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degenerative disorders

ALS: amyotrophic lateral sclerosis (Lou Gehrig’s disease)
-symptoms: stiffness of movement, exaggerated reflexes, muscular trophy, paralysis, terminal dicers (5-10 years after onset) no dementia
-mostly sporadic cases (1/20,000)
-misfolding of protein: chromosome 21 -> toxic gain of function
-neural substrate: degeneration of spinal cord motor neurons and cranial nerves.
-excitotoxicity: death of neurons because of too much stimulation/excitation
-treatment: no cure, drugs can decrease glutamate release and improve symptoms, gene therapy
- genetic not sporadic: can have gene but no symptoms

MS: multiple sclerosis
-symptoms: complex and very diverse. slowly evolving, not hereditary not contagious. more in women than men. loss of motor coordination, tremors, numbness
-neural substrate: autoimmune disease; degeneration of myelin and formation of sclerotic plaques
-treatment: genetic component (gypsies and Asians are low risk), environmental component (childhoods in cool climates are at a higher risk). influencing the immune system; no cure; partial recovery.

infectious diseases

encephalitis and meningitis
-symptoms: fever, irritability, nausea -> convulsion, delirium. 10% is terminal, 20% result in permanent brain damage, also deafness

neural substrate:
- viral infections (STDs or mosquitoes), bacteria, fungi
- encephalitis: affects the whole brain
- meningitis: affects the meninges

treatment: none in general
- herpes simplex: cold sores. virus that lives in spinal ganglion and breaks out periodically along the sensory nerves. encephalitis results from breakout to the brain (low key rare), frontal and temporal lobes. treatable (acyclovir) but no cure.
- polio: damage to all motor neurons (brain and spinal cord). vaccine (Jonas Salk)
- rabies: fever, headaches -> convulsions, seizures, death within a week, affects the cerebellum and hippocampus. there is a vaccine
- AIDS (not HIV): brain damage in 75% of cases (if untreated). due to excess of calcium through nACh receptors (excitotoxicity) hippocampus and cortex
- inability of neurons to sustain too much excitation
- meningitis: headache, stiff neck -> convulsion, death. infection of meninges, resulting in impaired blood/cerebrospinal fluid circulation. cranial nerve damage.
treatable by antibiotics. vaccine.
Schizophrenia:
- 1% total world population. Complex disease. Not strictly degenerative
- 3 types of symptoms:
  - Negative symptoms (lack of some behaviors)
  - Cognitive symptoms (disorder of information processing)
  - Positive symptoms (additional abnormal behaviors)
- Physical traits: Mild facial (larger heads, wide set eyeballs, low ears) and finger signatures
- Late onset: 20’s
- Symptoms appear gradually within 5 years of onset. Positive symptoms appear last.

Positive schizophrenia symptoms: Dopamine
- All positive symptoms may be preceded by short-lived ‘elation’ and ‘euphoria’
- Thought disorders: Irrational, disorganized thinking
- Delusions: Non-factual beliefs (persecution, contact with aliens, grandeur)
- Hallucinations: Sensory perception malfunction (auditory)

Reasons we know it deals with dopamine:
- Chlorpromazine blocks D2 receptors and blocks positive symptoms
- L-Dopa, cocaine, amphetamine: Agonists increase the positive symptoms
- A dysfunction of the meso-limbic dopaminergic system: Too much dopamine
  - VTA -> Nucleus accumbens and amygdala

Negative schizophrenia symptoms: Brain damage
- Absence of certain behaviors: Flat affect, flat motivation. Unusual facial expression, social inhibition, anhedonia, poor eye pursuit — follow a finger with eyeballs, deficit in eye-blink reflexes
- Enlarged ventricles: Large lateral (and third) ventricles -> Less gray matter (temporal, frontal lobes)
  - Ventricles have not increased in size, the brain around it died

Evidence from anatomy: The loss of brain tissue (cortical gray matter) is progressive after onset. More loss in schizophrenic patients
- Gray matter: Axons
- White matter: Cell bodies

Hypofrontality (less frontal lobe): Evidence from physiology
- Decrease of activity in dorsolateral frontal cortex
- Due to decrease in dopamine release
- Reduced frontal lobe activity

Hypofrontality: Evidence from animal studies
- Animal models: PCP (Angel dust) or ketamine produce schizophrenic like symptoms:
  - Indirect NADA antagonist: Decrease neural activity and dopamine modulation in prefrontal cortex
  - Lack of prefrontal activity/dopamine results in perseverating behaviors
  - Clozapine increases dopamine in prefrontal cortex and alleviate symptoms
towards an explanation and an effective treatment for the positive and negative symptoms

1. hypofrontality
   - less nada and da release in prefrontal cortex: less pac activity
   - negative symptoms
   - alleviated by indirect nada agonists
2. too little activity in pac triggers less inhibition of eta
   - more da release in nun accumbens
   - positive symptoms
   - alleviated by d2 antagonists
   - not enough da in frontal cortex, too much da in nov accumbens

Treatment: partial competitive da agonist: substance with a high affinity for dopamine but less efficient that dopamine itself. high binding capability but low threshold.

- atypical antipsychotics (clozapine, aripiprazol)
  - agonist in pac
  - antagonist in nut accumbens
  - alleviate all symptoms of schizophrenia

causes of schizophrenia: no single cause

viral source/cause:
- epidemiology: study of disease at the population level
- latitude effect: increase risk if birth occurs far from the equator
- seasonality effect: late winter/early spring birth — viruses more prominent during this season: not a cause but an increase in risk
- births after a flue epidemic on 2nd trimester of pregnancy
- births in cities: 3x more schizo. easy transmission of viruses

other risk factors:
- vitamin d deficiency (lack of sunlight or milk)
- smoking and alcohol consumption during pregnancy

developmental causes:
- lack of sociability and psychomotor skills in childhood are associated with schizophrenia
- monozygotic twin studies: if twinning occurs before day 4 -> separate placenta -> decrease likelihood of both twins developing schizo

Genetic cause:
- parental schizophrenia increase the risks of children developing schizophrenia by a factor 10
- twins fingerprints correlates with their concordance for schizo
- identical twins from 2 schizo parents: only 45% chance they both develop schizo (should be over 75% just proves more than one gene is involved
- multiple genes involved
cognitive symptoms: brain damage
- attention deficits
- slow reaction time (fingers, legs)
- deficit in learning and memory
- poor planning and problem solving
- deficit in abstract thinking

brain areas involved in ^: no clear neural correlate or mechanisms yet

aff ective disorders: mania and depression
- bipolar disorder: cycle between depression and mania
- depression: three times longer than mania
- mania by itself is rare
- depression (mdd) by itself is 2-3x more likely in women (7%) than men (3%) mdd: unworthiness, guilt, low energy, difficulty to fall asleep
- suicide attempts: 15% unipolar, 30% bipolar
- accompanied by sleep disorder: less slow wave sleep, more stage 1, earlier rem onset
- hereditary: one direct parent -> 10x increase in risk. no single genes
- seasonality effect: birth in may/june/july -> high risk for suicide

action reaction story for depression and mania cycle