

Neurobiological Syndromes and Developmental Disabilities

James Coplan, MD

Neurodevelopmental Pediatrics of the Main Line, PC

Rosemont, PA

610-520-2130

<http://www.DrCoplan.com>

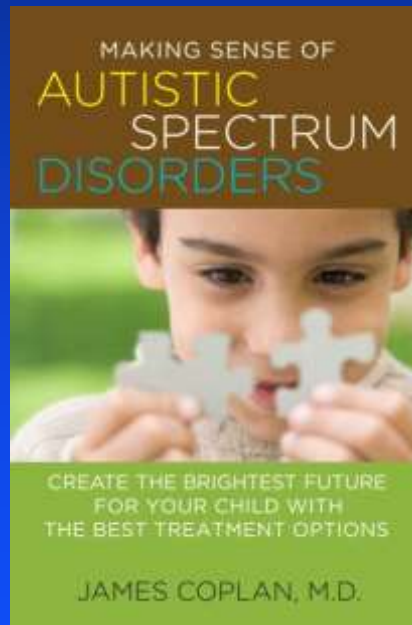
info@drcoplan.com

BCIU

11/8/2022

Disclosures

- Dr. Coplan is author of *Making Sense of Autistic Spectrum Disorders: Create the brightest future for your child with the best treatment options* (Bantam-Dell, 2010), and receives royalties on its sale

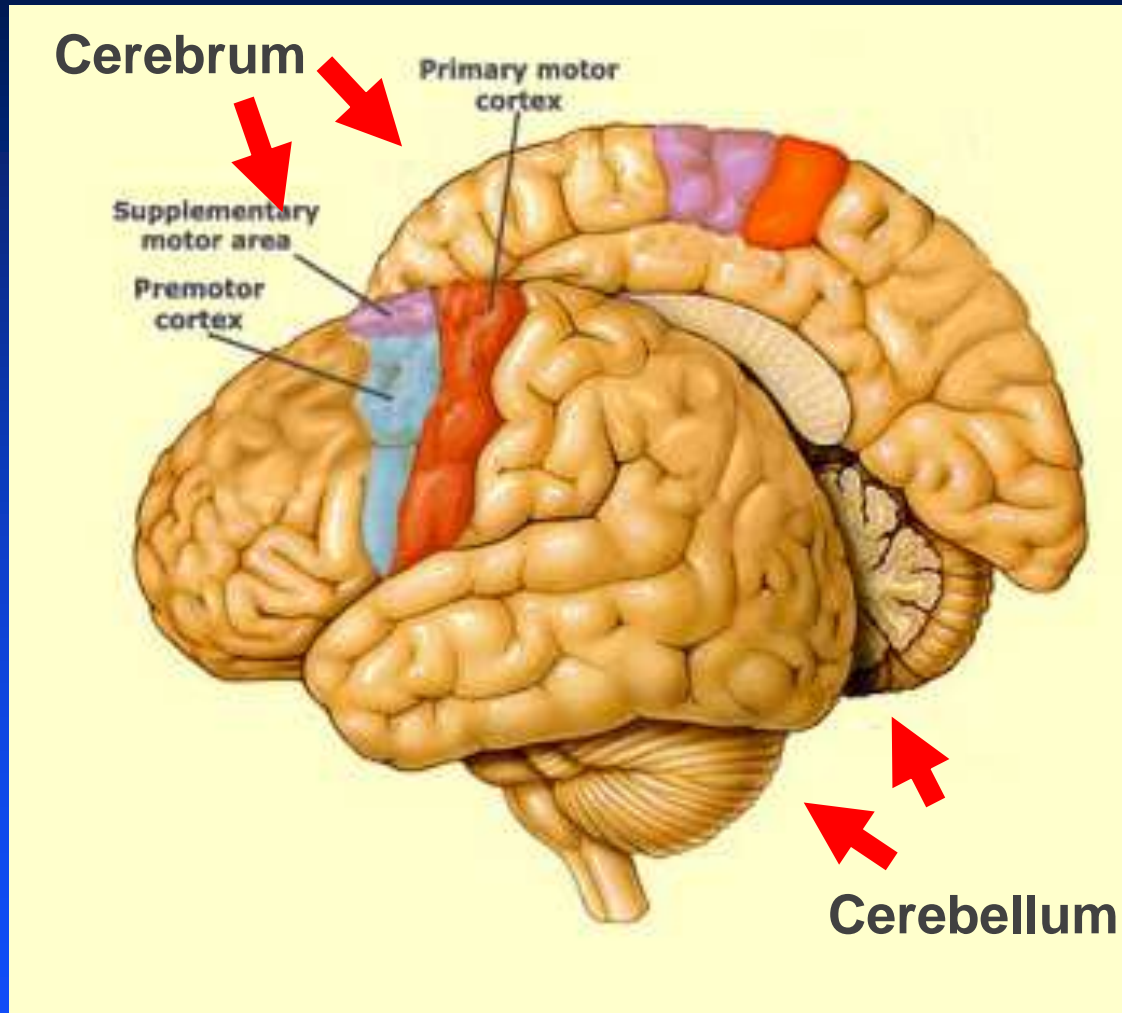


- This presentation will include a discussion of off-label drug use

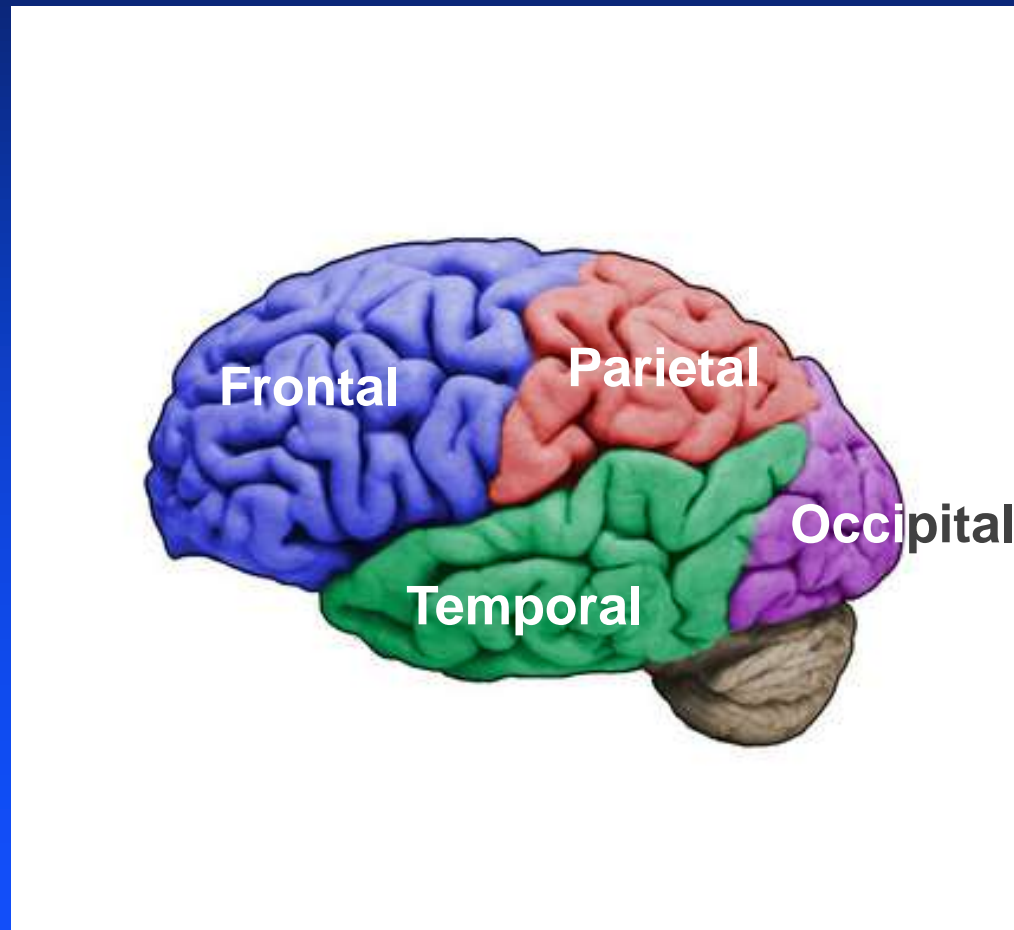
Classification Schemes

- **Anatomic**
 - Structural – Functional relationships
- **Physiologic**
 - Neurotransmitter pathways
- **Neural Networks**
 - Interrelationships between systems
 - “Final common pathways”
- **By developmental diagnosis**
- **By specific etiology** (genetic, metabolic, etc)

The brain



Lobes of Cerebral cortex (left side)

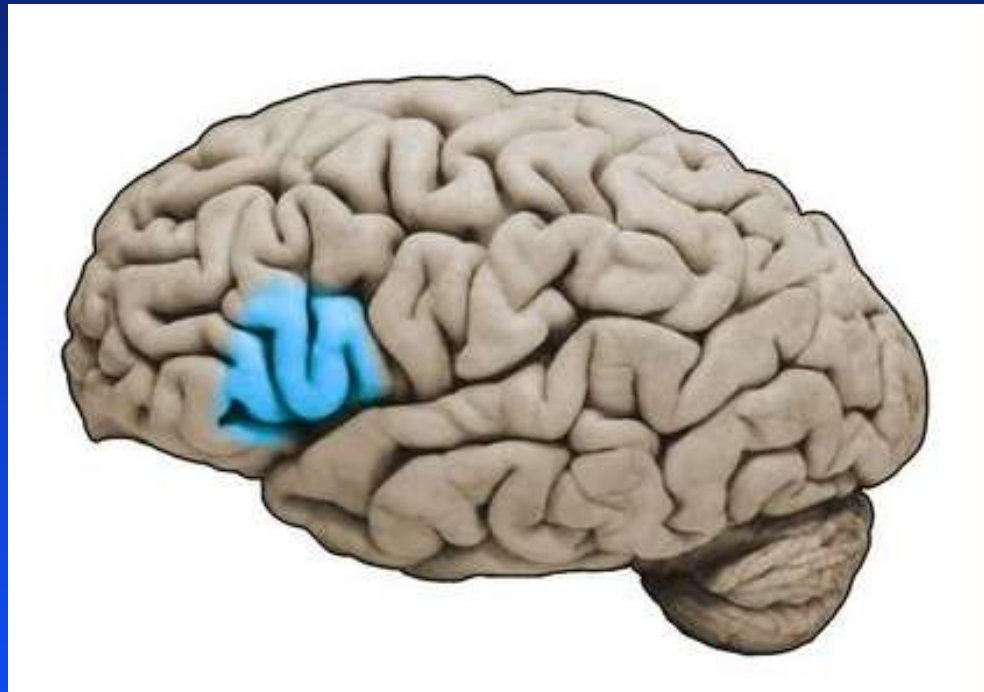


Anatomic Localisation

19th Century Model:

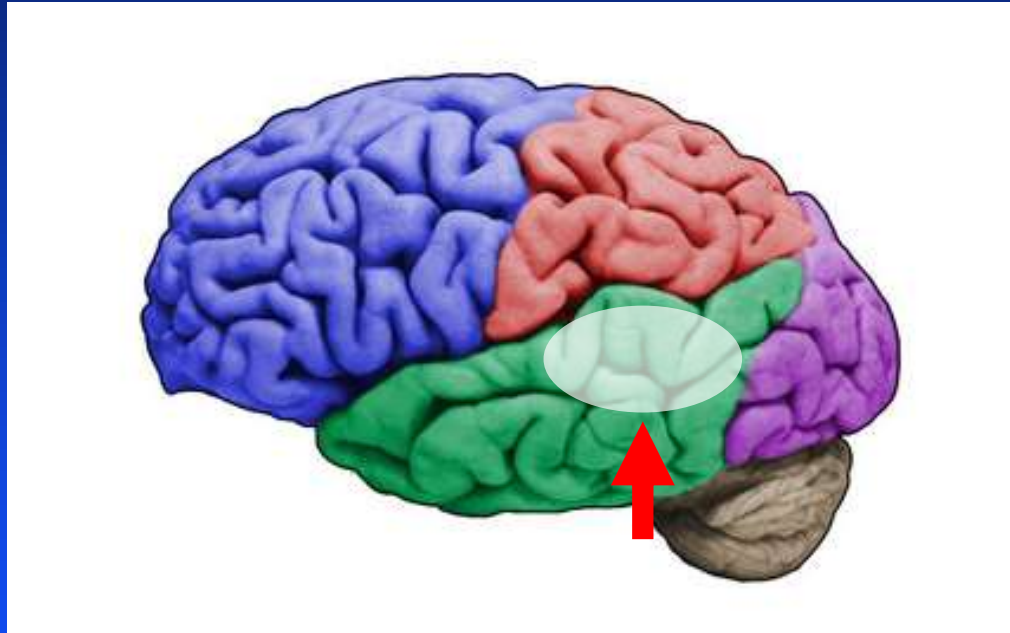
- Each brain region serves exactly one function, and each brain function arises from exactly one region
- Remove a region, and the function served by that region is lost
 - Stroke
 - Gunshot wound
 - Other trauma

Broca's Area



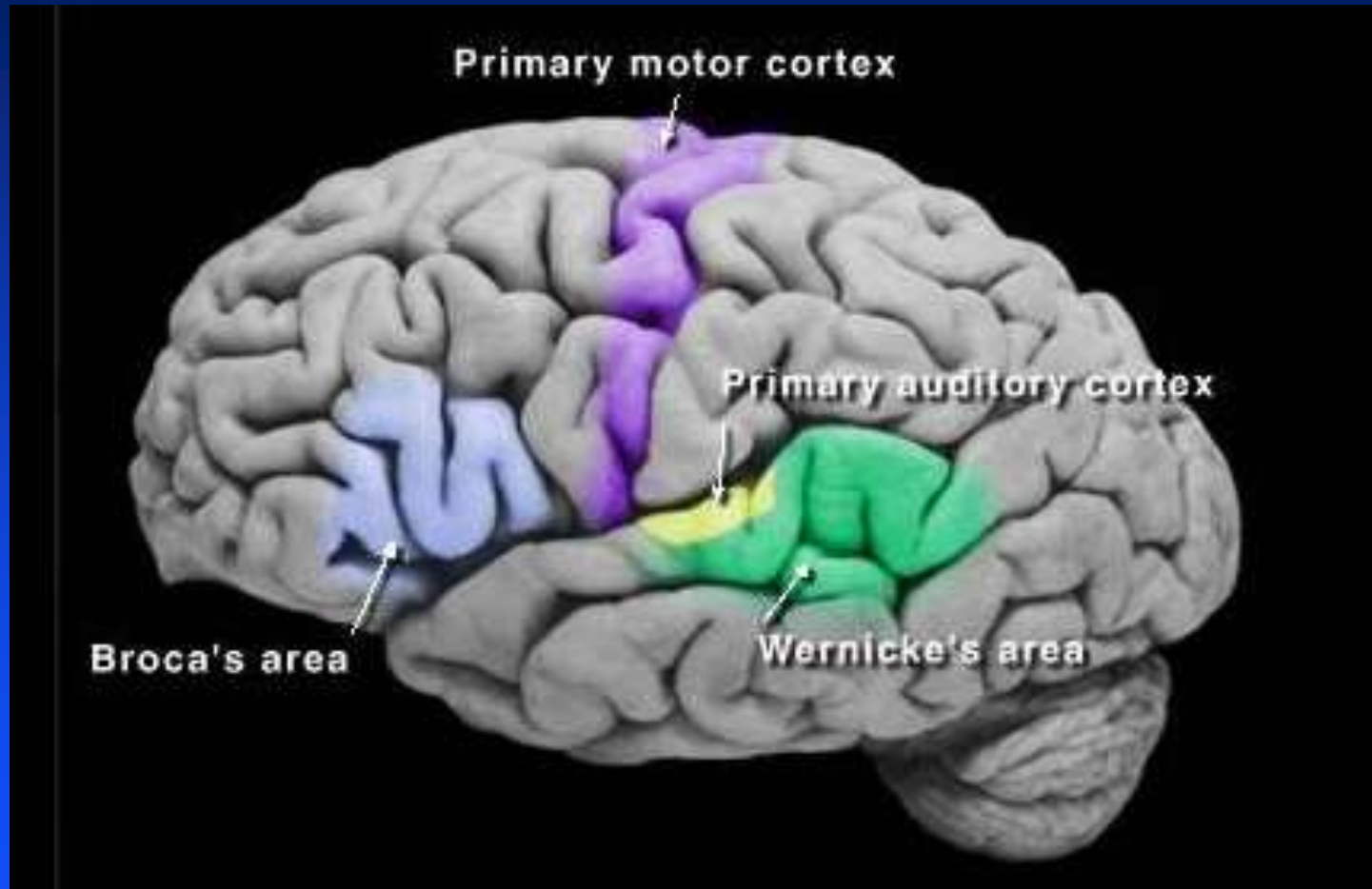
- Paul Broca, 1861
- Severe impairment of speech production
- Language comprehension remains intact (“Broca’s aphasia”)

Wernike's Area

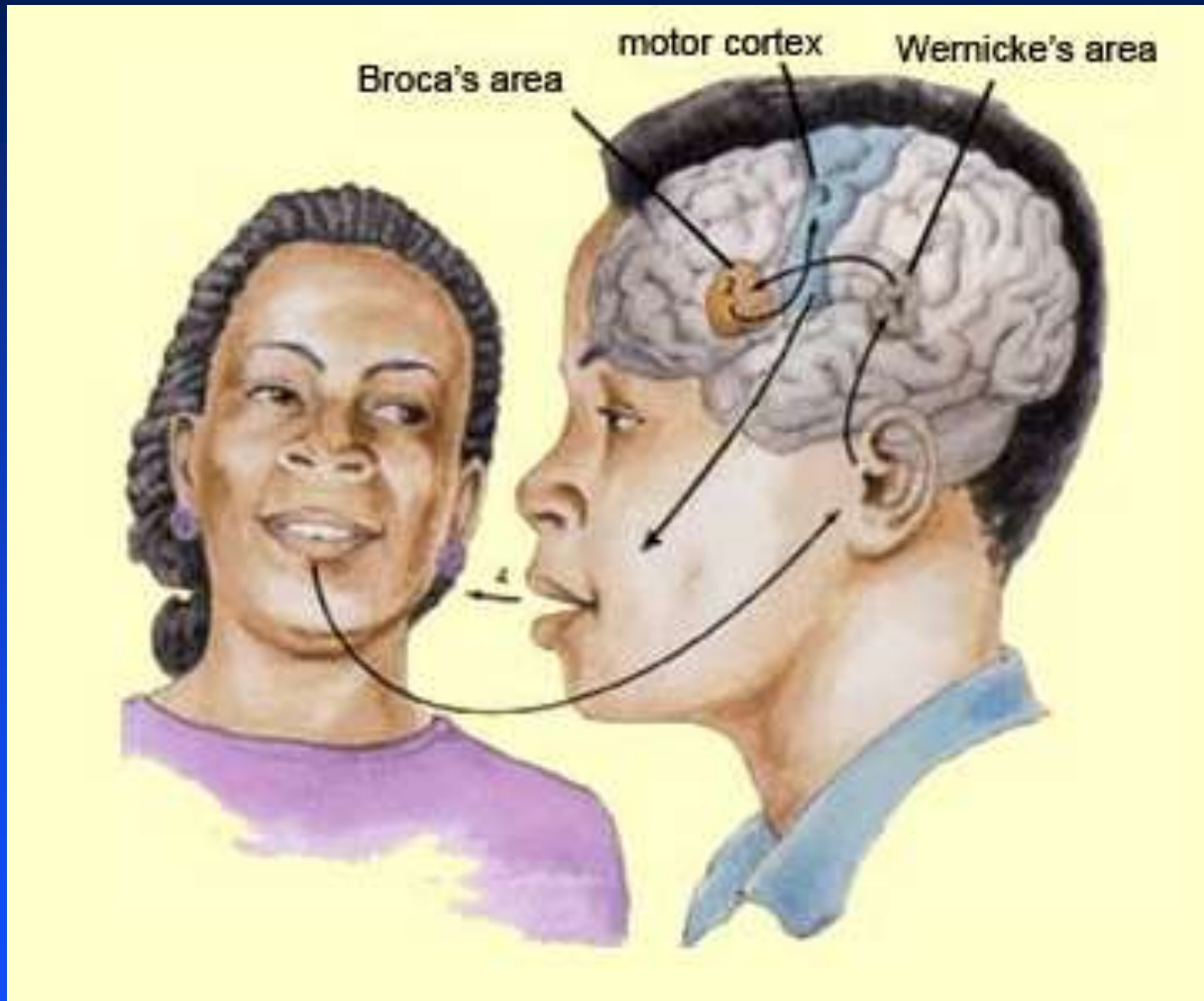


- Carl Wernicke, 1874
- Ability to speak remains intact, but language comprehension and ability to produce meaningful speech are impaired (“Fluent aphasia”)

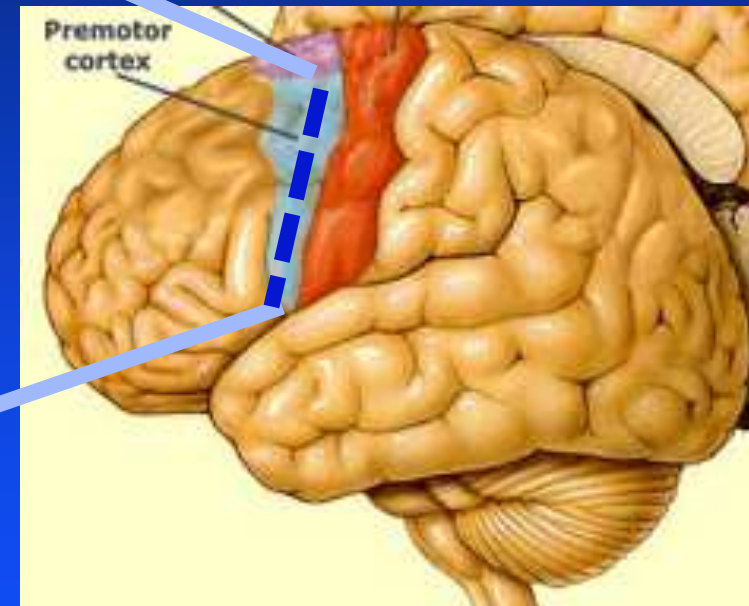
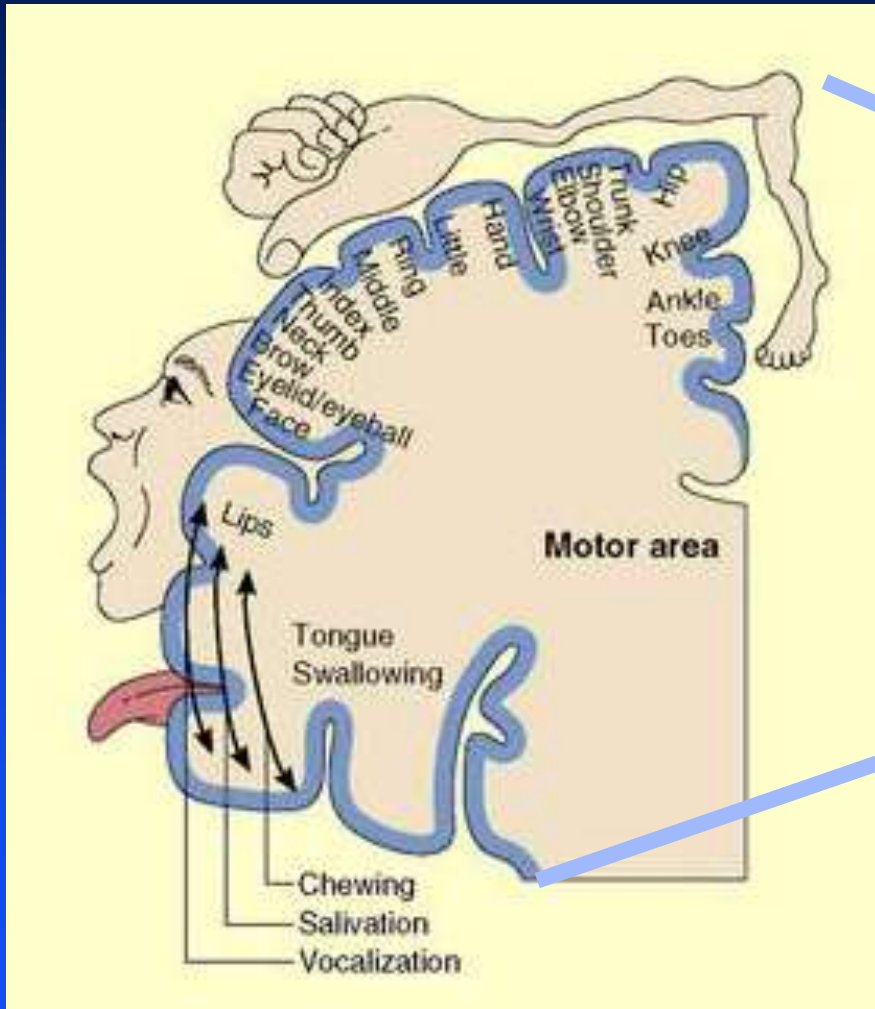
Speech-Language Circuit



Speech-Language Circuit



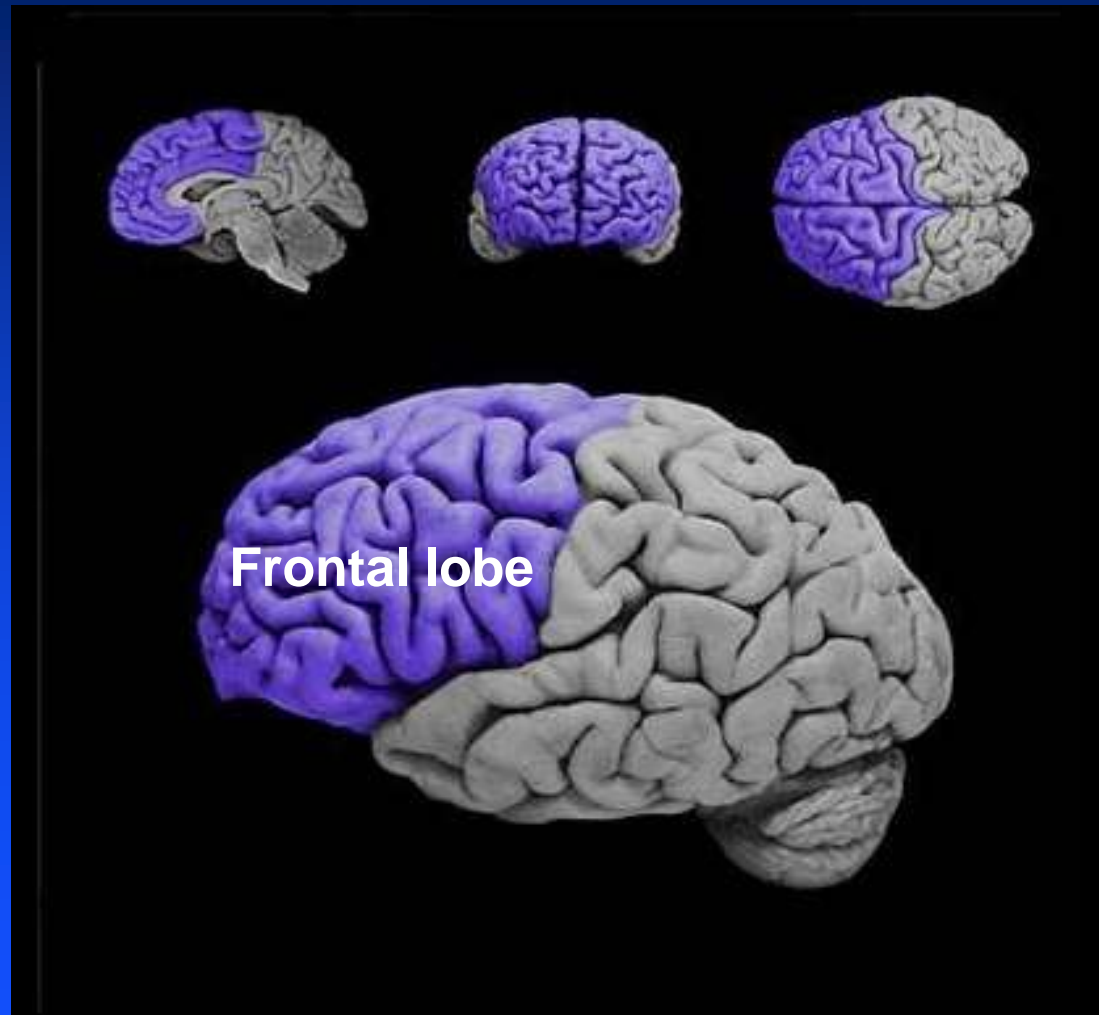
Motor & Sensory Homunculi



- Wilder Penfield; 1930s-50s
- Cortical stimulation / surgery



Regional Function



Phineas Gage (1848)



Horrible Accident – As Phineas P. Gage, a foreman on the Railroad in Cavendish, was yesterday engaged in tamping for a blast, the powder exploded, carrying an iron instrument through his head an inch and a fourth in circumference, and three feet and eight inches in length, which he was using at the time. The iron entered the side of his face, shattering the upper jaw, and passing back of the left eye, and out the top of his head.

The most singular circumstance connected with this melancholy affair is, that he was alive at two o'clock this afternoon, and in full possession of his reason, and free from pain.” – *Ludlow, Vt, Union*

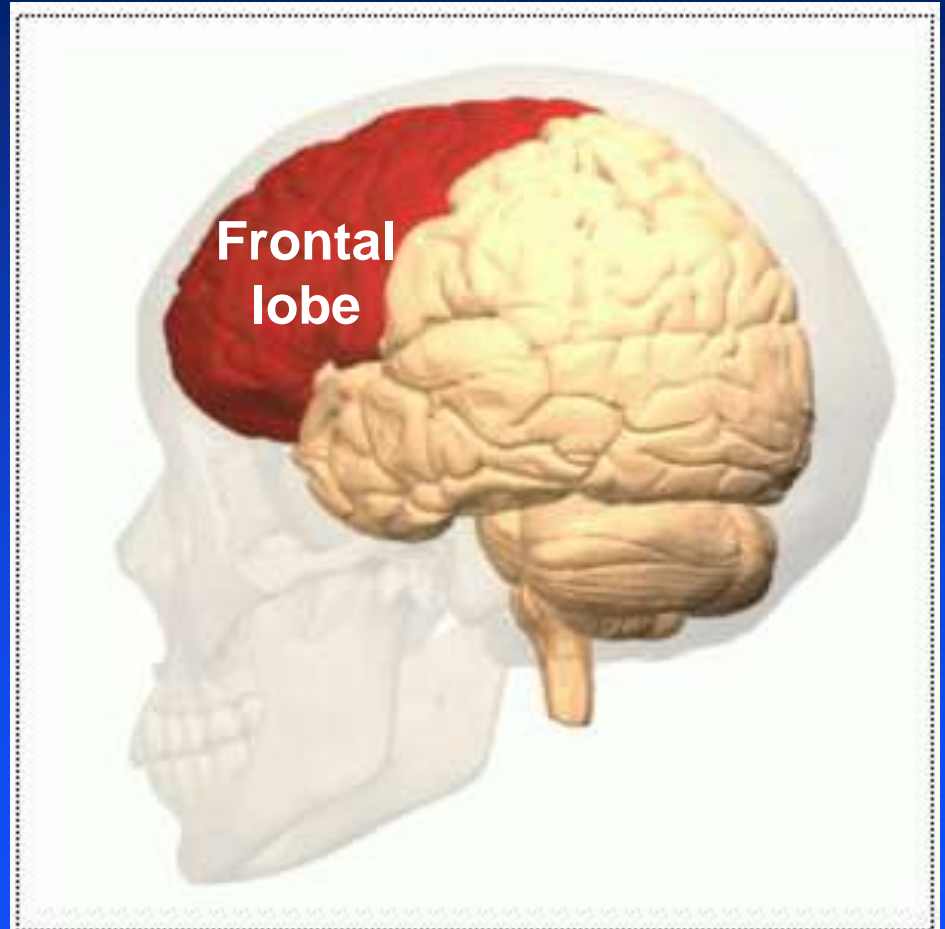
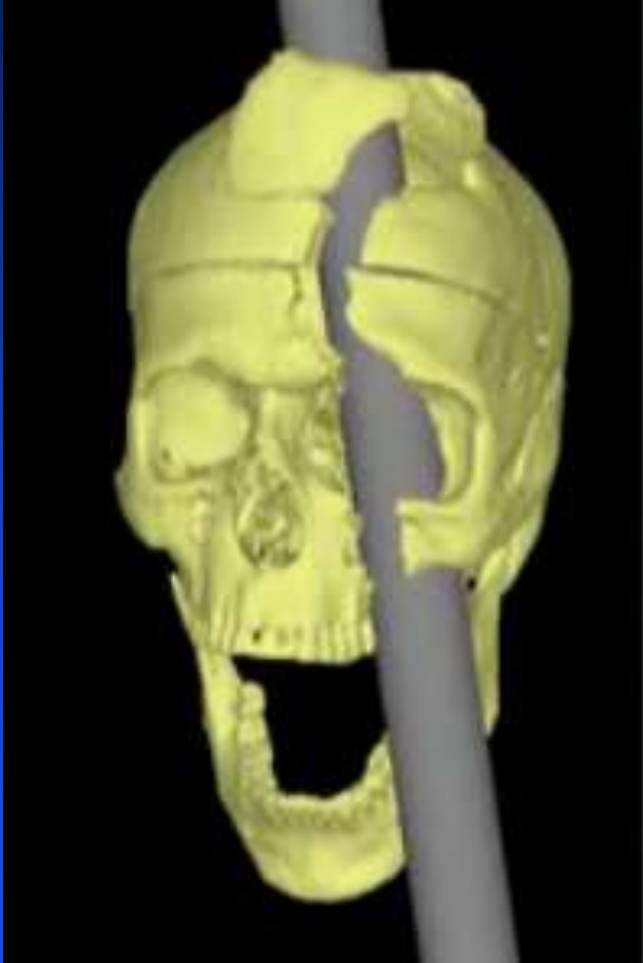
Phineas Gage 20 years later

His contractors, who regarded him as the most efficient and capable foreman in their employ previous to his injury, considered the change in his mind so marked that they could not give him his place again. He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint of advice when it conflicts with his desires, at times pertinaciously obstinent [sic], yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. In this regard, his mind was radically changed, so decidedly that his friends and acquaintances said he was "*no longer Gage.*"

Frontal Lobe Syndrome

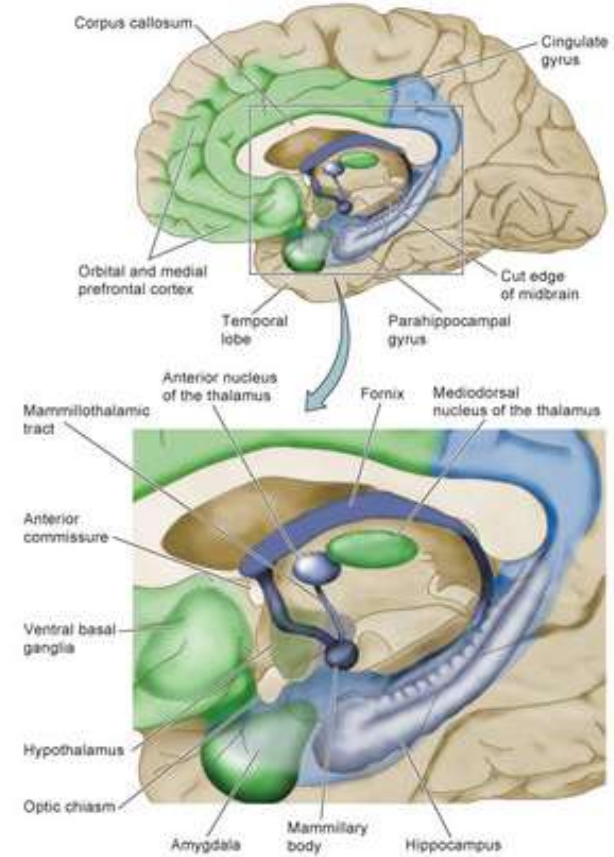
- **Cognitive: Impairment of**
 - Attention span
 - Memory
 - Planning
- **Emotional**
 - Mood lability (excitement, sadness, anger)
- **Behavioral**
 - Aggression, perseveration, hypersexuality

Phineas Gage





Prefrontal cortex 🔊



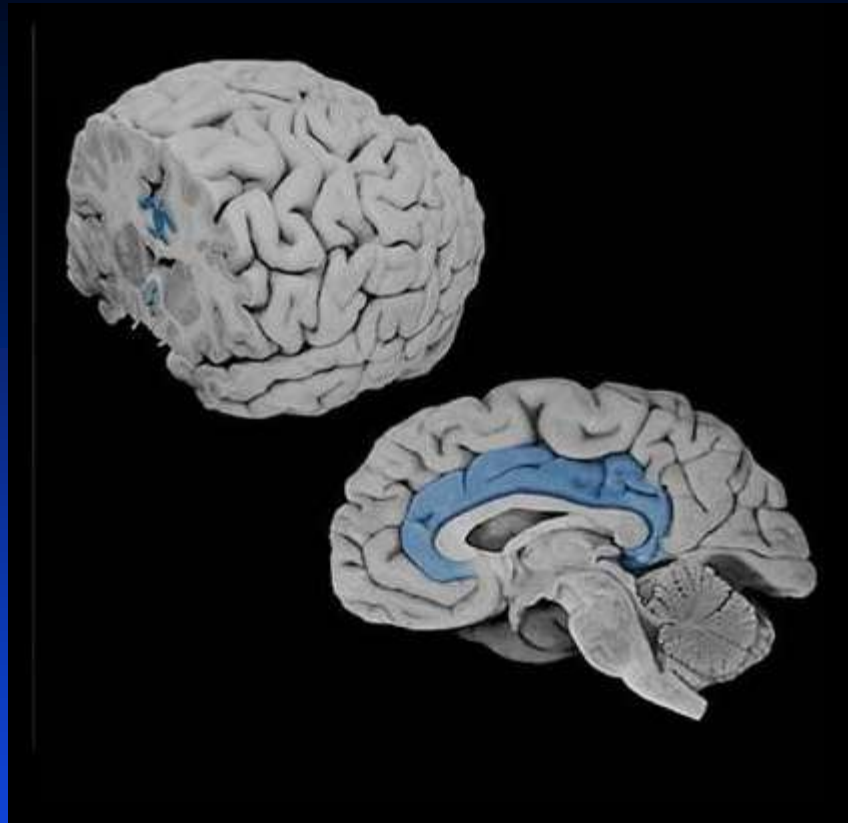
Prefrontal cortex 🔊

Cortical regions in the frontal lobe lying anterior to the primary and premotor cortices. The prefrontal cortex mediates a variety of executive functions, with a dorsal-lateral sector involved in working memory processes, planning and decision making, and a ventral-medial (orbitomedial) sector involved in emotion and the organization of personality and appropriate social behavior.

Location: anterior frontal lobe

Function: involved in associational functions related to cognition and executive control

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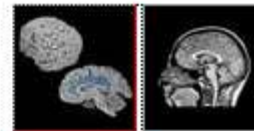
Cingulate gyrus 🔊

Prominent cortical component of the limbic system located on the medial aspect of the hemisphere superior to the corpus callosum.

Location:
medial forebrain

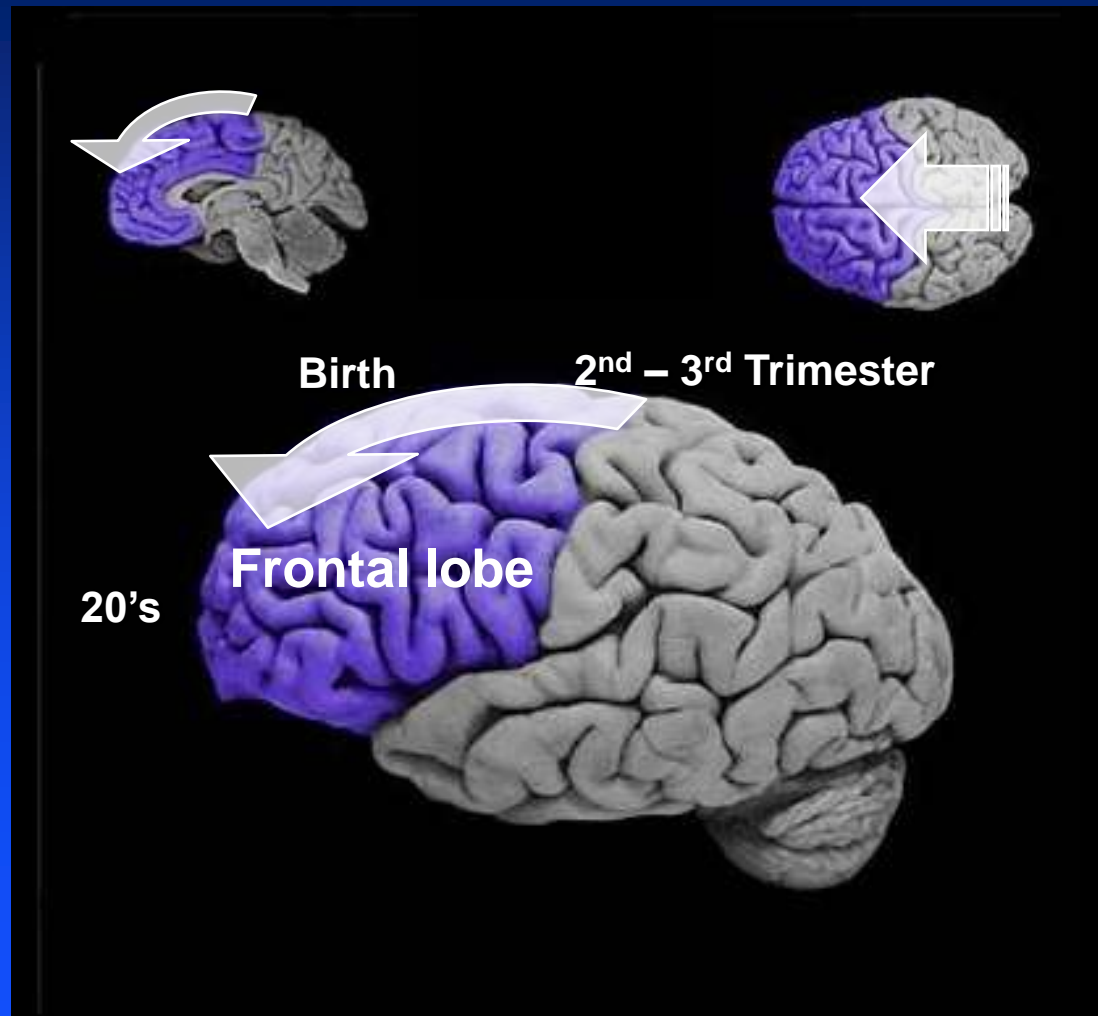
Function:
involved in emotional and cognitive processing

About this image:
Photographic images of a 3/4 view of a coronal section (top) and a midsagittal section of the right hemisphere (bottom) of the human brain.





Time line of myelination





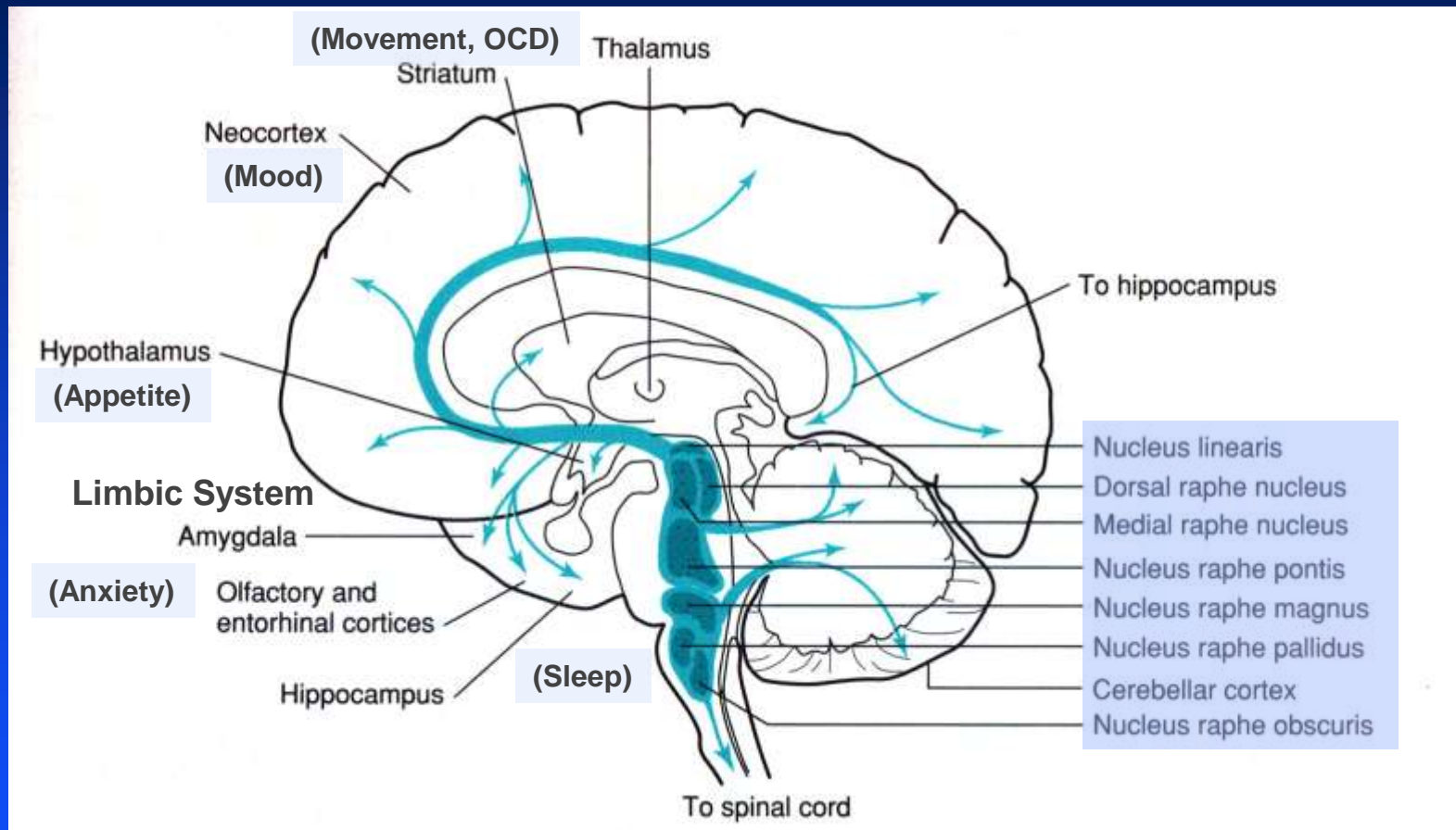
Neurotransmitter Systems

- GABA
- Glutamate
- Dopamine →→
- Norepinephrine (“noradrenergic”)
- Serotonin
- Acetylcholine

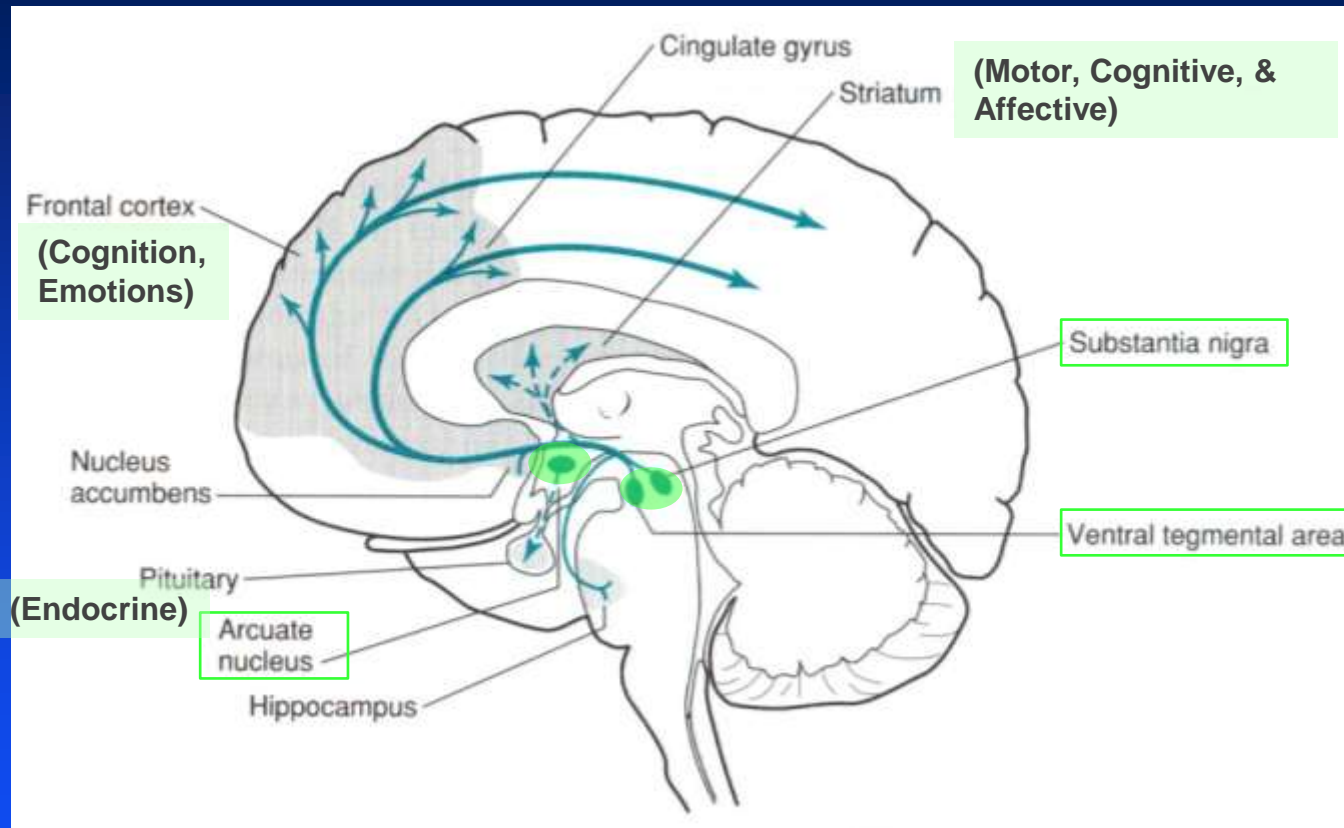
Brain-wide activity

- **Localization by biochemical properties of receptors on neurons**

Serotonin

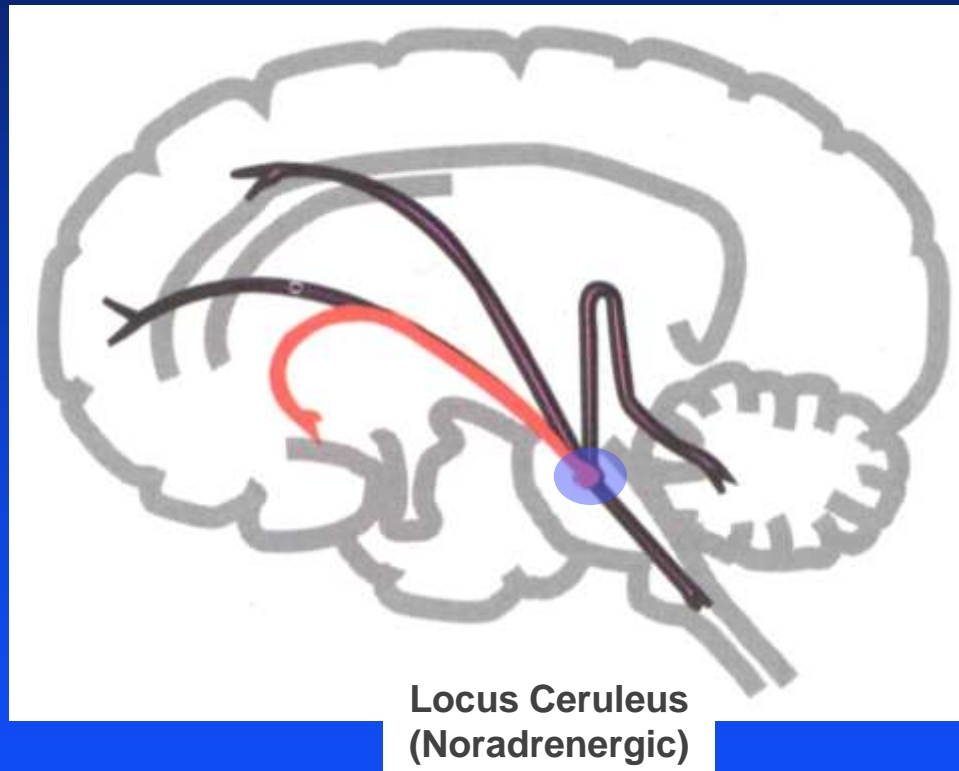


Dopamine



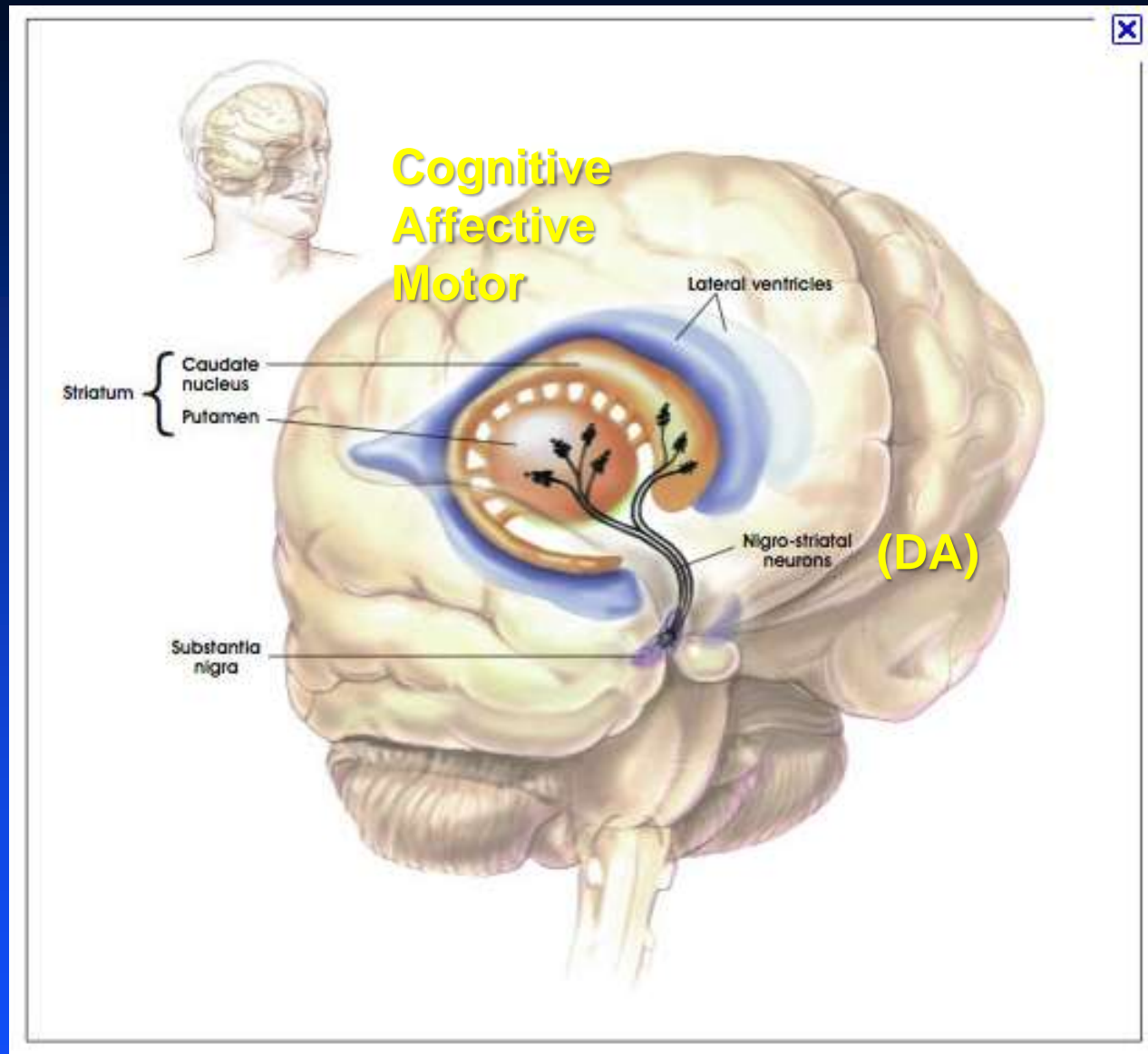
Substantia Nigra (“black stuff”), Ventral tegmentum, arcuate nucleus

Hypervigilance, Agitation

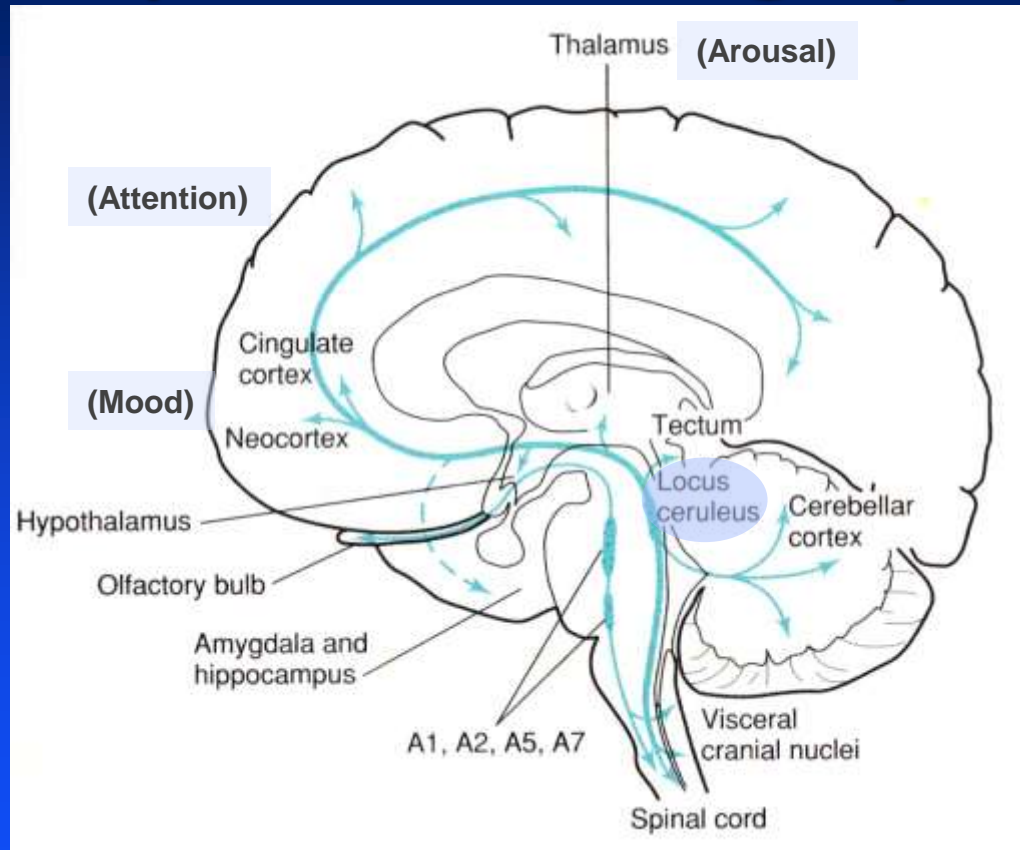


Excess Noradrenergic Activity → Hypervigilance, Agitation

Stahl, *Essential Psychopharmacology*, fig 5.26



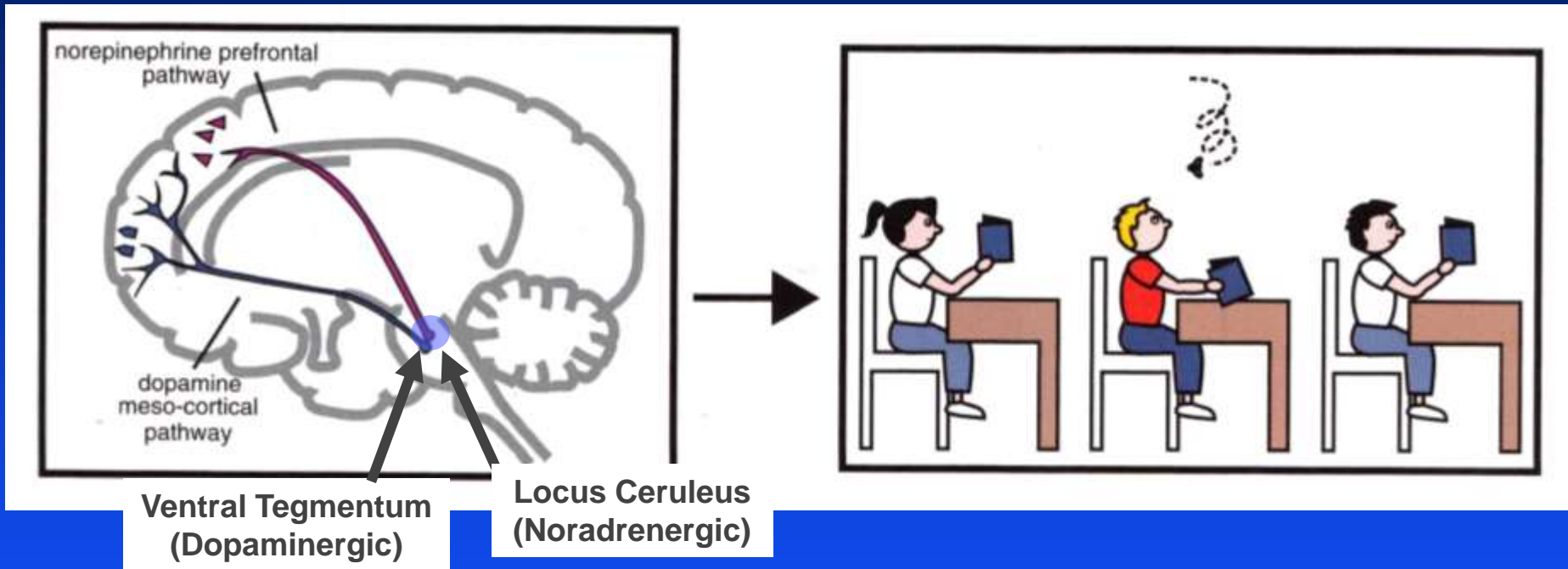
Norepinephrine (Noradrenergic)



Locus Ceruleus (“blue spot”): Principal noradrenergic source in brain.

Nestler, *Molecular Neuropharmacology*, Fig 8.5

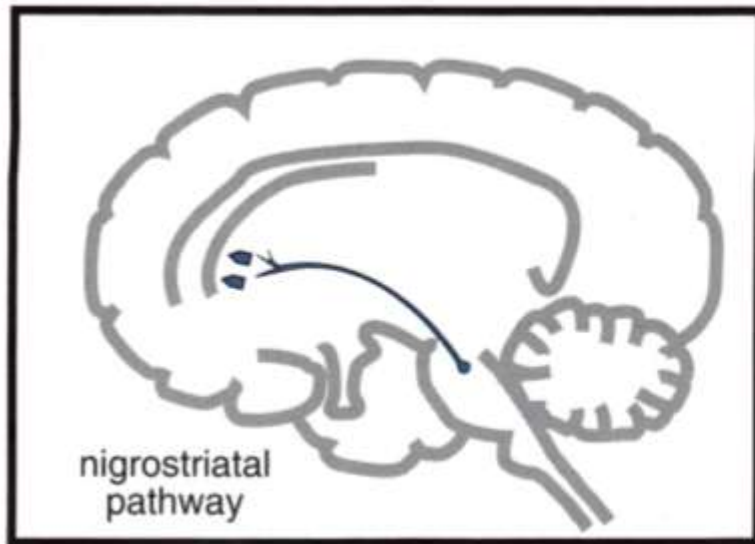
Inattention



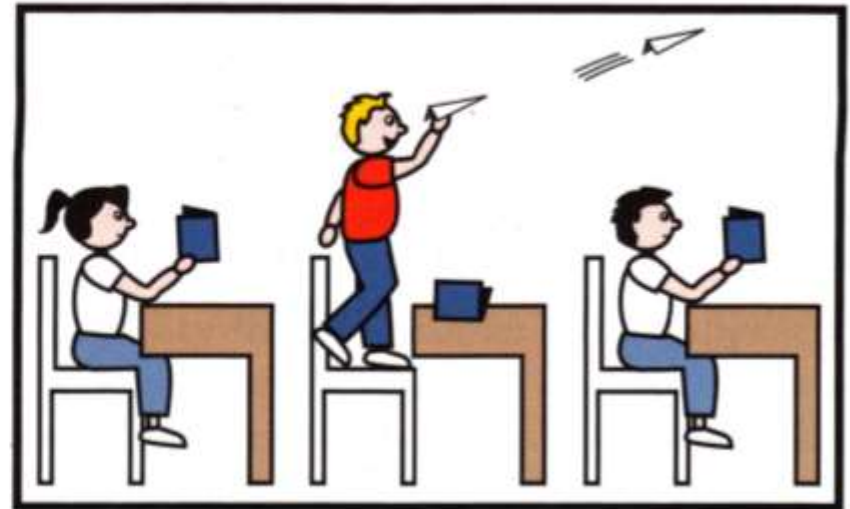
Insufficient activation of frontal cortex → → → Inattention

Stahl, *Essential Psychopharmacology*, fig 12.1

Hyperactivity



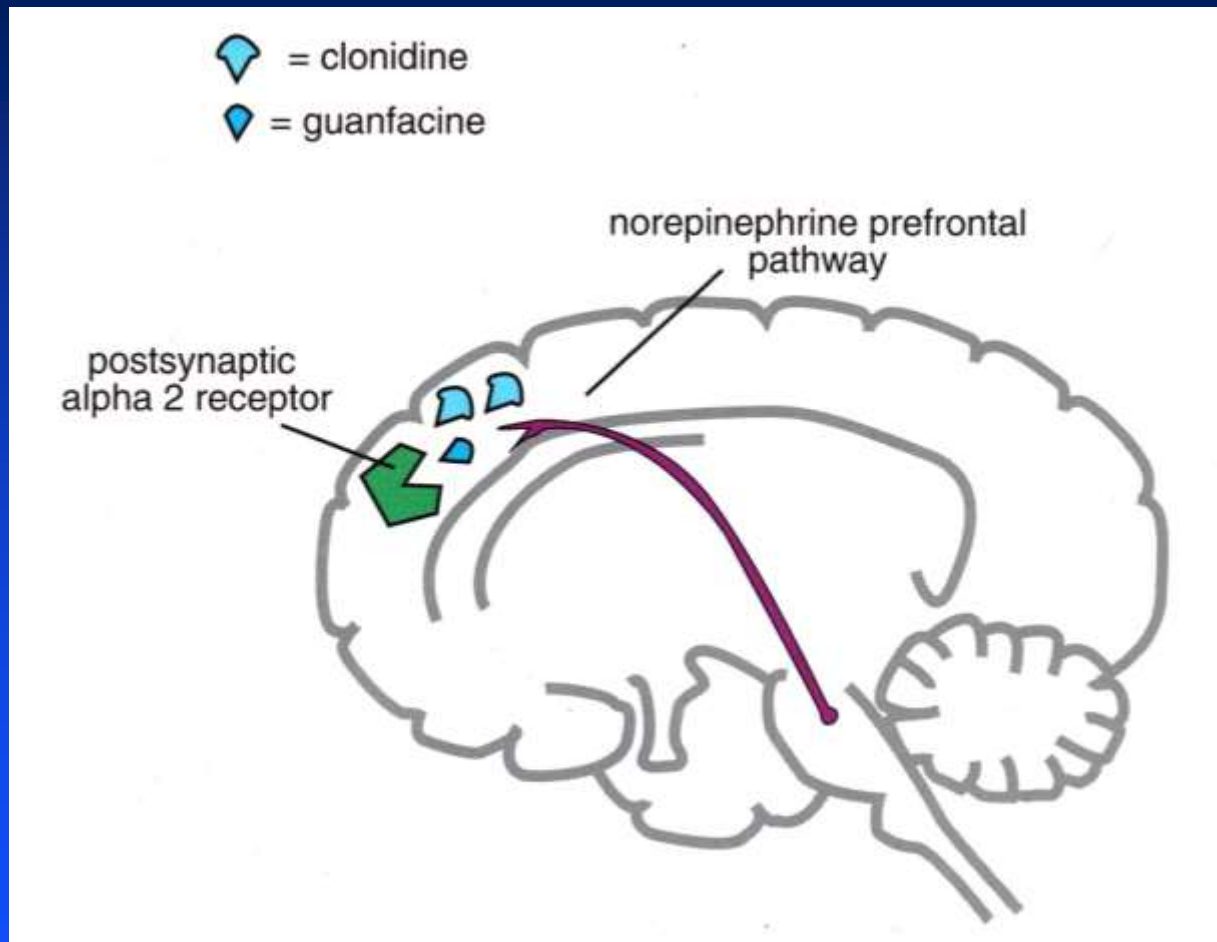
(Dopaminergic)



↑ Dopamine in children with ADHD → “Paradoxical” calming

Stahl, *Essential Psychopharmacology*, fig 12.1

Alpha-2 Agonists



Stahl, *Essential Psychopharmacology*, fig 12.6



Developmental Diagnosis

- **Autism Spectrum Disorder**
- **Mental Retardation (Intellectual Disability)**
- **ADHD**
- **Developmental Language Disorder**
- **Cerebral Palsy**
- **Tourette Syndrome**
- **Various syndromes with specific behavior patterns**

Developmental Diagnosis

Autism Spectrum Disorder

- **No one location in the brain is universally abnormal**
 - Cerebellum (vermis; cell packing; cerebellar-frontal pathways)
 - Brain stem
 - Temporal lobes
- **ASD probably = a “final common pathway” of behavioral symptoms, due to various abnormalities upstream (“My car won’t start” disorder: Battery? Gas? Fuel pump? etc.)**

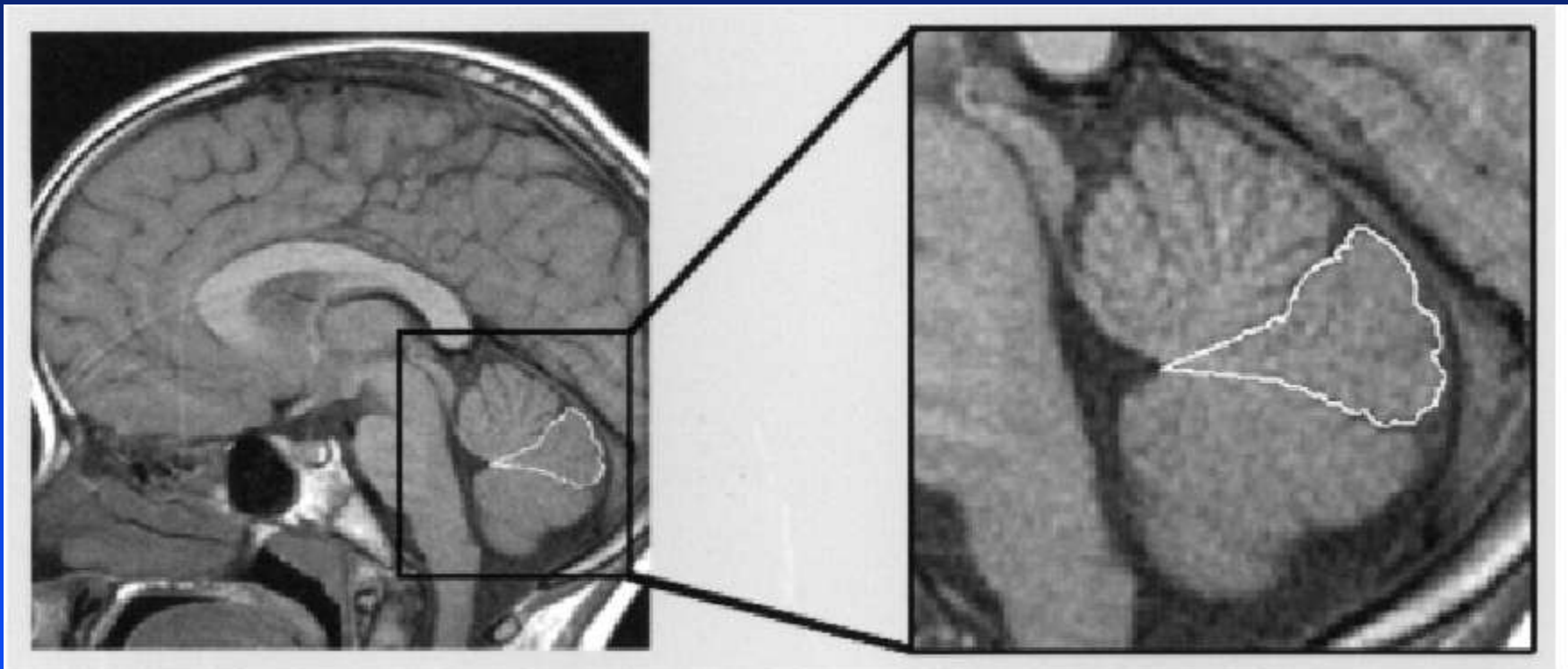
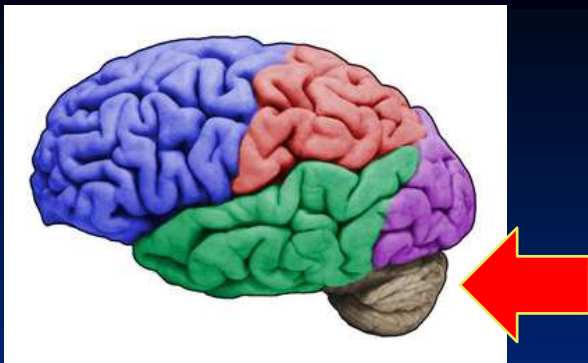
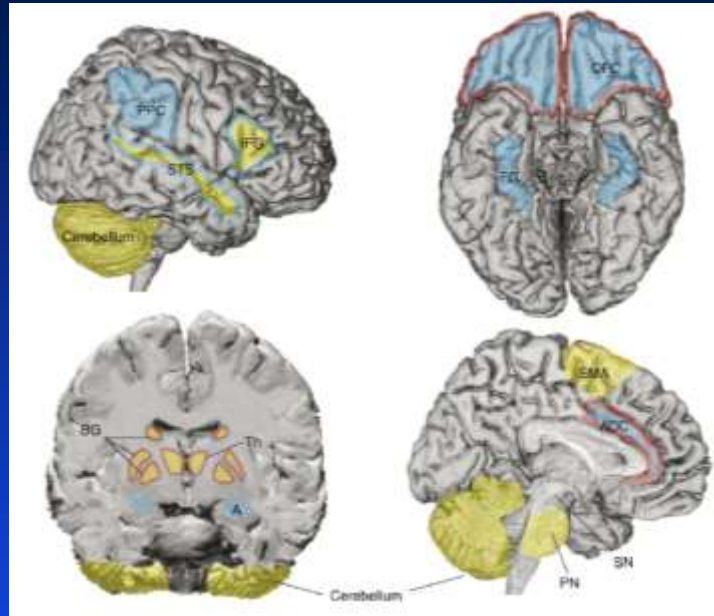


Fig. 2 Mid-sagittal, T₁-weighted image illustrating the anatomical boundaries used for measurement of cerebellar vermis lobules VI–VII.

Carper & Courchesne, Brain, 2000

Candidate Impairments in ASD



Social impairment	Communication deficits	Repetitive behaviors
<p>OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex FG – Fusiform gyrus STS – Superior temporal sulcus A – Amygdala mirror neuron regions IFG – Inferior frontal gyrus PPC – Posterior parietal cortex</p>	<p>IFG- Inferior frontal gyrus (Broca's area) STS – Superior temporal sulcus SMA – Supplementary motor area BG – Basal ganglia SN – Substantia nigra Th – Thalamus PN – Pontine nuclei cerebellum</p>	<p>OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex BG – Basal ganglia Th – Thalamus</p>



Developmental Diagnosis

Mental Retardation (Intellectual Disability)

- **Multiple causes**
 - Chromosomal (Trisomy 21)
 - Single Gene (Fragile X)
 - Teratogenic (Rubella, alcohol)
 - Metabolic (PKU)
 - Syndromes of unknown cause
- **Deficiency in number of neurons and/or number of interconnections**

Developmental Diagnosis

ADHD

- **No specific anatomic abnormality**
- **No specific lab abnormality**
- **Strongly genetic**
- **Defined on the basis of function**
- **Treatment: “Symptomatic”**
 - **Academic**
 - **Self-esteem / Social**
 - **Behavioral**
 - **Medication**

Developmental Diagnosis

Developmental Language Disorder

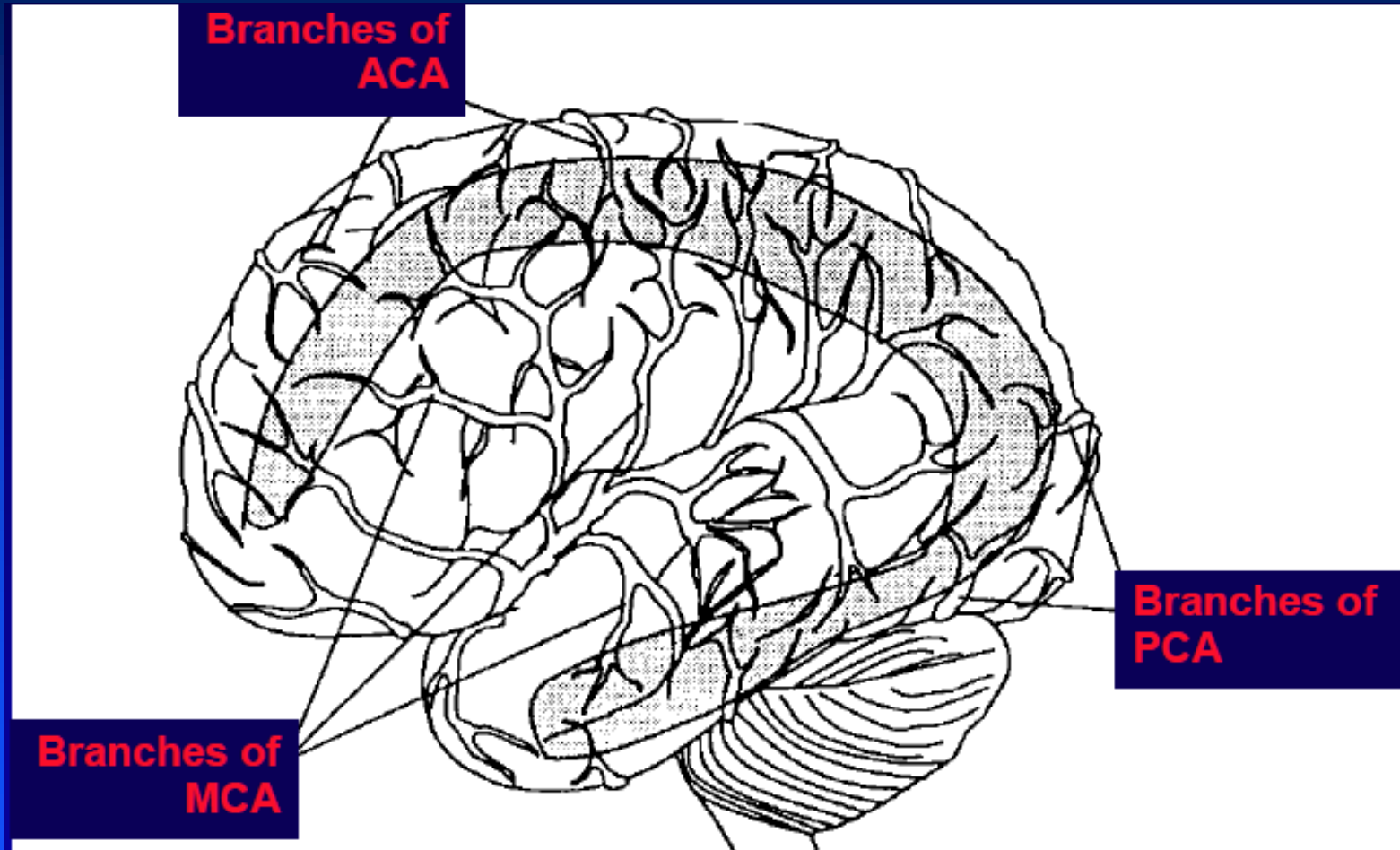
- **Not like Broca's or Wernicke's aphasia**
- **Congenital (no prior language base)**
- **Usually not due to focal brain damage**
- **Strongly genetic**
- **Some specific single gene abnormalities (FOXP2, e.g.)**
- **Functional brain imaging: Stay tuned....**

Developmental Diagnosis

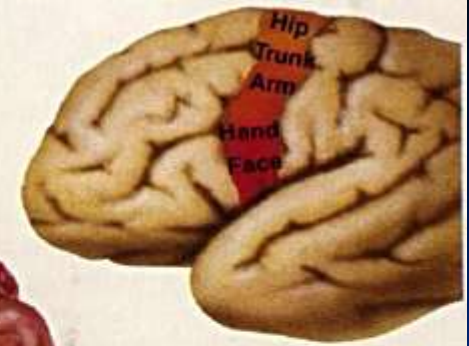
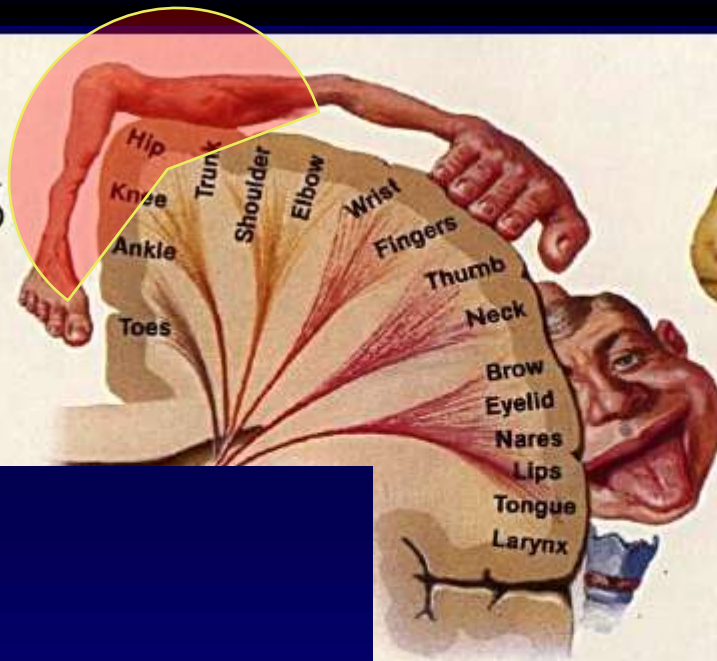
Cerebral Palsy

- **Perinatal: Hypoxic-ischemic encephalopathy**
- **Prenatal: Maternal infection / inflammation, activates TNF (tumor necrosis factor) with damage to fetal brain**
- **Anatomic abnormalities often present**
 - Watershed infarcts
 - Periventricular encephalomalacia
 - Cerebral atrophy

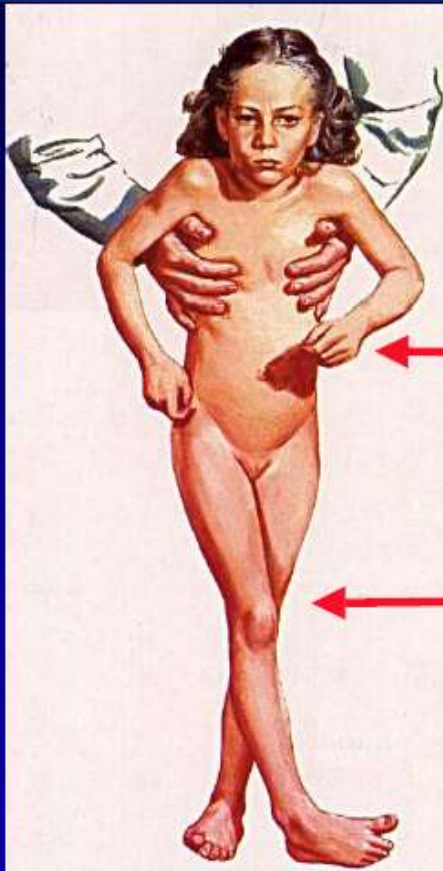
Watershed Infarcts



Primary motor cortex (area 4)



Lateral aspect of cerebral cortex to show topographic projection of motor centers on precentral gyrus



"Fisting"

**"Scissoring"
of lower limbs**

Developmental Diagnosis

Tourette Syndrome

- **Multiple tics, including vocal tics, for >12 mo**
 - Head, eyes, trunk
 - Involuntary (OCD-like) behaviors (Touching others)
- **Strongly genetic**
 - Family Hx: Anxiety D/O, OCD, Depression, ASD, TS
- **Associated Symptoms:**
 - ADHD
 - Anxiety / Depression
 - LD
- **Abnormal brain activation on imaging studies**



By Etiology

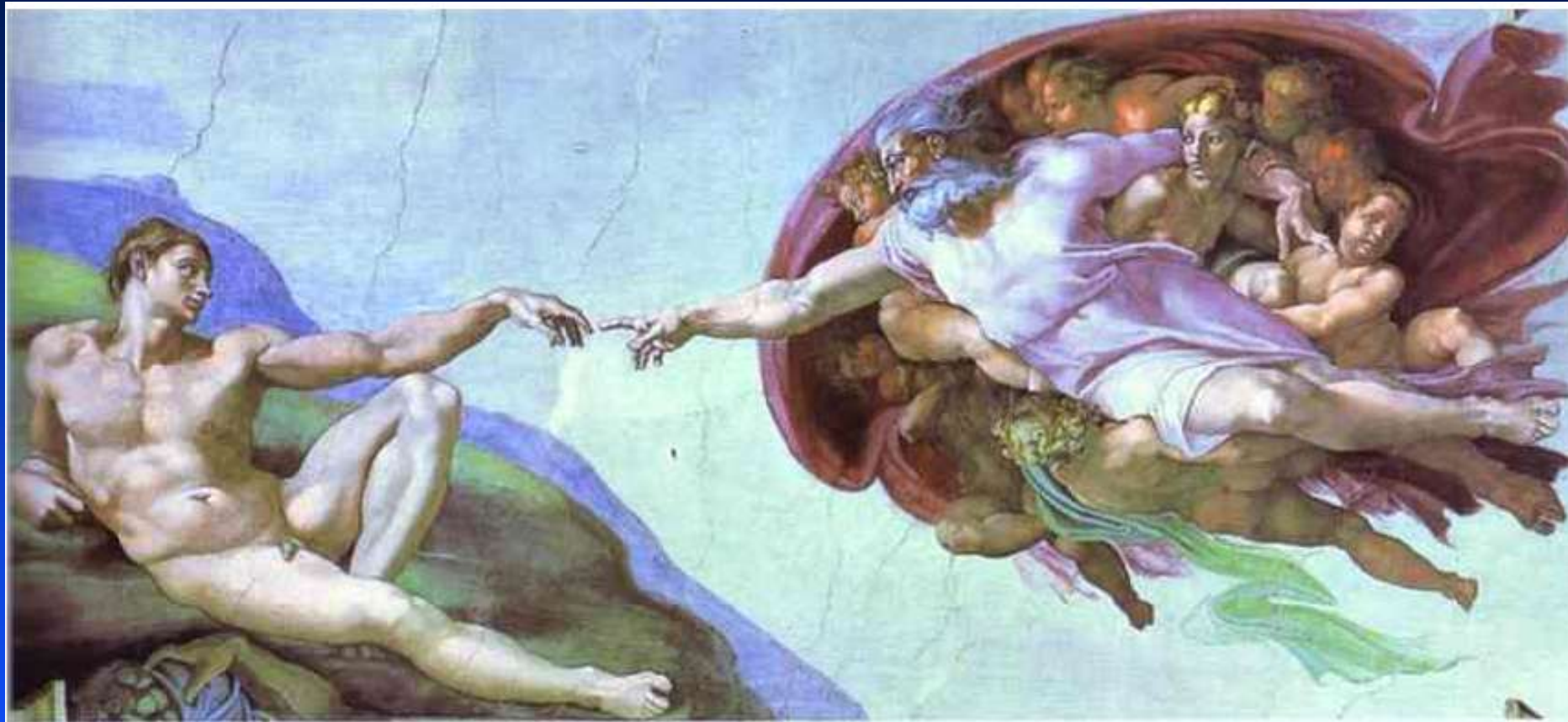
- **Syndromes with specific behavior patterns**
 - **Fragile-X: Autistic-like / anxiety / agitation**
 - **Prader-Willi: DD, neonatal hypotonia, voracious appetite**
 - **Angelman Syndrome: DD, del. speech, jerky movement, laughter**
 - **Williams Syndrome: Hyperverbal, ASD-like**
 - **Smith-Magenis Syndrome: Self-hugging, Self-injury, poor sleep**
 - **Rett Syndrome: Hand-wringing / Loss of hand function**
 - **Lesch-Nyhan Syndrome: Self-Injurious Behavior**
 - **Down Syndrome: 95% friendly & outgoing; 5% ASD (why??)**



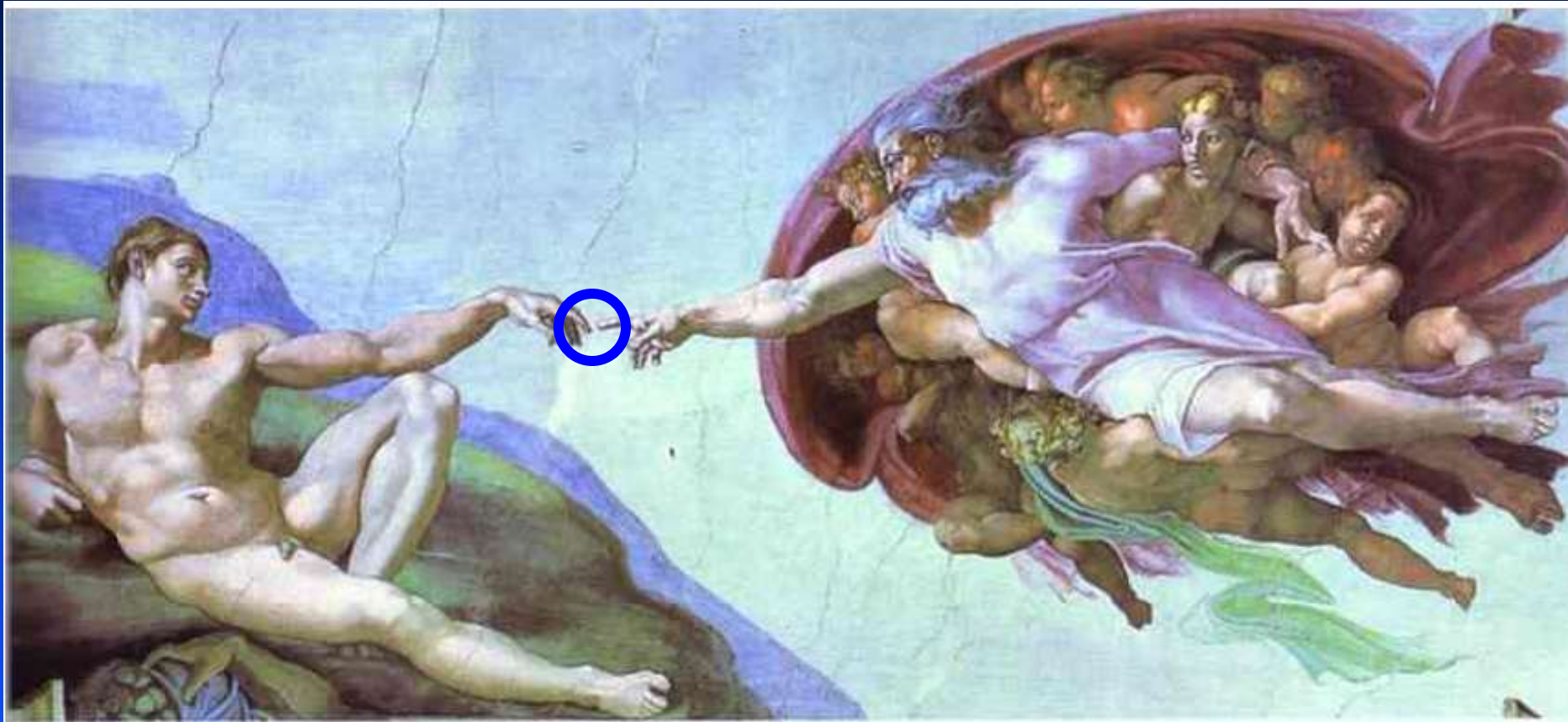
Summary

- **“Behavior” may not be just “behavior” in the child with a disability**
 - **Seek underlying neurodevelopmental drivers and treat accordingly**

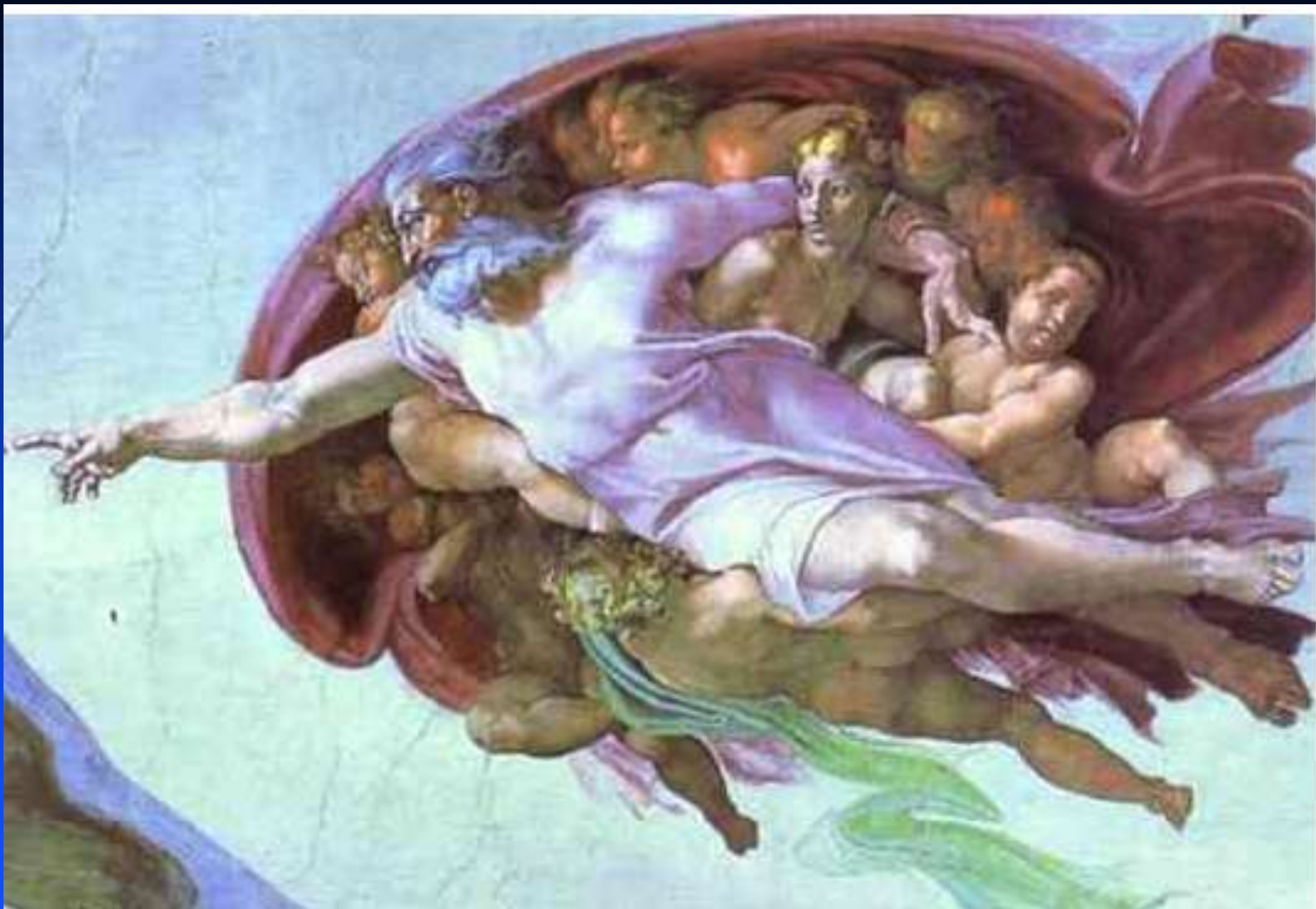
What God gave Adam...

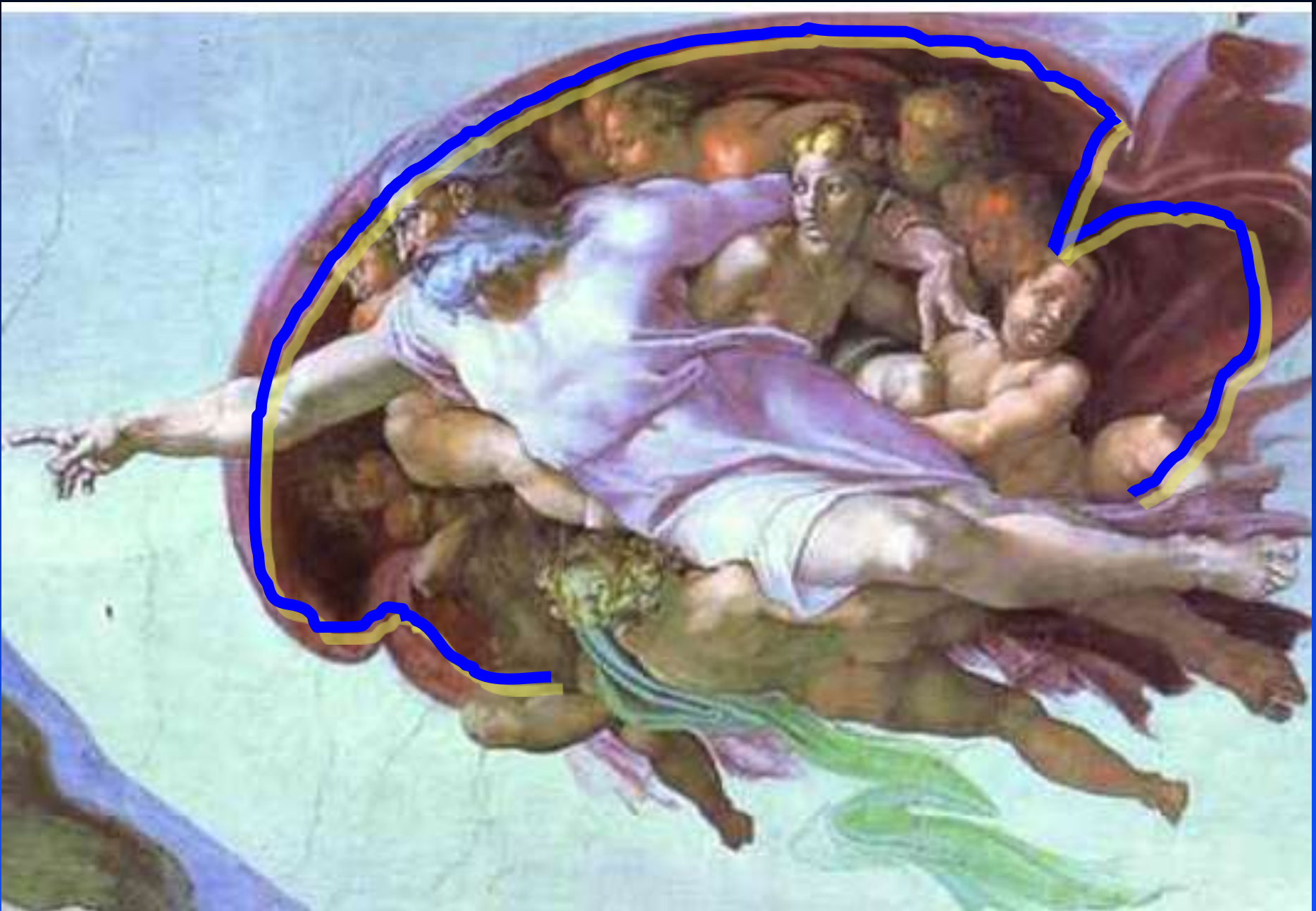


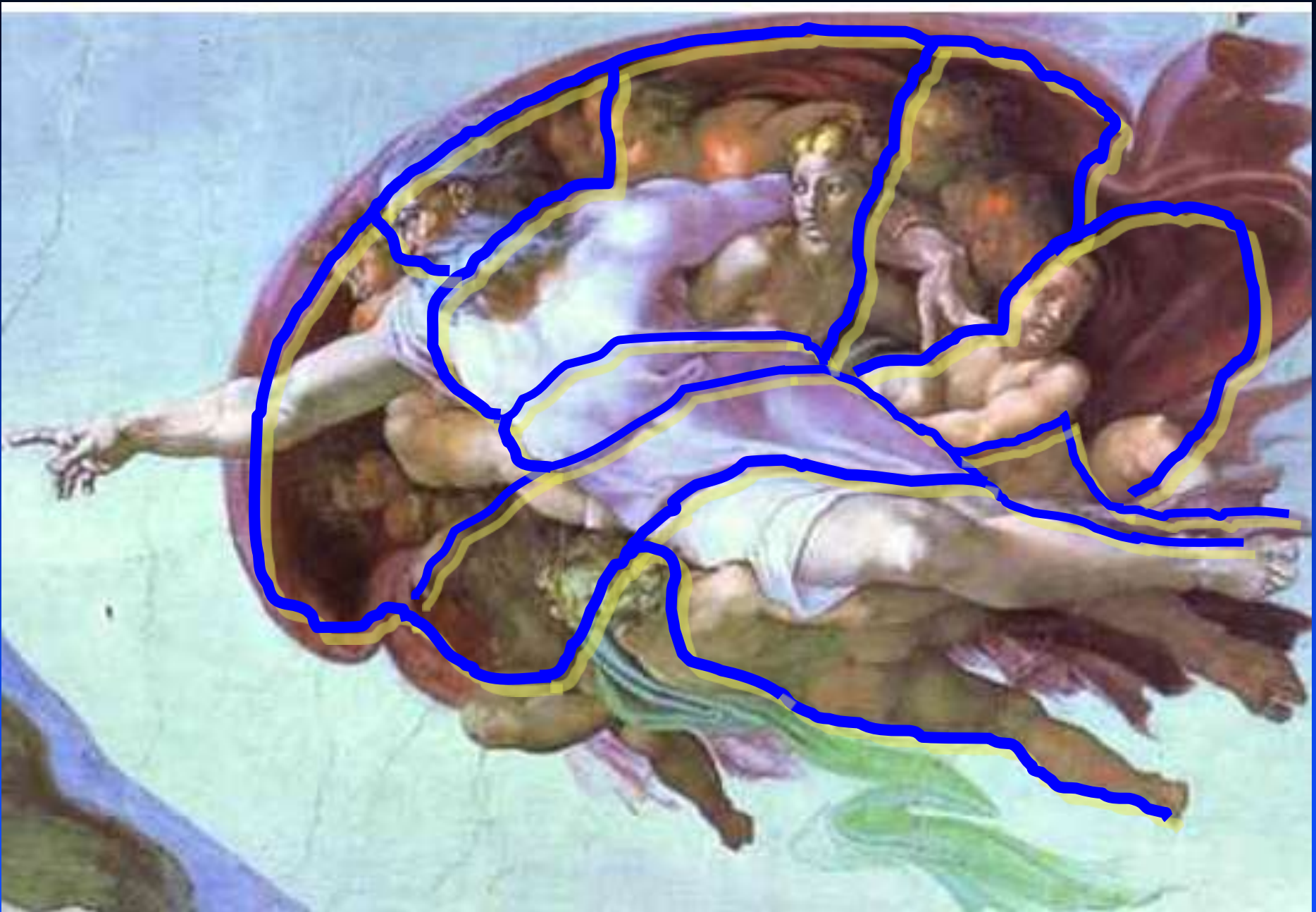
The spark of life...?

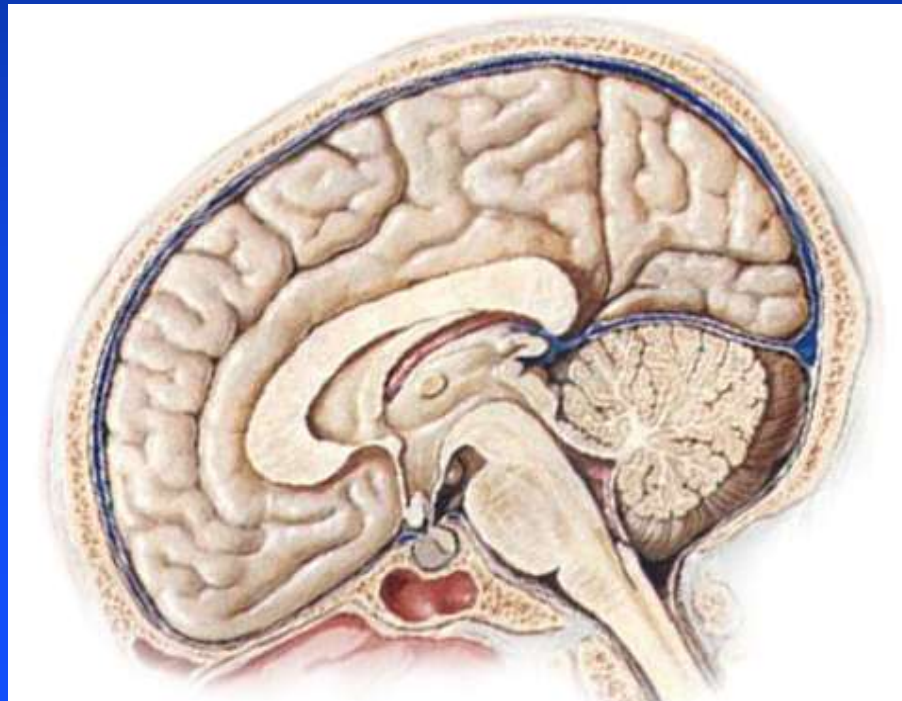
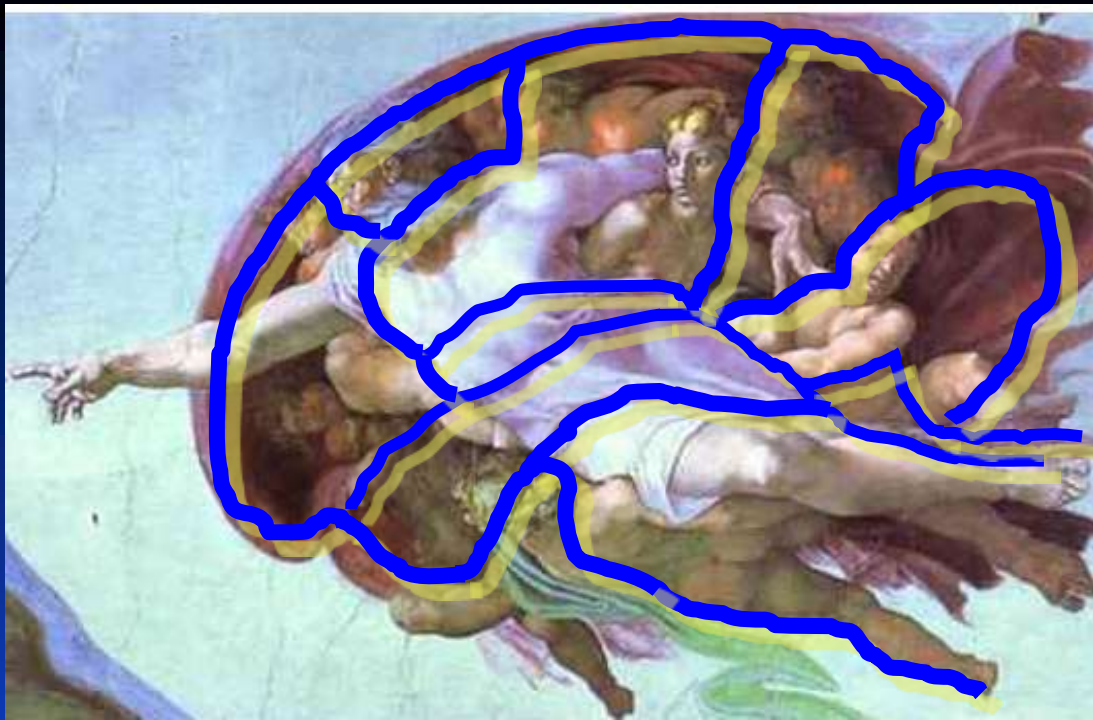


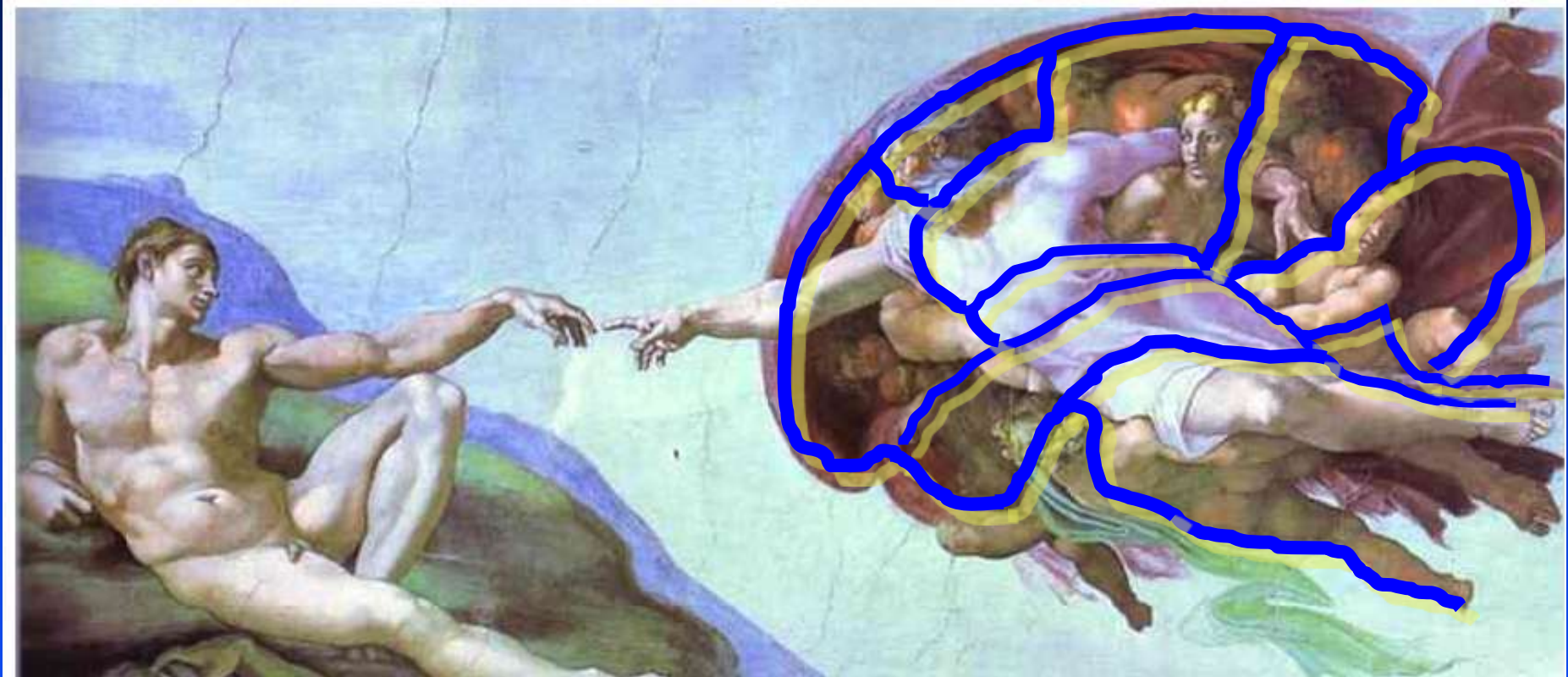
Or...











...the power of the Human Brain.



Thank you!