Brain Resource Creation Workshop:
Chapter 11 - Childhood Disorders

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Autism Spectrum Disorders (ASD)

- Autism
  - Autism is considered a spectrum because symptoms (many of which persist lifelong) range from mildly to severely disabling
  - Some with autism also have mood & anxiety disorders, seizures, intellectual disability, attention deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD).
  - >40% of people with autism have normal or above-average intelligence.
  - Some are unable to speak, while others are socially awkward but very articulate.
  - Autism spectrum disorders (ASD) are diagnosed based on 2 main criteria:
    i. impaired social communication & interaction
    ii. repetitive behaviors or narrow, obsessive interests

ASD (Cont.)

- Currently, about 1 in every 68 American 8 year olds meet the diagnostic criteria for an ASD.
- ASD prevalence has risen dramatically since the 1970s, but it's unclear if changes to diagnostic criteria & wider recognition of ASD have contributed to the increase in diagnoses.
- 4-5x more boys than girls are diagnosed with autism, however it's unclear if this pattern is attributable to underdiagnosis of girls.
- Environmental factors (like parents having kids later in life, fever & infection during pregnancy, and premature birth) are linked to an increased risk of autism in children.
- Many studies have found no correlation between childhood vaccination and the increase in autism diagnoses.

ASD (Cont.)

- Autism is believed to be partially driven by genetics
  - The genetics of autism are very complicated in most cases, involving many genes, leading to a unique condition in nearly every person.
  - If one twin out of a pair of identical twins is diagnosed with an ASD, the other twin >50% chance of also being diagnosed with ASD.
  - Children who have an older sibling on the spectrum have about a 1 in 5 chance of being diagnosed with ASD.
  - Recent research shows that many genes, each with a small effect, contribute to the inheritance of most ASDs, but such small effects make these genes hard to identify in genome-wide association studies.

ASD (Cont.)

- Scientists are now looking at the rare genetic variants associated with ASD, whose effects are larger and easier to detect.
  - Some of these rare mutations are in single genes whose impairment is already known to cause intellectual disability and social dysfunction.
  - These genes include FMR1 (codes for fragile X mental retardation protein); PTEN (codes for a tumor suppressor enzyme that regulates cell division); and TSC1 or TSC2 (tuberous sclerosis complex 1 and 2), which also code for proteins that help control cell growth and size.
- 50-60% of people with fragile X syndrome and about 40% of people with tuberous sclerosis complex have ASD.
- Children with a variant of the gene NF-1 develop tumors in childhood (neurofibromatosis) and nearly 10% met the criteria for autism.

ASD (Cont.)

- These ASD-related genes influence a major signaling pathway for regulating cell metabolism, growth, and proliferation, the mTOR pathway.
- This suggests potential for treating autism with drugs targeting the mTOR pathway
    - ex. mouse models with mutations in PTEN show traits similar to humans with these gene variants: altered sociability, anxiety, & repetitive behaviors. These behaviors can be relieved or reversed by drugs that inhibit the mTOR pathway
        - Clinical trials of these drugs (rapamycin and lovastatin) are underway.
- Autism genetics are so complex that they cannot be used to diagnose the condition, and there are no biochemical or other biomarkers of autism.
- Autism diagnosis is based on behavioral analysis, but efforts to use more objective criteria (like tracking eye movements and functional neuroimaging, which can even be done in infants) is underway.

ASD (Cont.)

- Parents often notice developmental issues before their child's 1st birthday, and autism can be reliably diagnosed based on behavioral characteristics at age 2, but most American children aren't diagnosed until they're about 4½ years old.
- Interventions are more effective the earlier they begin, so researchers hope more objective measures will lead to earlier diagnoses & interventions.
- It appears that ASD results from unusual cellular development within the cerebral cortex — a brain region that is essential to memory, attention, perception, and language.
- Both white and gray matter of the brain show consistent, but subtle, alterations in people with ASD.
- Studies also show that a minority of children on the autism spectrum have abnormally large brain volumes and faster brain growth.

ASD (Cont.)

- Other toddlers with autism have shown unusual development and network inefficiencies at the back of the cerebral cortex.
- Evidence shows that some atypical activity occurs in the cortex of people with ASD from older childhood into adulthood, and information might not be integrated in the usual way across distributed brain networks.
- No medications have been proven to reverse autism.
    - Some people get symptomatic relief from drugs designed for other uses, such as anxiety conditions, and several studies have reported social benefits from treatment with oxytocin — a hormone known to improve social bonding — but the findings have been mixed.
- Behavioral therapies are still the only proven treatments for autism, and early interventions are the most effective.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

- Attention deficit hyperactivity disorder (ADHD)
  - One of the most commonly diagnosed childhood conditions
  - 11% of American children ages 4-17 received an ADHD diagnosis in 2014.
  - ≥30% of those diagnosed still have the disorder during adulthood.
  - Characterized by extreme and lengthy inattentiveness, hyperactivity, and impulsive behaviors.
  - Kids with ADHD often struggle to form strong friendships, and grades in school can reflect their behavior rather than their academic ability.
  - Executive functions (finishing what they start, remembering to bring homework back to school, and following multistep directions) can be challenging.
  - Children with ADHD have lower rates of high school graduation & a higher risk of suicide compared to children who do not have ADHD.

ADHD (Cont.)

- ADHD diagnosis requires a comprehensive evaluation, including a clinical interview and parent & teacher ratings since no objective diagnostic test exists
- Problems with attention & hyperactivity can be caused by other conditions such as depression, sleep issues, and learning disorders. Careful evaluation is needed to determine whether ADHD is the cause of the symptoms.
- Attention and behavioral problems must be severe enough that they interfere with normal functioning.
- Behavioral issues must be present in more than one context (eg. home & school)
- Although ADHD tends to run in families, no well-defined set of genes is known to be responsible for the condition.
- Environmental risk factors can also be involved such as extreme early adversity, exposure to lead, and low birthweight.

ADHD (Cont.)

- People with ADHD do not demonstrate any obvious brain alterations, but research shows that they might have differences in the structure of brain cells & in the brain's ability to remodel itself.
- Some people with ADHD show unusual activity in brain cells that release dopamine, a chemical messenger involved in rewarding behavior.
- There's no cure, but treatments include drugs and/or behavioral interventions.
    - ADHD medications include stimulants like methylphenidate, as well as newer, non-stimulant drugs, both of which are available in long-acting formulations.
    - Determining the right drug & right dose might require a period of experimentation and support from a specialist since dosage is adjusted to how fast a child metabolizes the drug, and to minimize the side effects.
    - Effective behavioral treatments include organizational support, exercise, and meditation.

DOWN SYNDROME

- Down syndrome
  - Named for the English physician who first described it in 1866
  - 100 years later, scientists determined that possessing an extra copy of all or part of the 21st chromosome caused the condition.
  - People with this syndrome have, not two, but three copies of this genetic material.
  - In some cases, the extra copy, or trisomy, does not occur in every cell, producing what's known as mosaicism.
  - Currently, about 250,000 people in the US are living with Down syndrome.
  - There's no clear cause of the genetic glitch, although advanced maternal (as well as paternal) age is a major risk factor for Down syndrome
    - Mothers older than 40 are 8.5 times more likely to have a child with Down syndrome than mothers aged 20 to 24)

DOWN SYNDROME (Cont.)

- Fetuses can now be screened for Down syndrome by testing the mother's blood.
- In the past, the risk of test procedures meant that only older mothers (whose likelihood of having a Down syndrome child was known to be higher) should be screened; younger mothers didn't know until delivery whether their child would have Down syndrome.
- The new blood test, unlike amniocentesis and chorionic villus sampling, poses no risk to the baby, so it can also be used without a high risk of harm for younger mothers whose chances of having a child with Down syndrome are low
- Children born with Down syndrome have a flattened face and bridge of the nose, eyes that slant upward, and small ears.
- They usually have small hands & feet, short stature, and poor muscle tone.
- Their intellectual abilities are typically low to moderate. It is still possible to graduate from high school and college and successfully hold jobs.

DOWN SYNDROME (Cont.)

- Other symptoms include hearing loss & heart defects; most with Down Syndrome will develop early-onset Alzheimer's disease, in their 40s or 50s.
    - Chromosome 21 contains the gene that encodes amyloid precursor protein (APP), an Alzheimer's disease risk factor, and possessing an extra copy of this gene might cause the early onset of this fatal disease.
- People with mosaic Down syndrome seem to have milder symptoms and are more likely to live past 50.
- Currently, there is no real treatment, or any clear explanation of what occurs in the brain of someone with Down Syndrome.
- Poor connections among nerve cells in the hippocampus, the part of the brain involved in memory (and the first brain area affected by Alzheimer's disease), are supposedly a key factor in brain/intellectual differences in Down syndrome.
- Dysfunction in the mitochondria might also play a role in development of related disorders that involve energy metabolism, like diabetes and Alzheimer's

DOWN SYNDROME (Cont.)

- Scientists have grown stem cells from fetuses with Down Syndrome and used them to test potential treatments and confirm which molecular pathways are involved in the condition.
  - In one laboratory study, researchers took a gene that normally inactivates the second X chromosome in female mammals and spliced it into a stem cell that had three copies of chromosome 21.
  - In these cells, the inactivation gene muted the expression of genes on the extra chromosome 21, believed to contribute to Down syndrome.
  - The model is being used to test the changes and cellular problems that occur with the tripling of the 21st chromosome, in hopes of eventually finding a treatment.

DYSLEXIA

- Dyslexia is the most common of the learning disabilities, affecting 15-20% of all Americans.
- People with dyslexia have a pronounced difficulty with reading despite having normal intelligence, education, and motivation.
- Symptoms include trouble with pronunciation, lack of fluency, difficulty retrieving words, poor spelling, and hesitancy in speaking.
- People with dyslexia may need more time to orally respond to a question and may read slower than their peers.
- Dyslexia is usually diagnosed in elementary school when a child struggles with reading.
- Although reading skills and fluency can improve, dyslexia is a lifelong challenge.
- Deciphering printed letters and words and recalling their sounds and meaning involves many areas of the brain.

DYSLEXIA (Cont.)

- Brain imaging studies indicate these areas can be less connected in people with dyslexia compared to those without dyslexia
- One of these areas is a region on the left side of the brain called the "word-form area," which is involved in the recognition of printed letters and words.
- People with dyslexia also show less brain activity in the left occipitotemporal cortex, which is considered essential for skilled reading.
- It's believed that brain differences are present before the reading and language difficulties become apparent — although it is possible that people with dyslexia read less and, therefore, their brains develop less in regions associated with reading.
- Those with dyslexia appear to compensate for reduced activity on the left side of the brain by relying more heavily on the right side.

DYSLEXIA (Cont.)

- Genetic analyses have revealed susceptibility genes, which affect the migration of brain cells during development, leading to differences in brain circuitry.
- Dyslexia runs in families, with roughly half of dyslexics sharing the condition with a close relative.
- If a twin is diagnosed with dyslexia, the second twin is found to have the condition 55-70% of the time.
- However, the genetics of dyslexia are complex, and likely involve a wide range of genes and environmental factors.
- Treatment involves behavioral & educational intervention, especially exercises like breaking words into sounds and linking sounds to specific letter patterns.
- Some researchers use a child's ability to rapidly and automatically name things as an early indicator of dyslexia.
- Treatments targeting phonology and language skills show the greatest promise.

EPILEPSY

- If someone has ≥2 seizures without an apparent underlying medical condition (such as a high fever or low blood sugar) they are diagnosed with epilepsy.
- Epilepsy is from the Greek words “seize,” “attack,” or “take hold of.”
- 1% of American children and 1.8% of adults have been diagnosed with epilepsy.
- Seizures result from irregular activities in brain cells that can last five or more minutes at a time.
- Some seizures look like staring spells, while others cause people to collapse, shake, and become unaware of what is going on around them.
- The pattern of symptoms and after-seizure brain recordings using EEGs are used to distinguish between different types of epilepsy and determine whether the true cause of the seizures was epilepsy or a different medical condition.
- Seizures are classified by where they occur in the brain.

EPILEPSY (Cont.)

- Generalized seizures affect both sides of the brain.
  - They include absence/petit mal seizures, which can cause rapid blinking or a few seconds of staring into space, and tonic-clonic/grand mal seizures, which can make someone fall, have muscle spasms, cry out, and/or lose consciousness.
- Focal or partial seizures are localized to one area of the brain.
  - A simple focal seizure can cause twitching or a change in sensation, triggering strange smells or tastes.
  - Complex focal seizures can leave a person confused and unable to answer questions or follow directions.
- A person can also have secondary generalized seizures, which begin in one part of the brain but spread to become generalized seizures.

EPILEPSY (Cont.)

- With severe epilepsy, multiple types of seizure can occur at the same time.
- Epilepsy has many possible causes and thus is considered a spectrum.
- Causes include premature birth, brain trauma, and abnormal development due to genetic factors.
- Attributes of epilepsy patients such as head size, movement disorders, and family history suggest that genetics are involved.
- Seizures can also accompany or cause intellectual or psychiatric problems
    - For example, some seizures may suppress the growth of dendrites, leaving the person emotionally unsettled or with difficulty learning.
- Epilepsy treatments attempt to control seizures with medication or diet.
- For most patients, a single medication is enough to control seizures, although a significant minority cannot get adequate control from drugs.

EPILEPSY (Cont.)

- Half of epilepsy patients, particularly those with generalized epilepsy, can reduce their seizures by eating a ketogenic diet, which relies heavily on high-fat, low-carbohydrate foods, but it's unclear why this diet is effective.
- For severe cases that are not relieved by medication, doctors might recommend surgery to remove or inactivate the seizure-initiating part of the brain.
- In the most severe cases, if one side of the brain triggers seizures on the other side, surgeons may perform "split-brain surgery," cutting the corpus callosum, a thick band of white matter that connects the two sides of the brain.
- Once their seizures are controlled, people with epilepsy can resume their normal lives.

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We hope you enjoyed the workshop!

Any questions?

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