Huntington's disease

Within the striatum, the caudate and putamen contains medium spiny neurons.

Grey type I synapses have thicker pre-synaptic terminals, tend to be stimulatory

Grey type II have symmetric synaptic terminals, tend to be inhibitory

Dopaminergic neurons contain tyrosine hydroxylase, responsible for the synthesis of dopamine

Huntington's:

- Autosomal dominant inherited disorder on chromosome 4
- Symptoms: Early stage involves hyperkinesia, later stage becomes parkinsonian (akinetic), final stage involve dementia
- Diagnosis: enlarged lateral ventricle, shrinking of the caudate and putamen (striatum)
    - Dying of the medium spiny neuron, shrinking of the nucleus
- Mechanism:
    - Huntington's disease gene located in chromosome 4, spliced from 67 exons
    - Huntingtin polymorphic protein coding gene on the first exon of the chromosome, contains CAG repeats (gln)
    - General population contains up to 37 repeats, higher repeats lead to HD. Higher number —>earlier onset
    - Enkaphalin marker decrease before substance P decrease, GPe (indirect) degenerate before GPi (direct), assessed by in-vitro hybridisation, dorsal caudate nucleus degenerate before ventral putamen.
    - Loss of indirect pathway (inhibtion) followed by loss of direct pathway

Parkinson's:

- Symptoms: Bradykinesia, postual instability, loss of facial expression, rigid joints.
- Diagnosis:
    - Lesion of substantia nigra ventrolateral segment. Progress through the substantia nigra.
    - Putamen contains less dopamine than the caudate, dorsal region affected worse
    - Lewy body, dark spot in the cell with radiating filaments made up of α-synuclein
- Mechanism:
    - α-synuclein gene mutation or duplication of the gene on chromosome 4
    - All patients develop Lewy bodies containing α-synuclein with or without mutation
    - Loss of dopaminergic effects, less stimulation of direct pathway, increase in inhibitory effect in the indirect pathway.
    - Overstimulation of subtalamic nucleus causes parkinsonian synptoms,
        - Experimental evidence: injection of D1/D2 agonist rescues parkinson's symptoms
        - Experimental evidence: electrical inhibition of subthalamic nucleus rescues parkinson's symptoms

Schizophrenia:

Causes of phychosis: schizophrenia, sleep deprivation, drug use, stress anxiety.

- Symptoms:
    - Heterogenous symptoms: positive, negative and cognitive
    - Positive symptoms: hallucinations, delusions, disorganised thinking and behaviour (same as phychosis)
    - Negative symptoms: Reduced speech, motivation, anhedonia (lack of pleasure), social withdrawl
    - Cognitive: Loss of attention span, loss of working memory, early phases show declined cognitive abilities.
- Diagnosis:
    - Enlargement of lateral ventricles, decrease in cortical thickness.
    - Clinical assessment of symptoms based on various operational criterias.

        - Symptom + symptom duration
        - Effect of symptom on functioning of individual
        - Psychiatric history, substance misuse history
- Mechanism:
    - Environmental factors: urban populations, social isolation, drug use, premature birth
    - Genetic components: Indentical twins have 50% risk of developing SZ, suggest genetic + environmental
    - Neurotransmittor systems hypothesis:
        - Dopamine: SZ symptoms mimicked by amphetamines, increased release of dopamine
            - Chlorpromazine reduce SZ positive symptoms (side effect resemble PD), blocks D2 receptors in the nucleus accumbens, prevent overstimulation of the prefrontal cortex (aberrant salience/focus)
            - Clozapine targets 5HT receptors, improve both positive and negative syndromes
        - Glutamate: hypofunction of NMDA receptors: ketamine/antagonists of NMDA mimick SZ
            - Decrease in synaptic protrusions in patients with SZ, decrease in glutamertergic synapses.
    - Genetic risk factors: variations in dopamine D2 and glutamate receptors.

Alzheimer's

- Symptoms: stages
    - Mild cognitive impairment: Temporal lobe: short term memory loss
    - Mild Alzheimer's: Parietal lobe: Reading problem, object recognition
    - Moderate Alzheimer's: Frontal lobe: Poor judgement, impulsivity
    - Severe Alzheimer's: Occipital lobe: vision problem
- Diagnosis: β-amyloid accumulation, cell death
    - τ-proteins neurofibillary tangles, visualised in the hippocampus using phosphorylation stain
    - Extracellular β-amyloid plaque, cleaved from C-terminus of APP produce amyloid monomer, aggregate produce filament, insoluble form plaque.
    - Shrinking of temporal lobe and cortex
    - Enlargement of lateral ventricles
- Mechanism: autosomal dominant on chromosome 21.
    - Mutation on the amyloid precursor protein (APP) or trisomy 21 causes AD.
    - Increased expression of APP leads to AD
    - Risk factor for AD is apolipoprotein E4
    - Presinilin 1/2 mutation is an inheritable form of AD risk factor, subunit of γ-secretin
    - τ-tangles are associated with neuronal cell death, β-amyloid is the trigger
        - τ is a microtubule binding protein, and is alternatively
            - β-amyloid phosphorylate τ, dissociate from microtubule, form tangles, cytotoxic
    - Apolipoprotein protein variants are risk factors.
        - ApoE4 highest risk factor
        - ApoE3 neutral
        - ApoE2 protective

Autism Syndrome disorder

Features:

Withdrawl from social interactions, lack of joint attention, avoid eye contacts

Defects in language

Repetitive behaviours and limited interest, tend to follow strict rules

Resistance to change

Diagnosis:

- Behavioural characteristic diagnostic criteria, following developmetal stages and family history.
- MRI reveal abnormal brain growth, increase in cortical volume and total surface area.

Mechanism: genetic and developmental

Environmental risk factors:

- Prenatal and perinatal in utero stress (e.g. age of pregnancy, hypoxia, drug exposure e.g. valporate for epilepsy)

Genetic risk factors:

- Family history with ASD are more likely to have offsprings with ASD
- Identical twins are morel likely to have ASD compared to non-identical twins
- Common variations with additive effects that may cross the threshold of developing ASD
    - Autosomal recessive or variations in copy number
- Rare mutations with significant effects, highly penetrant
    - E.g. autosomal dominant mutations
    - Monogenic mutations that lead to ASD: generally thought to disrupt synaptic functions
        - Rett syndrome
        - Tuberous sclerosis
        - Fragile X (40% lead to ASD): decrease in synaptic protein synthesis
        - Phelan-Mcdermid syndrome: disruption in shank3 structural protein.
        - X-linked mutation in neuroligin 3 and 4, form trans-synaptic complex with neurexin
- Cohort gene sequencing found risk factors related to