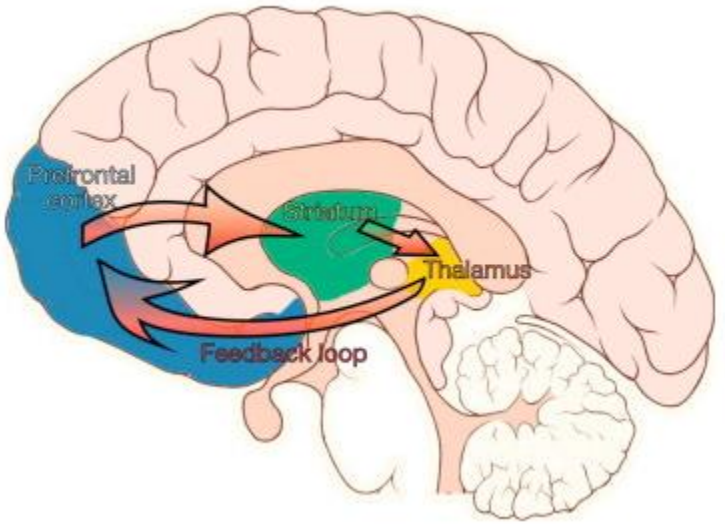
# Round 25: ADHD

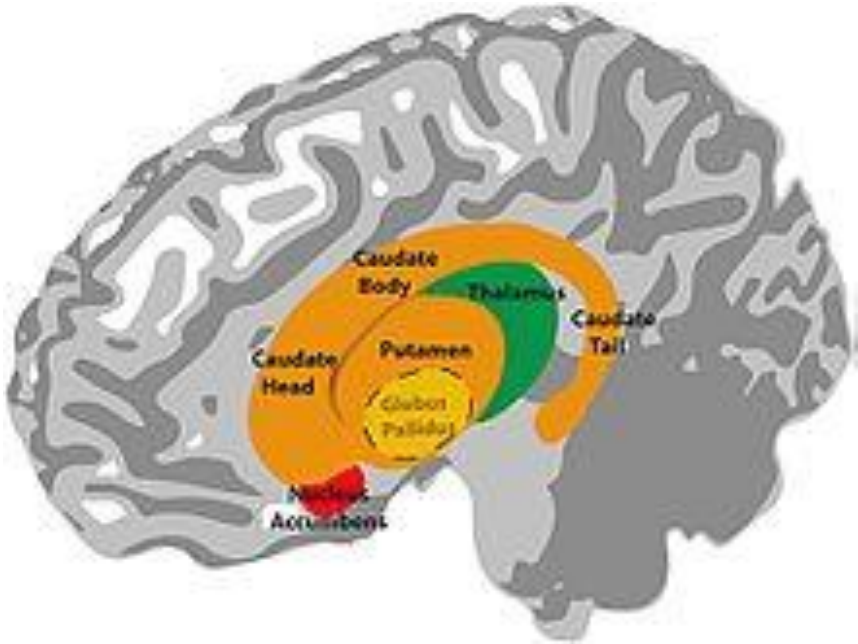
06/10/2021

Kristy Snyder Colling, PhD

# Related Disorders

- Cortico-Striato-Thalamo Circuit
  - OCD
  - Trichotillomania (Hair pulling)
  - Tourette's syndrome
  - ADHD




https://www.hindawi.com/journals/bmri/2016/3821579/

# Tourette's Syndrome

- Some forms of OCD may be genetically linked to Tourette's
- Tic-related OCD presents with counting, aggressive thoughts, symmetry, and touching compulsions

- Motor tics
  - Blinking
  - Coughing
  - Throat clearing
  - Sniffing
  - Facial movements

- Phonic tics
  - Coprolalia – utterance of obscene words or socially inappropriate, derogatory remarks

# Tourette's Syndrome

- Heritable
  - 10-100 times more likely among family members
  - 50-77% of identical twins only 10-23% of fraternal twins

- Risk factors
  - Advanced paternal age
  - Non-Hispanic white
  - Males are 3x more likely than females
  - Forceps delivery
  - Stress or severe nausea during pregnancy
  - Use of tobacco, caffeine, alcohol, or cannabis during pregnancy
  - Premature birth, low birth weight
  - PANDAS

- Prevalence
  - 1% of school-aged children
  - Typical onset is between 5-7 years old
  - Severity reaches a peak around 8-12 years old
  - Severity of tics decrease through adolescence

- Causes & Treatment
  - Combination of genetic & environmental factors
  - Dysfunction in neural circuits involving basal ganglia
    - Decreases in the indirect pathway

  - Antipsychotic drugs
    - Inhibit dopamine bc excess dopamine in basal ganglia may contribute to symptoms
  - Neurofeedback
    - Cz SMR training, theta inhibit

# Tourette's Syndrome

- May be considered an impulse control disorder
  - Failure to suppress unwanted or abnormal behaviors, obsessions, compulsions, hyperactivity, impulsivity, aggressions, rage
    - May be due to functional disconnectivity
      - Increased metabolic activity bilaterally in the premotor cortex & cerebellum
      - Decreased metabolism in caudate/putamen & orbitofrontal

  - OCD-related metabolic pattern
    - Reduced activity in anterior cingulate & dorsolateral prefrontal regions
    - Increased activity in precuneus and primary motor cortex
      - Role in self-awareness -> reflect pts efforts to resist tics

Imaging Highlights Brain Activity in Patients with Tourette... : Neurology Today (lww.com)

# Tourette's & ADHD

- ~60% of those with Tourette's also have ADHD
- ~50% of children with ADHD have comorbid tic disorder
- ADHD age of onset is b/t 4 & 5 y/o
- Tourette's average age onset of is 7
- Stimulant medications may cause tics or exacerbate pre-existing tics

- Impulsive actions in ADHD (sudden and unpremeditated, unfiltered behaviors often prompted by a sense of urgency) and tics (sudden stereotyped movements or noises usually prompted by unpleasant warning sensations) may suggest a neural circuitry "disinhibition," or release, of undesired patterns of behavior linked to emotion, sensation, movement, and cognition
- Likely two different sides of a coin
  - Disinhibition -> dysfunction in monoamine neurotransmitter systems in communications among the basal ganglia, the frontal cortex, and the thalamus
  - Stimulants for ADHD are believed to act by increasing dopamine activity, whereas excessive transmission of this monoamine is believed to cause or contribute to tics

Tourette syndrome associated with attention deficit hyperactivity disorder: The impact of tics and psychopharmacological treatment options (nih.gov)

Attention-Deficit/Hyperactivity Disorder and Co-Occurring Tics (contemporarypediatrics.com)

# ADHD

- Affect 3-7% of school-aged children
- In order to be diagnosed symptoms bust have occurred before the age of 7
- 2/3 continue to have impairing symptoms into adulthood

- 3 Subtypes
  - Inattentive
    - Girls more than boys
    - Easily distracted
    - Forgetful, misplacing items
    - Difficulty focusing/ staying on task

  - Hyperactive
    - Boys more than girls
    - Fidgety
    - Impatient
    - Impulsive
    - Overly talkative

  - Combined/Mixed

# ADHD

- Affective Components
  - Lack of emotional control
  - Poor/inappropriate motivation

- Attentional/Cognitive Components
  - Executive function -> the ability to control attention and action in the service of goals
    - Problem solving
    - Planning (including time estimation, temporal foresight)
    - Orienting
    - Alerting
    - Cognitive flexibility
    - Sustained attention
    - Response inhibition
    - Working memory

- Motor Components
  - Poor motor coordination
  - Poor handwriting
  - Clumsiness

# ADHD

- Strong genetic contribution
  - Hereditability between 60-90%
  - Genes implicated related to regulation of neurotransmitters

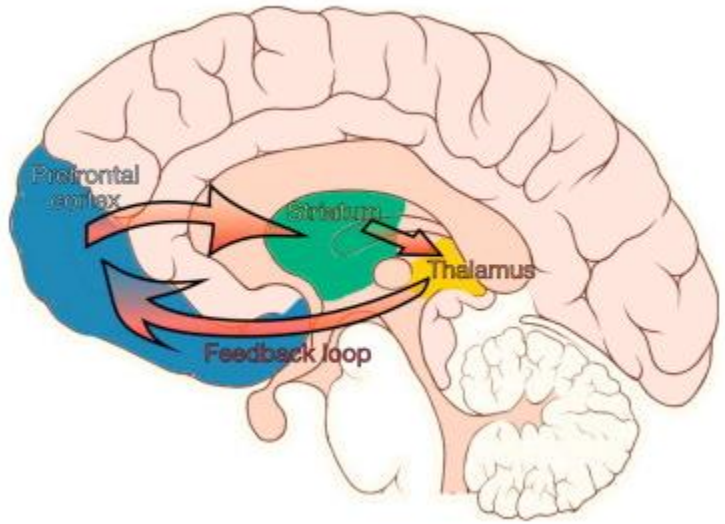
- Environmental factors
  - Prenatal factors
    - Maternal alcohol exposure
      - Structural brain anomalies in cerebellum
      - Children frequently hyperactive, disruptive, impulsive, increased risk of psychiatric disorders
    - Maternal smoking 2.7 fold increase risk for ADHD
  - Peri-natal factors
    - Very low birth weight
    - Pregnancy & birth complications
  - Post-natal factors
    - Nutritional deficiencies (essential fatty acids omega 3 & omega 6)
    - Deprivation of social environment

# ADHD

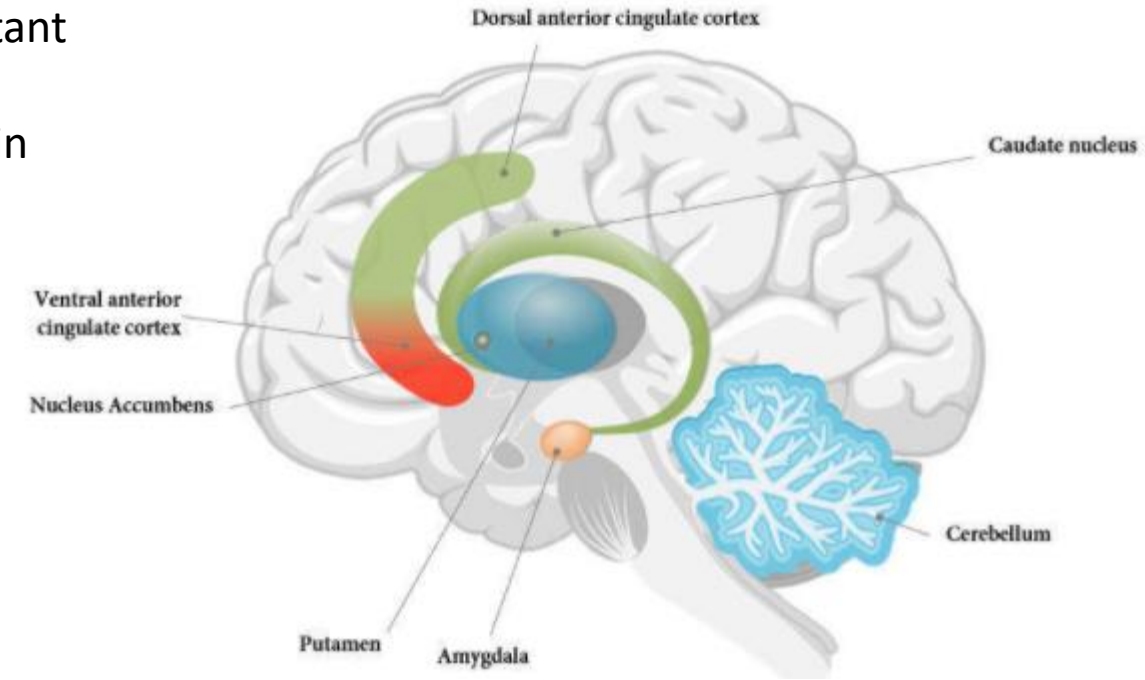
- ADHD is characterized by a delay in structural brain maturation

- Frontal-striatal circuitry abnormalities
  - Important for executive function and motivational control, but also include
    - Parietal
    - Temporal
    - Motor cortices
    - Cerebellum

- Volume reductions are in multimodal association cortices
  - Frontal lobes and its subregions
  - Premotor cortex
  - Posterior cingulate
  - Anterior and medial temporal lobes
  - Cerebellum
  - Basal ganglia structures (caudate, globus pallidus, putamen, ventral striatum)



- 1,713 ADHD /1,529 Control
- Reduction in volume of five regions
  - Caudate nucleus
    - Stores and processes memories and is important for learning.
    - Helps decide how to behave to achieve certain outcomes
  - Putamen
    - Movement and impulsive behaviors
  - Nucleus Accumbens
    - Reward processing and motivation
  - Amygdala
  - Hippocampus




- Striatum (e.g., Caudate, Putamen, Nucleus Accumbens)
  - Reward system
    - Helps control motivation, reward, and pleasure
    - Helps process thoughts, feelings, and experiences
  - Typically sends one piece of important information to the cortex at a time
  - In ADHD, sends several different random pieces of information -> difficulty focusing

https://www.sciencedaily.com/releases/2017/02/170216105919.htm

https://drcarolinebuzanko.com/normal-brain-vs-adhd-brain-whats-different-and-why/

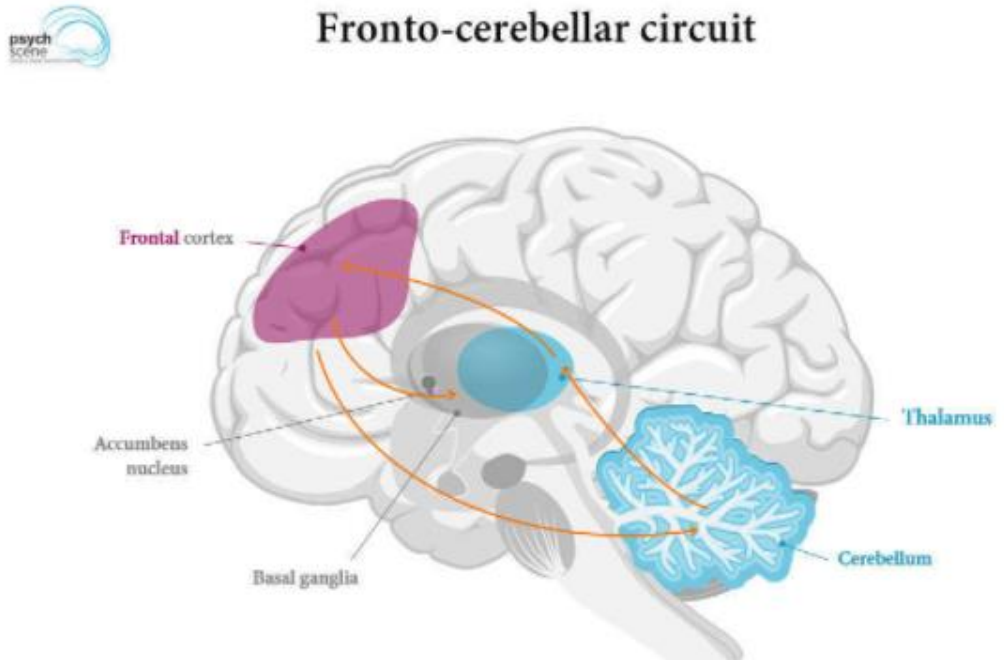
# ADHD – Delays in Structural Maturation

- Frontal–parietal cortical maturation in ADHD children differs depending upon the status of symptom expression and exposure to stimulant treatment

- ADHD children whose symptoms persisted into adolescence had thinner medial prefrontal cortex at an average age of 8.7 years compared to both ADHD children whose symptoms remitted and to controls
- Thinning of the right parietal cortex through childhood in ADHD children relative to controls
  - The difference disappeared in adolescence if symptoms resolved with increasing age
- Cortical maturation between 12.5 and 16.4 years was influenced by exposure to stimulant medication, such that unmedicated children showed greater cortical thinning than age-matched control children
- Comparison between medicated and unmedicated ADHD children showed that the right motor cortex, left ventrolateral prefrontal cortex, and right parietooccipital cortex were thinner in unmedicated ADHD children

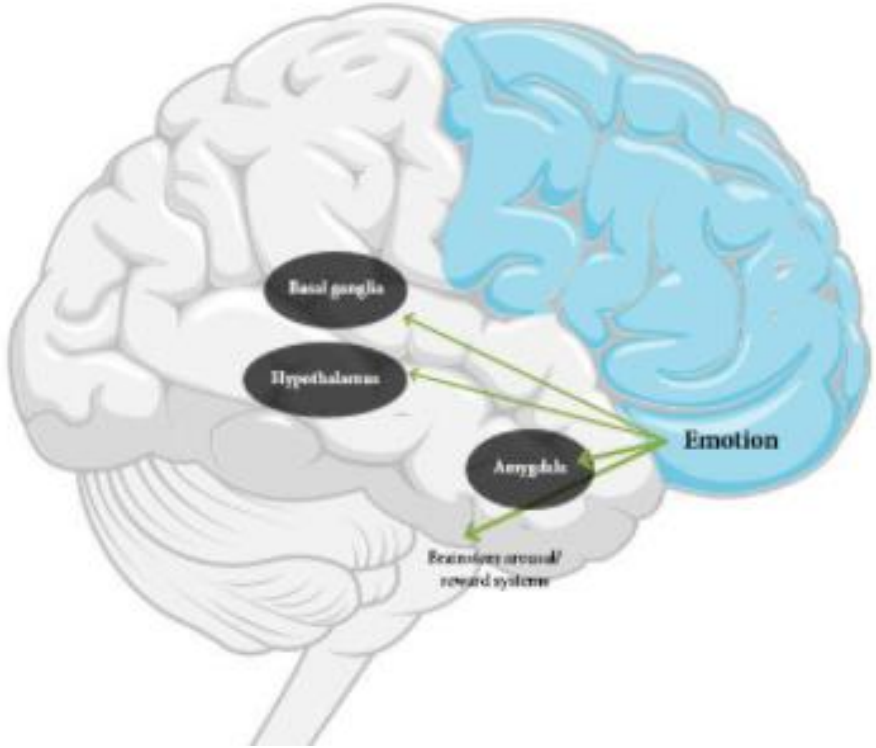
# ADHD – Networks

- Frontal-striatal-cerebellar Network
  - Circuit comprising regions in the
    - Frontal cortex (e.g., lateral prefrontal, premotor, anterior cingulate)
    - Dorsal striatum (e.g., caudate)
    - Cerebellum via thalamic projections
  - Important for the integrity of executive function
    - Response inhibition, interference suppression, working memory
  - Reduced volume of cingulum bundle and superior fasciculus
  - Reduced activation in lateral inferior frontal regions & dorsal anterior cingulate (inhibition)



# ADHD – Networks

- Limbic-frontal Network
  - Important for mediating motivation & regulating emotions
  - Ventral & medial portions
    - Regulate emotion




- The ventromedial prefrontal cortex has projections to amygdala, hypothalamus basal ganglia and brain stem arousal/reward systems and weakens reactions to disinhibited aggressive impulses and emotional dysregulation.

https://psychscenehub.com/psychinsights/neurobiology-of-adhd/

# ADHD – Networks

- Parietal-Temporal Network
  - Important for mediating attentional function

- Spatial working memory tasks
  - ADHD Children
    - Reduced activation of right inferior parietal cortex in
  - ADHD Adolescents
    - Reduced activation of superior parietal and temporal regions
    - Increased activation of medial parietal regions in ADHD adolescents
      - Greater medial parietal activation -> increased attentional resources necessary to perform difficult tasks, such as spatial working memory

# ADHD – Networks

- Oddball Involuntary Attention Tasks in adolescents with ADHD
  - Reduced activation in:
    - Bilateral and medial–parietal regions
    - Bilateral superior temporal gyri
    - Posterior cingulate
    - Parahippocampal gyrus
    - Amygdala

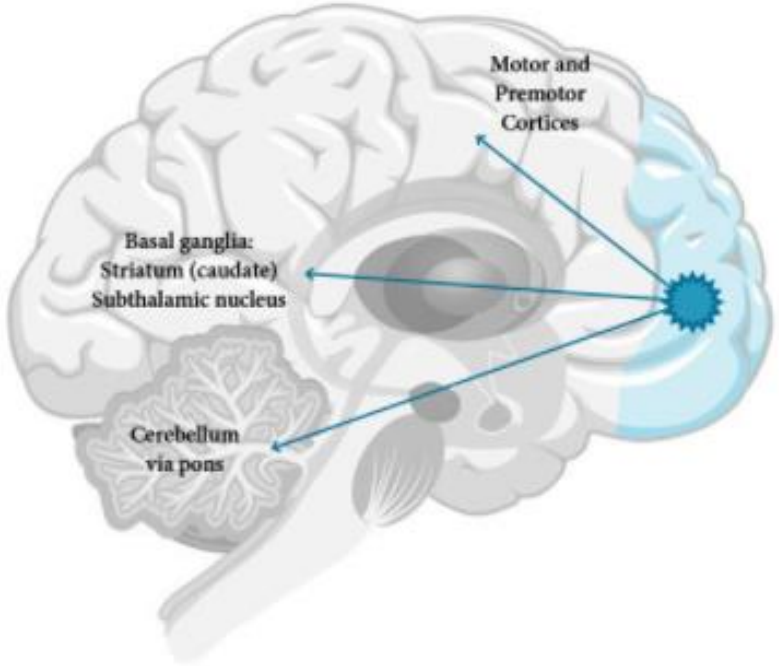
- Selective Attention Tasks
  - Reduced activation in:
    - Right superior parietal cortex in ADHD children
    - Left posterior middle temporal gyrus in ADHD adolescents

- Reduced posterior engagement during both voluntary and involuntary attentional tasks in ADHD suggests a general reduction of attentional resources in ADHD

# ADHD – Networks

- Dorsal and lateral prefrontal cortex -> Motor execution, Motor/Premotor regions
  - Regulate attention and motor responses
  - More variable trail to trial response latencies => immature motor circuitry
  - Reduced neural inhibition in the corticospinal tract in ADHD children
  - During self-paced finger-to-thumb movements, ADHD children showed reduced activation in contralateral motor cortex and right superior parietal cortex, relative to control children
    - Lower level motor abnormalities in ADHD -> likely to contribute to higher-order executive function deficits

The **right inferior prefrontal cortex** is specialized for behavioural inhibition through projections to the motor and premotor cortices, basal ganglia and cerebellum



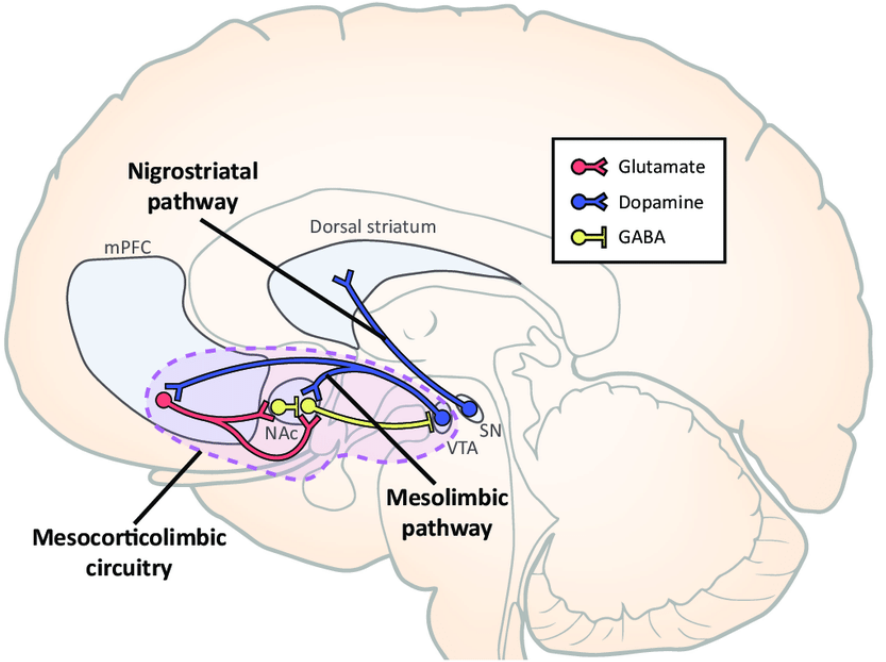
# ADHD – Neurotransmitters

- Dopamine
  - Too many dopamine transporters in the brain with not enough receptors
    - Dopamine moves too quickly for the messages in the brain to be picked up
    - … like millions of messages in bottles thrown into the ocean and only one or two actually being found and read - and the lucky messages found are likely not at all relevant or important…
  - Important
    - Control the brain's reward and pleasure center
      - Helps predict how rewarding a task will be
      - Inefficient dopamine systems => deficient delayed gratification
        - Do something now (e.g., homework) for a later reward (e.g., having a sleepover on the weekend).
        - Difficulty anticipating (future) pleasure and so constantly seek pleasurable experiences *now*.
    - Essential for sustaining attention and staying motivated

# ADHD – Neurotransmitters

- Mesolimbic Dopamine Circuitry
  - Ventral striatum, hippocampus, and orbitofrontal cortex
  - Reward-Related Decision Making
    - Important for encoding the salience of a stimulus and evaluating it in the context of making decisions

- Reduced activation -> processes may be evoked to a lesser degree or less efficiently in ADHD than in control subjects



# ADHD - Treatments

- Dysregulation of noradrenaline/ norepinephrine and dopamine neurotransmitter systems
    - Methylphenidate
        - Increases dopamine signaling
            - Blocking DA reuptake
            - Increases extra-cellular levels
            - Disinhibition of receptors
        - Inhibits norepinephrine reuptake
    - Dextroamphetamine
        - Increase synaptic activity of DA & NE
            - Increases release into synapse
            - Decrease reuptake

# ADHD - Treatments

- Common finding is elevated theta (4-8Hz) over frontal-central areas
  - SMR training to decrease theta and increase beta

- ADHD EEG profiles have been found with excesses of delta, theta, alpha, and beta
  - Elevated Beta (12.5–25Hz) -> symptoms of delinquent behaviors
  - Elevated frontal alpha (7.5–12.5Hz) -> markers of ritualistic obsessive behaviors

- Poor connectivity between the posterior cingulate cortex and the medial prefrontal cortex

- Inattentive subtype -> dysfunction of dorsolateral prefrontal cortex
  - A core node in the striatal and attentional pathways
- ADHD combined subtype is -> dysfunction of default mode network regions

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4633088/

https://mcgovern.mit.edu/2014/06/10/inside-the-adult-adhd-brain/

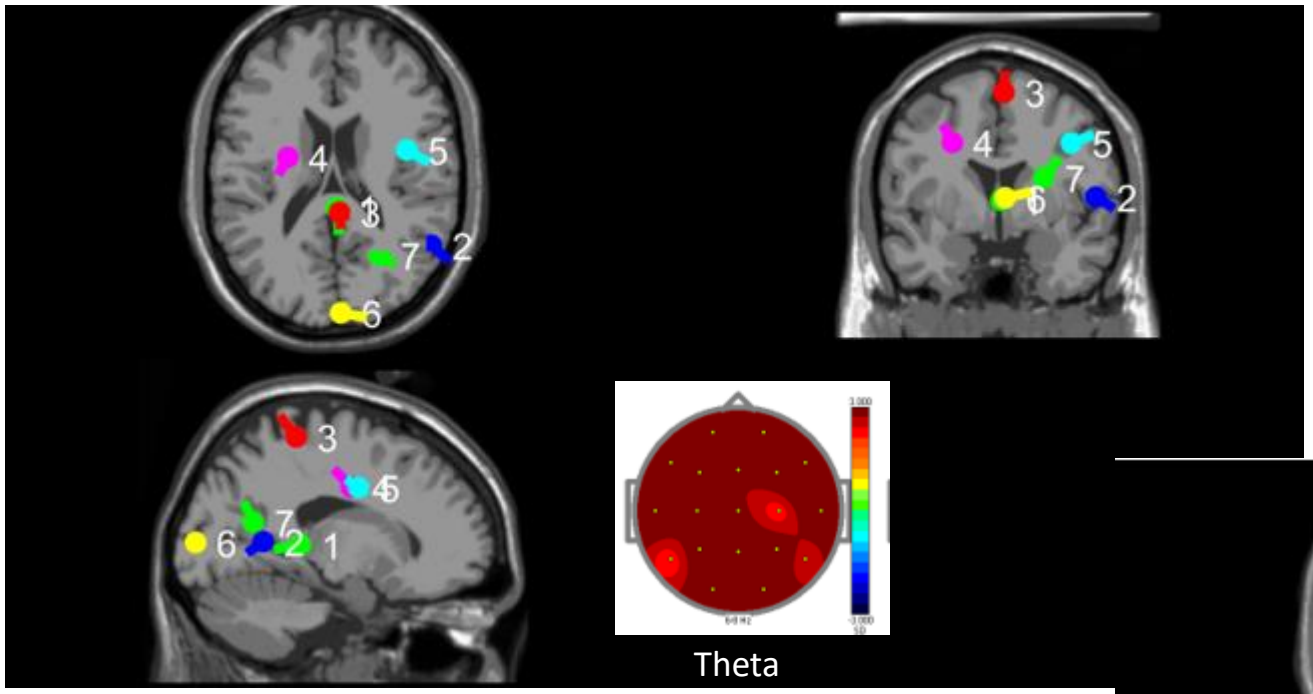
# Case Study 1

- 20 year old male
- Diagnosed with ADHD senior year of high school
- Prescribed stimulant medication but reported that it did not work to improve grades

- Neuropsychological Testing
  - Full scale attention – Mildly impaired
  - Auditory attention – Average
  - Visual Attention – Mildly impaired
  - Auditory Response – Mildly Impaired
  - Visual Response Control – Low Average
  - Sustained Auditory Attention – Severely Impaired

# Case Study 1

Eyes Closed

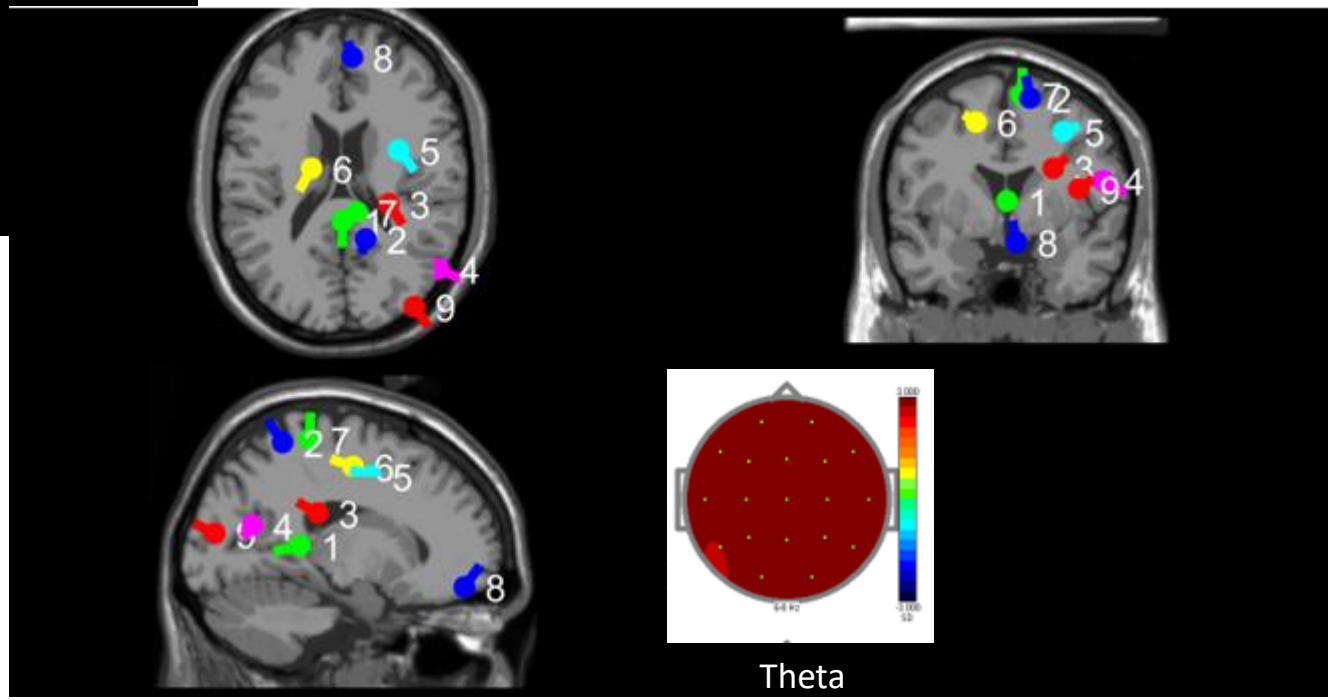





Theta

- 2: Area 39 - Wernicke’s area
- 3: Area 5 - Sensorimotor
- 7: Area 31 – Posterior CIngulate

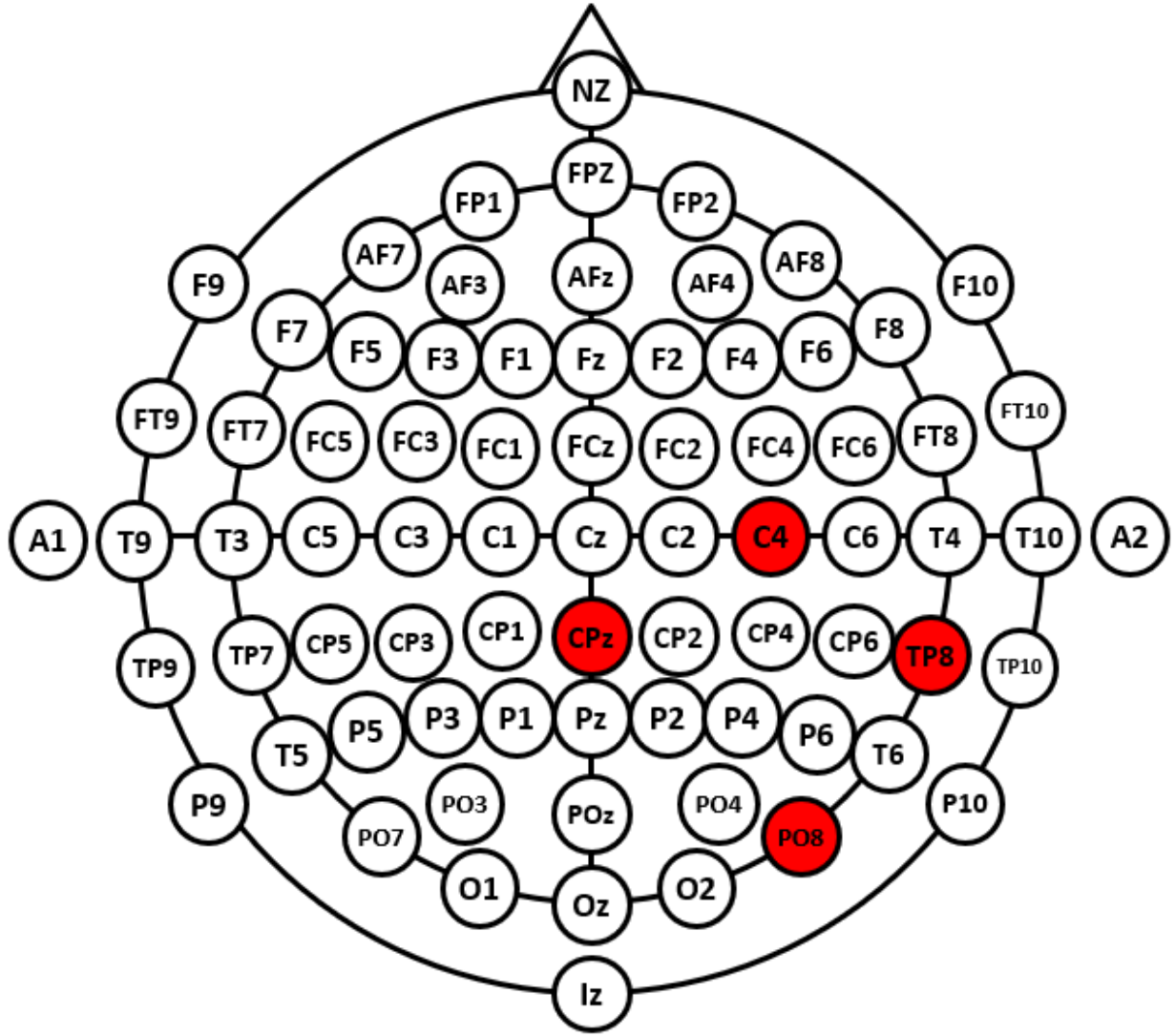
Eyes Opened





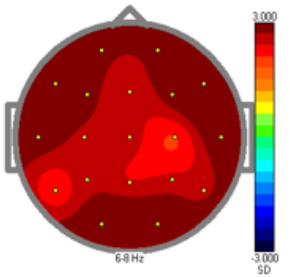

Theta

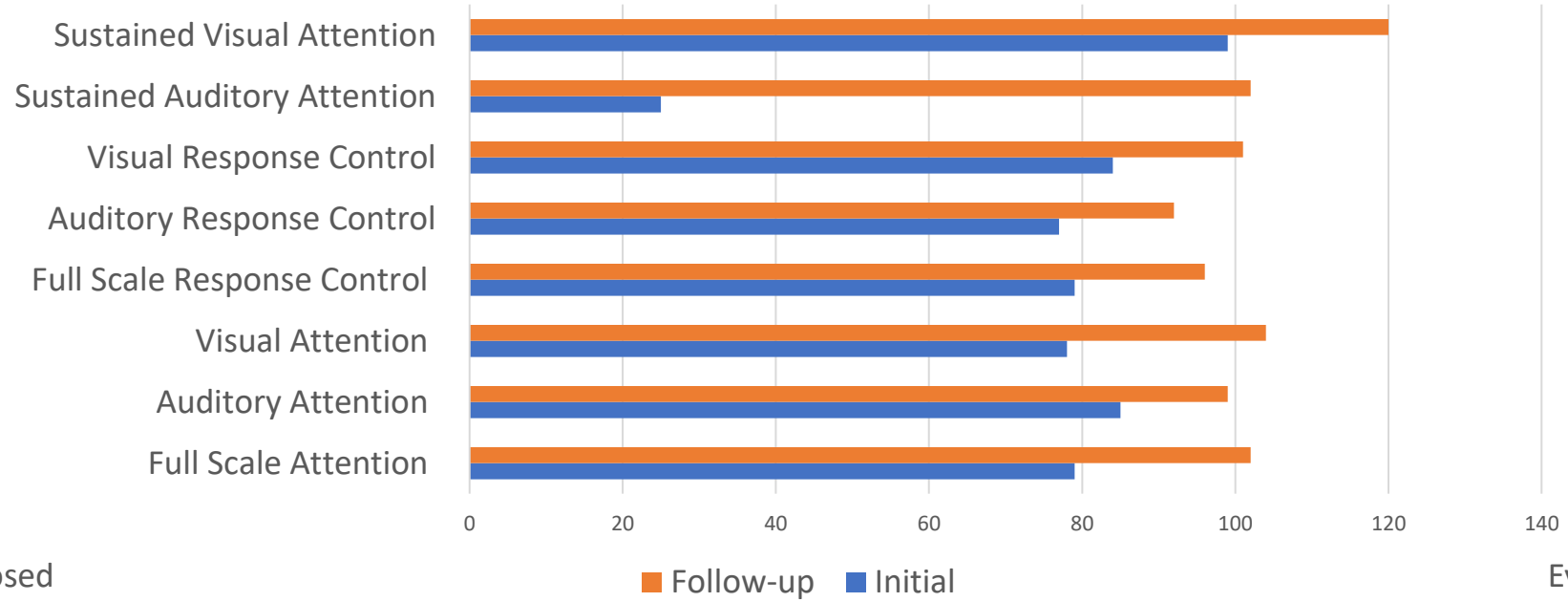
| | |
|---|---|
| Inhibit | 4-8 |
| Inhibit | 8-12 |
| Inhibit | 16-18 |
| Reward | 3-17 |

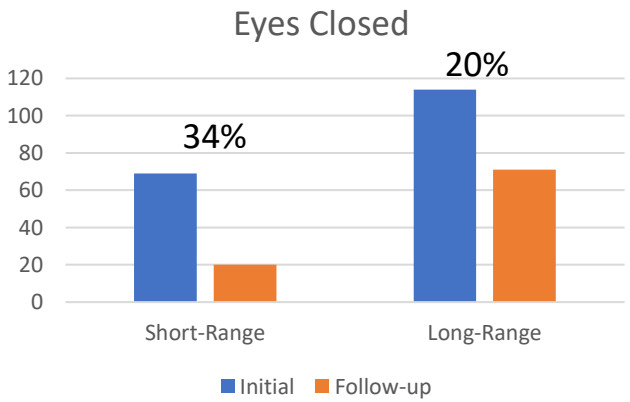


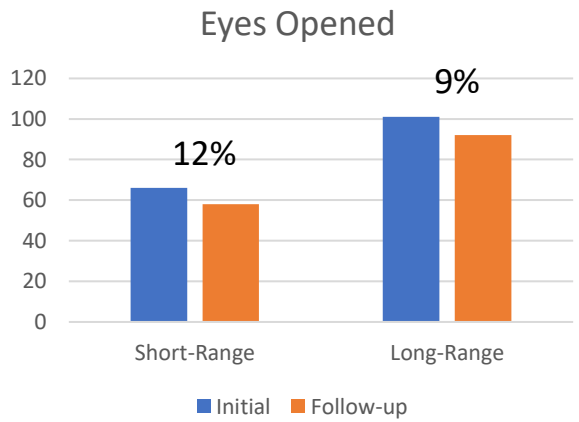
# Case Study 1

- Self-Report
  - Attention/Focus – improved
  - Concentration – much improved



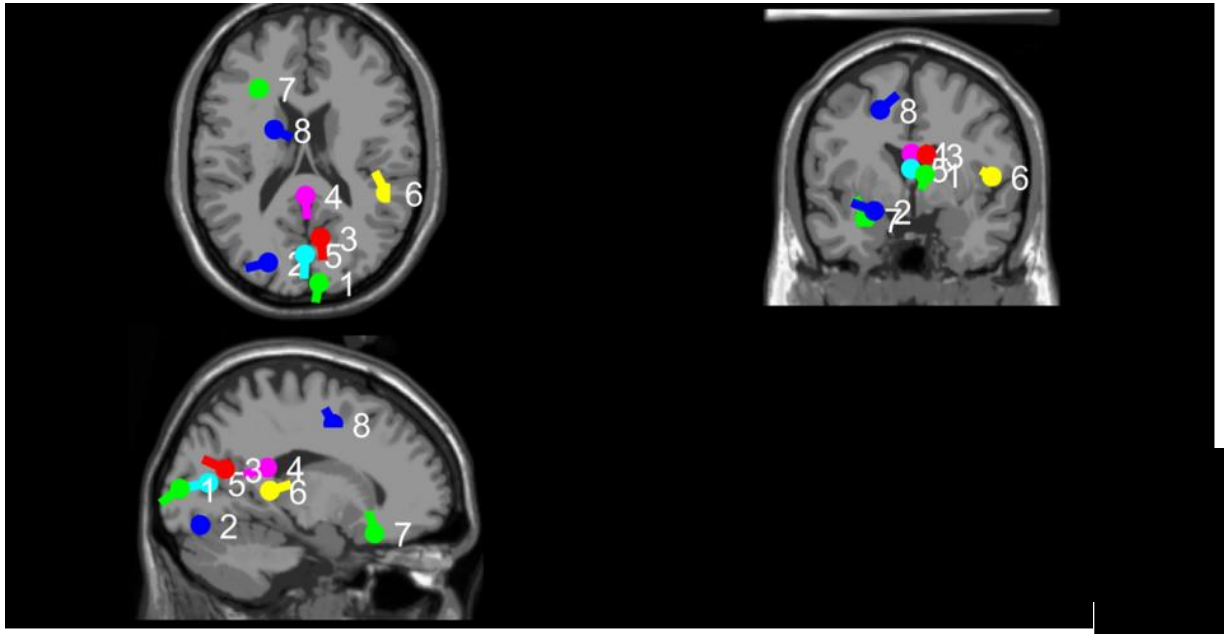
# Case Study 2

- 10 year old female

- Symptoms
  - Poor focusing
  - Difficulty staying on task
  - Following more than 2-step instructions
  - Regulating behavior
  - Speaking out of turn/interrupting teacher
  - Disruptive/ hard to manage

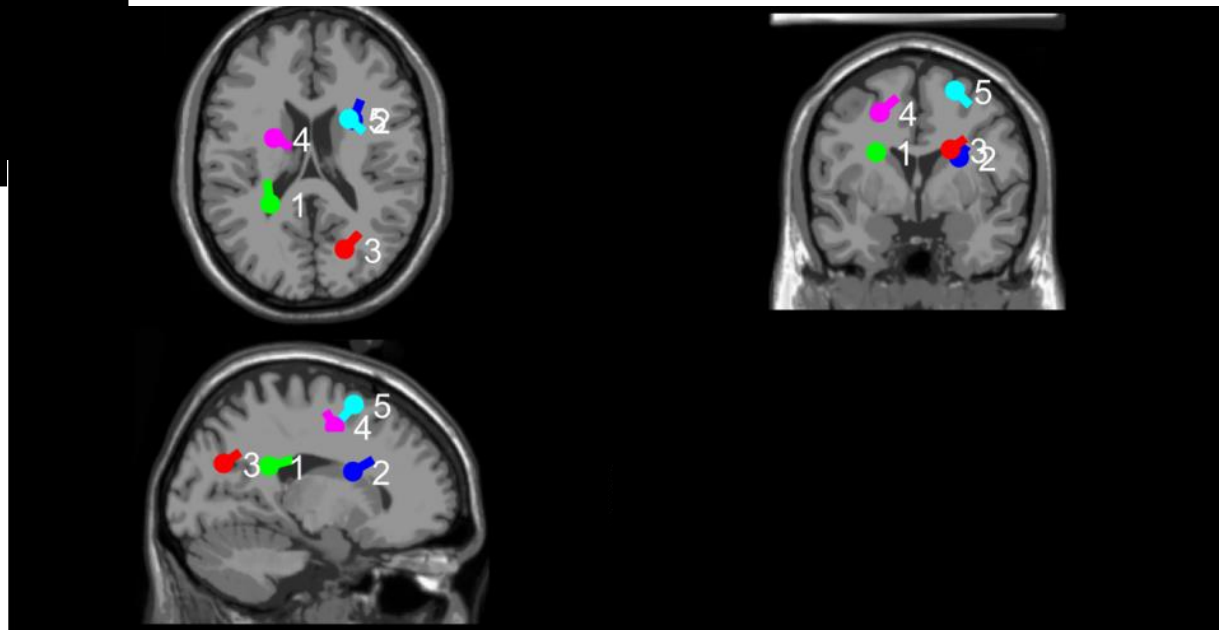
# Case Study 2

Eyes Closed

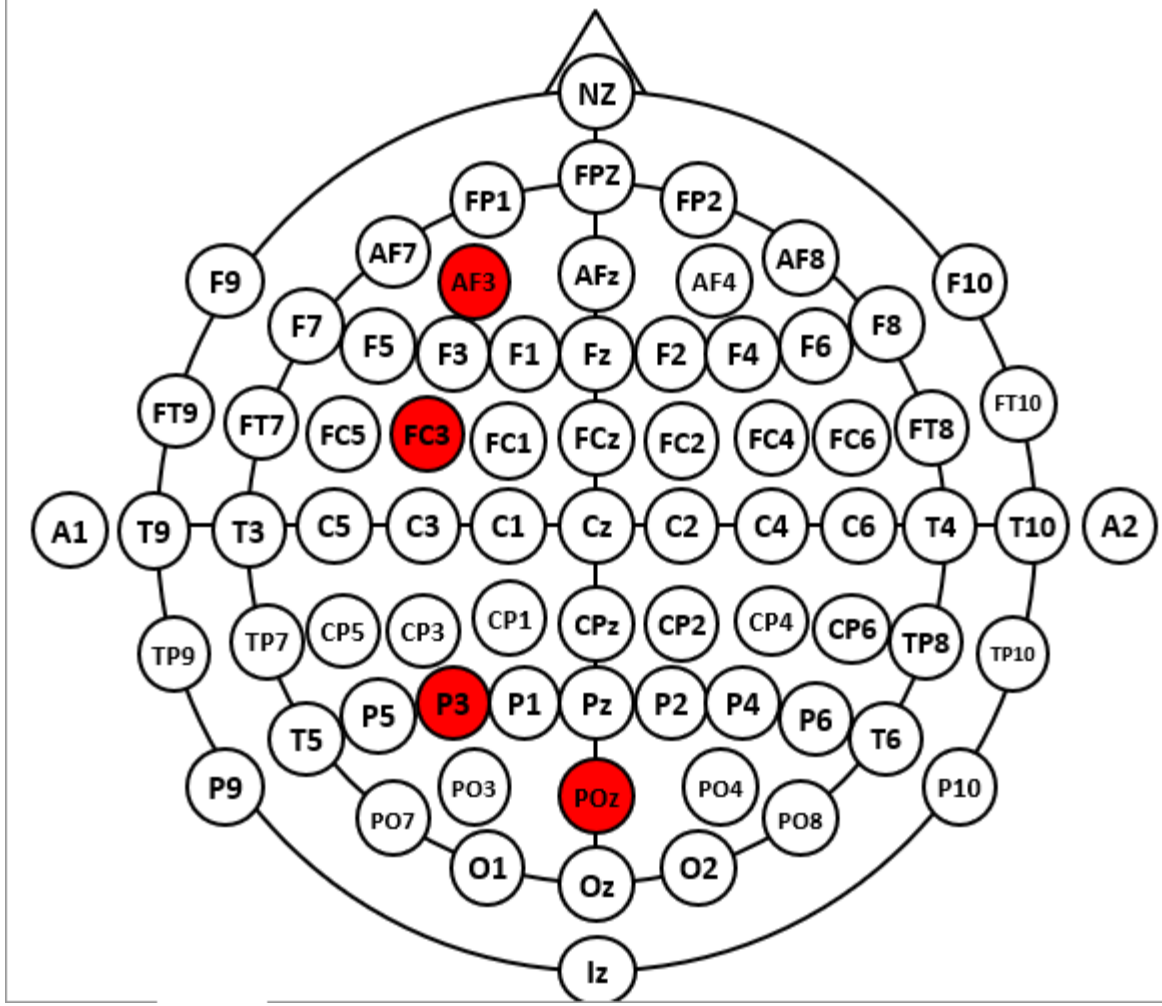


Spikes over P7 & F3

Eyes Opened



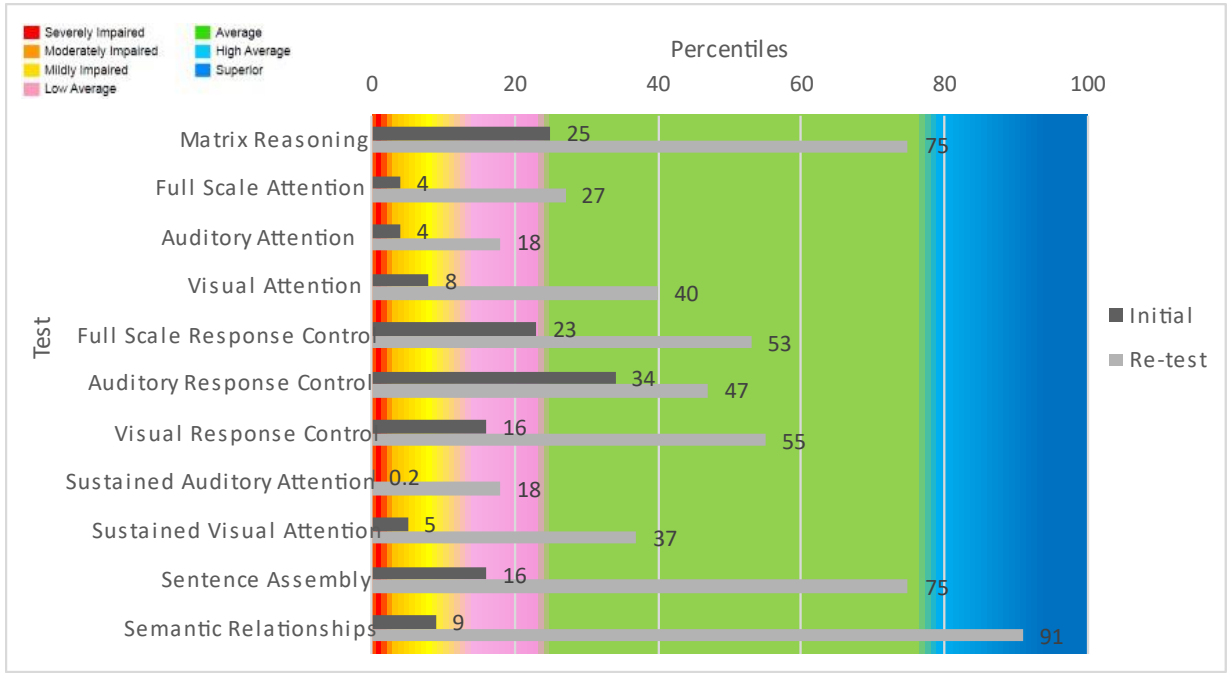
| | |
|---|---|
| Inhibit | 1-7 |
| Inhibit | 8-12 |
| Inhibit | 22-30 |
| Reward | 8-15 |

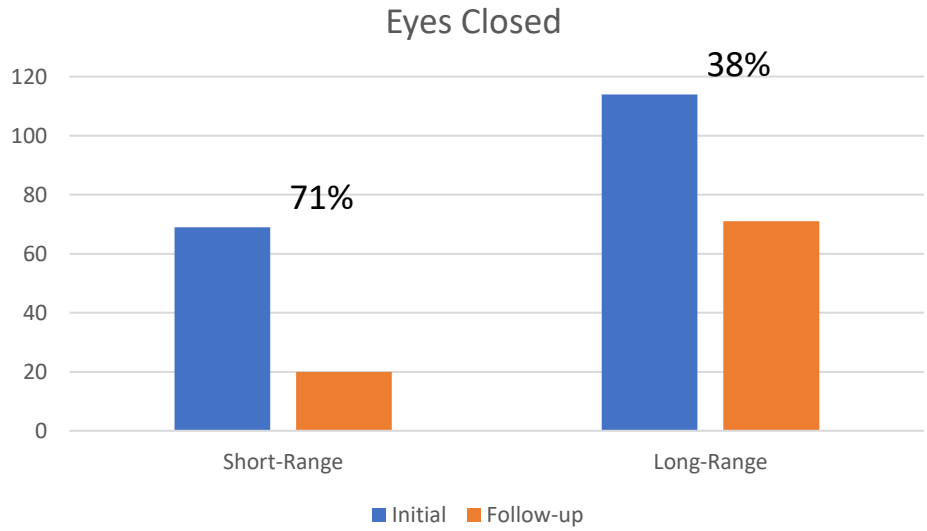


# Case Study 2

- Self/Parent-Report
  - Focus – Slightly improved
  - Verbalization of feelings – improved

No evidence of spikes at follow-up

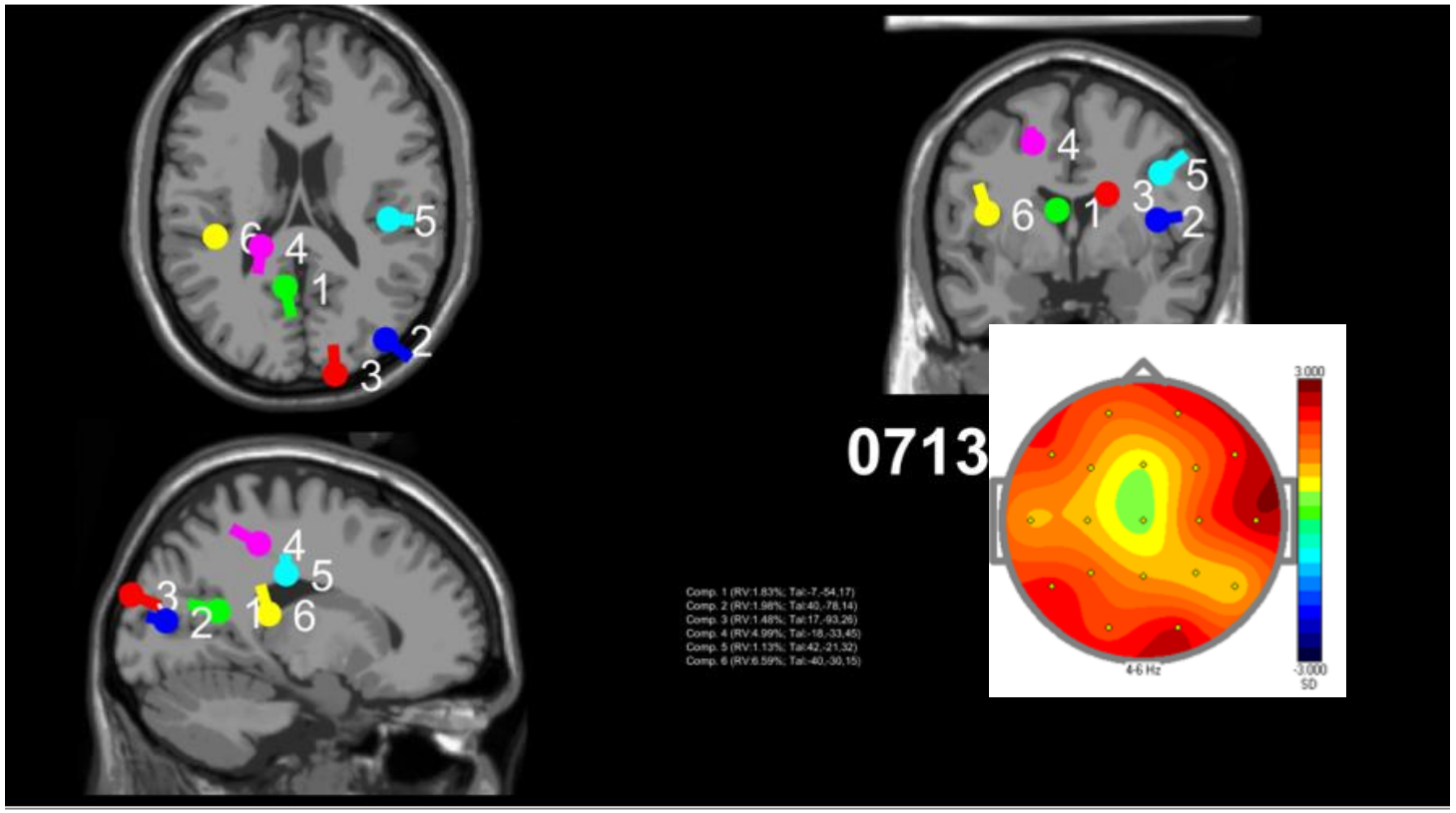


Thank You

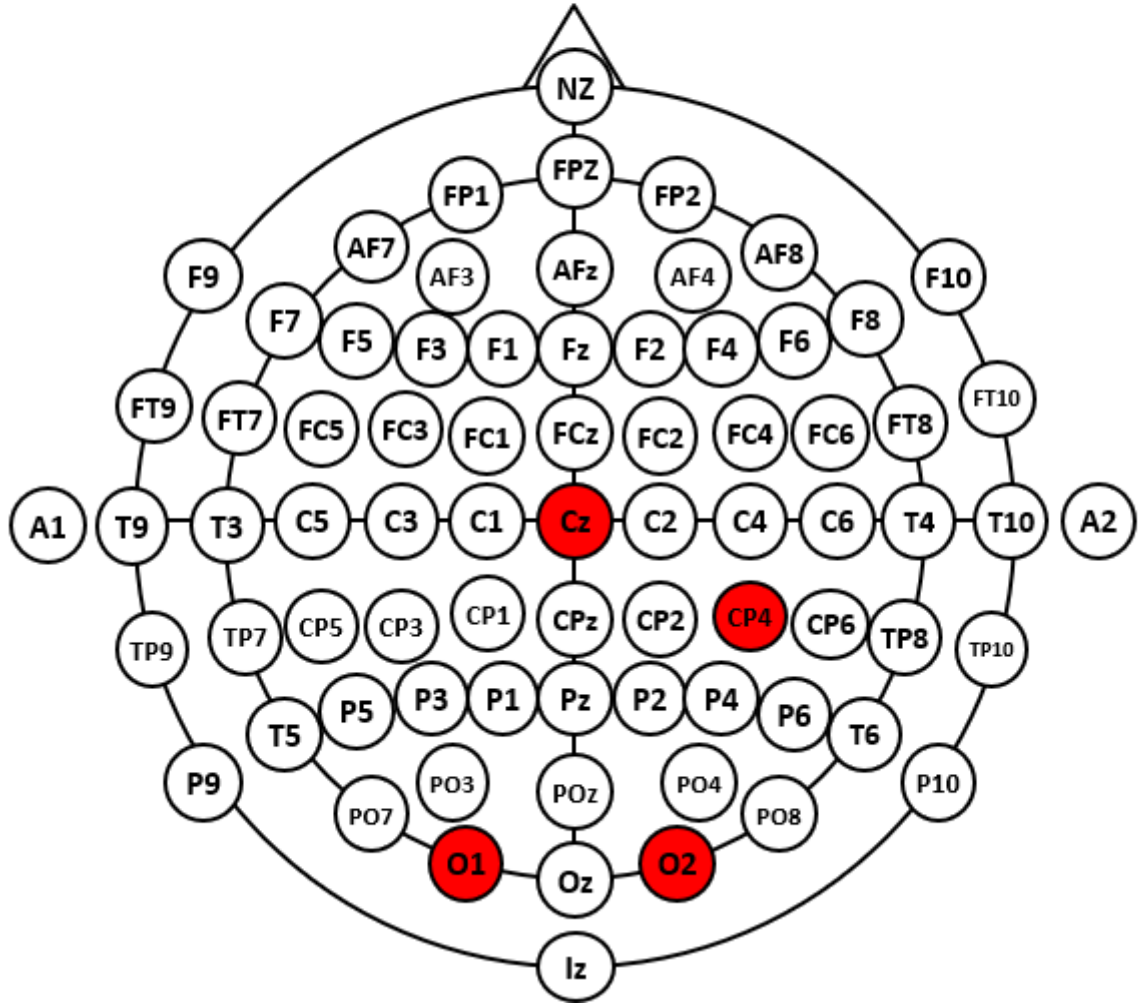
# Case Study

- 17 y/o male
- struggles with attention/focus, difficulty sitting still, fidgetiness, difficulty completing schoolwork, studying, and becoming overwhelmed with a lot of work
- Handedness was slightly delayed – may be ambidexterous officially right handed



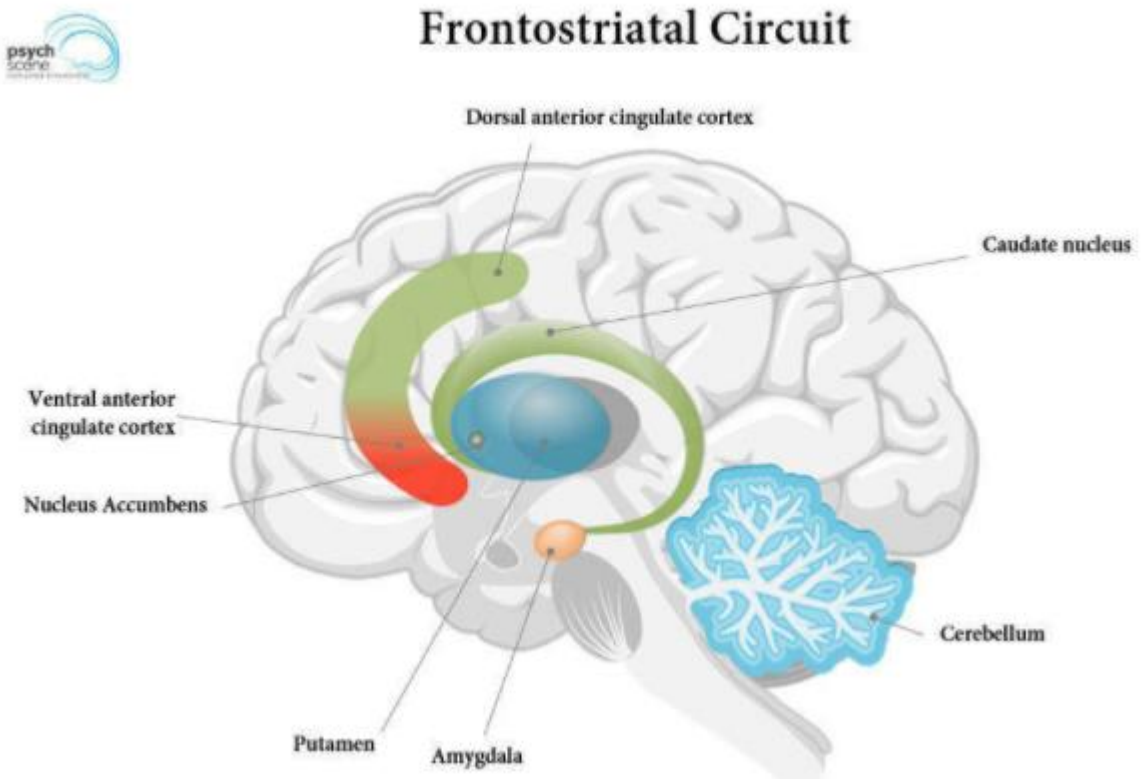

- 1 – posterior Cingulate
- 4 Area 5
- 5 area 2
- 6 area 41

| | |
|---|---|
| Inhibit | 1-6 |
| Inhibit | 7-12 |
| Inhibit | 22-30 |
| Reward | 8-24 |



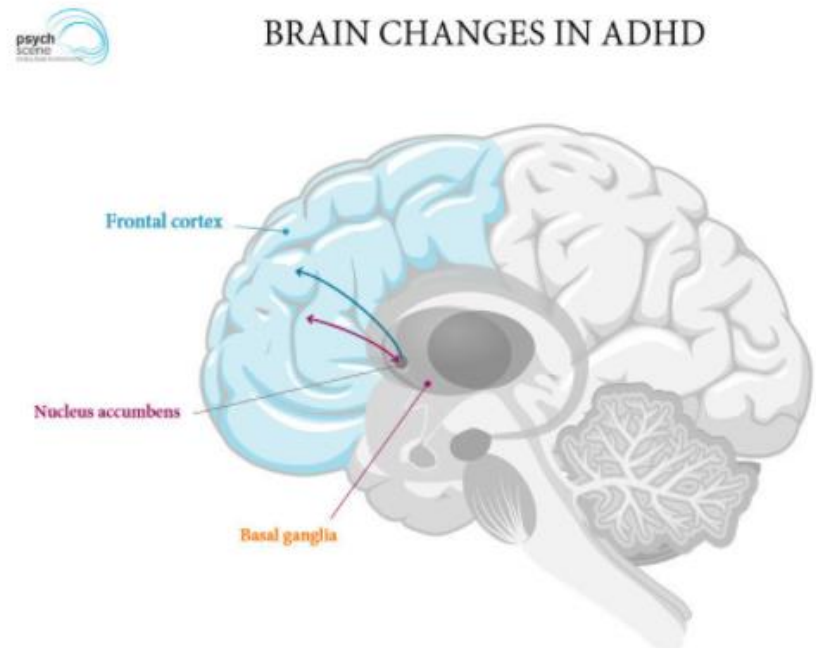
# ADHD

- Frontostriatal Network
  - Lateral prefrontal cortex, dorsal anterior cingulate cortex, caudate nucleus, putamen
- Hypoactivity
  - Anterior cingulate, dorsolateral prefrontal, inferior prefrontal, orbitofrontal, basal ganglia, thalamus, & parietal cortex
- Reduction in volume
  - Total cerebral volume, prefrontal cortex, basal ganglia, dorsal anterior cingulate, corpus collosum, & cerebellum




- Delay in brain maturation
  - Grey matter peaks 3 years delayed – most prominent in prefrontal regions
- White matter abnormalities
  - Corpus collosum, inferior parietal, occipito-parietal, inferior frontal, inferior temporal cortex
  - Decrease the speed of neuronal communication

7. fMRI shows reduced activation of prefrontal cortex and striatal regions.




**Reduced activation of prefrontal and striatal regions (nucleus accumbens and basal ganglia structures)**

- Symptoms of the disorder first become apparent in preschool years and persist into adulthood in approximately 60% of the cases
- Current diagnostic criteria require that symptoms appear prior to the age of 7 years and are expressed in at least two settings for at least 6 months
- the developmental progression of symptoms parallels the emergence of control processes mediated by the maturation of the prefrontal cortex. Thus, age-inappropriate levels of hyperactivity/impulsivity and inattention in ADHD children could reflect a maturational course that is atypical or typical but delayed

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329889/

ADHD comorbid oppositional defiant disorder (ODD) (comorbidity rates up to 60%) on these neuroanatomical differences is scarcely studied, while ODD (in combination with conduct disorder) has been associated with structural abnormalities of the frontal lobe, amygdala, and insula

structural and functional magnetic resonance imaging studies showed that ADHD and OCD have disorder-specific functional and structural abnormalities in basal ganglia and insula, which were reduced in ADHD but increased in OCD relative to controls, and in frontal regions, where rostro-dorsal medial frontal regions were disorder-specifically decreased in structure and function in OCD but ventrolateral prefrontal regions were disorder-specifically underfunctioning in ADHD

https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2526239