Mechanism of Antipsychotic Action

Specific role of 5-HT2 and NMDA receptors

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Possible conflict of interest

- Speakers fee from Servier
- Unrestricted research grant from Servier

Structure and function of the forebrain

- Cortical regions for analysis and response
  - Posterior brain for processing input
  - Anterior brain for generating output
  - Temporal lobe for regulating input to output

- Subcortical and brainstem structures
  - Extrapyramidal structures regulating magnitude and velocity
  - Ascending activating systems regulating awareness and consciousness
  - Ascending brain stem structures regulating alertness and response readiness

Site of Action of Antipsychotics

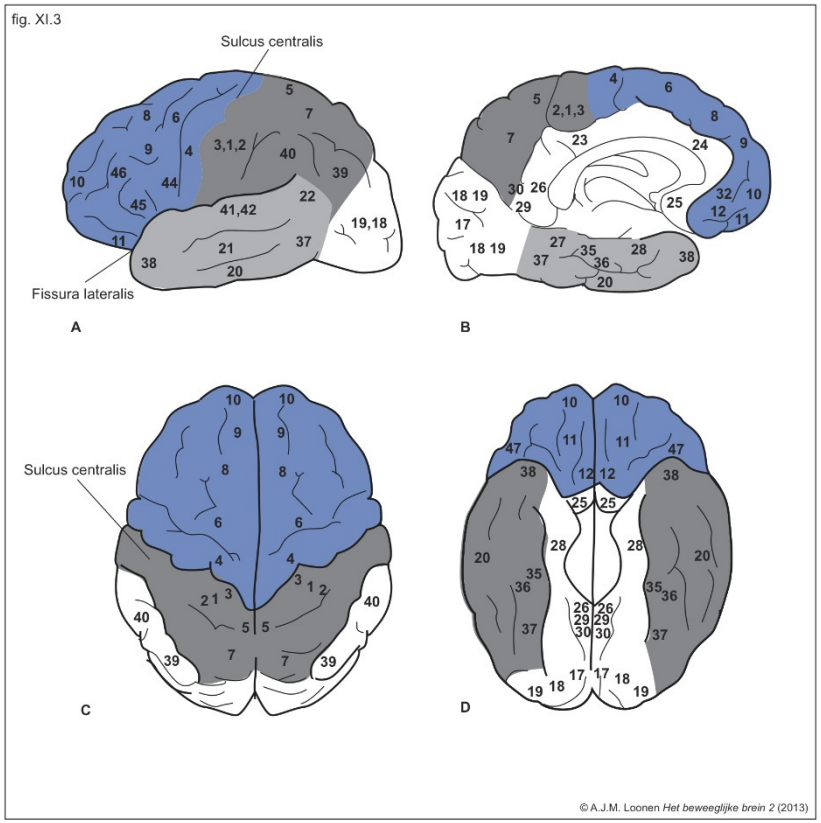
- Extrapyramidal circuits
  - Caudate: antimanic activity
  - Putamen: Parkinsonism, dystonia, dyskinesia
  - Accumbens: Anti-agitation, akathisia
- Temporal lobe
  - Hippocampal complex: anti-hallucinatory
  - Amygdaloidal complex: anti-delusional
- Prefrontal cortex
  - Combating negative and cognitive symptoms

Neurotransmitter systems involved

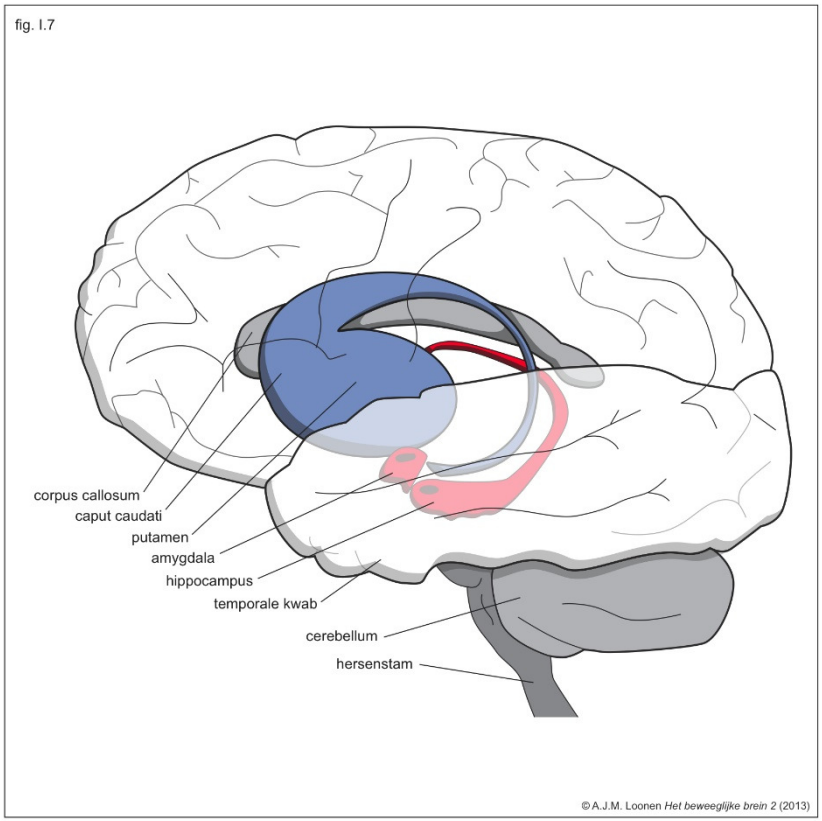
- Extrapyramidal systems
  - Glutamate and GABA serially connected
  - Dopamine, norepinephrine and serotonin
- Temporal lobe
  - Glutamate serially connected
  - GABA interneurons
  - Dopamine
- Prefrontal cortex
  - Glutamate serially connected
  - GABA interneurons
  - Dopamine, norepinephrine and serotonin

Structure of the forebrain

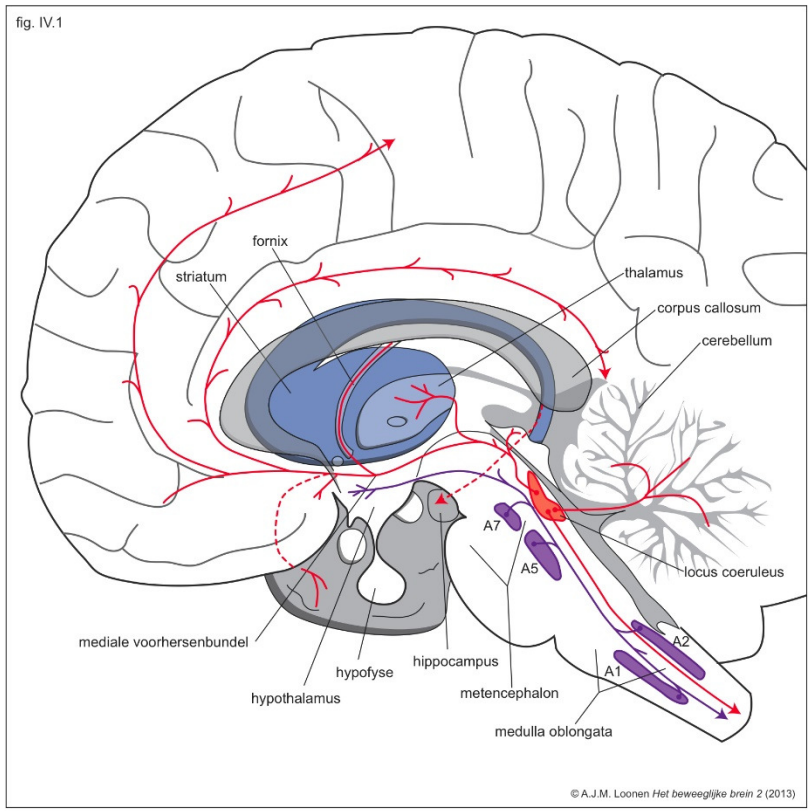
The outer component



The inner component

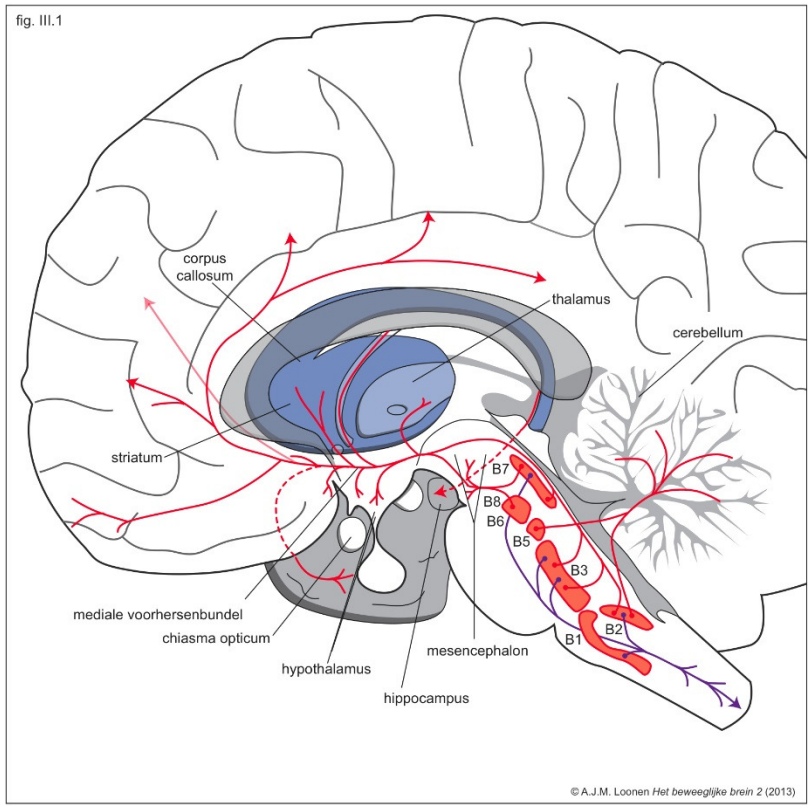


The adrenergic influence on the forebrain



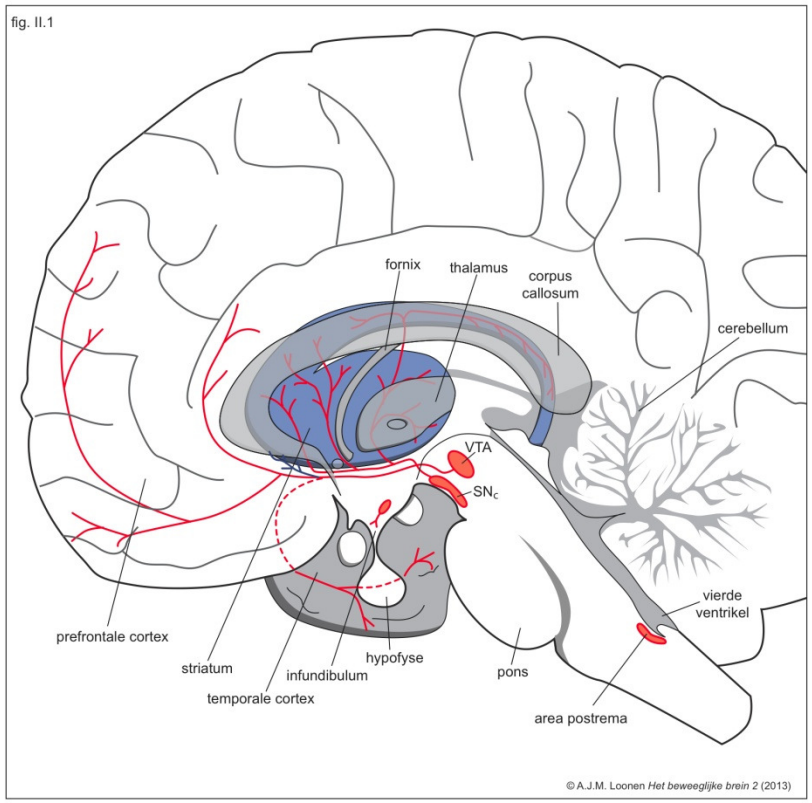
- Autonomic nuclei
  - Hypothalamus
- Locus coeruleus complex
  - Basal forebrain
  - Anterior cortex

The serotonergic influence on the forebrain



- Rostral raphe nuclei
  - Basal forebrain
  - Basal ganglia
  - Temporal lobe
  - Frontal cortex
- Caudal raphe nuclei
  - Cerebellum
  - Spinal cord

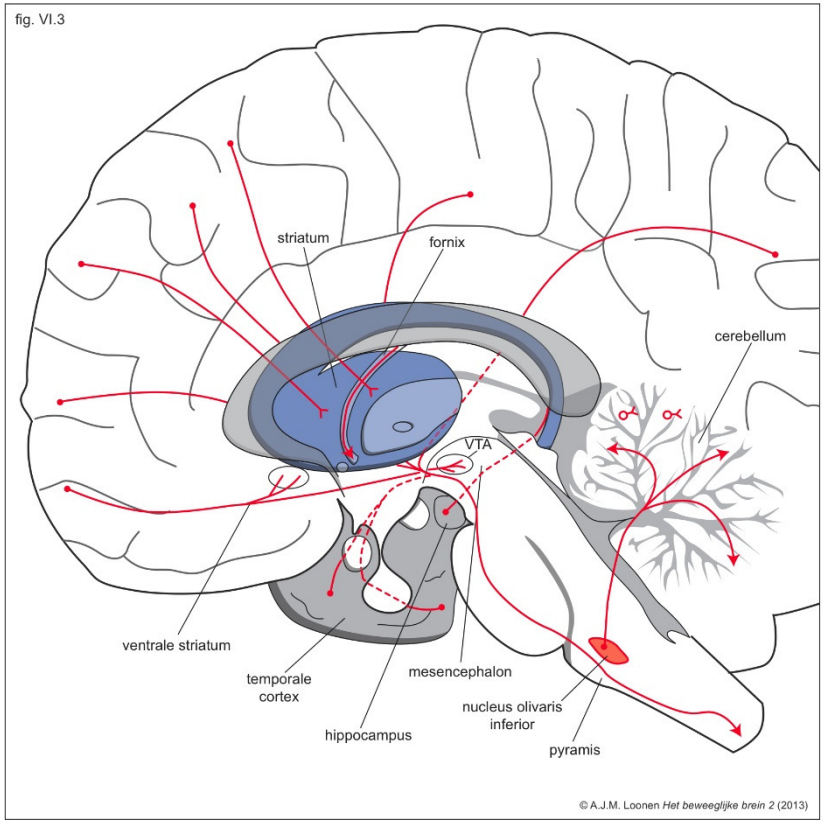
The dopaminergic influence on the forebrain



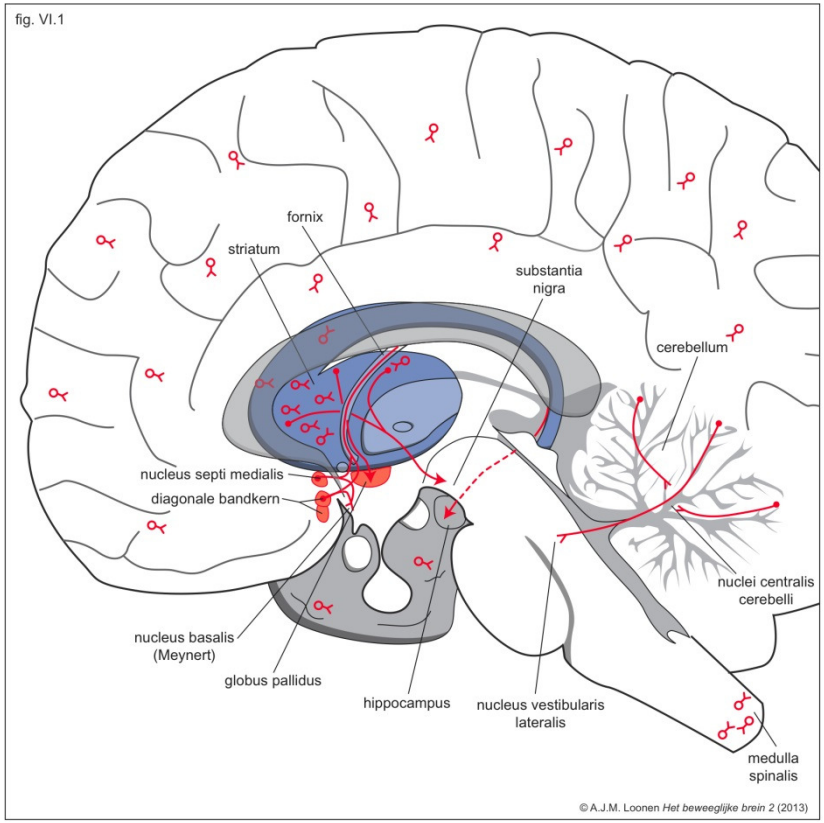
- Ventrale Tegmental Area (VTA)
  - Basal ganglia
  - Frontal cortex
  - Temporal lobe
- Substantia nigra pars compacta (SNc)
  - Basal ganglia
- Area postrema
- Infundibilum

The main players within the forebrain

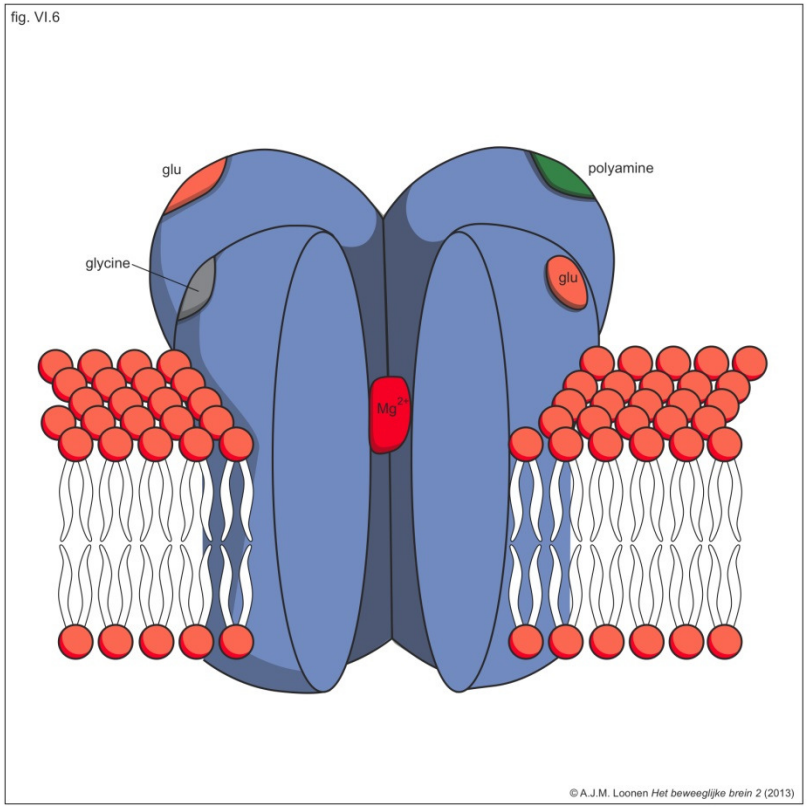
Glutamate



GABA



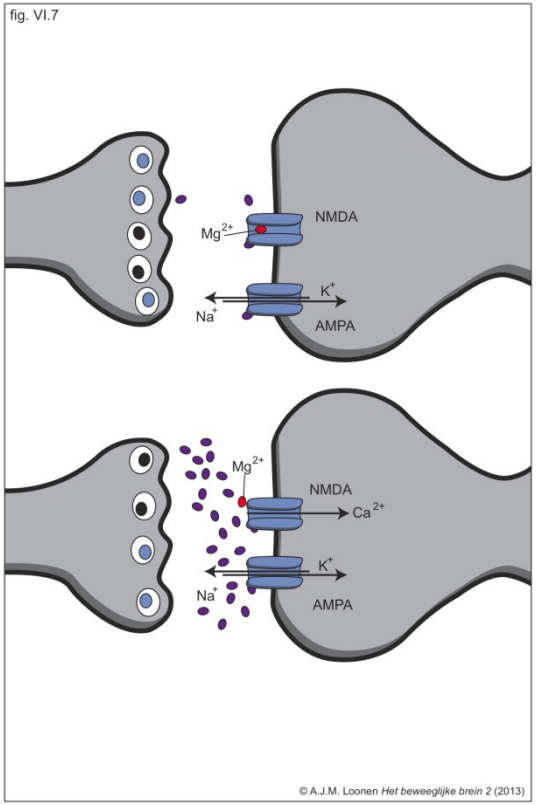
Glutamatergic neurotransmission



› Ionotropic receptors
  - AMPA
  - NMDA

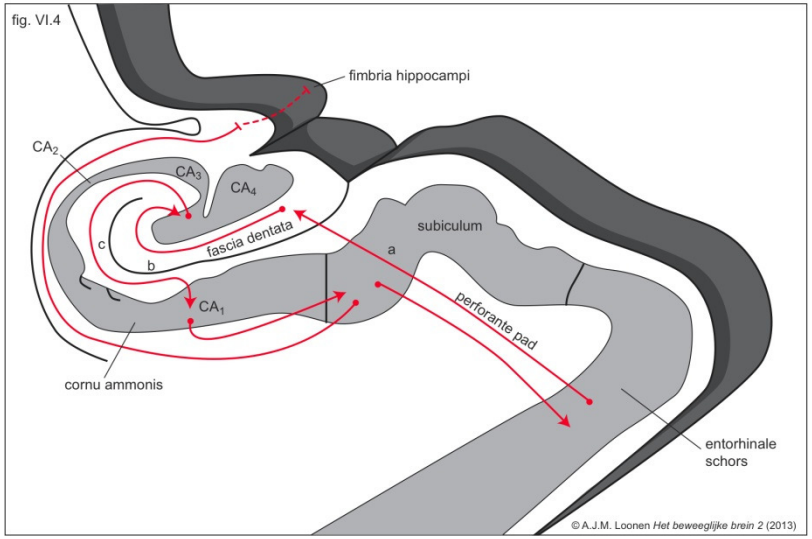
› Metabotropic receptors
  - mGlu receptors

Long-term potentiation (LTP)



- Normal acivation
  - AMPA receptors
    - Na & K flux
- Strong activation
  - AMPA receptors
  - NMDA receptors
    - Also Ca flux

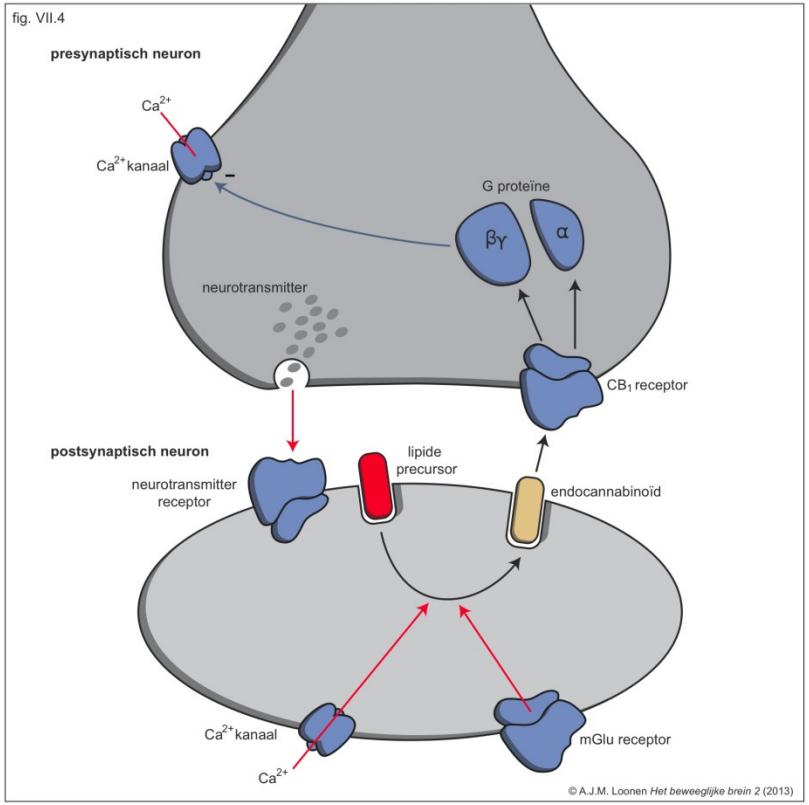
Long-term potentiation (LTP) in hippocampus



- Converging fibers
- Concomitant activity

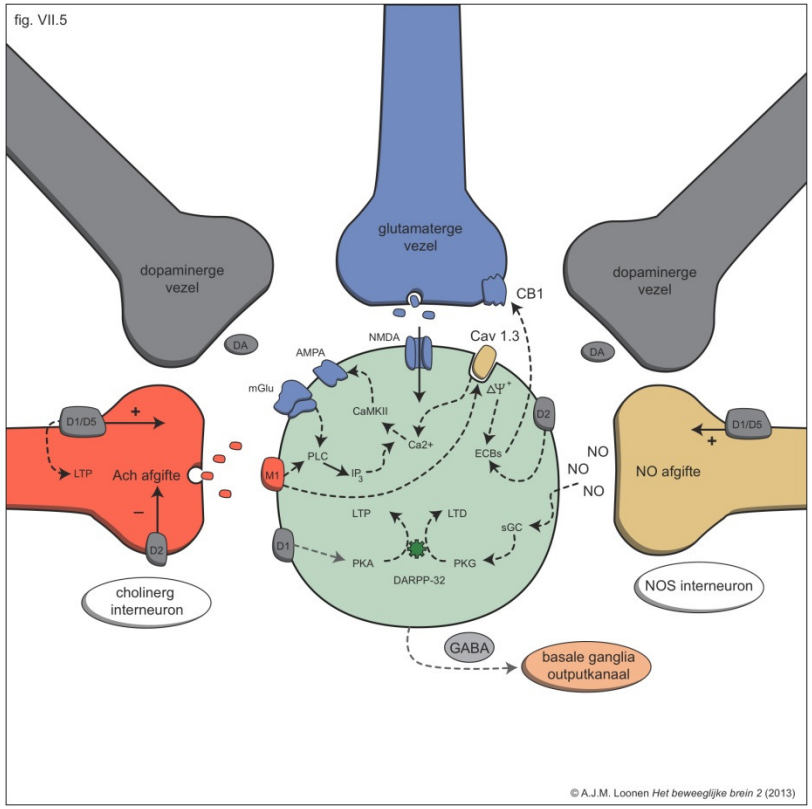
- Increased sensitivity
- Preferred tracks

Long-term depression (LTD)



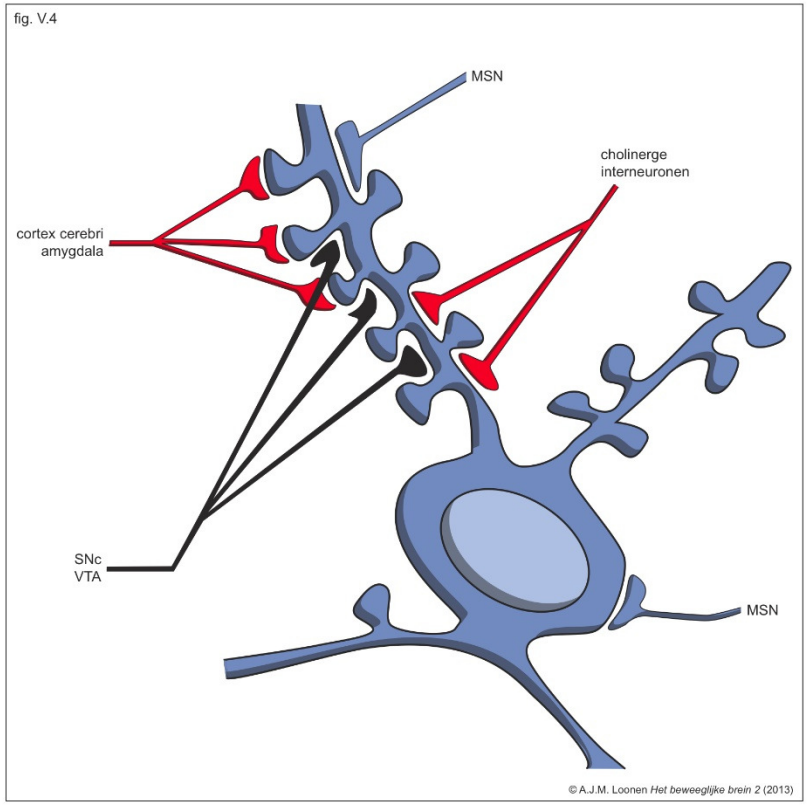
- Postsynaptic activity
- Synthesis endocannabinoid
- Release endocannabinoid
- Stimulation CB1R
  - Presynaptic receptor
  - G-protein activation
- Blocking Ca influx
- LTD of presynaptic activity

Long-term depression in corticostriatal synapses



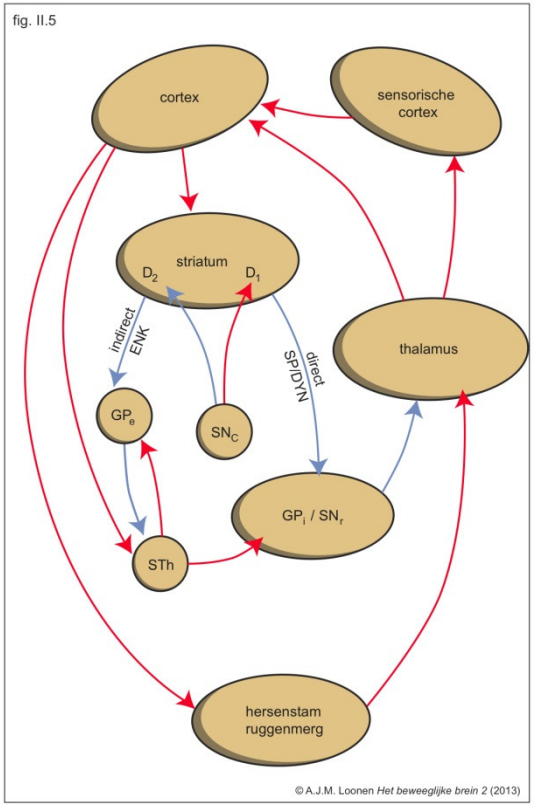
- Glutamatergic synapse
- Activation DRD2 & CHRM1
- Endocannabinoid pathway
- LTD of glutamatergic synapse

Corticostriatal connections



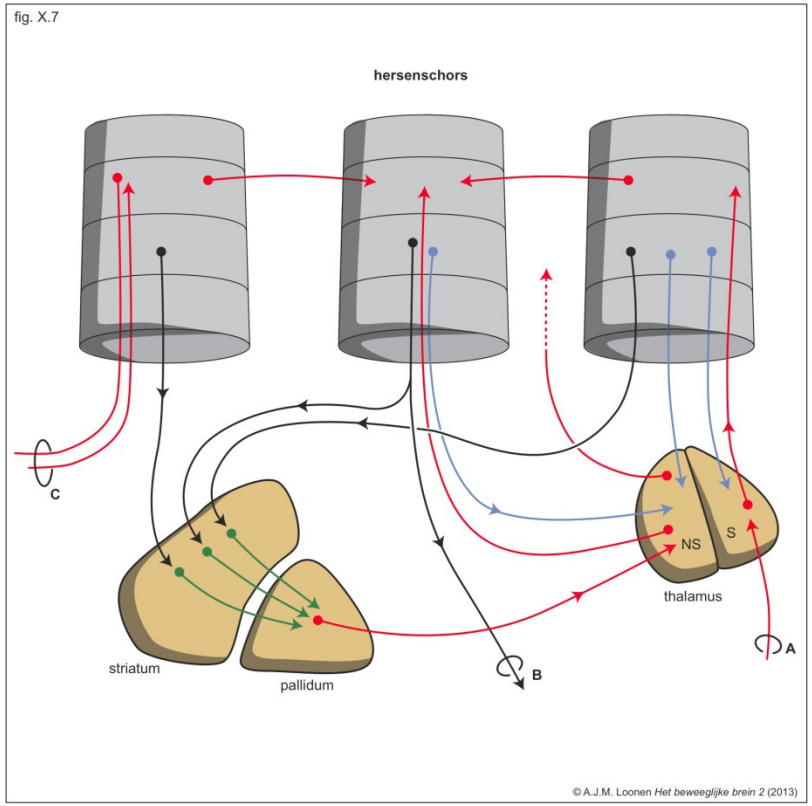
- Medium Spiny Neurons (MSN)
- Input:
  - Glutamatergic fibers (Ctx)
  - Dopaminergic fibers (SNc)
  - GABAergic interneurons
  - Cholinergic interneurons
- Output:
  - Globus pallidus (Gpe/Gpi)
  - Substantia nigra, pars reticulata (SNr)

Learning by LTP and LTD



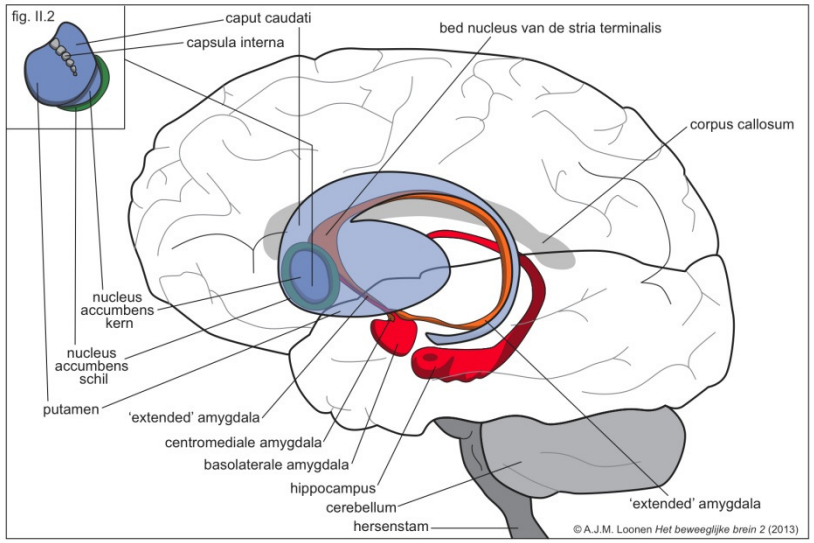
- Medium Sized Neurons
  - Direct pathway
    - Stimulates cortical endpoint
  - Indirect pathway
    - Inhibits cortical endpoint

Learning in cycles



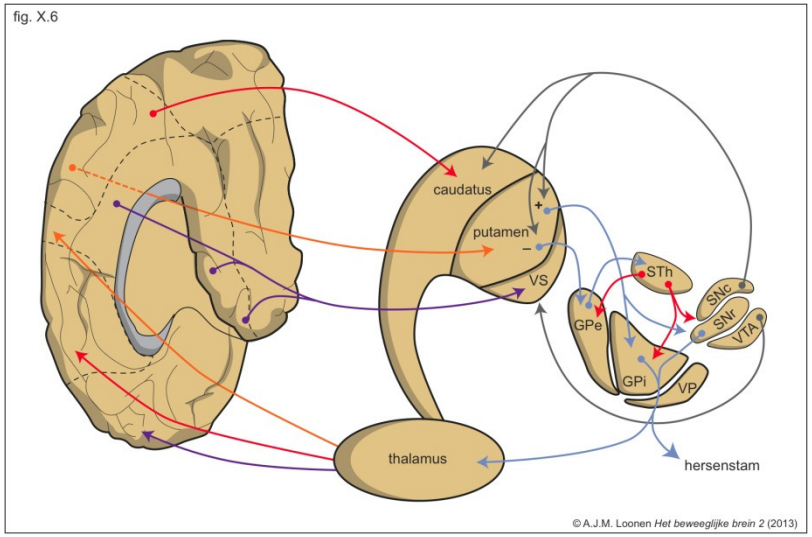
- Intracortical connections
  - Serial connections
  - Connecting many areas
  - Programming output
- Infracortical connections
  - Parallel connections
  - Connecting same areas
  - Adaptation of output

Position of basal ganglia within the forebrain



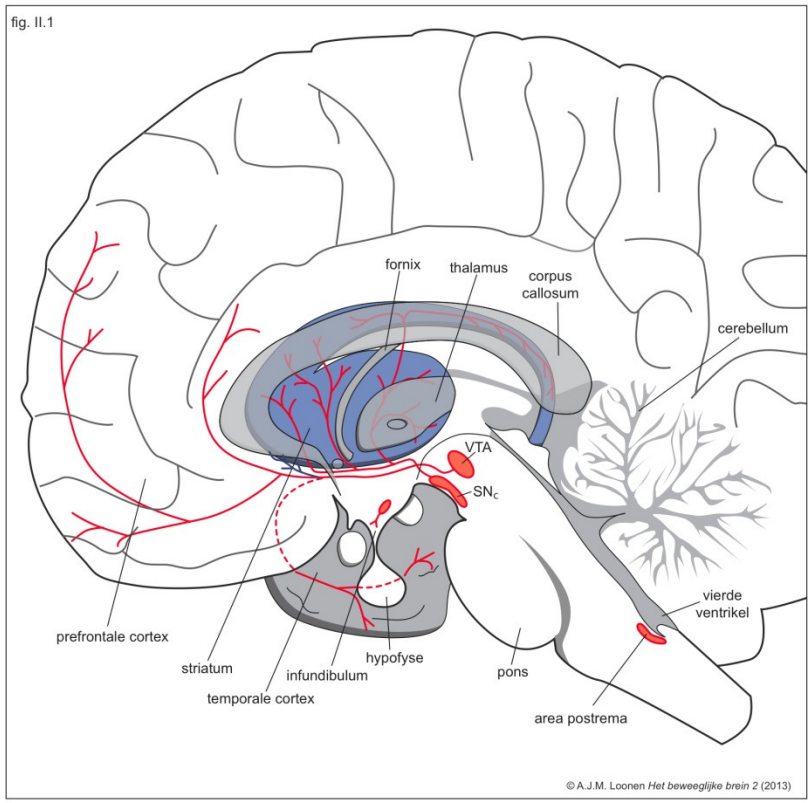
- Striatum
  - Caudate
  - Putamen
  - Accumbens
- Amygdala (limbic)
  - Centromedial part
  - Extended amygdala
  - Bed nucleus of the Stria terminalis

Topographical arrangement



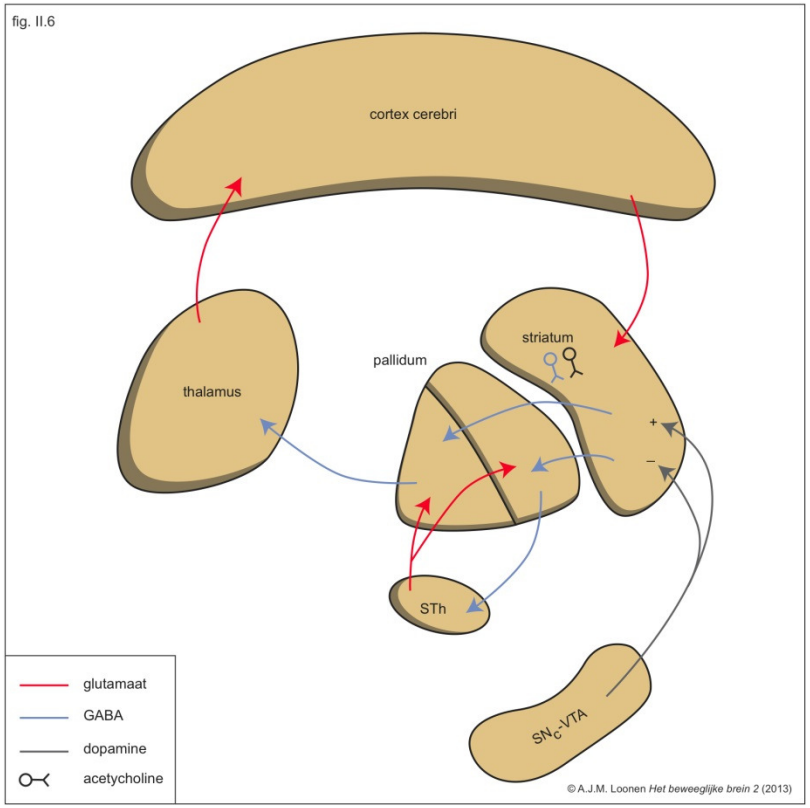
- Motor circuit
  - Putamen → MFC
- Cognitive circuit
  - Caudate → dl-PFC
- Motivational circuit
  - Accumbens → m-PFC

Distribution of dopaminergic fibres



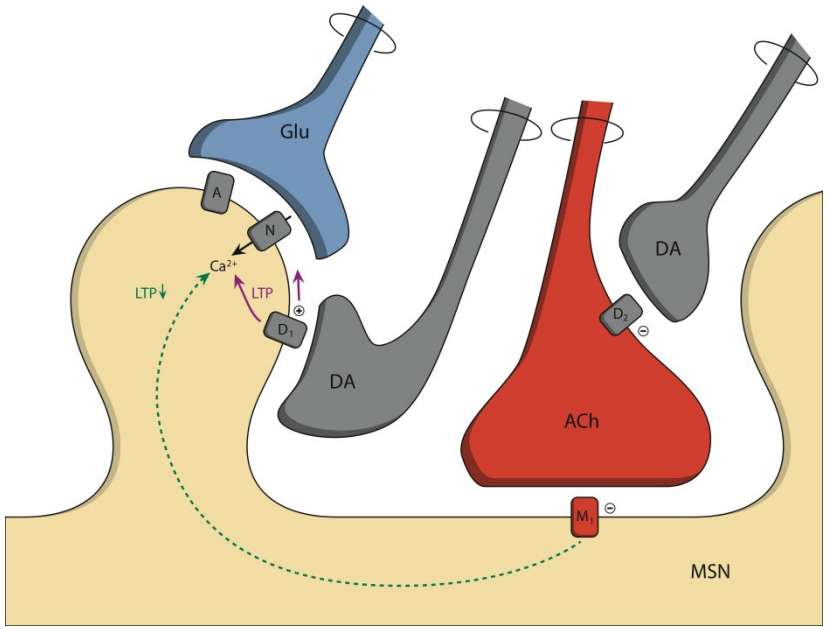
- Ventrale Tegmental Area (VTA)
  - Basal ganglia
  - Frontal cortex
  - Temporal lobe
- Substantia nigra pars compacta (SNc)
  - Basal ganglia

Dopaminergic fibres regulate striatal activity



- Extrapyramidal circuit
  - DRD1 increase activity
  - DRD1 in direct pathway
- Extrapyramidal circuit
  - DRD2 inhibit activity
  - DRD2 in indirect pathway
- DA increases output

Dopaminergic terminals regulate LTP/LTD

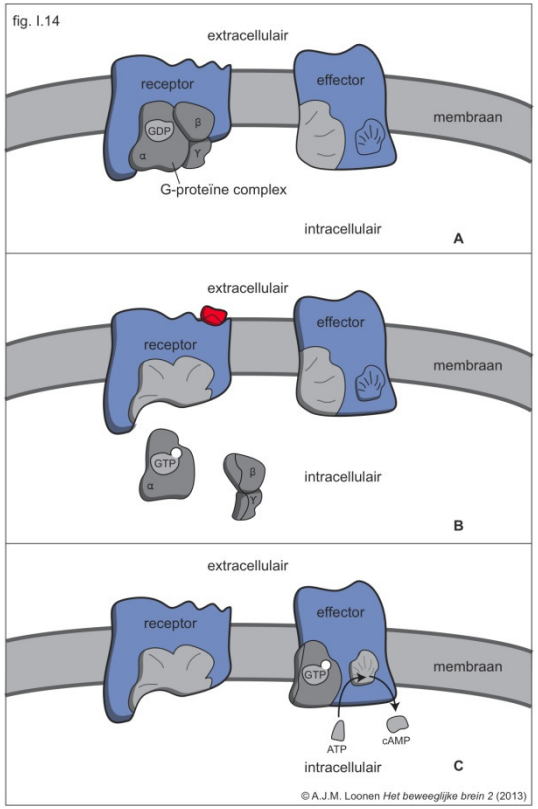


- Stimulation DRD1
  - Facilitates LTP
  - Direct pathway
- Stimulation DRD2
  - Inhibition ACh interneurons
  - Inhibition CHRM1 stimulation
  - Inhibition of LTP
- Stimulation DRD2
  - Inhibits LTP
  - Facilitates LTD
  - Indirect pathway

Serotonin (5-HT) receptors

- Type 1: 5-HT1a receptor (anxiety/depressie)
- Type 2: LSD receptor (delirium/biorythm)
  - Type 2A: inhibits dopamine
  - Type 2B: neurotrophic effects (embryo)
  - Type 2C: inhibits dopamine
- Type 3: ionotropic receptor (emesis)
- Type 4: cAMP (dementia, eating disorder)
- Type 5: cAMP (unknown)
- Type 6: cAMP (dementia, psychosis, obesity)
- Type 7: cAMP (depression, psychosis, anxiety)

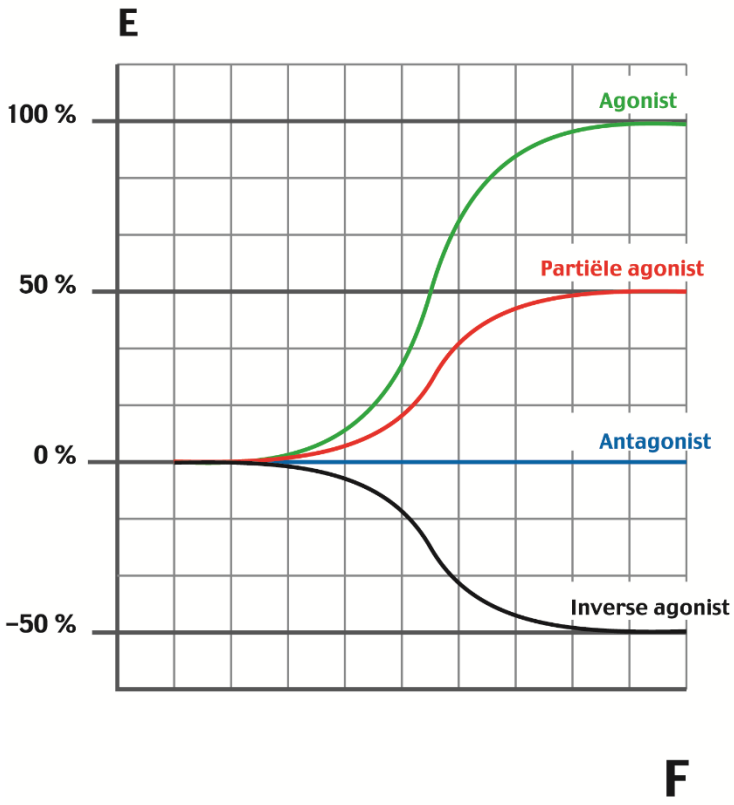
5-$HT_{2A/2C}$ receptors



› Metabotropic receptors

- Agonist activates receptor
  - G protein dissociates
- G protein parts leave receptor
  - alpha part binds GTP
  - Beta-Gamma part
- Effector is bound by alpha part
  - Effector is activitated
  - GTP → GDP ends binding

5-$HT_{2A/2C}$ receptors



- Excitatory receptors
  - Agonists increase activity
    - Agonist
  - Constitutive activity
    - 5-HT_{2C} >> 5-HT_{2A}
  - Antagonists decrease activity
    - Inverse agonist

5-HT_{2C} Antagonists act as inverse agonists

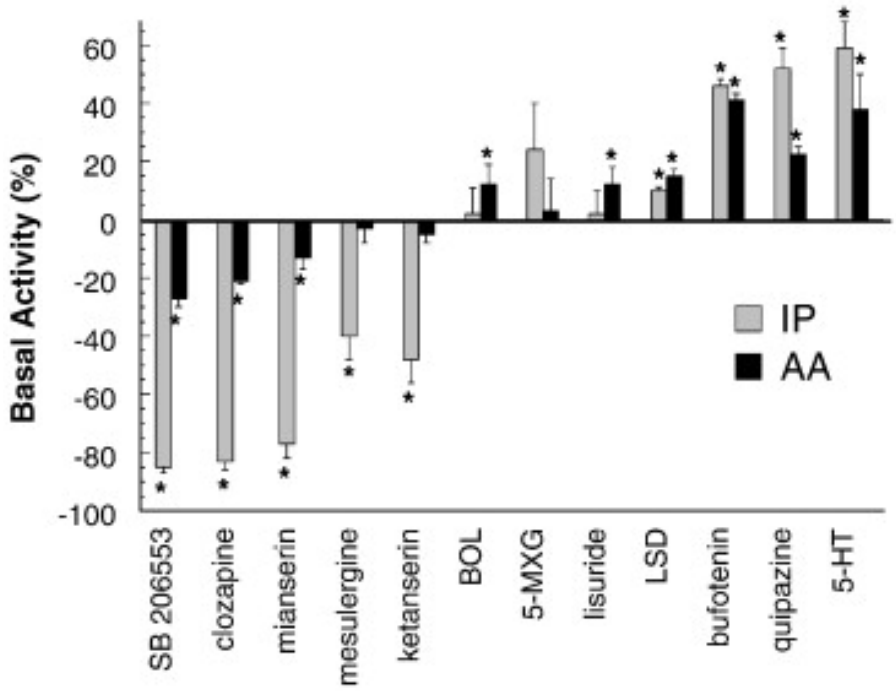
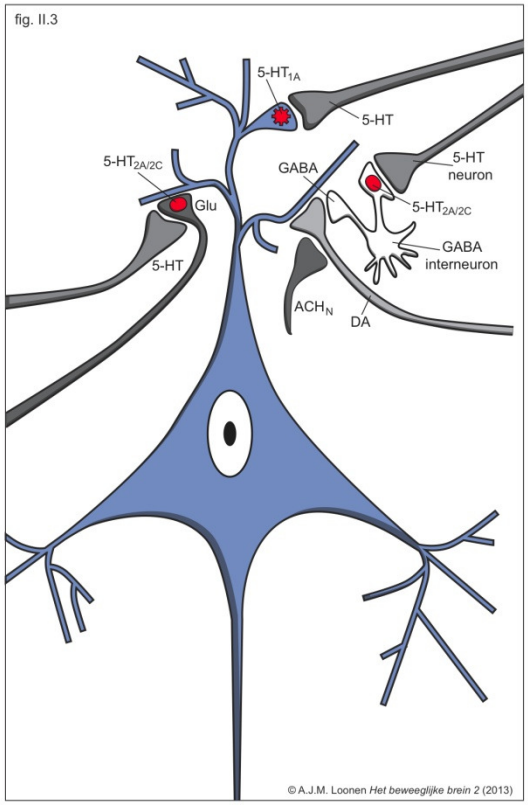


Fig. 3 Response-dependence of 5-HT 2C receptor inverse agonist efficacy: CHO-1C7 cells are optimized to detect inverse agonist properties of ligands since they express a high density of the human 5-HT 2C receptor (10–20 pmol/mg protein) and thus have a r...

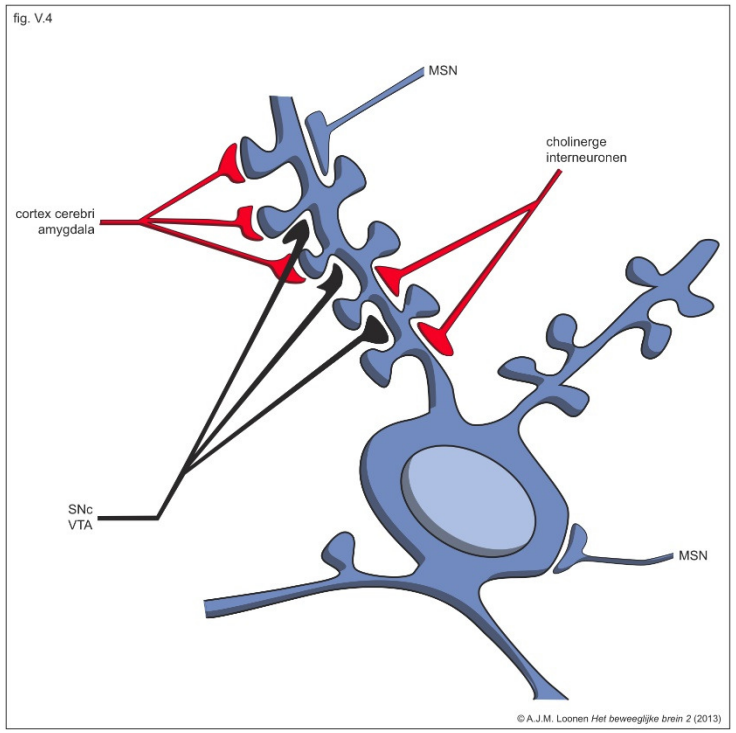
V.J. Aloyo , et al. Pharmacology & Therapeutics Volume 121, Issue 2, 160 – 173.

Serotonine 2A/2C receptors in cortex



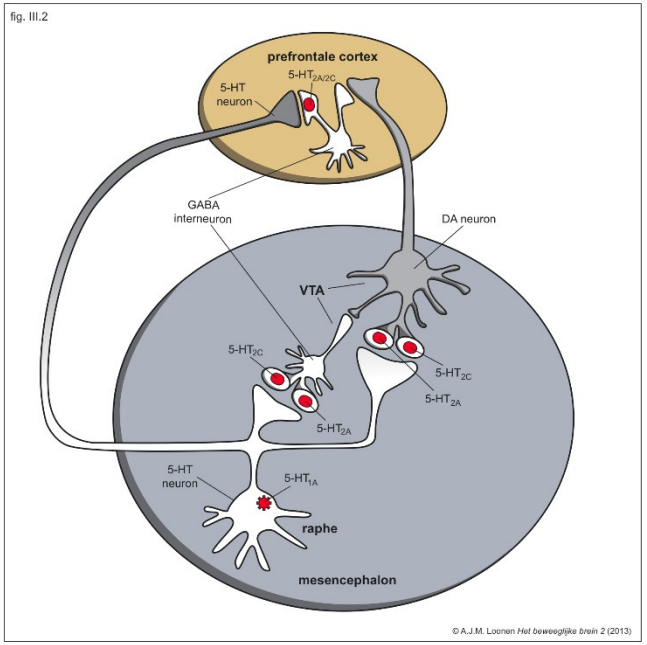
- Stimulates GABA-interneurons (HTR2A)
  - GABA inhibits DA fibres
  - GABA inhibits pyramidal cell
  - Antagonist disinhibits DA
- Stimulates MA fibers
  - Facilitates release
- Stimulates pyramidal cells
  - Excitatory activity

Serotonine 2A/2C receptors in striatum



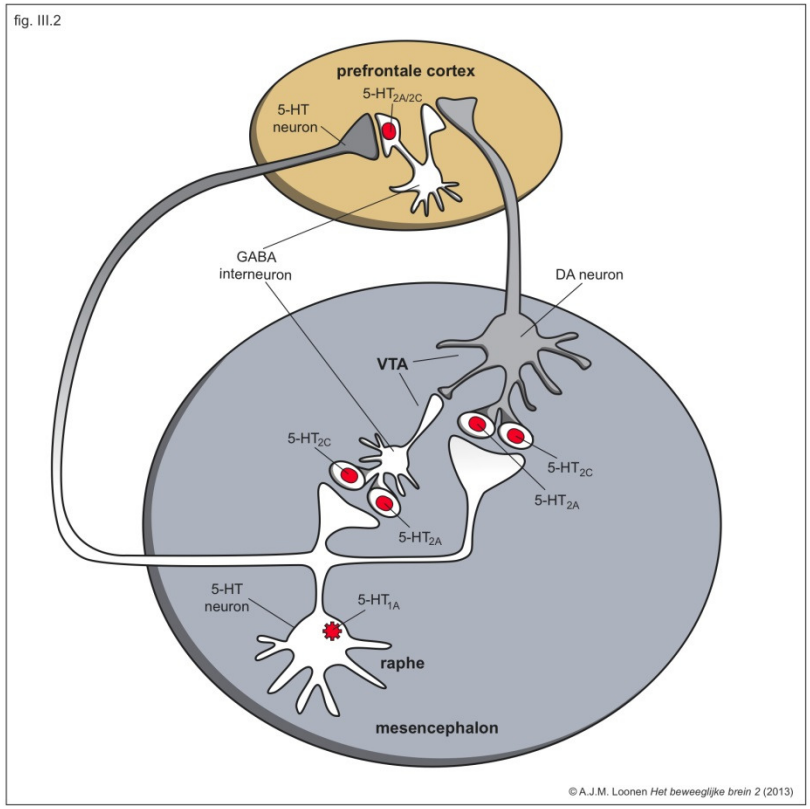
- Stimulates GABA-interneurons (HTR2C)
  - GABA inhibits DA fibres
  - GABA inhibits MSN
  - Antagonist disinhibits DA
- Stimulates MA/Ach/Glu fibres (HTR2A/2C)
- Stimulates MSN (5-HT2C/HTR2A)
  - Constitutive (rest) activity
  - Antagonist → invers agonism

Serotonine 2A/2C receptors in midbrain



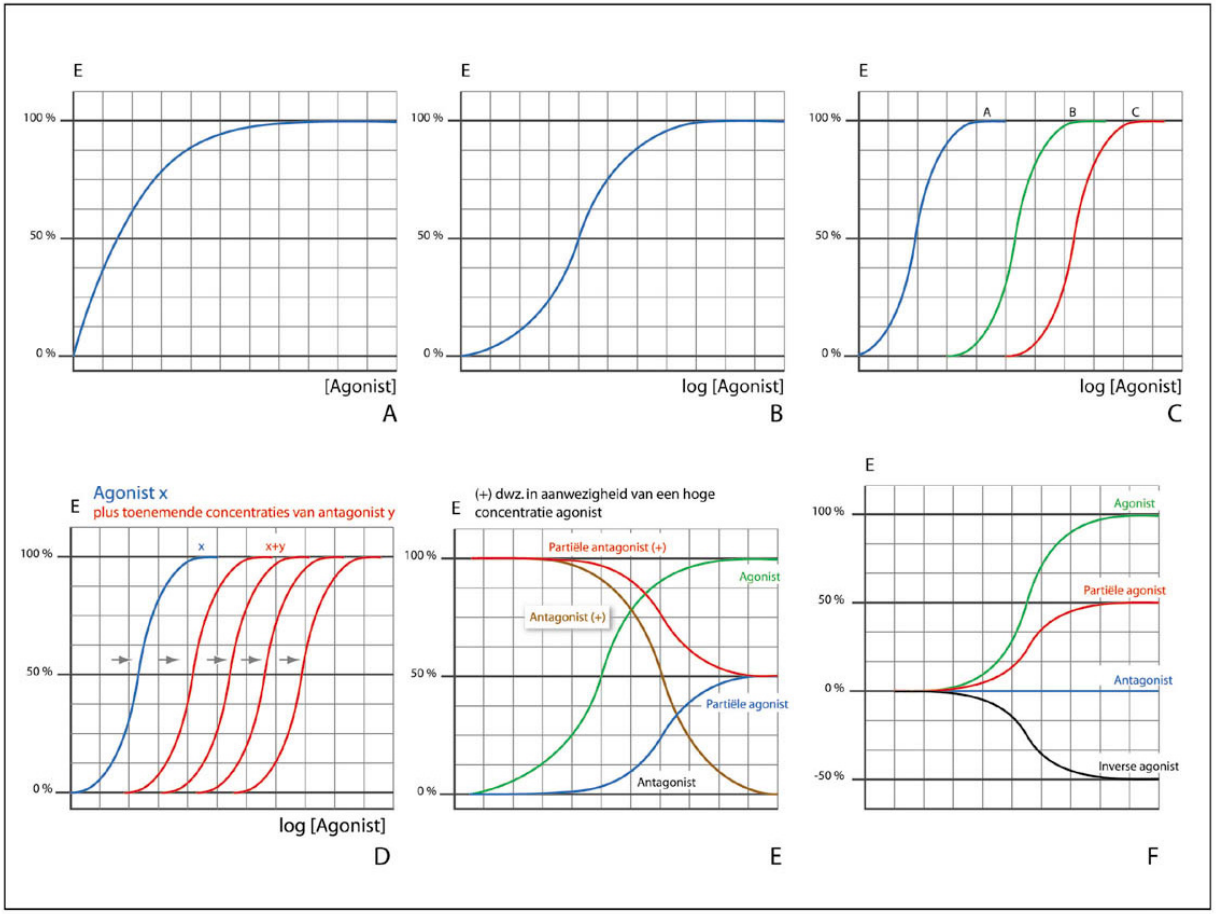
- Ventral tegmental area (HTR2A)
  - Stimulate DA neurons
  - DA release within Accumbens/Cortex
  - Antagonist → inactivity
- Substantia nigra, pars compacta
  - Stimulates GABA-interneurons (HTR2C)
  - GABA inhibits DA neurons
  - DA release within putamen/caudate
  - Constitutive (rest) activity
  - Antagonist → invers agonist

5-$HT_{2A/2C}$ receptors regulate dopamine release



- VTA
  - HTR2A on DA neurons
- SNc
  - HTR2C on GABA interneurons
- Striatum
  - HTR2C on GABA interneurons
  - HTR2A on MSN (and terminals)
  - HTR2C on MSN (and terminals)
  - HTR2A not on GABA interneurons
- Cerebral cortex
  - HTR2A on GABA interneurons
  - HTR2A on pyramidal cells
  - HTR2A on MA terminals
  - HTR2C idem, but
  - HTR2C not on GABA interneurons

Drug receptor interactions



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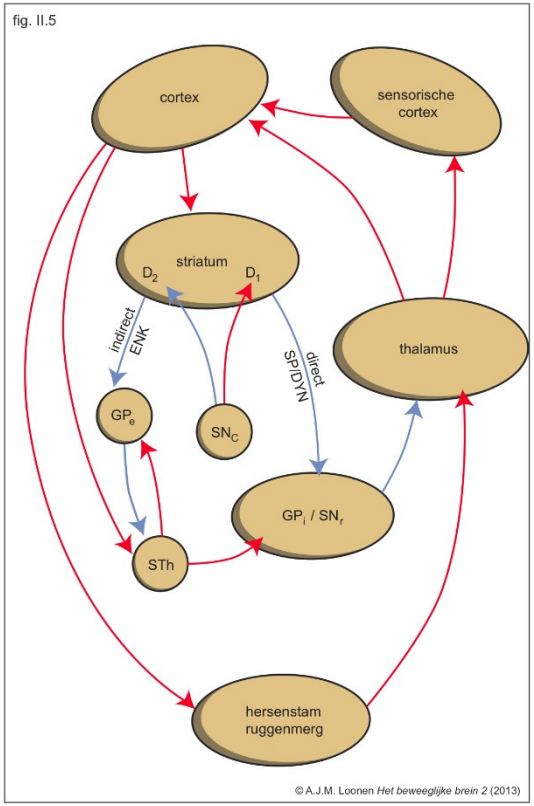
AJM Loonen. Het beweeglijke brein. Badhoevedorp: Mension, 2004.

Receptor binding affinity of antipsychotics

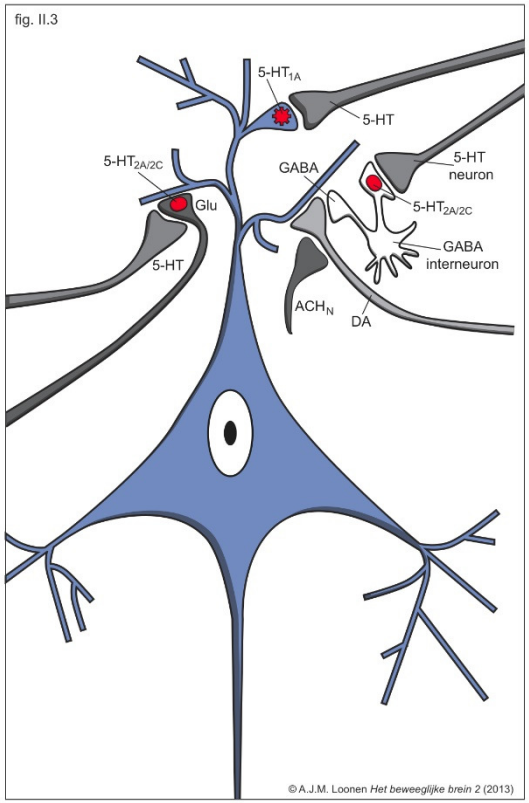
Receptor	Clozapine	Olanzapine	Quetiapine	ziprasidone	Sertindole	Aripiprazol	Asenapine	Risperidon	Paliperidon	Pipamperon	Ritanserin	Haloperidol
D1	85	31	455	9.5	12	265	1.4	75	670	-	-	25
D2	*125*	*11*	*160*	*4.8*	*0.45*	*0.34*	*1.4*	*3*	*4.0*	*124*	*70*	*1*
D3	473	49	340	7.2	12	0.8	0.42	10	7.5	-	-	2
D4	9	27	1600	32	11	44	1.1	7	30	-	-	5
D5	235	90	1738	152	-	1675	-	16	29	-	-	147
5-HT_{2A}	12	4	220	0.4	0.2	3.4	0.07	0.6	0.25	7	1.0	78
5-HT_{2C}	*8*	*11*	*615*	*1.3*	*0.51*	*15*	*0.034*	*26*	*71*	*54*	*9.3*	*3085*
α_1	7	19	7	10	1.4	57	1.2	2	4.0	62	97	46
H_1	6	7	11	47	440	61	1.0	155	10	>>	35	3630
M_1	1,9	1.9	120	>>	260	>>	>>	>>	3570	2.500	-	1475

Effects atypical antipsychotics in striatum I



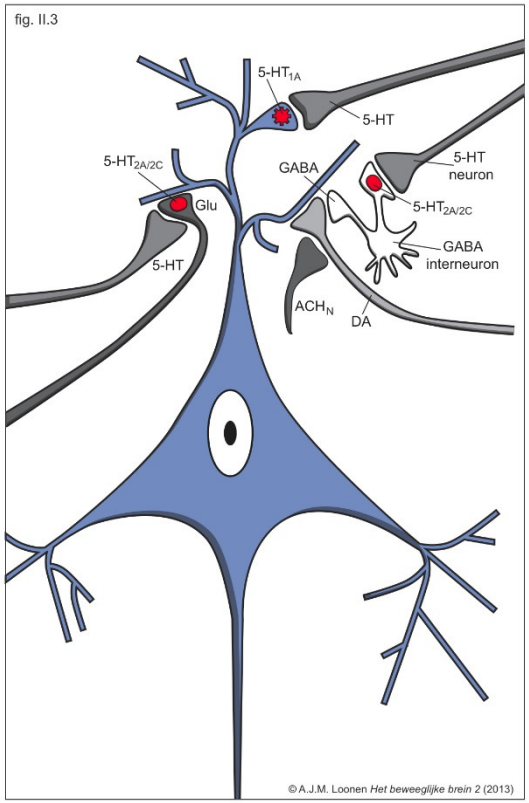
- Antagonism on DRD2 receptors
  - No influence on direct pathway (increases activity)
  - Less inhibition of indirect pathway (decreases activity)
    - Decreases activity of extrapyramidal circuit → bradykinesia
    - Compensatory release of dopamine at DRD2 → Neurotoxicity MSN

Effects atypical antipsychotics in striatum II



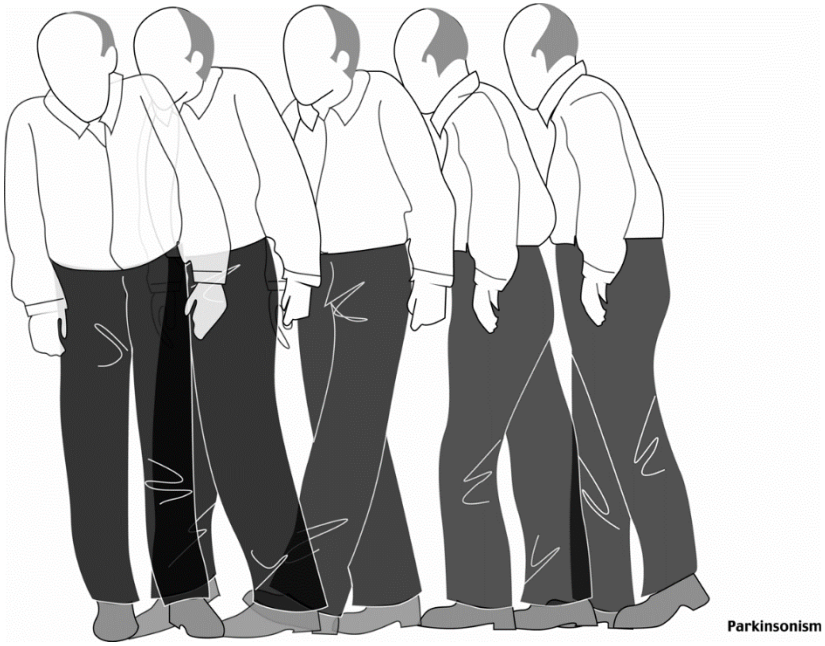
- Antagonism HTR2A
  - No effect on GABA interneurons (inhibit)
  - No excitation terminals
  - No excitation of MSN
    - Decrease DA, Glu activity
    - No direct effect on MSN

Effects atypical antipsychotics in striatum III



- Inverse agonism HTR2C
  - Decrease activity GABA interneurons (inhibit DA release)
    - DA stimulates only DRD1
    - Increased direct pathway activity
  - Inhibition Glu/DA terminals
    - Less LTP at indirect pathway MSN (DRD2 is blocked)
  - Inhibition of MSN
    - No compensation at indirect pathway MSN
    - Less neurotoxicity at indirect pathway MSN

Parkinsonism and atypical antipsychotics



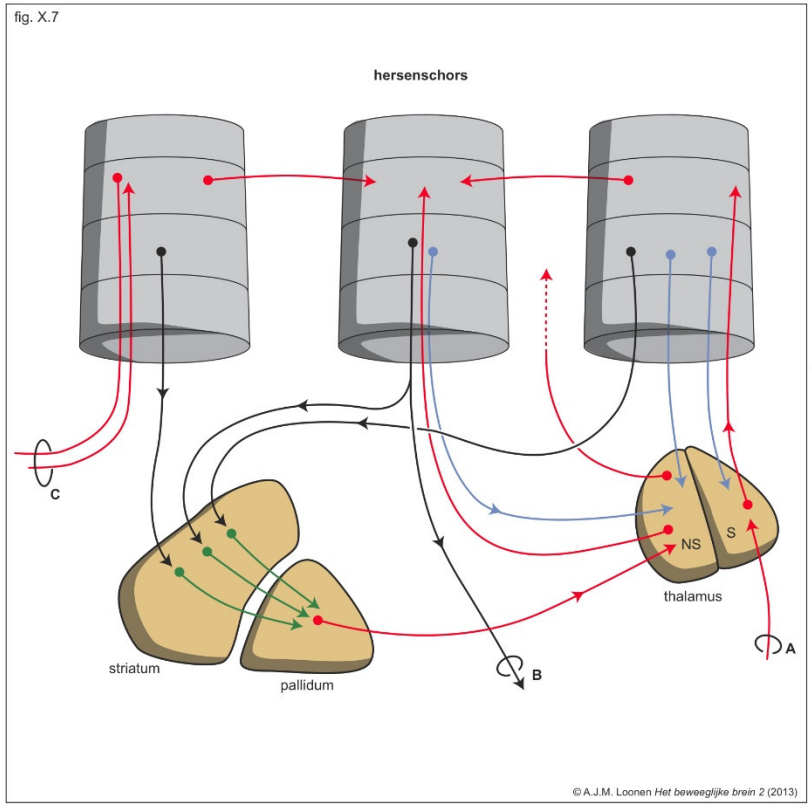
Parkinsonism >

- Putamen
  - DRD2 antagonism indirect pathway (bradykinesia)
  - HTR2A antagonism no effect
  - HTR2C inverse agonism →
    - increased DA release
      - Stimulation DRD1 on direct pathway (less bradykinesia)
    - Inhibition of Glu terminals
      - Decreased activation MSN [mainly indirect pathway (less bradykinesia)]
    - Inhibition of MSN
      - Decreased activation MSN [mainly indirect pathway (less bradykinesia)]
- Substantia nigra, pars compacta
  - HTR2C inverse agonist →
    - Inhibition of GABA interneurons → Increased release of DA in putamen.
  - HTR2A has no effect

Tardive dyskinesia and atypical antipsychotics

- Putamen
  - DRD2 antagonism indirect pathway
    - Insensitive for DA stimulation
    - Compensatory DA release
    - Increased intracellular oxidative stress → neurotoxicity
  - HTR2A antagonism no effect
  - HTR2C inverse agonist →
    - increased DA release
      - Increased oxidative stress
    - Inhibition of Glu terminals
      - Decreased activation MSN (less LTP → less excitotoxicity)
    - Inhibition of MSN
      - Decreased activation MSN (less LTP → oxidative toxicity)
- Substantia nigra, pars compacta
  - HTR2C disinhibits DA activity → increased DA release in putamen (causes tardive dyskinesia)

Dystonia and atypical antipsychotics



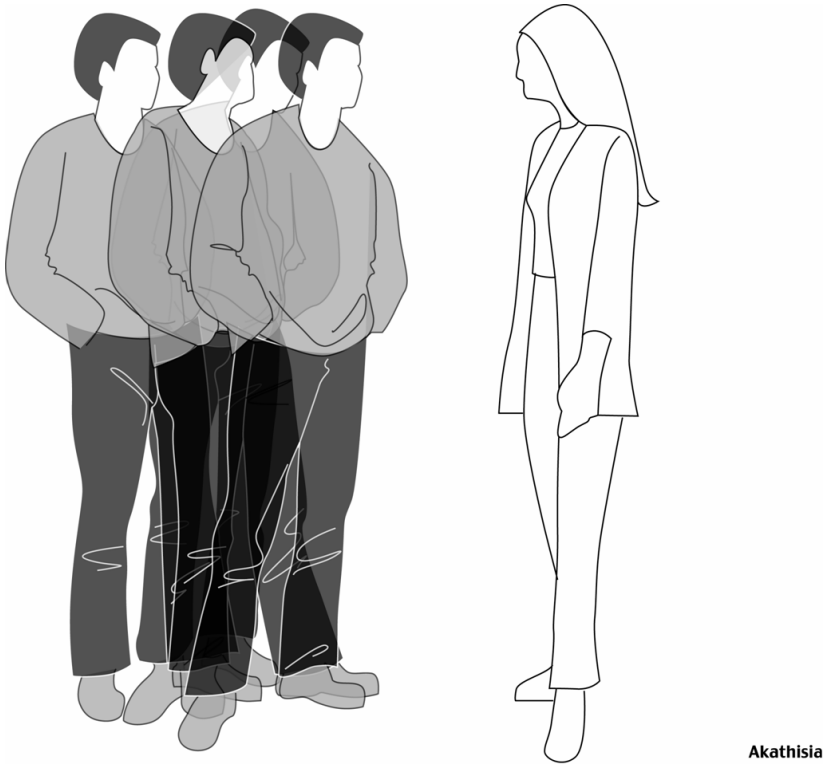
- Putamen
  - Mismatch between direct and indirect pathways.
    - DRD2 antagonism indirect pathway (inhibition)
    - Compensatory DA release stimulates DRD1 on direct pathways
  - Acute effect on cholinergic interneurons
    - Mismatch within converging extrapyramidal circuits → aberrant activation patterns
    - Antagonism of CHRM1 inhibits influence extrapyramidal circuits
  - Long-term effects on MSN
    - Mismatch between LTP/LTD at indirect pathway MSN → aberrant inhibition paterns
  - HTR2C inverse agonism →
    - Inhibition of LTP → decreased learning ability of activation patterns during exposure with DRD2 antagonist

Dystonia and atypical antipsychotics

Dystonia

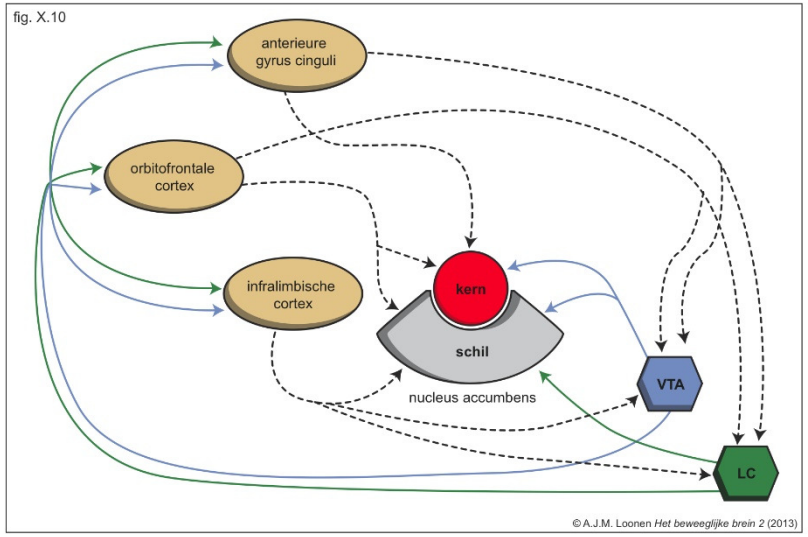
- Putamen
  - Mismatch of extrapyramidal activity
  - Aberrant movement patterns
- Anticholinergic drugs
  - Decrease influence of extrapyramidal circuit
- Atypical antipsychotics
  - CHRM1 antagonism gives acute effect
  - HTR2C inverse agonism inhibits learning

How about akathisia?



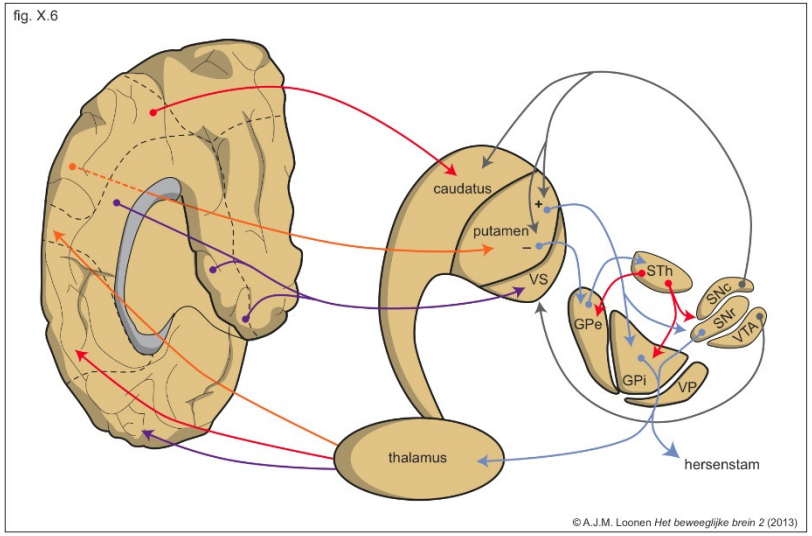
- Hypermotivation to get started
  - Urge to move the legs
  - Unpleasant feelings (dysphoria) when resisting this urge.
  - Movement are reaction to this urge/dysphoria
- Side effect of all antipsychotics
  - Classical > atypicals
- Can lead to aggression
  - Suicide
  - Hostility

Akathisia and agitation



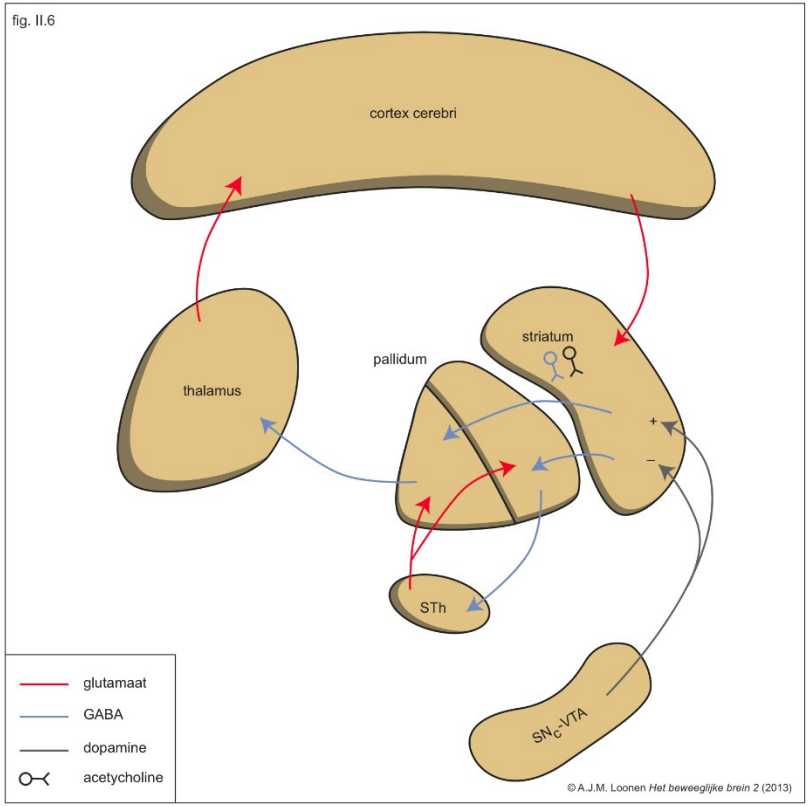
- Nucleus accumbens core
  - Stimulation by VTA → DA
  - DRD2 on direct pathway
  - DRD1 on indirect pathway
  - DRD2 antagonism
    - Inhibition of motivation
    - Inhibition of agitation
- Nucleus accumbens shell
  - Stimulation by VTA (idem)
  - Stimulation by LC (ADRB1)
  - Facilitates dysphoria
  - Facilitates akathisia

How about the caudate nucleus?



- Cognitive circuit
  - Regulates reasoning
  - Regulates associations
- Neurobiology caudate
  - Same as putamen
- Dorsolateral PFC
  - Endpoint of cognitive circuit
  - Target of atypicals
    - Blocking HTR2 → DA release
    - Blocking HTR2 →
      - increased intracortical activity
      - Increased corticofugal activity

Antimanic and cognitive effects



- DRD2 antagonism in caudate nucleus
  - Antimanic effects
  - Bradyphrenia
- Blocking HTR2 in caudate nucleus, SNc
  - Less bradyphrenia
- Blocking HTR2 in dl-PFC
  - Cognition enhancing
- Blocking HTR2 in m-PFC
  - Motivation enhancing
  - Initiative enhancing

Conclusion action of atypical antipsychotics

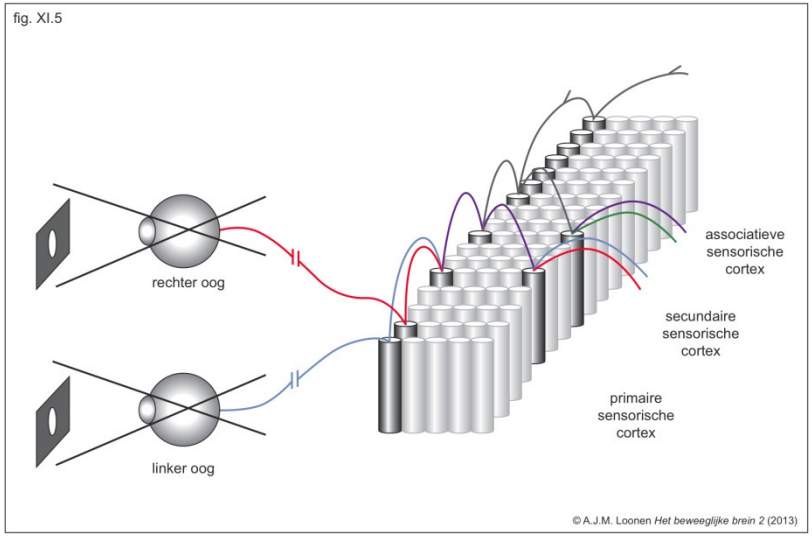
- Extrapyramidal circuits:
  - Caudate: anti-manic activity (DRD2)
  - Putamen:
    - Parkinsonism (DRD2, compensated HTR2 by stimulating DRD1 and directly inhibiting indirect pathway MSN),
    - Dystonia (topographical mismatch, CHRM1 by disabling extrapyramidal control and HTR2 by decreasing LTP),
    - Dyskinesia (DRD2, compensated HTR2C inhibiting neurotoxicity at indirect pathway MSN)
  - Accumbens: anti-agitation (DRD2), akathisia (ADRB1)

- Prefrontal cortex
  - Combating negative and cognitive symptoms (DRD1 and HTR2).

Anti-delusional and anti-hallucinatory effect

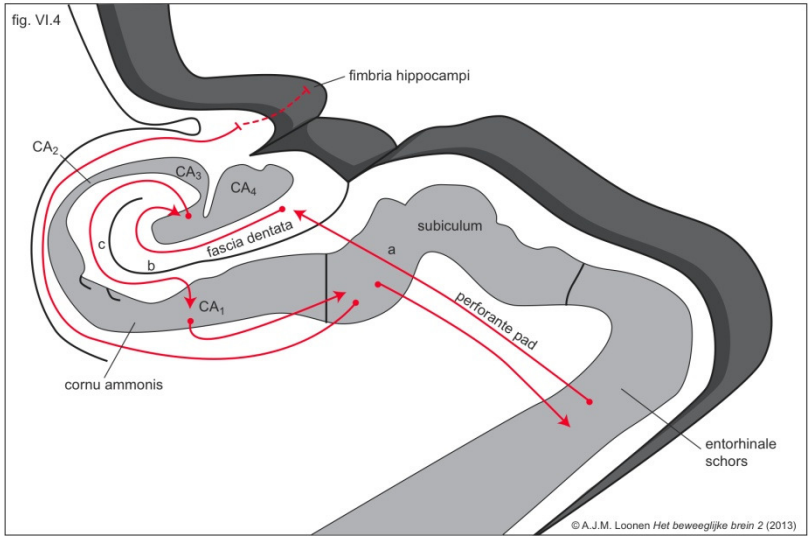
- Influencing the functioning of the temporal lobe
  - Identification of sensory information
    - Identification of non-existing input (= hallucination)
  - Dysregulation of salience (selecting relevant items)
  - Feelings of insecurity or grandness
    - Cognitive construct to explain these feelings (=delusion)

Visual input, recognition and memory



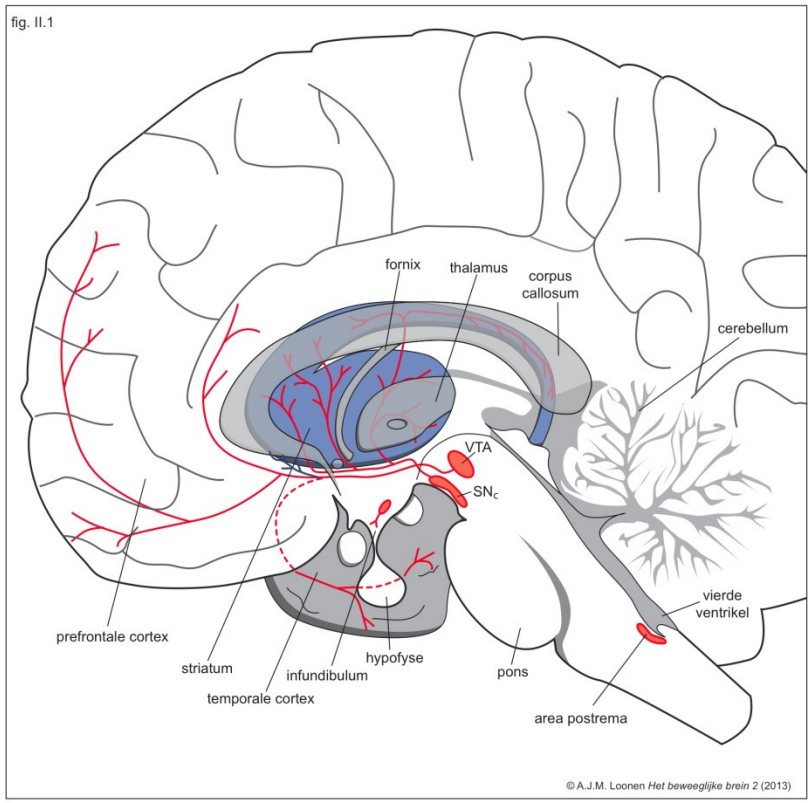
- Sensory cortex
  - Stepwise analysis
- PTO association area
  - Combining information
- Hippocampal complex
  - Recognition
- Back to sensory cortex
  - Memory formation

Recognition in hippocampus (learning by LTP)



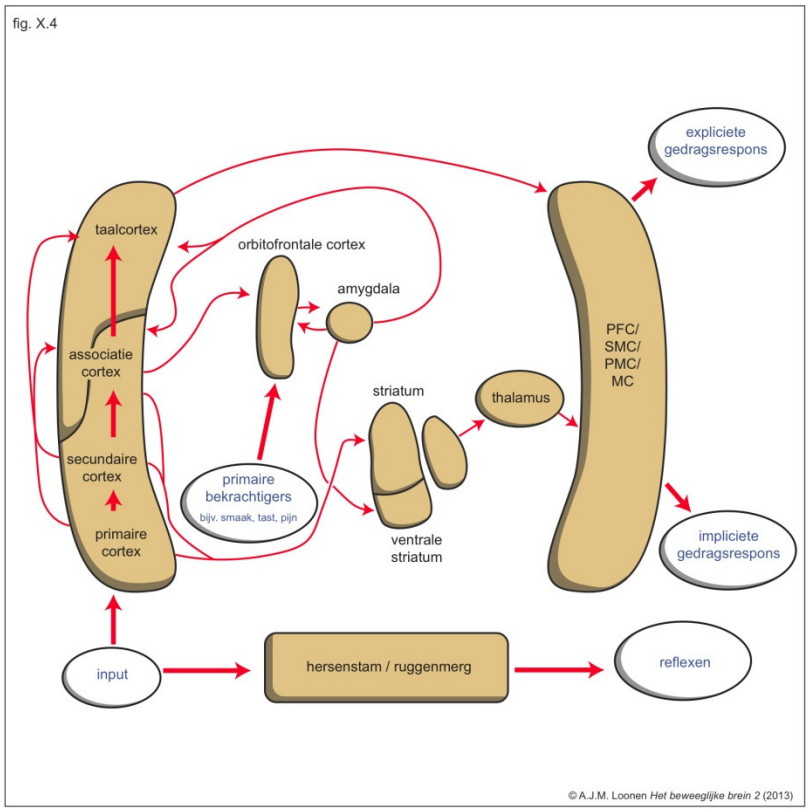
- Sensory cortex
  - LTP
- Parahippocampal ctx
  - LTP
- Cornu ammonis
  - LTP
- Parahippocampal ctx
  - LTP
- Sensory ctx

Antihallucinatory effect



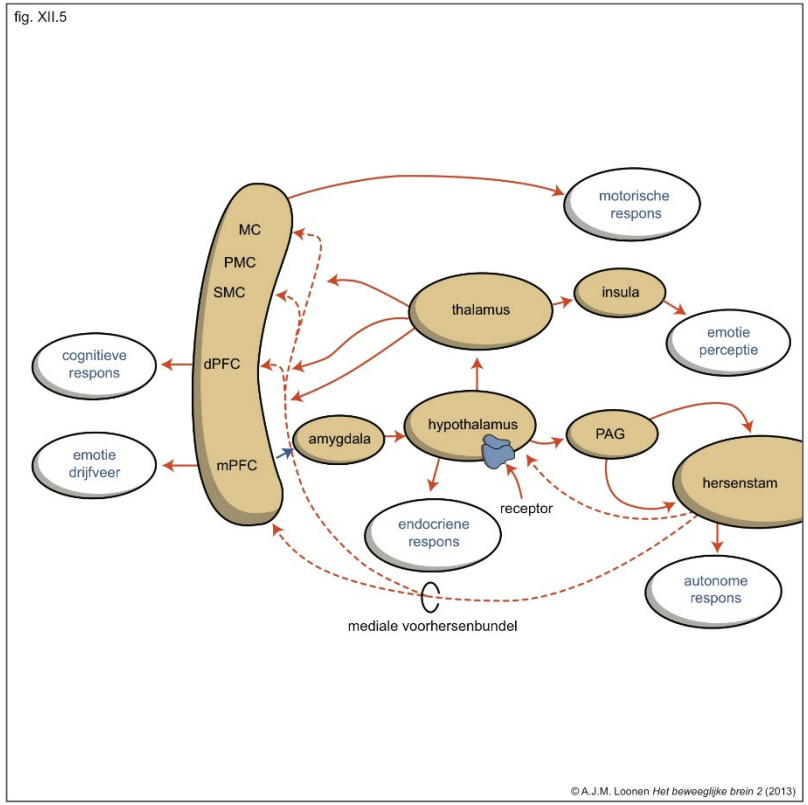
- Dopamine stimulates parahippocampal ctx
  - Illusion
    - Recognition without identification
  - Hallucination
    - Recognition without presence of input

Complex behavioural response



- Explicate response
  - Constructed
  - Planned and skilled
  - Motivation based
- Implicate response
  - Conditioned
  - Intuitive
  - Drive based

Emotional response type



- Hypothalamus
  - Controler
- Amygdala
  - Salience selector
- Prefrontal cortex
  - inhibitor

Anti-delusional effect

- Amygdala attributes to much significance to certain sensory stimuli (salience dysregulation)
- Prefrontal cortex inhibits emotional response insufficiently
- Dopamine stimulates amygdala too much
  - Facilitates emotional response (DRD2)
  - Facilitates conditioning response (DRD2)
- Delusion is cognitive construct explaining feeling
- Antipsychotics block DRD2 in amygdala

Conclusion: site of action of antipsychotics

- Extrapyramidal circuits
  - Caudate: antimanic activity
  - Putamen: Parkinsonism, dystonia, dyskinesia
  - Accumbens: Anti-aggitation, akathisia
- Temporal lobe
  - Hippocampal complex: anti-hallucinatory
  - Amygdaloid complex: anti-delusional
- Prefrontal cortex
  - Combating negative and cognitive symptoms

Conclusion: receptor interactions involved

- Antidelusional: DRD2 antagonism
- Antihallucinatory: DRD2 antagonism
- Anti-aggitation: DRD2 antagonism
- Akathisia: DRD2 antagonism + ADRB1 stimulation
- Cognitive: DRD1 stimulation + 5-HT2A antagonism
- Parkinsonism: DRD2 antagonism
  - Antiparkinson: HT2A/2C antagonism
- Dyskinesia: excitotoxicity indirect pathway MSN
  - Prevention: inverse agonist HTR2C on MSN
- Dystonia: mismatch LTP of MSN direct/indirect pathway

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Thank you very much

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