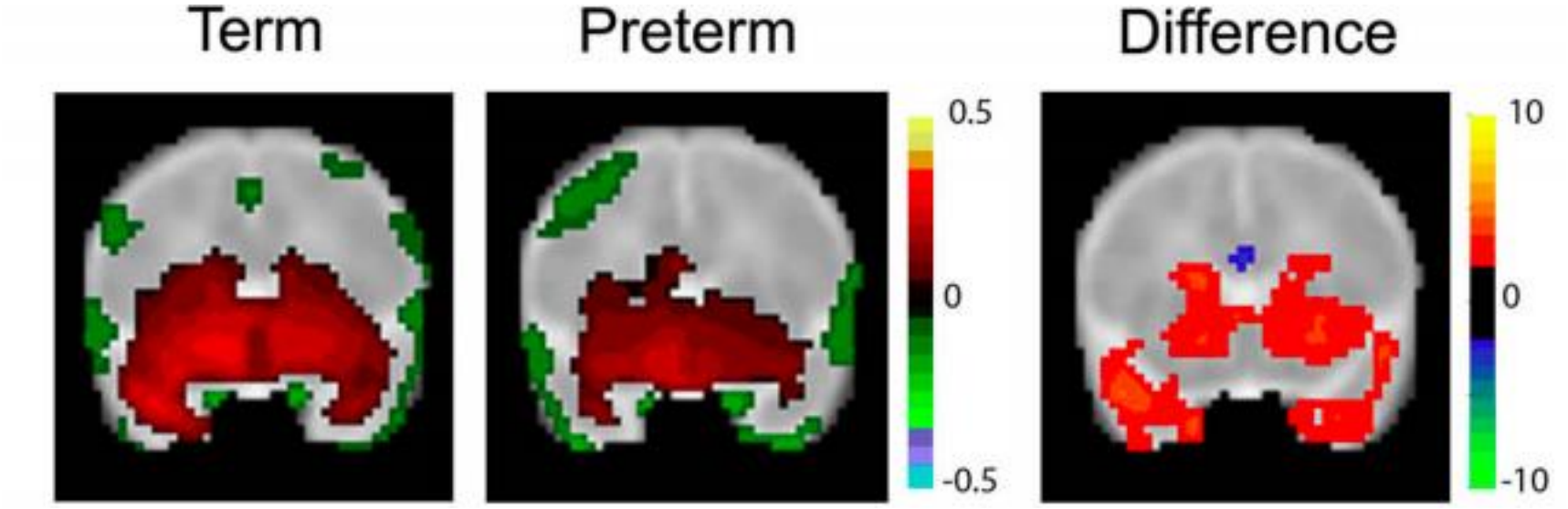


Apoptotic marker fractin is related with widespread axonal degeneration

“Preterm behavioral phenotype”

- Attention-deficit hyperactivity disorder (ADHD), anxiety, and autism spectrum disorder (ASD) are 2-4 times more common than full-term children

Amygdala resting state-functional connectivity correlation maps with rs-fMRI

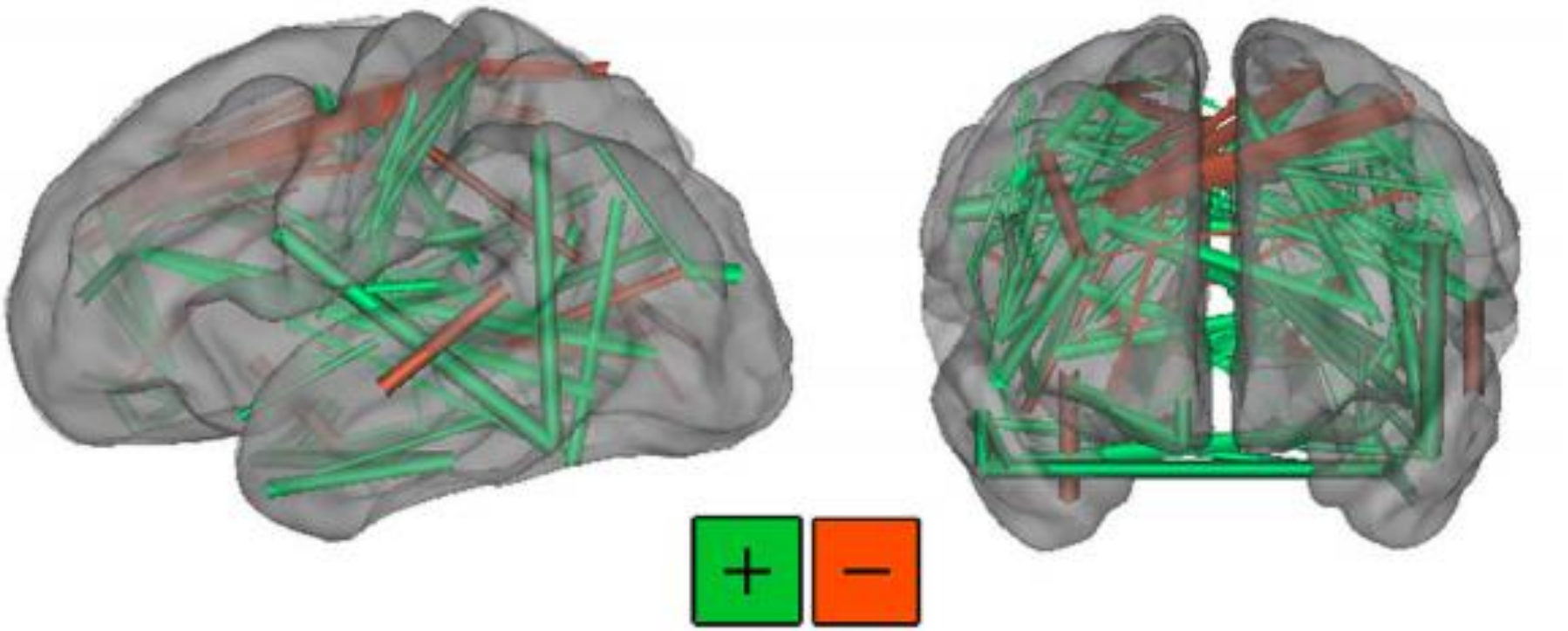


Functional connectivity differences between term and very preterm infants:

weaker intrinsic brain activity

Connections stronger in term infants (in green) vs in very preterm infants (in orange)

(d-MRI)



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