*Seminarhold d. 23. februar 2015*

# Transmittersystemer II
# Dopaminsystemet

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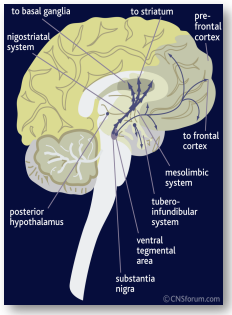
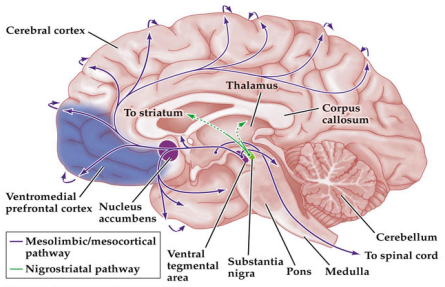





## Dopamin-systemet




*PRINCIPLES OF COGNITIVE NEUROSCIENCE 2e*, Figure 14.3
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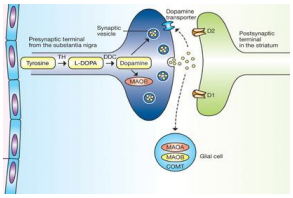
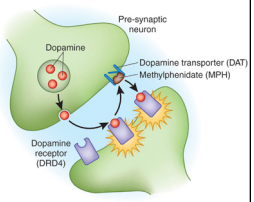
## Dopaminsynapsen




Nedbrydning (bl.a.)
- COMT: Catechol-O-methyl transferase
- DAT: Dopamine transporter

*Neuropsychopharmacology* (2010) **35**, 278–300; doi:10.1038/npp.2009.120





## Parkinsons sygdom

Gowers, 1878

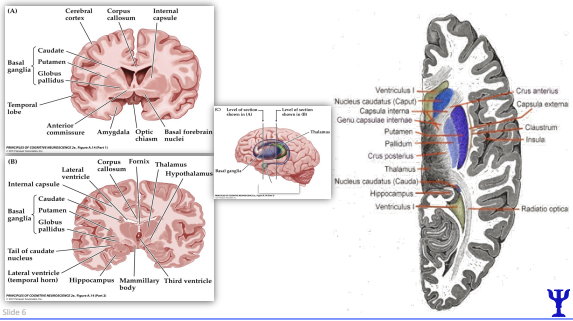
- Akinesi
- Rigiditet
- Hviletremor
- Postural instabilitet



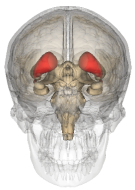


## ADHD

## Basalganglierne



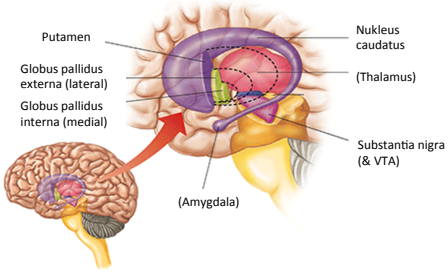
# Nucleus caudatus







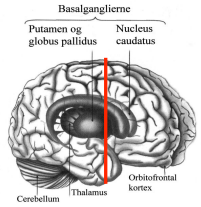
# Basalganglierne








# Striatum



Dorsale striatum
= caudatus og putamen

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Ventrale striatum
= nucleus accumbens

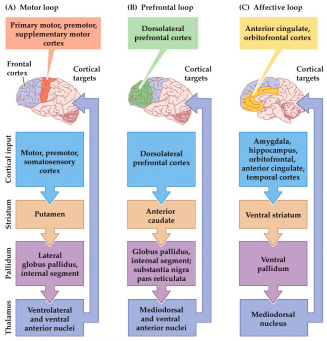




Frontostriatale kredsløb

Motoriske frontostriatale kredsløb - læsion giver mangel på bevægelser: akinesi

Limbiske frontostriatale kredsløb - læsion giver mangel på motivation: apati




PRINCIPLES OF COGNITIVE NEUROSCIENCE 2e, Figure 13.7
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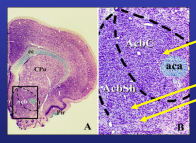
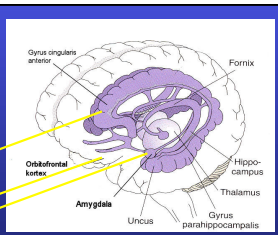
# Nucleus accumbens input




Det limbiske system - hjernens emotionssystem

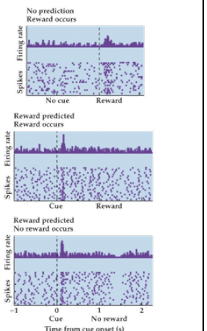
VTA
(dopamin)
("forstærker-signal")

.. Affektiv overbevisning om, hvad der er *"virkeligt, sandt og vigtigt"* MacLean, 1970



Dopamin
– forudsigelse og belønning

Aktivitet i midthjernens (VTA) dopaminerge neuroner (Schultz et al., 1997)

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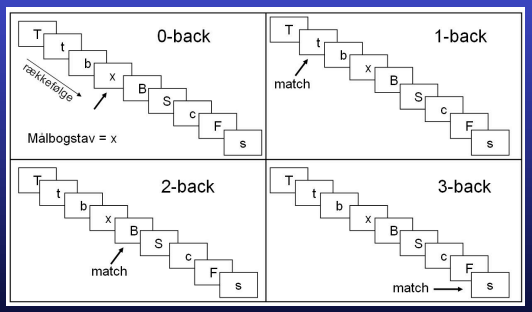
## Arbejdshukommelse - N-back opgaven






## COMT (catechol-O-methyltransferase)

- **Catechol-*O*-methyltransferase** (**COMT**) er et enzym, som nedbryder katekolaminerne dopamin, noradrenalin og adrenalin
- Mængden og effektiviteten af COMT påvirker således hvor meget de pågældende katekolaminer kan influere på den postsynaptiske celle
- COMT er særlig vigtig for reguleringen af dopamin i hjerneopråder, hvor dopamin transporteren (DAT) ikke forekommer i store mængder og derfor ikke kan regulere mængden af tilgængelig dopamin - fx i præfrontal kortex
- Hos mennesker koder COMT genet for COMT proteinet

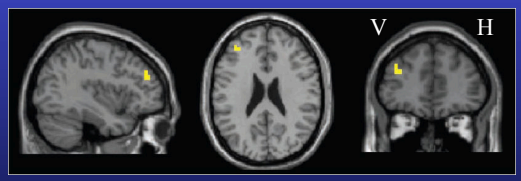


## COMT genet: Val$^{158}$Met polymorfismen

- En funktionel SNP (single-nucleotide polymorphism) i COMT genet, som resulterer i en punktmutation (udskiftning af et enkelt basepar: A → G) ved position 158
- Udskiftningen medfører, at det ikke er aminosyren valin (Val, codon: GUG) som indgår i proteinet, men derimod aminosyren methionin (Met, codon: AUG)
- Val varianten af COMT nedbryder dopamin op til fire gange hurtigere end Met varianten
- Met variantens lavere nedbrydningsrate medfører højere synaptisk dopamin-niveau og dermed en større dopaminerg stimulation af den post-synaptiske celle

## Dextroamfetamin, COMT-varianter og arbejdshukommelse

(N: 25: 9 val/val; 10 val/met; 6 met/met – matchede)



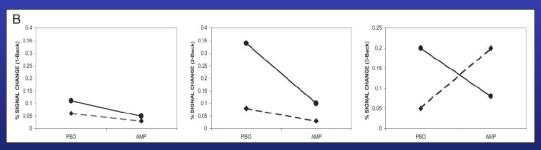

(Gruppeanalyse: COMT x medicin interaktion i fMRI)

Mattay et al. (2003). *PNAS, 100*: 6186-91
#a957g

## Dextroamfetamin, COMT-varianter og arbejdshukommelse

BOLD-ændring i venstre PFC ved

1-back 2-back 3-back




Val/val

Met/met

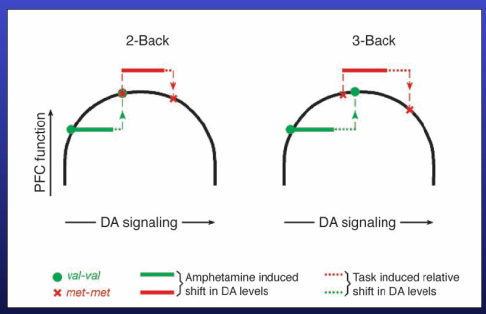
Kortere RT; uændret antal fejl

Længere RT; flere fejl

Mattay et al. (2003). *PNAS 100*: 6186-91
#a957g

Gade

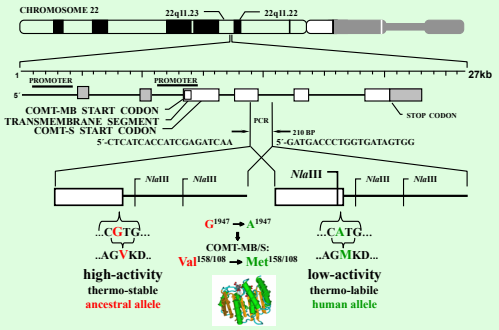
## Dextroamfetamin, COMT-varianter og arbejdshukommelse



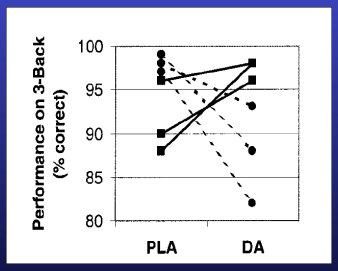

Mattay et al. (2003). *PNAS 100*: 6186-91
#a957g (also Arnsten 2007, #a376c; Diamond, 2007, #a376b)

Gade

## The COMT Gene




## Dextroamfetamin og arbejdshukommelsens effektivitet: Individuelle baseline forskelle




Performance ved Baseline (placebo):

Høj

Lav

Mattay et al. (2000). *NeuroImage 12*: 268-275

#a957g