Disorders of the central nervous system
Neurobiology & pathophysiology of addiction
Multiple sclerosis (MS)

- MS: autoimmune inflammatory demyelinating and neurodegenerative disorder of the CNS; which affects young adults with certain genetic background upon environmental influences
- This progressive inflammatory process affects the white and gray matters of the brain & spinal cord; in addition to myelin damage, axons and neurons are also destroyed, often early in the disease course
- Four types of MS are described
  - Relapsing and remitting MS (85%), which can lead to secondary progressive MS in 40% (mainly with neurodegeneration)
  - Primary progressive MS: steady decline of neurological function
  - Progressive relapsing MS: rare and the worst
Etiology

Genetic factors

Increased the risk of MS (e.g., northern Europeans or inhabitants of northern climates)

- HLA I A3 and B7 antigens
- HLA II polymorphisms: Dw2 and DR2
  (DRB1*1501 allele: antigen presentation, T cell repertoire selection and myelin basic protein [MBP] recognition (molecular mimicry)
- Interleukin 2 & 7 gene receptor polymorphism
  The receptors are critical for thymocyte differentiation and survival of CD4+ CD8+ cells
  F > M = 1.8 : 1
  Greater risk for relatives (31% for monozygotic twins and approx. 5% for dizygotic twins)
  Resistant groups in high risk areas never get MS: Hutterites, Maoris, Hispanics, Asians, Native Americans, Gypsies, Eskimos

Environmental factors

MS is more common above 37 parallel

- Vitamin D and sunlight exposure, high 25OH vitamin D level – lower risk
- DOB (northern hemisphere):
  November – less MS than in May
  Low vitamin D exposure in young females in Iran
  Risk appears to be related to where childhood was spent; later generation appear to take on the risk of the area

- Smoking – female smoking (?)

Transmissible agent

HHV-6 (EBV), HHV-6 (roseola infantum or exanthema subitum) and Chlamydia pneumoniae

MS is more frequent who have had infectious mononucleosis or have high anti-EBV antibodies
MS prevalence

Atlas multiple sclerosis resources in the world 2008. (WHO)
Pathophysiology of MS

**Th**\(_2\) cytokines (IL-4,5,6,10,13, TGF-β)

- *Soluble factors released by macrophages and microglia include TNF-α, leukotrienes, thromboxanes, proteases, and complement components*

**Th**\(_1\) cytokines ↑
- (TNF-α, IFN-γ, IL-2,12,15,17,23,27)
- Co-stimulatory molecules ↑,
- Th, chemokine receptors ↑

**Activated T (CD4\(^+\), CD8\(^+\)), B cells and macrophages\(^*\)

**Environmental factors**

**MBP** (molecular mimicry)

**HHV-4,6 antigens**

**BBB damage by inflammatory mediators** (occludin, cadherin, claudin)

**B cells & Ig-s entry into the CNS**

**Early immune activation outside the CNS**

**MS**

**Demyelination**

**Neurodegeneration**

**Exposition of myelin antigens**

*Environmental factors: activated T (CD4\(^+\), CD8\(^+\)), B cells and macrophages.**

**Th1 cytokines:**
- TNF-α, IFN-γ, IL-2, 12, 15, 17, 23, 27
- Co-stimulatory molecules increase, Th cell chemokine receptors increase

**Th2 cytokines:**
- IL-4, 5, 6, 10, 13, TGF-β

**IFN-β**

**Activated T cells (CD4\(^+\), CD8\(^+\)), B cells, and macrophages**

**Environmental factors**

**MBP (molecular mimicry)**

**HHV-4,6 antigens**

**BBB damage by inflammatory mediators** (occludin, cadherin, claudin)

**B cells & Ig-s entry into the CNS**

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**MS**

**Demyelination**

**Neurodegeneration**

**Exposition of myelin antigens**

*Soluble factors released by macrophages and microglia include TNF-α, leukotrienes, thromboxanes, proteases, and complement components.*
In demyelinated regions action current is short-circuited so further propagation of the action potential is blocked. In partially demyelinated axons exhibit Uhthoff phenomenon: worsening of vision with increased body temperature or exercise. Mechanical stimulation of demyelinated axons can generate de novo action potentials in the axon. This may explain the Lhermitte phenomenon: electric shock-like sensations in the spine on flexing the neck. Spontaneous action potentials can be recorded from demyelinated axons (symptoms of trigeminal neuralgia, myokymia [involuntary movement of the eyelids], paraspinal muscle spasms, and visual phosphenes (visual sensations when the eyes are closed).
Lesions in the CNS
Optic nerves, periventricular white matter, corpus callosum, brainstem, cerebellar white matter and spinal cord

Clinical investigation of MS by evoked potentials
- Visual evoked potentials
- Brainstem auditory evoked potentials
- Somatosensory evoked potentials

Example of the course of the disease
Clinical symptoms of MS

- **Unifocal**
  - Optic neuritis: inflammation of optic nerve causing pain/visual disturbances – diplopia (double vision)
  - Internuclear ophthalmoplegia: impaired horizontal eye movement with weak adduction of the affected eye and abduction nystagmus of the contralateral eye (dysfunction of the medial longitudinal fasciculus)
  - Facial hypesthesia or trigeminal neuralgia (*tic douloureux*)

- **Multifocal**
  - Spinal cord lesions: upper motor neuron dysfunction: paresthesia (pain, numbness), spasticity, paralysis
  - Cerebral symptoms: progressive weakness, fatigue, ataxia
  - Breathing, speech, swallow, bowel & bladder problems (incontinence)

- **Classic (Charcot) triad in MS:** nystagmus, intention tremor, and scanning or staccato speech
<table>
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<tr>
<th>Disease</th>
<th>Mode of transmission</th>
<th>Clinical features</th>
<th>Affected brain regions</th>
<th>Genes involved</th>
<th>Protein accumulation</th>
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</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Sporadic (95%) or familial (5%)</td>
<td>Progressive dementia</td>
<td>Hippocampus, cerebral cortex → basal forebrain, brain stem</td>
<td>APP, PSEN1 &amp; 2 APOE ε4</td>
<td>Amyloid-β, tau</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Sporadic (90%) or familial (10%)</td>
<td>Movement disorder</td>
<td>Substantia nigra, hypothalamus, cortex</td>
<td>SNCA, LRRK2 PRKN, DJ1, PINK1</td>
<td>α-synuclein, tau</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Familial (autosomal dominant)</td>
<td>Dementia, motor and psychiatric problems</td>
<td>Striatum, cerebral cortex</td>
<td>HD</td>
<td>Huntingtin (polyglutamine)</td>
</tr>
<tr>
<td>Frontotemporal lobar degeneration (FTLD) &amp; Amyotrophic lateral sclerosis (ALS) disease spectrum</td>
<td>Sporadic (90%) or familial (10%)</td>
<td>Personality, behavior &amp; language disturbances</td>
<td>Focal degeneration of frontal/temporal lobe</td>
<td>MAPT GRN C9orf72 TARDBP FUS</td>
<td>Tau Prprogranulin G4C2 expansion TDP-43 FUS</td>
</tr>
<tr>
<td>Creutzfeldt-Jacob’s disease</td>
<td>Sporadic (90%) or familial (8%) or infectious (2%)</td>
<td>Weakness with upper or lower motor neuron signs</td>
<td>Spinal &amp; cortical motor neurons, brainstem</td>
<td>SOD-1 C9orf72 MAPT, TARDBP FUS</td>
<td>SOD-1 G4C2 expansion Tau, TDP-43 FUS</td>
</tr>
</tbody>
</table>

APP - amyloid beta (A4) precursor protein; PSEN1 & 2 – presenilin; APOE ε4 – apolipoprotein E; SNCA - α-synuclein, LRRK2 – leucine-rich repeat kinase 2; PRKN – parkin, DJ1 – DJ-1; PINK1 – PTEN-induced putative kinase 1; HD – Huntingtonin; MAPT – mictotubule-associated protein tau; C9orf72 – chromosome 9 open reading frame 72; TARDBP – TAR DNA-binding protein; GRN – granulin; FUS – FUS RNA-binding protein; SOD-1 – superoxide dismutase 1, soluble; PRNP – prion protein
Alzheimer’s disease (AD)

- First described in 1906 by the German physician Alois Alzheimer
  - The most common form of dementia, accounts for > 80% of dementia cases worldwide. A progressive, degenerative disease with loss of intellectual function (thinking, remembering and reasoning)
  - The fourth leading cause of death in adults, after heart disease, cancer and stroke
  - Currently 25-30 million people suffer from AD triplicate by 2040
  - Cases are doubling every 5 yrs after 65
Alzheimer’s is worse than a disease – it takes the soul of a human being first.
### Etiology of AD

- **Age, head trauma, surgery etc**
- **Vascular factors: cholesterol ↑, blood pressure ↑**
- **Education**
- **Environment: unhealthy diet, lack of exercise, smoking**
- **Genes**

### Genes and AD

<table>
<thead>
<tr>
<th>Increased risk</th>
<th>Protective genes</th>
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<tbody>
<tr>
<td><strong>Autosomal dominant: Early onset (&lt; 60 yrs) AD</strong></td>
<td>• ApoE2 (ε2)</td>
</tr>
<tr>
<td>• Amyloid precursor protein (APP gene) mutation</td>
<td>• Disease resistant APP mutations</td>
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<tr>
<td>• APP is implicated in synaptic formation, repair signaling and cell adhesion</td>
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<tr>
<td>• Down trisomy</td>
<td></td>
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<tr>
<td>• PSEN-1 &amp; PSEN-2 gene mutations</td>
<td></td>
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<tr>
<td>• γ-secretase complex</td>
<td></td>
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<tr>
<td>• &gt; 160 other, rare mutations</td>
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<tr>
<td><strong>Co-dominant</strong></td>
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<tr>
<td>• ApoE4 (ε4): allele mutation (strongest risk factor for sporadic AD) ApoE4</td>
<td></td>
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<tr>
<td>• ApoE4: less efficient in membrane lipids and neuronal repair and acts as</td>
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<tr>
<td>• ApoE acts as a cholesterol transporter in CNS &amp; binds to amyloid-β</td>
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<tr>
<td>• ApoE3 (ε3): the most common isoform</td>
<td></td>
</tr>
</tbody>
</table>
• Forms of AD
  ○ Early onset (< 60 yrs) AD
  ○ Late onset (> 65 yrs) AD; sporadic disease
    ■ Heritability: ~80%
      □ Other variants/mutations of APP, PSEN 1&2
      □ Abnormal lipid metabolism: ApoE4 (ε4)
      □ Inflammatory response
γ-secretase complex cleaves APP to promote neuronal plasticity, and with β-secretase (BACE) generates amyloid β (Aβ) peptide. **Mutations** in presenilin-1 enhance γ-secretase activity, amyloid-β peptide (Aβ) formation and perturb endoplasmic Ca balance. Aggregated Aβ stimulates membrane-associated oxidative stress and with disturbed Ca balance → neurodegeneration.
Familial AD
Mutations in APP and PSEN genes

Life-long production & accumulation of Aβ/tau

Aβ plaque formation + Hyperphosphorylated tau

Microglial activation
Oxidative stress; inflammatory response

Neuronal dysfunction with transmitter deficits

DEMENTIA

Sporadic AD
ApoE4, other gene mutations; ageing and environmental risk factors

Failure of Aβ clearance & gradual accumulation of Aβ/tau in brain

DEMENTIA
Parkinsonian syndrome

Primary

- Parkinson’s disease
- Parkinson “plus” diseases

Sporadic Familial

Secondary

Parkinsonism secondary to medications (neuroleptic-induced parkinsonism) and various medical conditions (e.g., encephalitis, stroke)

See Neurology
- Multisystemic atrophy
- Progressive supranuclear palsy
- Parkinson’s syndrome in dementias (Alzheimer, frontotemporal dementia)
Parkinson’s disease (PD)

- PD is a progressive neurodegenerative movement disorder.
- 1. Classical motor triad of PD:
  - 1. resting tremor
  - 2. rigidity & postural instability
  - 3. bradykinesia, akinesia (difficulty in initiating willed movement)
- 2. Nonmotor symptoms
  - Depression, hyposmia, sleep disturbances, constipation
- 3. Neurodegeneration: development of Lewy bodies (LBs) and Lewy neurites (LNs) in surviving neurons often with spreading pathology
  - Intracellular aggregations of lipids and proteins (ubiquitin and α-synuclein)
Symptoms of motor triad of PD result from the profound and selective loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc), however non-dopaminergic neurons (ascending NA, cholinergic and 5-HT) are also involved in neurodegeneration → nonmotor symptoms.
### Braak stage

<table>
<thead>
<tr>
<th>Braak stage</th>
<th>1-2</th>
<th>3-4</th>
<th>5-6</th>
</tr>
</thead>
</table>
| Clinical features | • Hyposmia  
• Sleep disturbances (REM sleep; restless leg) | • Resting tremor  
• Rigidity & postural instability  
• Bradykinesia, akinesia | • Neuropsychiatric symptoms  
• Cognitive impairment |

Unilateral or asymmetric onset of a bradykinetic syndrome with resting tremor, masked face, hypovolemic speech, swallowing difficulty, micrographia, start hesitancy (akinesia), freezing, festination (rapid shuffling steps forward-flexed posture when walking)

Dopaminergic innervations decrease: ~ 60-80%
Etiology

● PD is not a single entity: genetic, environmental and age-related risk factors have been identified
  ○ Definite
    ■ Age-related: 1% → 4% (from 60 → 80 yrs)
    ■ Male gender ~1.5x
  ○ Highly likely
    ■ Monozygotic twins with early-onset PD
  ○ Probable
    ■ Positive family history
  ○ Possible
    ■ Herbicides, pesticides, heavy metals, solvents, proximity to industry, rural residence, well water, repeated head trauma, etc.
● Possible protective effect: smoking (nicotine), caffeine (adenosine A2a receptor)
• Genetics abnormalities in familial PD leading to deficits in mitochondrial and ubiquitin proteasome system (UPS)
  ○ **Autosomal dominant PDs**
    ■ Two gene abnormalities (SNCA, LRRK2) affect common pathways leading to widespread α-synuclein deposits and autophagic impairment resulting in mitochondrial dysfunction in several brain areas
      □ LRRK2: the most common gene defect in autosomal dominant PD leading to late onset PD in general population as well as in Ashkenazi Jews and people of Mediterranean origin leading to typical late-onset PD
      □ SNCA (α-synuclein): earlier onset & more aggressive than LRRK2; leading to nonmotor signs and spreading pathology (besides classical PD symptoms)
- **Autosomal recessive PDs**
  - PRKN, DJ1, and PINK1 gene abnormalities produce neuronal cell loss, generally without protein aggregation and leading to early-onset PD (< 45 yrs) with slow course (restricted to brainstem) and with low-risk for cognitive decline
    - PRKN alone accounts for ~50% of early-onset PDs
    - Normally these genes are key mediators of mitochondrial homeostasis and mitophagy (degradation of mitochondria via autophagosome formation)
Normal mitochondrial function: parkin, DJ-1, PINK-1
Pathophysiology of PD

● 1. Two main pathways of cellular toxicity
  ○ Protein misfolding and aggregation
    ■ ↑ production of α-synuclein and/or ↓ elimination of toxic proteins (proteasome dysfunction)
  ○ Mitochondrial dysfunction

● 2. Vulnerability of DA neurons, Free radical formation
  ■ Some environmental toxins and pesticides can inhibit complex-I and lead to mitochondrial dysfunction, whereas alterations in mitochondrial DNA (mtDNA) may influence mitochondrial function. Impaired mitochondrial function leads to oxidative stress, deficits in ATP synthesis, and α-synuclein aggregation, which may contribute to UPS dysfunction
  ■ Oxidative stress may also influence the antioxidant function of DJ-1, can impair parkin function, and may promote dopamine oxidation
  ■ Excess dopamine metabolism (oxidation of cytosolic DA) may further promote oxidative stress
  ■ Mitochondrial and UPS dysfunction, oxidative stress, and α-synuclein aggregation ultimately contribute to the demise of DA neurons in PD
Mitochondrial dysfunction, oxidative stress, and impairment of the UPS may underlie the molecular pathogenesis of familial and sporadic PD, and these pathways may be linked together at multiple levels.
Huntington’s disease (HD)

- **Hyperkinesia** (jerky, involuntary movements), **Chorea** (from the Greek choreia for „dance“)
- **Dyskinesia** (impaired movement), **Dementia**, **Depression**
- **Degeneration of the neurons in the striatum and other regions**, Dominant, incurable
- **Chromosome 4** (Huntingtin gene mutation) – Huntingtin protein
  - CAG triplet (glutamine) repeats (11-34 normal; from 37 to 150 in HD)
    - The longer the repeat, the earlier the disease presents
    - The repeat appears to cause precipitation of protein
- **Decreased GABA, acetylcholine and glutamate in striatum**
  - Mutations may enhance the glutamate toxicity
Normal brain

Huntington’s disease; atrophy of caudate nucleus (and putamen)
Tremors

Physiological tremor

Resting tremor
Parkinson’s disease
Disappear with movement

Intentional tremor
Cerebellar damage

Chorea
Huntington’s disease
quick, irregular, involuntary

Athetotic movement
much slower; almost writhing
movement of neck and trunk
Frontotemporal lobar degeneration (FTLD) & amyotrophic lateral sclerosis (ALS) disease spectrum

- **FTLD**
  - Progressive deterioration of frontal / anterior temporal lobes with heterogeneous pathological, clinical and genetic picture
  - The second most common presenile dementia after AD with progressive behavioral changes, language impairment and/or executive dysfunction
  - 40% of FTLD cases present measurable motor dysfunction, 15% is diagnosed with ALS

- **ALS (Lou Gehrig’s disease)**
  - The loss of motor neurons from brain and spinal cord leads to fatal respiratory paralysis within 1-5 yrs
  - 50% of ALS patients show functional impairment in frontal lobe tests; 15% is diagnosed with FTLD
Genetics of FTLD & ALS

● The number of genes discovered (> 20) and understanding their function is not proportionate

● Pure FTLD
  ○ MAPT (tau) and GRN (progranulin) mutations

● Middle ground
  ○ Mutations leading to cytoplasmatic accumulation/aggregation of RNA-binding proteins (TARDBP [TDP-43]), FUS [FUS/TLS]) and DNA hexanucleotid [G₄C₂] repeats (C9orf72)
    ■ C9orf72 the most frequent mutation in familial (FTLD [20%] & ALS [40%]) and sporadic (5-7%) cases
    ■ G₄C₂ repeats (up to 24 normal, from 700 → neurotoxicity)

● Pure ALS
  ○ SOD1 mutation

* FUS / TLS suppressor protein injected by viral vector inhibits paralysis / neurotoxicity in animal experiments
Circulatory disorders in the brain

- **Brain ischemia**
  - Global ischemia
    - Anemic form: cardiac standstill, circulatory collapse
    - Hyperemic form: venous circulatory obstruction (strangulation)
  - Focal ischemia
    - Narrowed brain vessels
    - Thrombosis / embolism, transient ischemic attack (TIA)

- **Brain hemorrhages**
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
  - Secondary hemorrhage of the ischemic part
1. Stroke: an acute episode of focal dysfunction of the brain, retina or spinal cord lasting longer than 24 hr, or of any duration if imaging (CT, MRI) or autopsy show focal infarction or hemorrhage relevant to the symptoms

  ○ Typical symptoms: sudden unilateral weakness, numbness or visual loss; diplopia; altered speech, ataxia; vertigo
  ○ Atypical symptoms: binocular blindness, amnesia, anosognosia, dysarthria, dysphagia, stridor, foreign accent or headache; hemiballismus*; altered consciousness

*Damage to the subthalamic nucleus; inhibitory GABAergic function decreases → contralateral involuntary flinging motions of the extremities
2. Transient ischemic attack (TIA)
   ○ A clinical syndrome characterized by an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours due to inadequate cerebral or ocular blood supply as a result of low blood flow, arterial thrombosis or embolism associated with diseases of the arteries, heart or blood. There is NO imaging evidence of infarction or hemorrhage. TIAs can predict an impending stroke
   ○ 1. Carotid system TIA
      ■ Unilateral weakness or sensory (aphasia, monocular vision loss) symptoms
   ○ 2. Vertebrobasilar system TIA
      ■ Bilateral weakness or sensory symptoms
         □ Diplopia, vertigo, ataxia without weakness
         □ Dysphagia only in combination; not as an isolated symptom
Classification/subtypes of stroke

- Pathological /pathophysiologic subtypes
  - Acute ischemic (occlusive) and hemorrhagic stroke

- Clinical stroke syndromes
  - Five major stroke syndromes
Pathological /pathophysiological subtypes

**Stroke**

- **Acute ischemic stroke** 85%
  - Cerebrovascular atherosclerosis 60%
    - Stenosis (flow reduction)
    - Ulcerated plaque (artery-to-artery emboli)
  - Penetrating artery disease (lacunes) 20%
    - Dissection, migraine, oral contraceptive use in smokers, meningovascular syphilis, cocaine and amphetamine use, associated with prothrombotic states
  - Cardiogenic embolism 15%
    - Atrial fibrillation
    - Acute MI
    - Rheumatic heart disease
    - Ventricular aneurysms
    - Artificial valve, other
- Other, unusual causes 5%
- **Acute hemorrhagic stroke** 15%
  - Intracerebral hemorrhage (10%)
  - Subarachnoid hemorrhage (5%)
Acute ischemic (occlusive) stroke

Causes of occlusion

Thrombosis – the most common type of stroke
Atherosclerosis, hypertension

Embolism
Blood clots (neck or heart and lodges in the cerebral artery), air bubbles, tumor fragments, fat particles
Development of acute ischemic stroke

6 hr

Infarct

Ischemic penumbra

12 hr

24 hr

Infarct
Lack of ATP, IC acidosis, tissue necrosis

The tissue damage partially reversible if circulation is restored within 3 hours

Isoelectric EEG, but some function may remain
Clinically neurological symptoms can be detected
Mechanism of ischemic cell death

Excitotoxicity
Inhibited glutamate re-uptake $\rightarrow$ NMDA/AMPA receptor binding $\rightarrow$ Ca influx $\uparrow$ $\rightarrow$ PL and protease activation $\rightarrow$ membrane degradation

Peri-infarct depolarization
Infarcted tissue expand at the expense of penumbra. Hypothermia, NMDA, glycin antagonists may $\downarrow$ ischemic lesion

Inflammation
Main inflammatory mediators: iNOS, COX-2, IL-1, MCP-1

Apoptosis
Mild ischemia may cause apoptosis only, however necroptosis is more frequent
Caspase-dependent apoptosis is confined to penumbra (caspase requires ATP)
Caspase-independent apoptosis can be induced by NMDA receptor activation
Other consequences of brain ischemia

- Ischemic penumbra
- No reflow (abnormal microcirculation)
  - Aggregation of blood cells
  - Endothelial swelling
  - Astroglial swelling around small vessels
- Reperfusion injury (oxidative and nitrosative stress)
  - Due to activated neutrophils
- Diaschisis
  - Decrease in blood flow away from the lesion
- Autoregulation does not work properly
- Ischemic neuronal damage, abnormal gene expression and development of ischemic brain edema (cytotoxic and vasogenic)
Treatment of acute ischemic stroke
• Endovascular thrombectomy of large artery occlusion
• Recombinant tissue plasminogen activator (rtPA) can be used for within 3-5 hours
• Benefits of aspirin in preventing early recurrence of ischemic stroke
Acute hemorrhagic stroke
1. Intracerebral hemorrhage
   ○ Bleeding deep into brain tissue
     – usually caused by chronic hypertension
   ○ Lobar hemorrhage (i.e. peripheral, not subcortical)
     ■ No past history of hypertension (amyloidosis, structural lesion to the vessels or anticoagulation)
     ■ APOE gene ε2 and ε4 forms

2. Subarachnoid hemorrhage
   ○ Blood around brain hemispheres
   ○ Usually caused by ruptured aneurysm
   ○ Surgical emergency
     ■ Cerebral angiography followed by aneurysmal clipping
   ○ Symptoms with sudden onset
     ■ Severe headache
     ■ May or may not have mental distortion
     ■ Seizures and stiff neck
     ■ Light intolerance, nausea, vomiting
Lacunar infarcts

Brain hemorrhage

Subarachnoid hemorrhage
• Major risk factors of stroke
  ○ Prior stroke or transient ischemic attacks
  ○ High blood pressure, hypercholesterolemia, carotid stenosis, atrial fibrillation (treatment shown to reduce the incidence of stroke)
  ○ Cigarette smoking, excessive alcohol use, insulin resistance, diabetes mellitus (likely causal risk factors)
Repetito est…
Anterior circulation system

Posterior circulation system
Five major stroke syndromes

- Anterior circulation syndromes (supplied by carotid artery)
  - 1. artery cerebri media (middle cerebral artery)
  - 2. aerteria carotis interna (internal carotid artery)
- 3. Posterior circulation syndromes (supplied by vertebral and basilar arteries)
- 4. Lacunar stroke syndromes
- 5. Watershed (or borderzone) infarcts (~5%)
  - Watershed infarcts involve the junction of distal regions of two arterial systems.
  - The clinical presentation is heterogeneous
Anterior circulation syndromes

The most frequently affected vessel during stroke

arteria cerebri media

arteria carotis interna

arteria cerebri anterior
Aphasia (loss of speech)

- The dominant cerebral hemisphere is the side that controls language function.

Signs: variable from mild to very severe (malignant stroke: brain edema, herniation)

- Contralateral hemiparesis, hemihypesthesia, hemianopsia
- Ipsilateral conjugated head and eye deviation ("patients look at lesion")

- Contralateral multimodal hemineglect (visual, motor, sensitive, spatial, auditory)
- Anosognosia (denial of illness)
- Anosodiaphoria (indifference to illness)
- Asomatognosia (lack of awareness of a part of one’s body)
2. Arteria carotis interna

- Embolic or progressive atherosclerotic occlusion of the vessel
- Embolic form is usually more severe
- Retinal ischemia from emboli can be transient (*amaurosis fugax*) or persistent
3. Posterior circulation syndromes

• Clinical symptoms:
  ○ Preceding TIAs and strokes, ipsilateral headache,
  ○ Dizziness, diplopia, dysarthria, dysphagia, dystaxia
• Dysconjugate, conjugate gaze, gaze palsy
  ○ Nystagmus (involuntary eye movement)
  ○ Bernard-Horner’s syndrome (myosis, mild ptosis of the upper and lower eyelid, and hemifacial anhydrosis)
- Hemi- or quadriplegia
- Sensory loss in hemibody or all 4 limbs
- Crossed signs (dropping eyelid and mouth on one side; body other side)
- Diplopia, conjugate or disconjugate gaze, gaze palsy, anisocoria
- Vertigo, tinnitus, unilateral deafness
- Nausea, vomiting

- Truncal gait ataxia
- Limb ataxia
- Nausea, vomiting
4. Lacunar stroke syndromes

- Chronic hypertension, diabetes, old age, smoking – risk factors
- Lacunes are small subcortical infarcts (< 1.5 cm) in perforator territories (capsula interna & externa, putamen, thalamus, brainstem)
- Motor and ataxic hemiparesis (lesion: contralateral capsula interna, thalamo-capsular region and pontine lesion)
- Sensory stroke (face, arm, leg numbness) (lesion: contralateral thalamus)
Cerebral edema

- An increase in brain volume due to an increase in the water content of the brain
- Major forms of cerebral edema
- 1. Vasogenic cerebral edema; EC edema – develops in white matter
  - Due to blood-brain barrier damage
    - Due to sudden increase in blood pressure (hypertension)
    - Protein-rich fluid enters into the brain tissue – with subsequent fluid movement (due to osmotic effect)
  - Due to cerebral vascular endothelial damage
    - Lead poisoning
2. Cytotoxic edema; IC edema – affects astrocytes & neurons; develops in the gray matter
   ○ Due to failure of ATP-dependent Na+ pumps (hypoxia, head trauma, cerebral circulatory problems, metabolic disturbances: hepatic failure; osmotic disturbance: hyponatremia) cell membrane damage develops
   ○ In the brain cells Ca, Na and H₂O ↑, EC fluid moves into cells – IC edema

Vasogenic and cytotoxic edema often occur together in head trauma and cerebral infarction

3. Interstitial edema
   ○ Due to liquor outflow damage (hydrocephalus)
   ○ Passive movement of CSF from the ventricles into the surrounding periventricular regions
Vasogenic cerebral edema

Energy deficiency

Cytotoxic edema

Interstitial edema
Consequences of cerebral edema
Increased intracranial pressure (herniation), decrease in cerebral blood flow and secondary brain damage
“Pain is a more terrible lord of mankind than even death itself.”
Albert Schweitzer (1931)

**Pain** defines as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective
### Classification of pain states

<table>
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<th></th>
<th>Acute pain</th>
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<tr>
<td><strong>Duration</strong></td>
<td>Chronic pain</td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
<td>Mild (1-3), moderate (4-5), severe (6-10) pain</td>
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<tr>
<td><strong>Anatomic source</strong></td>
<td>Somatic pain</td>
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<tr>
<td></td>
<td>Visceral pain</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Nociceptive pain (somatic or visceral)</td>
</tr>
<tr>
<td></td>
<td>Neuropathic pain (central or peripheral)</td>
</tr>
<tr>
<td></td>
<td>Mixed pain</td>
</tr>
<tr>
<td></td>
<td>Dysfunctional pain</td>
</tr>
<tr>
<td>Acute pain</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Protective sensation, processing of brief, noxious stimuli that resolves after successful intervention or healing</td>
<td>Pain that continues to last <strong>longer than 6 months</strong> despite treatment or healing; chronic pain serves no biologic purpose. Autonomic hyperactivity is rare; irritability, lack of energy and concentration, anxiety, insomnia, depression is frequent. Affects ~30% of adults worldwide</td>
</tr>
<tr>
<td>Onset usually sudden and related to an actual or impending tissue injury</td>
<td>Chronic pain results from altered neuronal activity</td>
</tr>
<tr>
<td>Displays predictable response caused by autonomic hyperactivity: tachycardia, tachypnea, increased peripheral blood flow and blood pressure; pallor, dilated pupils and diaphoresis</td>
<td>Peripheral sensitization: primary afferents (Aβ, δ &amp; C-fibers) become hyper excitable by inflammatory mediators</td>
</tr>
<tr>
<td></td>
<td>Central sensitization: reduction in the threshold of what is perceived as painful by the CNS</td>
</tr>
<tr>
<td></td>
<td>Types of chronic pain: inflammatory pain (chronic arthritis), cancer pain, headaches, lower back pain; neuropathic pain</td>
</tr>
</tbody>
</table>
Neuroinflammation in the spinal cord drives pain via neuron-glial interaction and central sensitization.

- Nerve & spinal cord injury
- Arthritis-induced inflammation
- Cancer

→
- Neuroinflammation in the spinal cord
- Infiltration & activation of immune cells and glial elements
- Release of pro-inflammatory mediators (chemokines, cytokines, growth factors, proteases, WNT ligands) and gliotransmitters (ATP, glutamate)

→
- Altered synaptic plasticity

←
- Chronic pain

- Central sensitization
- Anti-inflammatory mechanisms (IL-4,10, TGFβ, resolvins, protectins, lipoxins)
Major features of chronic pain

- **Hyperalgesia**: see inflammatory pain
- **Hyperesthesia**: increased sensitivity to stimulation
- **Allodynia**: pain triggered by a stimulus which does not normally provoke pain (light touch, puff of wind)
- **Dysesthesia**: an unpleasant sensation (throbbling, sharp), whether spontaneous or evoked
- **Paresthesia**: an abnormal sensation (tingling, itching), whether spontaneous or evoked
- **Hemiagnosia**: Inability to identify the source of the pain stimulus on one side of the body. Associated with stroke patients who have muscle paralysis and hypersensitivity to pain on the affected side.
- **Lancinating pain**: spontaneous or evoked pain with an “electric shock” like quality
- **Phantom pain**: If the neural pathway from amputated limb is stimulated along its pathway, the impulse travels to the CNS and allow the interpretation and perception of pain in the affected (amputated) limb
- **Myofascial pain**: injury to muscles and fascia
Acute, traumatic, nociceptive pain
## Nociceptive pain

Direct stimulation of peripheral nerve endings by noxious stimuli

<table>
<thead>
<tr>
<th>Somatic pain</th>
<th>Visceral pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superficial pain from cutaneous and subcutaneous tissues</strong></td>
<td>• Most viscera receives bilateral innervation and are innervated by two sets of afferent nerves (vagal &amp; spinal)</td>
</tr>
<tr>
<td>Skin alone: tingling, sharp, cutting or burning</td>
<td>• Visceral pain is a complex experience: diffuse, poorly localized, often referred to somatic regions (next slide)</td>
</tr>
<tr>
<td>Vessels involved: throbbing pain</td>
<td>Severity of pain doesn’t always reflect the disease severity (mild/no pain in colon cancer vs passing a stool or wind in IBS)</td>
</tr>
<tr>
<td><strong>Deep pain from muscles, tendons, ligaments, bones, joints and arteries. Pain is more diffuse and tends to radiate to adjacent areas</strong></td>
<td>• Develops due to internal organ dysfunction: abnormal stretching / flow obstruction → capsular/organ distension; spasm; traction or direct neural invasion of tumor; ischemia; inflammation</td>
</tr>
<tr>
<td>Joint: well localized, sharp or burning</td>
<td>• Associated with strong emotional reactions: vagal &amp; spinal activation of the anterior cingulate cortex</td>
</tr>
<tr>
<td>Bone: dull, aching or soreness</td>
<td>• Associated with exaggerated autonomic reactions: reflex spasm in abdominal wall (muscle guarding, <em>defance musculaire</em>), nausea, vomiting, sweating, blood pressure changes</td>
</tr>
<tr>
<td>Muscle: dull ache or cramp</td>
<td></td>
</tr>
</tbody>
</table>

Mechano-, thermo-, chem- prurireceptors and polymodal nociceptors

Mainly distension-sensitive nociceptors; lower density of other types of pain receptors
Referred pain: pain originating from one site in body but perceived as being localized at a different site
The area expressing the referred pain is supplied by the same spinal segment as the actual pain site
Referred pain is explained by convergence-projection theory
Two types of afferents (visceral afferents & skin/subcutaneous or muscle afferents) enter DRG segment and converge onto same sensory projection cells & the brain doesn’t know the actual source and projects to the somatic site
Neuropathic pain

Neuropathic pain: lesion or disease of the **somatosensory system**
- Affects 7-10% of the general population (more frequent in ♀ and age >50)
- Mechanisms: imbalances between excitatory/inhibitory somatosensory signaling → hyperexcitability
  - Alteration in ion channels (Na, Ca↑, K↓) & changes in second-order nociceptive neurons (nociceptive neurons activated by Aβ, δ & C afferents; convey enhanced sensory information to the CNS [central sensitization: ↑NMDA/AMPA ; loss of GABA-releasing interneurons])
  - Impaired inhibitory modulation of pain messages in the CNS
    - Decrease in inhibitory interneuron activity in the brain: anxiety, depression, sleep problems
    - Defective descending pain-control system
      - NA mediates conditioned pain modulation[CPM] (one painful stimulus inhibits another through descending pathways)
      - CPM lost/damaged (NA inhibition↓; 5-HT↑)
      - Temporal summation ↑(↑pain intensity upon repetitive identical nociceptive stimuli) due to central sensitization of ascending pain pathways
- Expectancy-induced analgesia (phenotyping neuropathic pain patients)
Central neuropathic pain
   Spinal cord injury (> 50% w pain), syringomyelgia, demyelinization (multiple sclerosis), *neuromyelitis optica*
   Post stroke pain

Peripheral neuropathic pain (A\ß,\δ & C fibers affected)
   Trigeminal (facial, intra-oral trigeminal territory), postherpetic (one/more dermatomes or ophthalmic trigeminal division [*r. ophthalmicus*]), ilioinguinal, genitofemoral neuralgia
   Infra- & supra orbital, occipital, intercostal, brachial, ulnar, femoral neuritis
   Painful diabetic, HIV-associated, chemotherapy-related polyneuropathy („glove and stocking” pain)
   *Meralgia paresthetica*: damage to the lateral femoral nerve
   *Cervical, lumbar radiculopathy* (innervation territory of the affected nerve root)
   Carpal tunnel syndrome
   Neuroma
   Inherited channelopathies (K or Na): erythromelalgia (episodic block of vessels w inflammation)
Comparison of nociceptive and neuropathic pain

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nociceptive pain</th>
<th>Neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Tissue or potential tissue damage</td>
<td>Nerve injury or peripheral /central sensitization</td>
</tr>
<tr>
<td>Descriptors</td>
<td>Throbbing, aching, pressure-like</td>
<td>Lancinating, shooting, electrical-like, stabbing</td>
</tr>
<tr>
<td>Sensory deficits</td>
<td>Infrequent</td>
<td>Frequent (numbness, tingling, pricking)</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>May have pain-induced weakness</td>
<td>Neurologic weakness may be present if motor nerve affected</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Uncommon except in the immediate area of an acute injury</td>
<td>Pain frequently evoked with non-painful (allodynia) or painful stimuli (hyperalgesia)</td>
</tr>
<tr>
<td>Radiation</td>
<td>Proximal radiation frequent</td>
<td>Distal radiation common</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>Less common, associated with activity</td>
<td>Common and unpredictable</td>
</tr>
<tr>
<td>Autonomic signs</td>
<td>Autonomic signs uncommon in chronic nociceptive pain</td>
<td>Color, temperature changes, swelling, or sudomotor activity in 1/3-½ of patients</td>
</tr>
</tbody>
</table>
Mixed pain
- Cancer pain (neuropathic drug-induced)
- Ischemic pain
- Low-back & neck pain
- Headache (cephalgia)

Dysfunctional pain
- Fibromyalgia, IBS: augmented sensory perception and altered central neurotransmission
Headache (cephalgia)

- Pain sensitive tissues
  - All extra cranial tissues (scalp, muscles, periosteum (etc)
  - Cranial and intracranial venous sinuses
  - Parts of dura at base of brain and arteries within dura
  - Trigeminal, facial, vagus and glossopharyngeal nerves
  - Cervical nerves C1 and C3

- Tentorium cerebelli divides cranium into supratentorial (2/3) and infratentorial (1/3) part
  - Supratentorial pain occurs in anterior portion of head (frontal and temporal)
  - Infratentorial structures refer pain to occipital area of head and neck
General mechanisms that seem responsible for evoking headache
- Distention or displacement of blood vessels
- Traction of blood vessels
- Contraction of head and neck muscles
- Stretching of periosteum
- Degeneration of upper cervical spine with compression of cervical nerve roots
- Deficiency of enkephalins
Common types & causes of headache

● Primary headache
  ○ Neurovascular-type headache
    ■ Migraine 16%
    ■ Cluster headache 0.1%
  ○ Tension-type headache 69%
  ○ Other

● Secondary headache
  ○ Systemic infection (fever) 63%
  ○ Head injury 4%
  ○ Other
Key structures involved in headaches:
1. Large intracranial vessels and dura mater innervated by
2. Peripheral terminals of trigeminal nerve
3. Trigemino-cervical complex: central terminals of trigeminal nucleus & dorsal horns of C1 and C2
1. Neurovascular-type headache

- Migraine
  - Unilateral dull ache and then throbbing or pulsating pain that may become bilateral
    - Frontal and temporal lobes – most frequent (trigeminal nociceptive afferents: ophthalmic divisions)
    - 2-4 attacks/month lasting for 1-2 days – most common
  - The trigemino-vascular system and its connections act as a feed forward system to facilitate attacks, the fundamental problem is in the brain
  - Neuroanatomical processing of vascular head pain:
    - Ophthalmic branch of trigeminal nerve → trigeminal ganglion → trigeminal nucleus → thalamus → cortex
    - Modulatory areas: midbrain (PAG), hypothalamus
○ Vascular headache involving vasodilatation and localized inflammation which sensitizes arteries to pain (CGRP and SP ↑)
○ Two types of migraineur
  ■ Migraine without aura – immediate onset of headache
    □ Multifactorial disease: genetic + environmental factors
  ■ Classic migraine: prodrome, aura, headache, postdrome
    □ Aura – due to cortical spreading depression & ionopathy: Na, Ca channel and ATP genes
    □ Aura is seen in ~ 30% of patients
Classic migraine

Phase 1 (The Prodrome): up to 24 hours prior to the headache
Roughly half of all migraine sufferers experience this stage, which is characterized by symptoms of heightened or dulled perception, irritability or withdrawal, and food cravings.

Phase 2 (The Aura): up to 1 hour prior to the headache
One out of five migraine sufferers experience this stage of visual disturbances. There may be flashing lights, shimmering zig-zag lines, and luminous blind spots, as well as non-visual sensations like numbness and pins and needles in the hands.

Phase 3 (The Headache): 4-72 hours long
Characterized by:
- Severe aching, often pulsating or throbbing pain on one or both sides of the head
- Intolerance of light (photophobia)
- Intolerance of noise (phonophobia)
- Nausea and vomiting
- Sensitivity to movement
- And less commonly, speech difficulties

Phase 4 (The Postdrome): up to 24 hours after the headache
Most migraine sufferers experience aching muscles and feel tired and drained after the headache, although some few go through a period of euphoria.
● Cluster headache
  ○ Onset: 2-3 hrs after falling asleep (REM sleep) lasting minutes to hours; recurrence for a few weeks or months then absent for years
    ■ PET changes: hypothalamus, cingulate & prefrontal cortex
  ○ Pain: constant, severe, non-throbbing unilateral and often retroorbital or side of head (the most painful human condition) with ipsilateral parasympathetic activation
  ○ Precipitating factors: alcohol, stress, change in climate, hay fever
  ○ Male : female=3 : 1
2. Tension-type headache

- Pathophysiology: incomplete
  - Sustained contraction of scalp, forehead and neck muscles accompanied by constriction of extracranial arteries
  - Primary disorder of CNS pain modulation
- Pain: band-like tightness around head and tenderness in occipito-cervical area
- Very common – 69%
  - Episodic form
    - Associated with temporary stress, anxiety or fatigue
  - Chronic type
    - Lasts from months to years
    - Often associated with anxiety, depression and repressed feelings
    - More common in women
Seizures and epilepsy

- Epilepsy: Chronic neurological disorder characterized by recurrent, transient and unpredictable seizures; followed by impaired consciousness. The 2nd most common neurologic disorder after cerebrovascular accident
  - Most seizures begin at an epileptogenic focus
    - The epileptogenic focus: Group of abnormal neurons (neurons in cortex – pyramidal cells [PC] or hippocampus) that spontaneously depolarize
      - Epileptogenetic activity at the cellular level determined by balance of excitatory and inhibitory activity. Increase in excitatory activity or a decrease in inhibitory activity can lead to massive, rapid firing of PCs
Axons project to basal ganglia, cerebellum, brain stem and spinal cord
Hippocampal PCs fire bursts of action potentials and then remain susceptible to subsequent activation for a brief period
  ○ The activation of epileptogenic focus may recruit normal neurons → propagation
  ○ Seizures are associated with abnormal
    ■ Motor activity (convulsion)
      □ Episode of widespread motor activity - May or may not be associated with loss of consciousness
      □ Can be limited – partial seizure
      □ If broader recruitment – generalized seizure
      □ Focal seizures can spread in seconds or minutes and become a secondary generalized seizure
    ■ Sensory activity - abnormalities of sensation of mental function (sensory seizure)
    ■ Autonomic activity
    ■ Psychic activity
Mechanism

- Abnormal voltage-operated channels
- Abnormal receptor-operated channels
- Alterations in extracellular ionic environment
- Recruitment of normal neurons via anatomical circuits

Steps in seizure

- Focal epileptogenesis
- Synchronization
- Propagation

Seizure Sequence
Patterns of seizure activity

- Epileptic seizures have relatively predictable pattern
  - Prodrome – set of symptoms that warns of seizure’s approach minutes, hours or days prior
  - Aura – as seizure begins
    - Mental, sensory or motor phenomena that person later remembers
    - Aura and first observable characteristics useful in pinpointing area(s) where seizure initiated
  - Seizure – a set of sensory, mental and/or motor activities
    - Fairly consistent for given individual
    - Persist for fairly constant period and then resolve
  - Post seizure state – differs for each person and seizure type
Epileptic seizure foci

● Motor cortex
  ○ Movements on contra lateral side according to the somatotopic location of the seizure focus

● Somatosensory cortex
  ○ Epileptic aura in which a sensation is experienced

● Visual cortex
  ○ Visual aura (scintillations, colors)

● Auditory cortex
  ○ Auditory aura (humming, buzzing, and ringing)

● Vestibular cortex
  ○ Feeling of spinning

● Temporal lobe
  ○ Complex behaviors

● Olfactory cortex
  ○ Malodorous aura

● Hippocampus – particularly susceptible and a frequent source of epileptic activity
Aura
Complex partial seizure
Generalized seizure
Normal EEG

Tonic convulsion

Clonic convulsion

amplitude

frequency

$\alpha$ 8-12Hz

$\beta$ 12-30Hz
Neurobiology and pathophysiology of addiction
Occasional use of abusable drug
Frequent user (binge drinking: 4-5 drinks within 2 hours)
Substance abuse/dependence
Addiction / dependence: a compulsive behavior that is harmful to the individual and its environment
Continuous urge to perform a certain behavior (drug taking, eating, gambling, theft, sex, exercise, religion ..)
Development of tolerance
Unsuccessful attempts to quit; repeated relapses
Withdrawal symptoms: physical and psychological symptoms
Changes in intrinsic values (personality changes: the subject is over valued)
Development of pathological conditions: physical and mental illness

Forms of addiction: chemical addictions (harmful drug use) and behavioral addictions (harmful behavior)

Chemical addiction / psychoactive substance dependence / drug addiction
Psychoactive drugs / drugs: natural or synthetic substances which can alter the CNS functions acutely or chronically
Drugs: agents are mainly of plant origin (rarely animal). In Hungary, drugs are considered as illegal psychoactive substances (kábítószerek); alcohol and cigarettes are not drugs.
Drug abuse: the drug is taken by the user (excessively, for non-medical purposes, user-specified ways)
Long-term abuse leads to chronic damage
Simultaneous abuse
Nicotine + alcohol, alcohol + heroin, heroin + barbiturates, heroin & cocaine, benzodiazepines + cocaine
Brain reward system

Rewards
Natural rewards: Social bond, food, sex
Drugs of abuse: “hijack reward system”; activate reward system far more strongly and persistently than natural rewards
Parts of the brain reward system

1. Ventral tegmental area (VTA)
   Located in the midbrain; part of the meso-cortico-limbic dopaminergic (DA) system;
   DA terminals to: nucleus accumbens (NAcc), prefrontal cortex (PFC) and amygdala

2. Nucleus accumbens (part of ventral striatum)
   Dopaminergic input from VTA
   - DA is important in reward attribution, associative learning and conditioning (hard-wiring of addiction, relapse)
   - DA release is regulated directly and indirectly by other neurotransmitters (serotonin, GABA, glutamate, and endogenous opioids & cannabinoids)

Glutamatergic innervations from three areas
   - Hippocampus (declarative memory, the memory of persons, places, or things). With the help of amygdala, it establishes drug-related memories (important in relapse)
   - Basolateral amygdala (conditioned learning with emotional context) it associates environmental cues with emotional context (rewarding, neutral or aversive experience), for example, remembering what accompanied finding food or fleeing a predator. It also interacts with the VTA-NAcc DA pathway
   - Prefrontal cortex [PFC], (decision making, executive control „what we want“) control impulses from PFC are integrated in the medium spiny neurons of NAcc (plasticity) and in the striatum
In the early stages of addiction the NAcc shell plays an important role:
Functions connected to the limbic system (emotion, motivation)
   Incentive phase, DA is released at this stage followed by enjoyment (gratification stage) produced by endogenous opioids
At a later stage of addiction the role of the core portion is more important
   Integration of motor functions (relapse)
3. PFC is the most complex and the least known area
   • Orbitofrontal cortex (OFC)
     Rapid changes in behavior, comparing experiences
     Lesion: it is difficult to learn if an impulse is followed by reward or punishment
   • Ventromedial prefrontal cortex (vmPFC)
     Risky decisions
     Lesion: a social and emotional behavior deteriorates, memory and language difficulties, but executive functions are intact
   • Anterior cingulate cortex (ACC)
     Analysis of conflicting processes; regulation of the reward response
     Enhanced activity: “something is not right” feeling
Addiction is a chronic relapsing brain disorder

1. Intoxication (impaired self-awareness) and loss of control in limiting intake (binging)
   - Activation of brain reward system (ventral striatum [n accumbens], extended amygdala and its networks)
   - Desensitization of specific neurochemical mechanisms (dopamine, opioids, GABA, endocannabinoids) in the brain reward system

2. Emergence of negative emotional state (withdrawal)
   - Activation of brain stress system (CRF, NE) and dysregulation of the brain anti-stress system (NPY)

3. Compulsion to seek and take drugs (craving)
   - Altered reward set point is maintained by changes in the reward and stress system
Intoxiation/binge / Addiction is a reward deficit disorder

Meso-cortico-limbic DA system and its terminals in the ventral striatum are involved in the positive reinforcing effects, to drive goal-oriented behavior or activation in general.

Major transmitters: dopamine (increased assignment of incentive salience to drug-associated environmental cues) and opioid peptides.

Upon repeated exposure the transmitters are depleted (negative hedonic effects):
- DA↓ dysphoria;
- opiates↓ pain;
- serotonin↓ dysphoria;
- GABA↓ anxiety, panic attacks.

Euphoria, reward (ventral striatum [VS], including n accumbens)
Habits, perseverations (dorsal striatum [DS], glubus pallidus [GP], thalamus [Thal])
<table>
<thead>
<tr>
<th>Drugs of abuse</th>
<th>Neurotransmitters</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine and amphetamines</td>
<td>Dopamine (\gamma)-aminobutyric acid (GABA)</td>
<td>Nucleus accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Dopamine (\gamma)-aminobutyric acid (GABA)</td>
<td>Nucleus accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Opioid peptides</td>
<td>Ventral tegmental area</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Dopamine (\gamma)-aminobutyric acid (GABA)</td>
<td>Nucleus accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Opioid peptides</td>
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</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>Ventral tegmental area</td>
</tr>
<tr>
<td></td>
<td>Endocannabinoids</td>
<td>Nucleus accumbens Amygdala</td>
</tr>
<tr>
<td>(\Delta^9)-tetrahydrocannabinol</td>
<td>Endocannabinoids</td>
<td>Ventral tegmental area</td>
</tr>
<tr>
<td></td>
<td>Opioid peptides</td>
<td>Nucleus accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>Ventral tegmental area</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Dopamine (\gamma)-aminobutyric acid (GABA)</td>
<td>Nucleus accumbens Amygdala</td>
</tr>
<tr>
<td></td>
<td>Opioid peptides</td>
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</tr>
<tr>
<td></td>
<td>Endocannabinoids</td>
<td>Ventral tegmental area</td>
</tr>
</tbody>
</table>
Acute effect
Opioids → µ opiate receptors → activation of G-protein-dependent K channels↑, AC↓ → cell hyperpolarization & inhibition of GABA release in VTA (inhibition of DA ↓) → euphoria due to increased DA release

Withdrawal
VTA DA neurons inhibited due to increased GABA release → withdrawal signs

Neuroadaptation
µ opioid receptor degradation↑, AC activity ↑ GABA release ↑; euphoric effect ↓
Effect of acute ethanol consumption
- Increased efficacy of GABA on its receptors → intoxication, relaxation
- Increased dopamine (DA)/serotonin (5-HT) level (joy of being drunk)
- Decreased glutamate release in N. accumbens & amygdala
- Decreased glutamate effect on NMDA receptors, ↓ Ca$^{2+}$ influx to the cells → analgesia, amnesia, intoxication

Ethanol withdrawal
- GABA: anxiety, seizures
- NMDA: dysphoria, hallucinations
- Ca$^{2+}$ channel: Ca-mediated excitotoxicity, seizures

Withdrawal syndrome „Delirium tremens“
- Insomnia, tremors, increased reflexes, weakness, anorexia, orthostatic hypotension, sweating
- Delirium: auditory and visual hallucinations; disorientation, paranoid delusions, seizures „status epilepticus“
- Dehydration, heart failure → death

Neuroadaptation
- Changes in GABA receptor subunits
- Increased L-type Ca$^{2+}$ channel synthesis & membrane exposure

Hangover – „mild withdrawal“ (headache, dehydration)

Development of tolerance
Physical and psychological dependence
Acute effects
NE, DA and mild 5-HT release
Impaired DA and 5-HT synaptic re-uptake.
Later, activation of DA$_2$ receptors: DA synthesis ↓

Withdrawal
Decreased transmitter synthesis and increased clearance from the synaptic cleft due DA transporters ↑.
Fatigue, dysphoria and anhedonia (inability to feel pleasure) develops

Neuroadaptation
Increased amount of DA transporters and reduced amount of postsynaptic DA receptors
Tolerance develops to the euphoric effect
Withdrawal/negative-affect stage / Addiction is a stress surfeit disorder

Neuronal systems implicated in the positive reinforcing effects are depleted
Stress system is over-active during withdrawal and protracted abstinence
CFR system is activated during withdrawal
  Withdrawal signs can be ameliorated by injecting CRF or kappa opiate antagonists
  The effect of extrahypothalamic CRF becomes stronger and the hypothalamic weaker during withdrawal

Decreased reward (ventral striatum [VS], including n accumbens)
Malaise, dysphoria, negative feelings
(amygdala [AMG], bed nucleus of the stria terminalis [BNST])
Subjective effects of craving, executive function (anterior cingulate [AC], medial-prefrontal [mPFC], and orbitofrontal [OFC] cortex)
Conditioned cues (basolateral n of the amygdala)
Conditioned contextual cues (hippocampus [Hippo])

**Craving / Addiction is self-regulatory disorder**

Mainly dependent upon cortical brain circuits using glutamate neurotransmission
Decreased activity of the reward and PFC circuits
Compulsive drug seeking involves dorsal-striatal, dorsal-pallidal, thalamo-cortical networks
Brain stress system stays active
Dopamine receptors (D2) are lower in addiction

- Cocaine
- Methamphetamine
- Alcohol
- Heroin

Control  Addicted
Long-term alterations in metabolic demand and dopamine activity in the cocaine abuser’s brain
During intoxication, drug-induced activation of the brain’s reward regions (in blue) is enhanced by conditioned cues in areas of increased sensitization (in green). During withdrawal, the activation of brain regions involved in emotions (in pink) results in negative mood and enhanced sensitivity to stress. During preoccupation, the decreased function of the prefrontal cortex leads to an inability to balance the strong desire for the drug with the will to abstain, which triggers relapse and reinitiates the cycle of addiction.

The compromised neurocircuitry reflects the disruption of the dopamine and glutamate systems and the stress-control systems of the brain, which are affected by corticotropin-releasing factor and dynorphin. The behaviors during the three stages of addiction change as a person transitions from drug experimentation to addiction as a function of the progressive neuroadaptations that occur in

Addiction cycle

Genetic contribution to risk for addiction ~ 50%
Environmental factors
Stress (childhood abuse, separation, isolation)
Conditioning

Intoxication
Acute reinforcement/limited access

Bingeing
Rewarding effect

Dependence
Neuroadaptation

Withdrawal
Dysphoria, irritability, anxiety

Crawling

Relapse