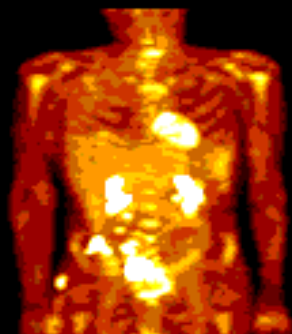


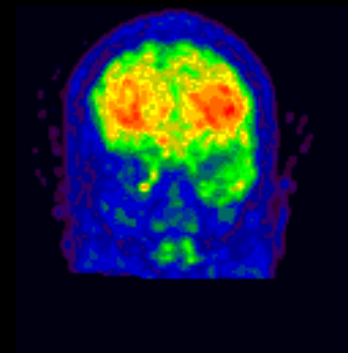


# PositronenEmissionsTomographie oder “homöopathische Chemie heute”

Institut für Kernchemie  
Universität Mainz



Markus Piel





## Einleitung



*Albrecht Dürer: Adam und Eva*

Wer sind wir?

In einem körperlichen Sinne:

- Anatomie und Physiologie
- Bau und Funktionen der Organe
- Bau und Funktionen der Zelle

Klinische Diagnostik:

- Röntgenuntersuchungen
- Magnetresonanztomographie (MRT)
- Computertomographie (CT)

⇒ Morphologie



## Einleitung



Idee der PET:

Visualisierung eines biochemischen  
Prozesses ohne ihn dabei zu beeinflussen



geeignete „Sonde“



Sehr hohe, störungsfreie  
Nachweismöglichkeit



**Radioaktive Sonden**



# Inhalt

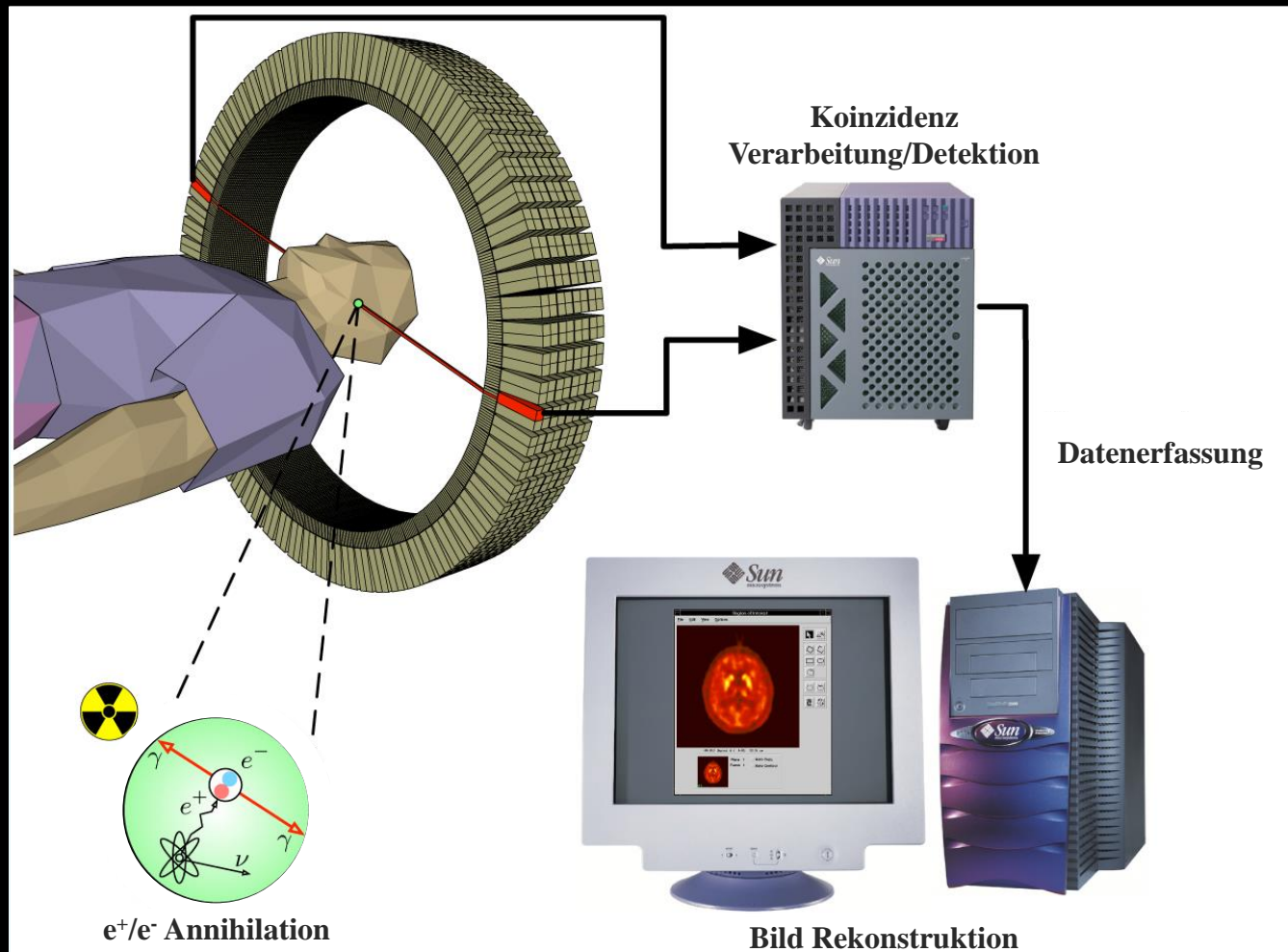
- 1. Messprinzip und Messung der Signale**
- 2. Herstellung geeigneter Radioisotope**
- 3. Biochemische Konzepte**
- 4. Synthese geeigneter Moleküle**
- 5. Medizinische Bewertung (Diagnostik)**



- 1. Messprinzip und Messung der Signale**
- 2. Herstellung geeigneter Radioisotope**
- 3. Biochemische Konzepte**
- 4. Synthese geeigneter Moleküle**
- 5. Medizinische Bewertung (Diagnostik)**



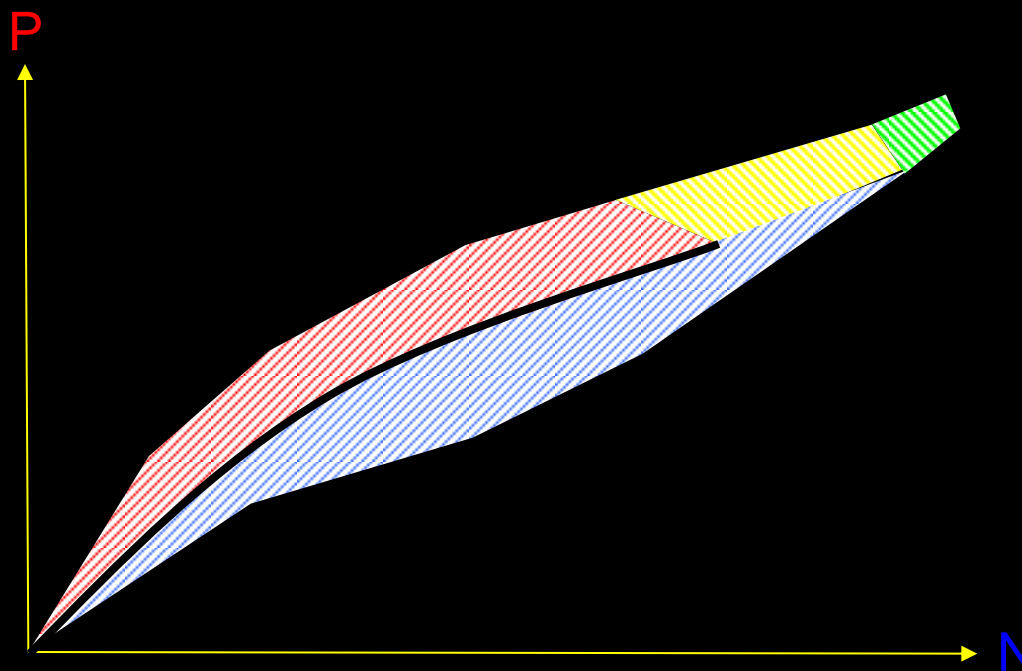
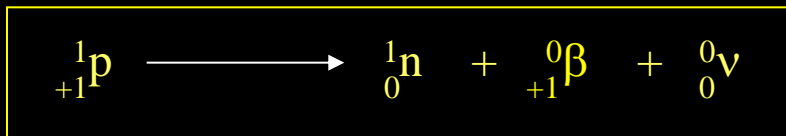
## Schema des Messverfahrens





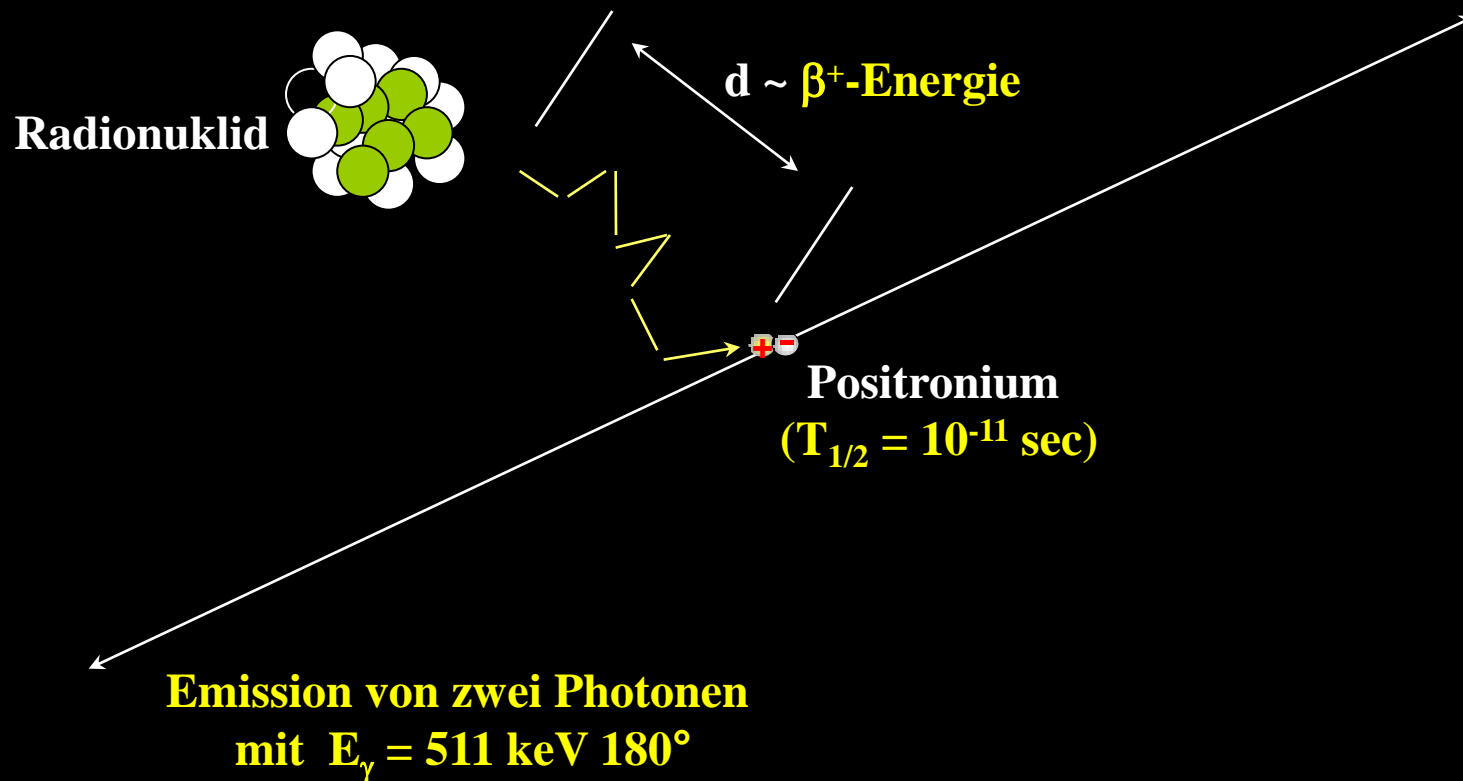
## Geeignete Radionuklide

**Positronenemission:** Variante des  $\beta$ -Zerfalls neutronendefizitärer Kerne





## Schema der Positronenemission

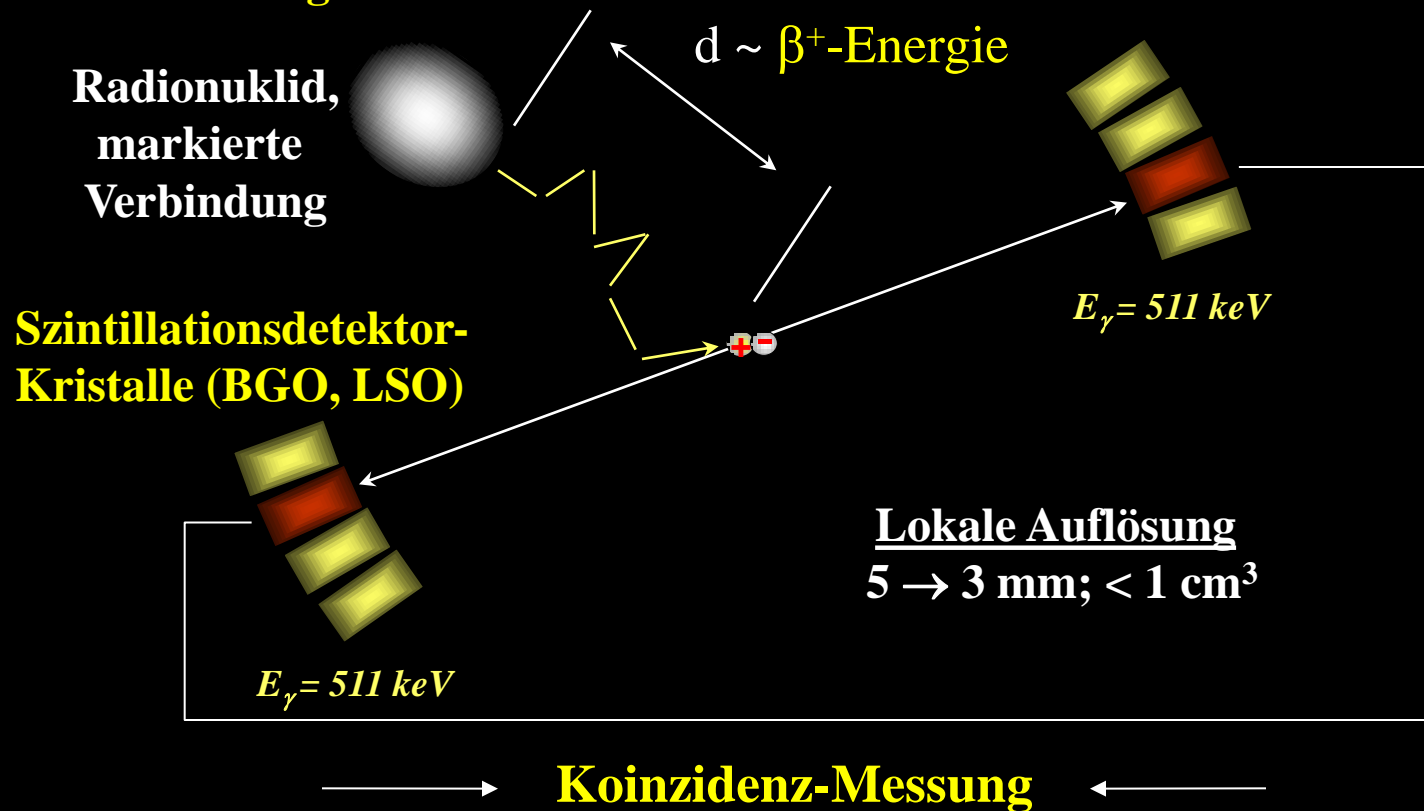






## Prinzip der Koinzidenzmessung

### 1. Emissionsmessung



### 2. Transmissionsmessung: Schwächungskorrektur

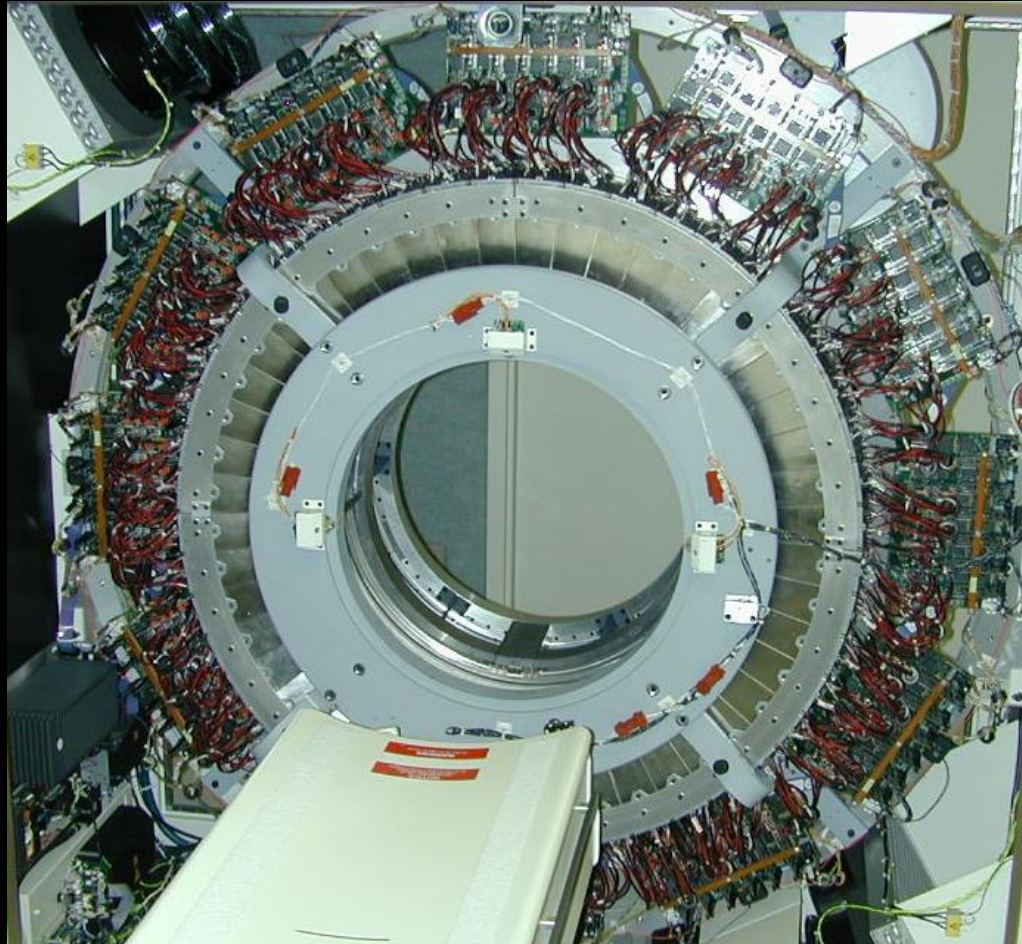


## Aufbau einer PET-Kamera



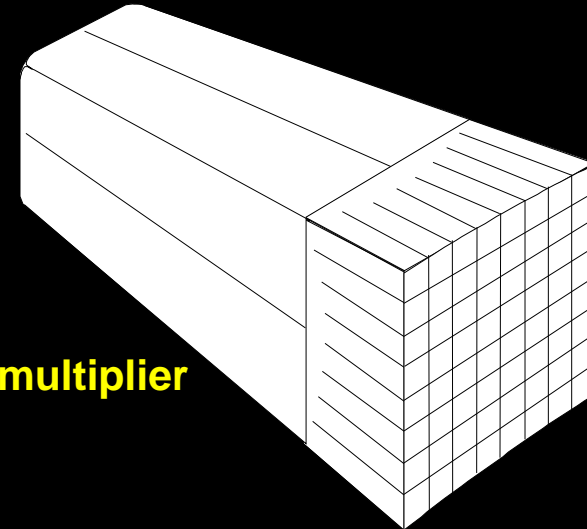
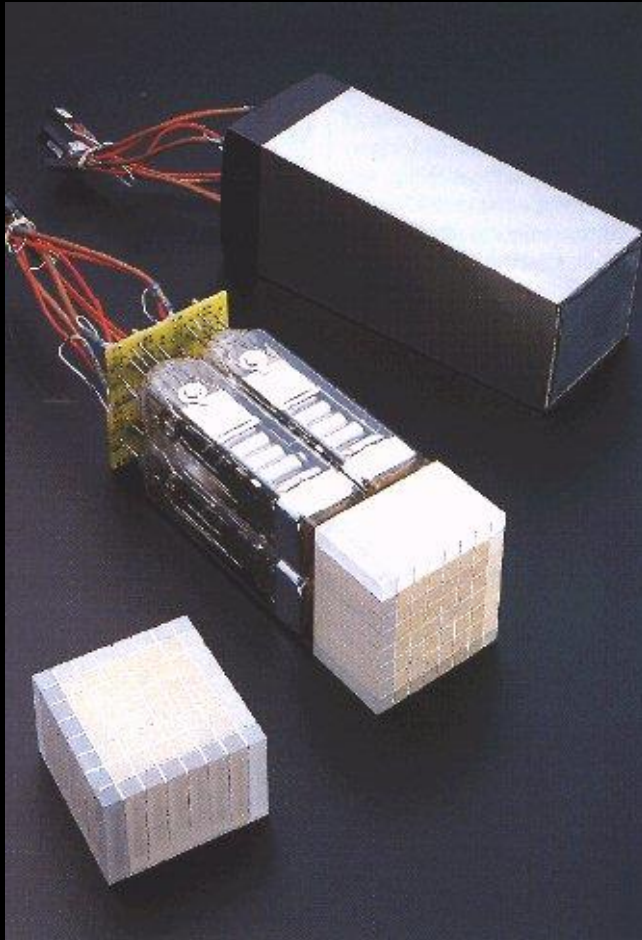


## Aufbau einer PET-Kamera





## Aufbau des Blockdetektors



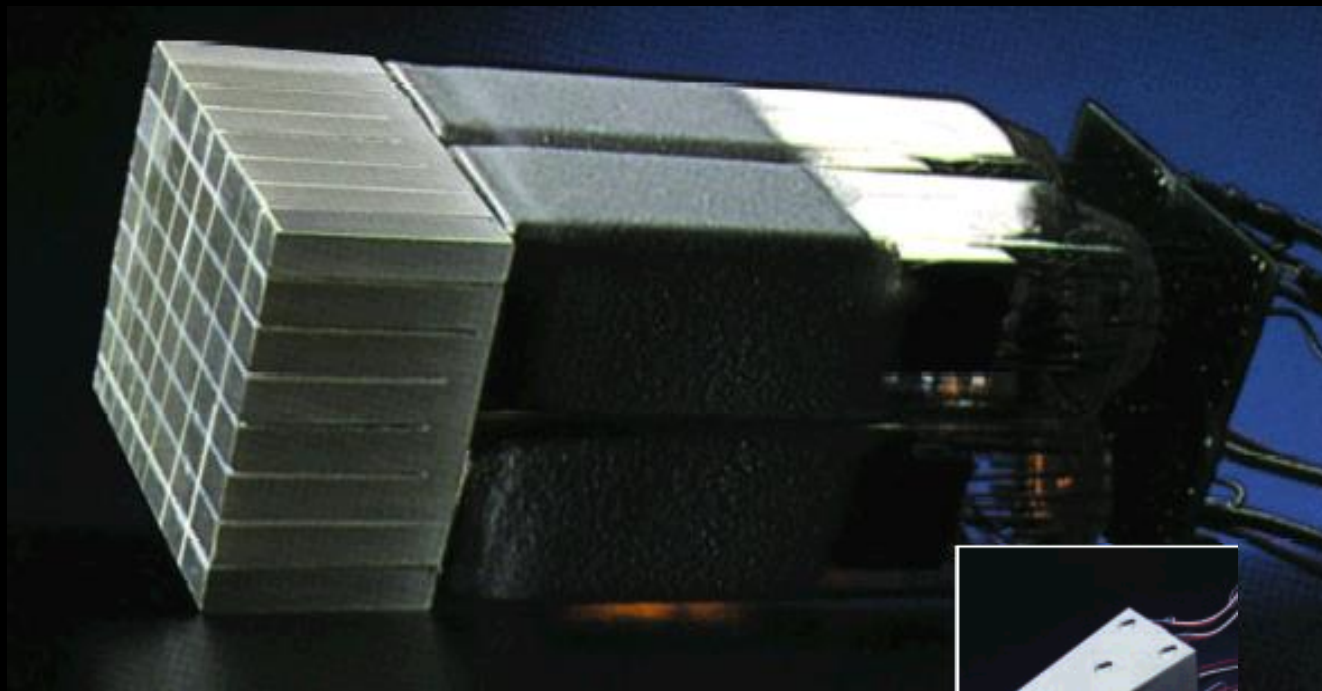
**4 Photomultiplier**

**8 x 8 Detektoren**

**Detektorgröße:  $6.75 \times 6.75 \times 20 \text{ mm}^3$**



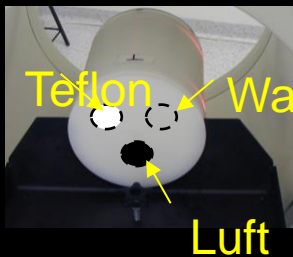
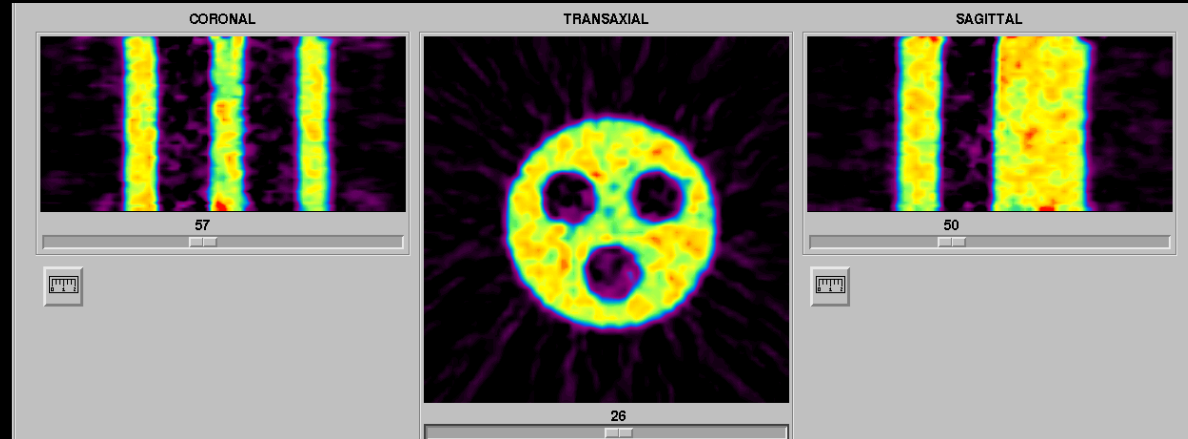
## Funktionsweise eines Blockdetektors



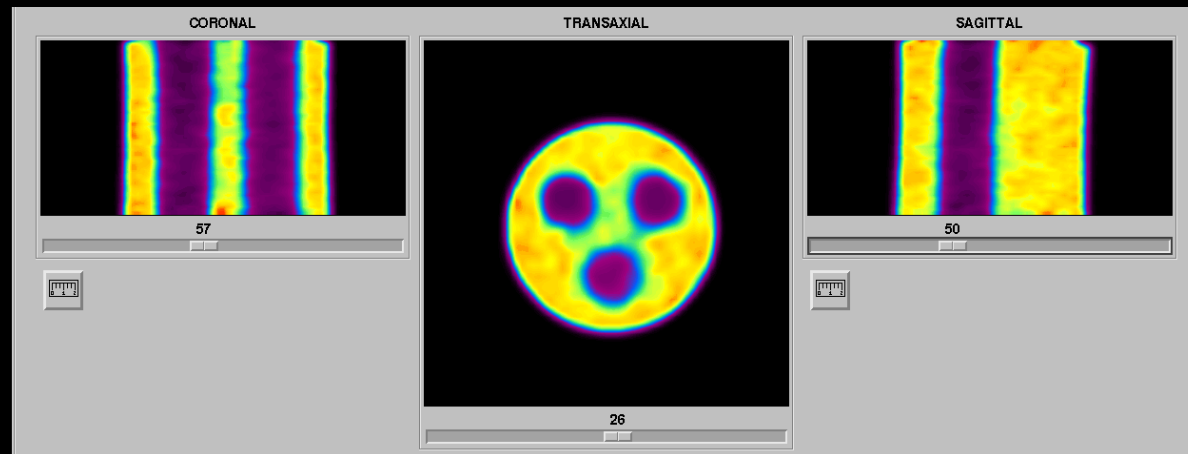


# Bildrekonstruktionsverfahren

FBP



OSEM  
2 it / 8 sub

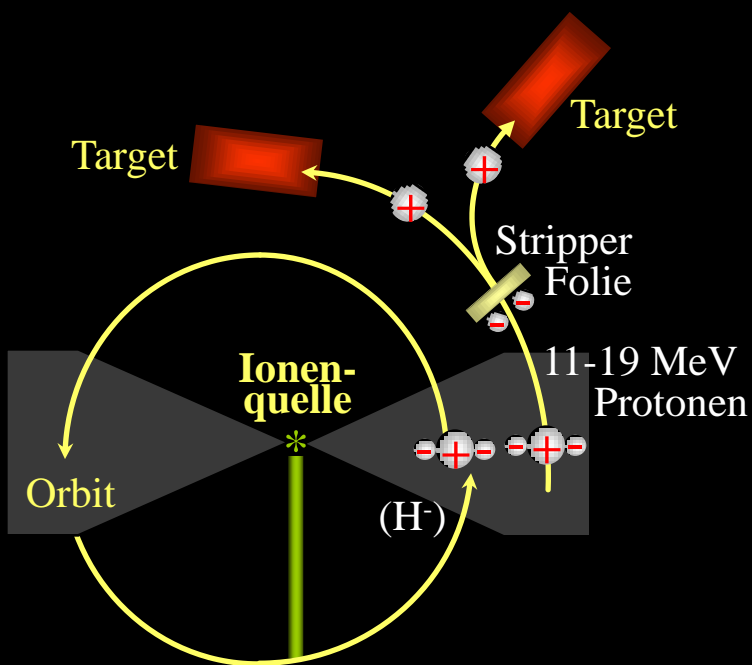




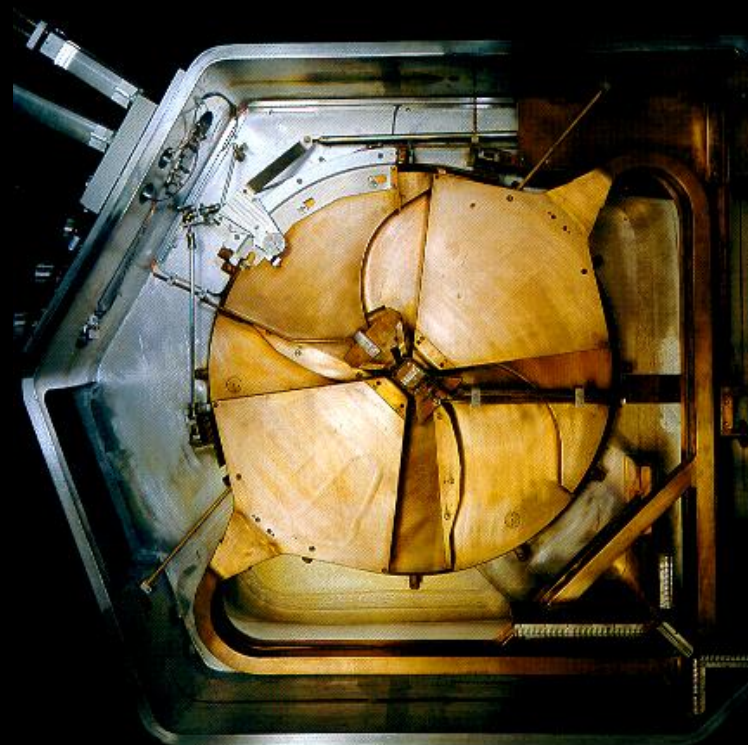
1. Messprinzip und Messung der Signale
2. Herstellung geeigneter Radioisotope
3. Biochemische Konzepte
4. Synthese geeigneter Moleküle
5. Medizinische Bewertung (Diagnostik)



## Produktion von Positronenemittern



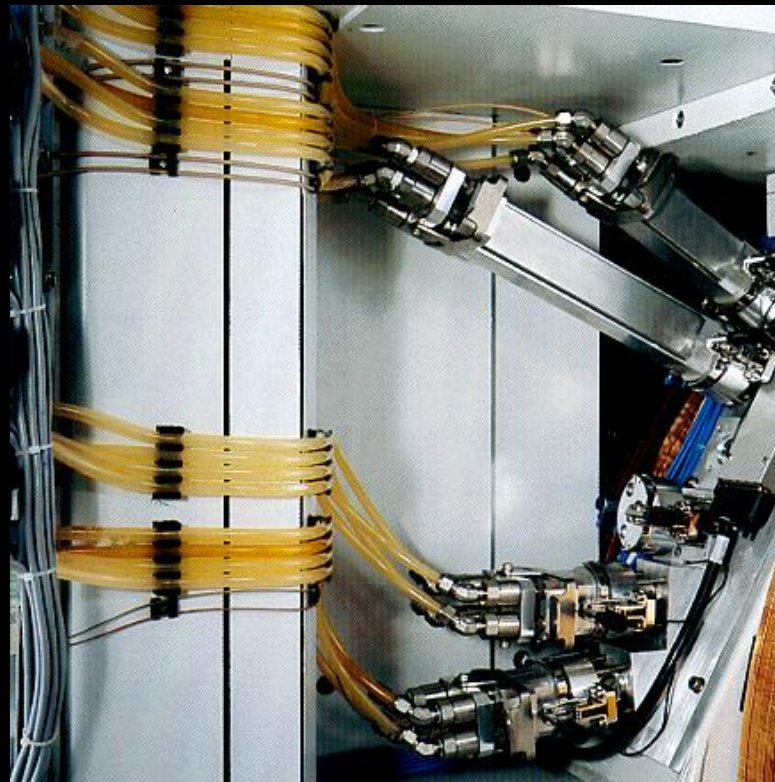
**Negativionenbeschleuniger**







# Herstellung der Positronenemitter

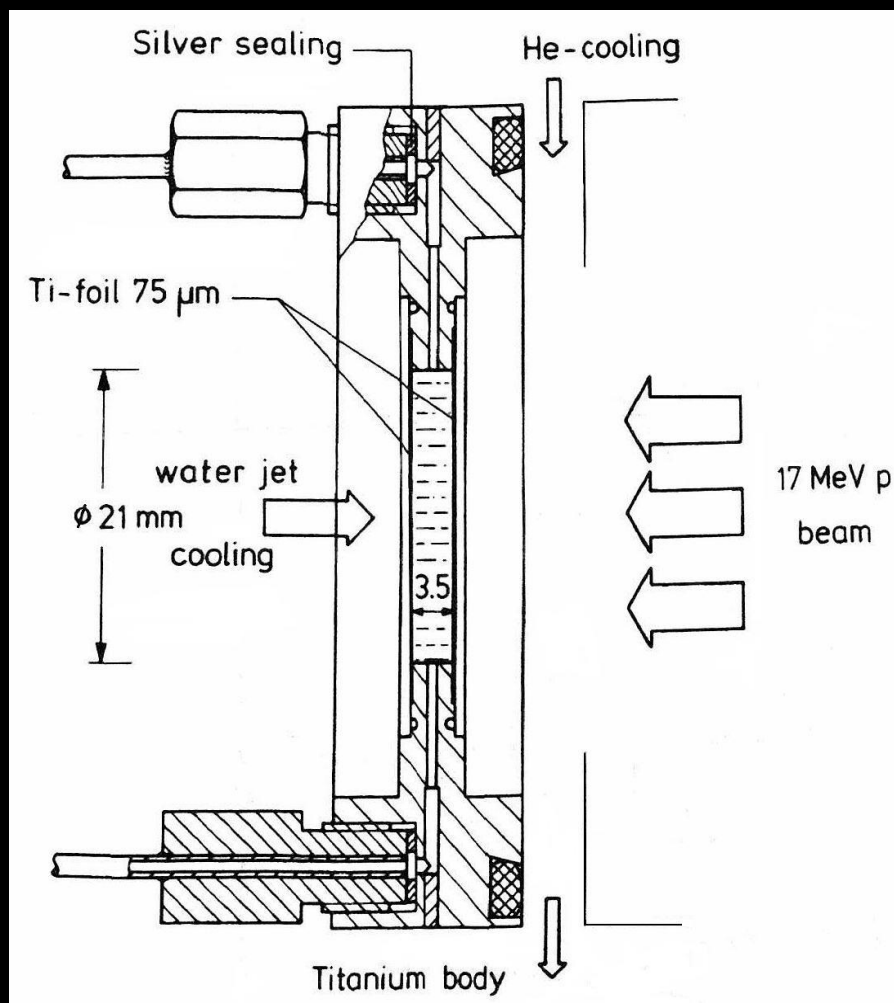


## Wichtige Kernreaktionen

Target	Radioisotop	Kernreaktion	Produkt
$^{14}\text{N}_2$	$^{11}\text{C}$	$^{14}\text{N}(p,a)^{11}\text{C}$	$[\text{C}^{11}]\text{CO}_2$
$\text{H}_2^{16}\text{O}$	$^{13}\text{N}$	$^{16}\text{O}(p,a)^{13}\text{N}$	$[\text{N}^{13}]\text{NH}_3$
$^{15}\text{N}_2$	$^{15}\text{O}$	$^{15}\text{N}(p,n)^{15}\text{O}$	$[\text{O}^{15}]\text{O}_2$
$\text{H}_2^{18}\text{O}$	$^{18}\text{F}$	$^{18}\text{O}(p,n)^{18}\text{F}$	$[\text{F}^{18}]\text{F}^-_{\text{aq}}$
$\text{Ne} + 0.1\%\text{F}_2$	$^{18}\text{F}$	$^{20}\text{Ne}(d,a)^{18}\text{F}$	$[\text{F}^{18}]\text{F}_2$



## Aufbau eines $\text{H}_2^{18}\text{O}$ -Targetts





## Wichtige Positronenemitter

Isotop	$T_{1/2}$ [min]	$\beta^+$ -Zweig	$E_{\beta^+}$ , mittl. [MeV]	Reichw. $\beta^+$ , mittl. [mm]	Quelle
$^{11}\text{C}$	20.38	> 99%	0.39	1.6	Zyklotron
$^{13}\text{N}$	9.96	> 99%	0.49	2.2	Zyklotron
$^{15}\text{O}$	2.03	> 99%	0.74	3.3	Zyklotron
$^{18}\text{F}$	109.7	96.9%	0.24	1.0	Zyklotron, (Reaktor)
$^{82}\text{Rb}$	1.27	95%	1.41	5.8	g ( $^{82}\text{Sr}$ : 25.6 d)
$^{62}\text{Cu}$	9.74	97%	1.28	5.3	g ( $^{62}\text{Zn}$ : 9.26 h)
$^{68}\text{Ga}$	68	90%	0.70	3.3	g ( $^{68}\text{Ge}$ : 271 d)

**Wahl des Radioisotops ist abhängig von untersuchtem biochemischen Prozess  
(biologische Halbwertszeit des Prozesses, Struktur des Moleküls, Hirngängigkeit, etc...)**



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4. Synthese geeigneter Moleküle
5. Medizinische Bewertung (Diagnostik)



**ZNS-Diagnostik**

**Tumordiagnostik**

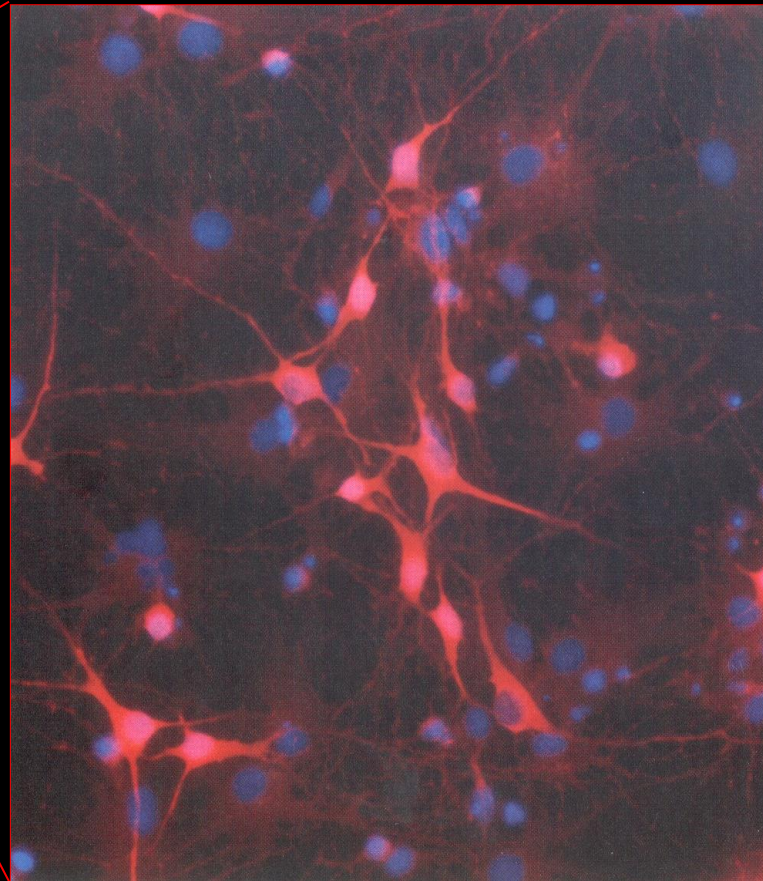
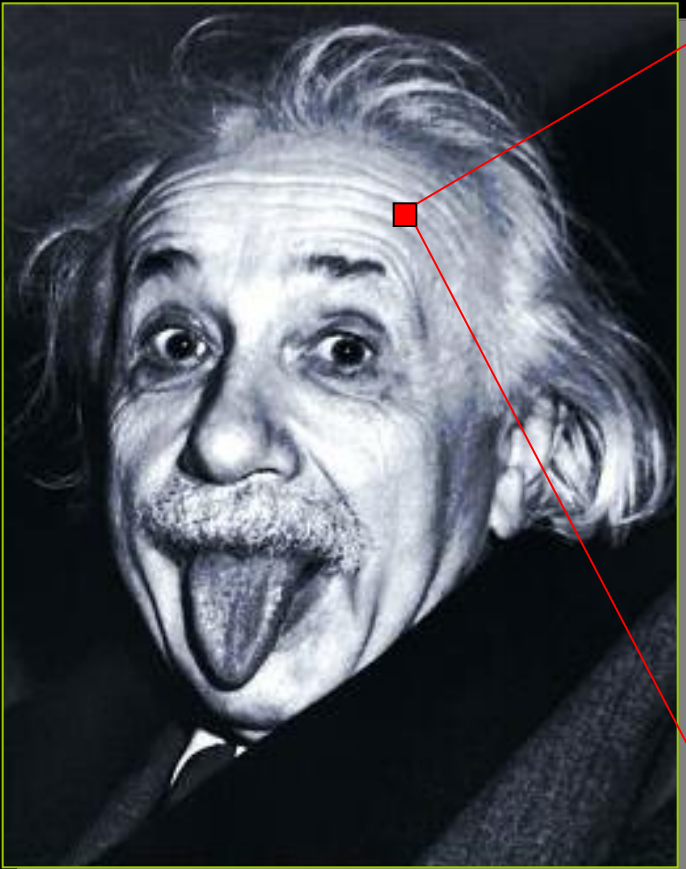


## Das zentrale Nervensystem

	Gehirn	Computer
Anzahl der Verarbeitungselemente	$10^{11}$ Neuronen	$10^9$ Transistoren
Schaltzeit der Elemente	$10^{-3}$ s	$10^{-9}$ s
Schaltvorgänge	$10^3$ s	$10^9$ s
Schaltvorgänge insgesamt (theor.)	$10^{14}$ / s	$10^{18}$ / s
Verarbeitungsart	Massiv parallel	Primär seriell
Vernetzungsfaktor	$10^3$	1

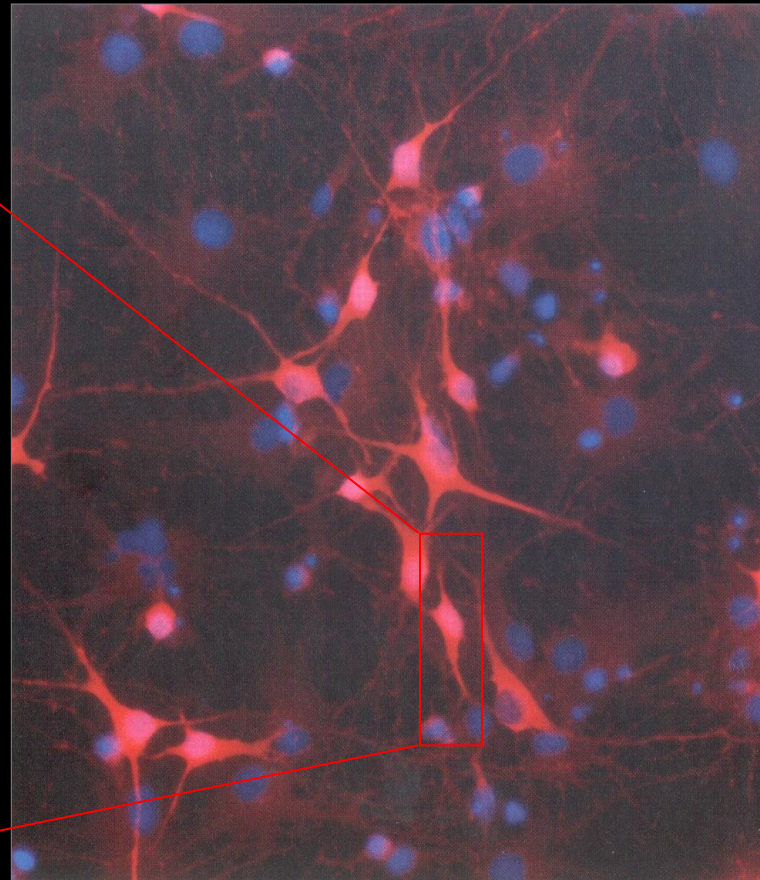
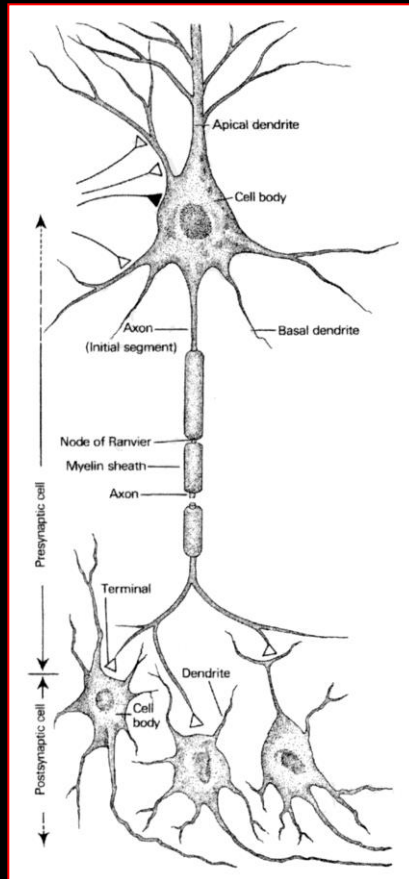


## Das zentrale Nervensystem





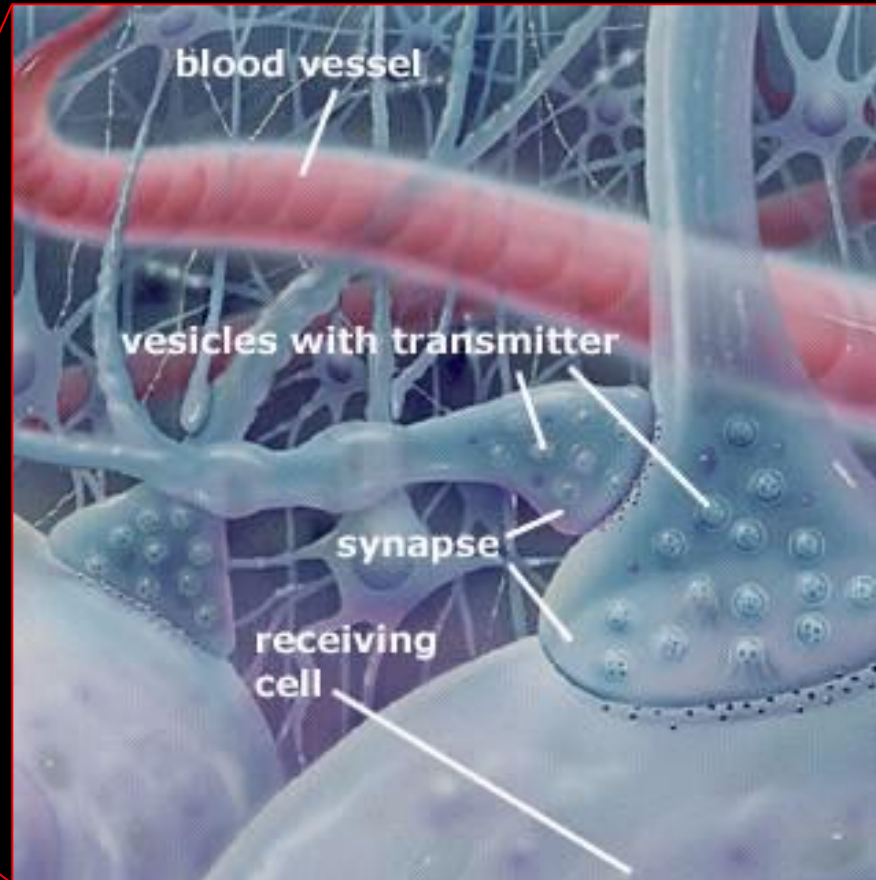
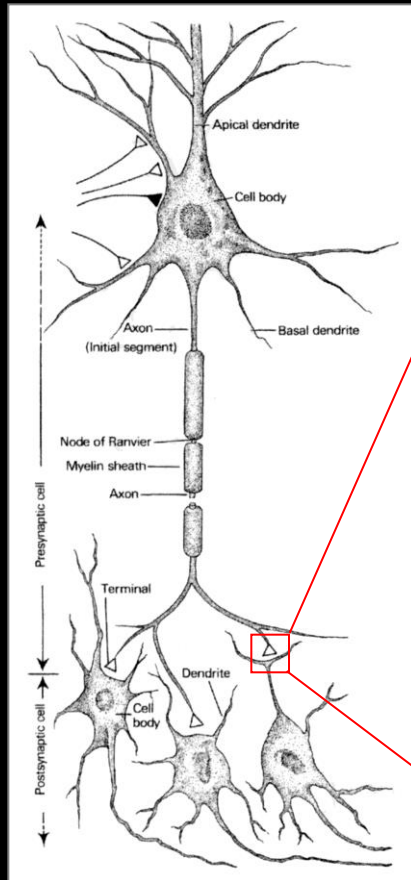
# Das zentrale Nervensystem





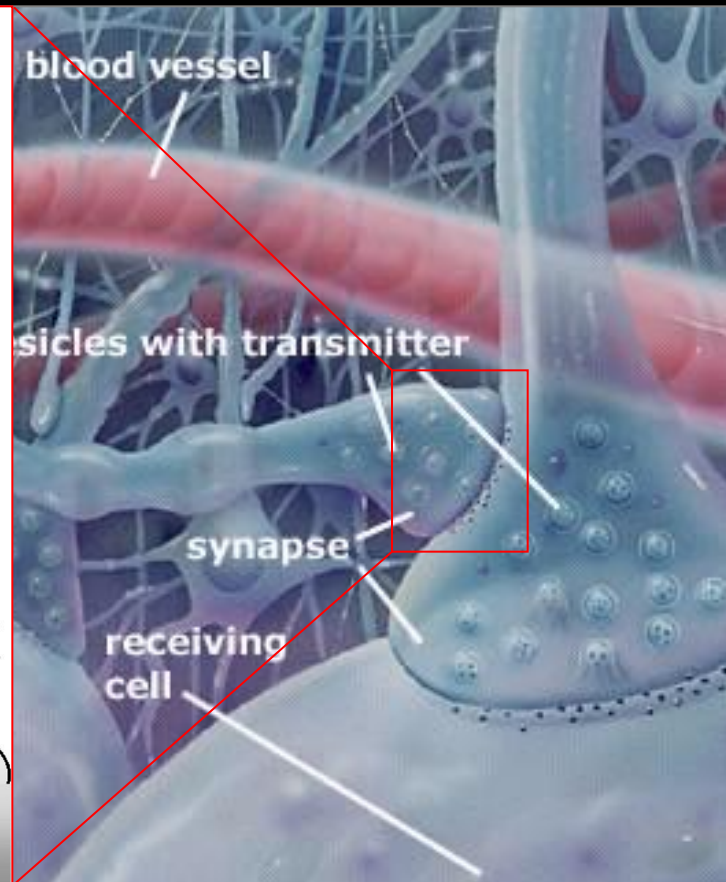
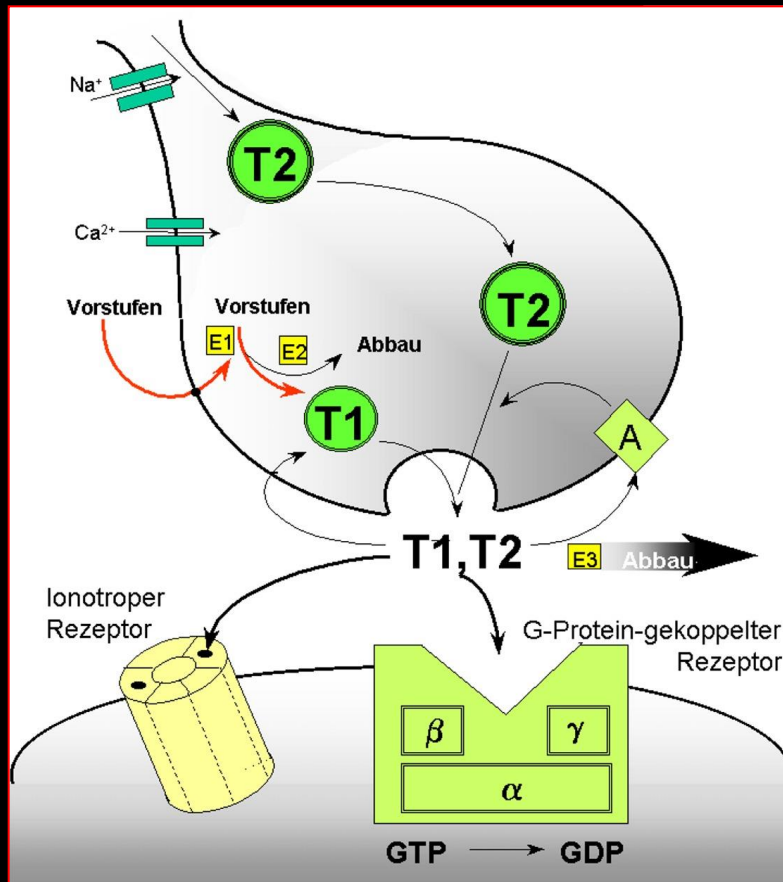


# Das zentrale Nervensystem





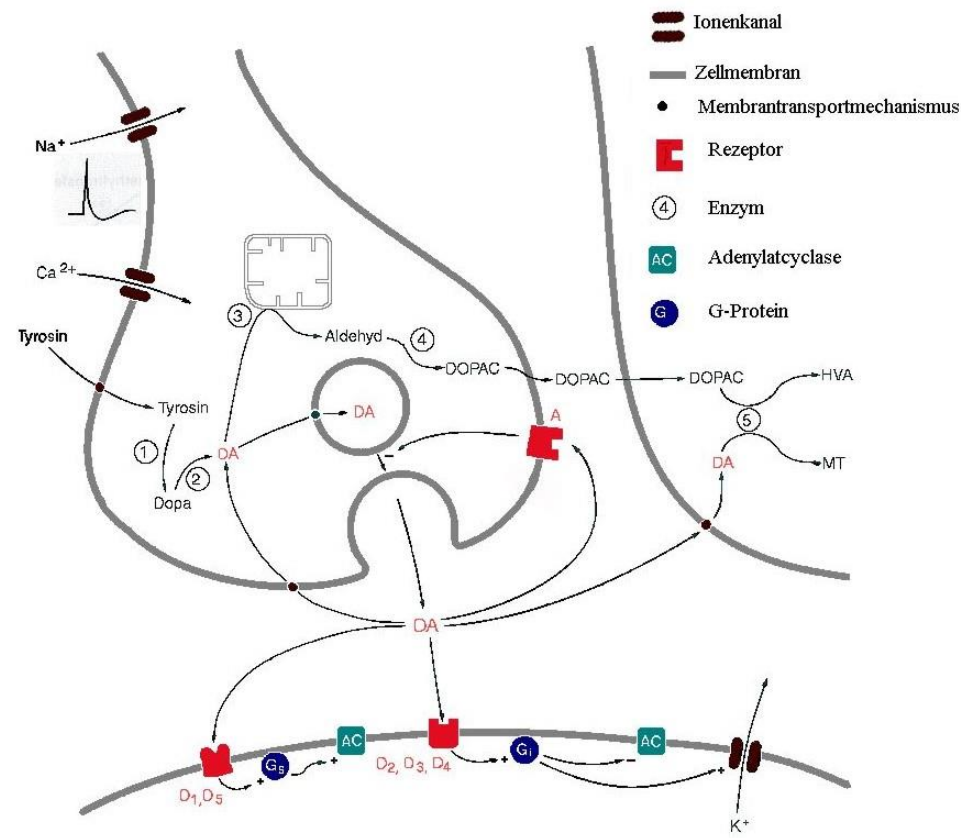
# Das zentrale Nervensystem





# Das dopaminerge System

- Dopamin ist einer der 12 wichtigsten Transmitter
- 3 große dopaminerge Systeme im ZNS:
  - nigro-striatal: Steuerung der Motorik
  - mesolimbisch: Empfindung von Lust & Freude
  - tubero-infundibular: Hemmung der Prolaktinsekretion
- **Relevante Krankheitsbilder**
  - Parkinson
  - Schizophrenien
  - Suchterkrankungen (Alkoholismus, etc.)



GTP

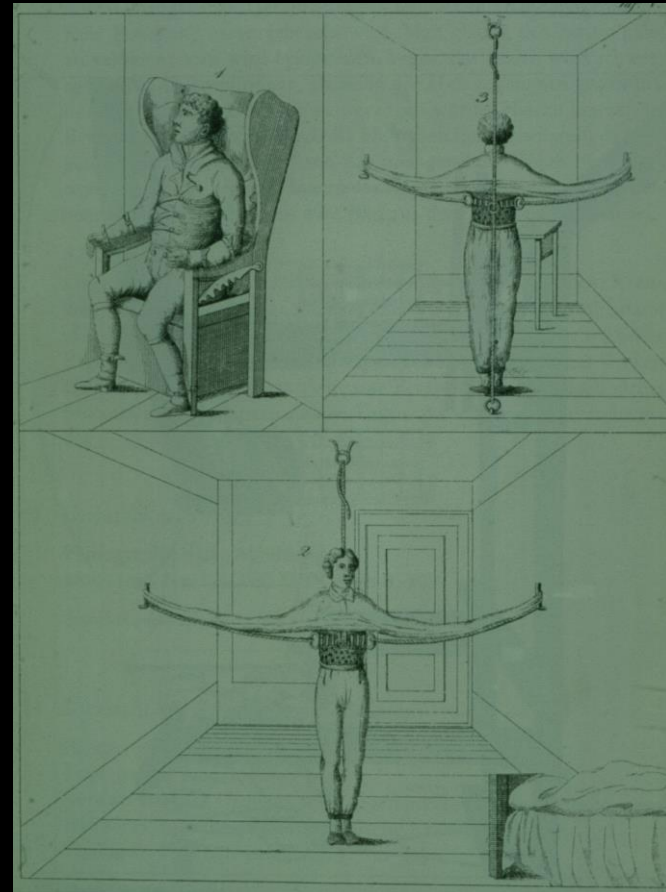


# Schizophrenien





# Schizophrenien





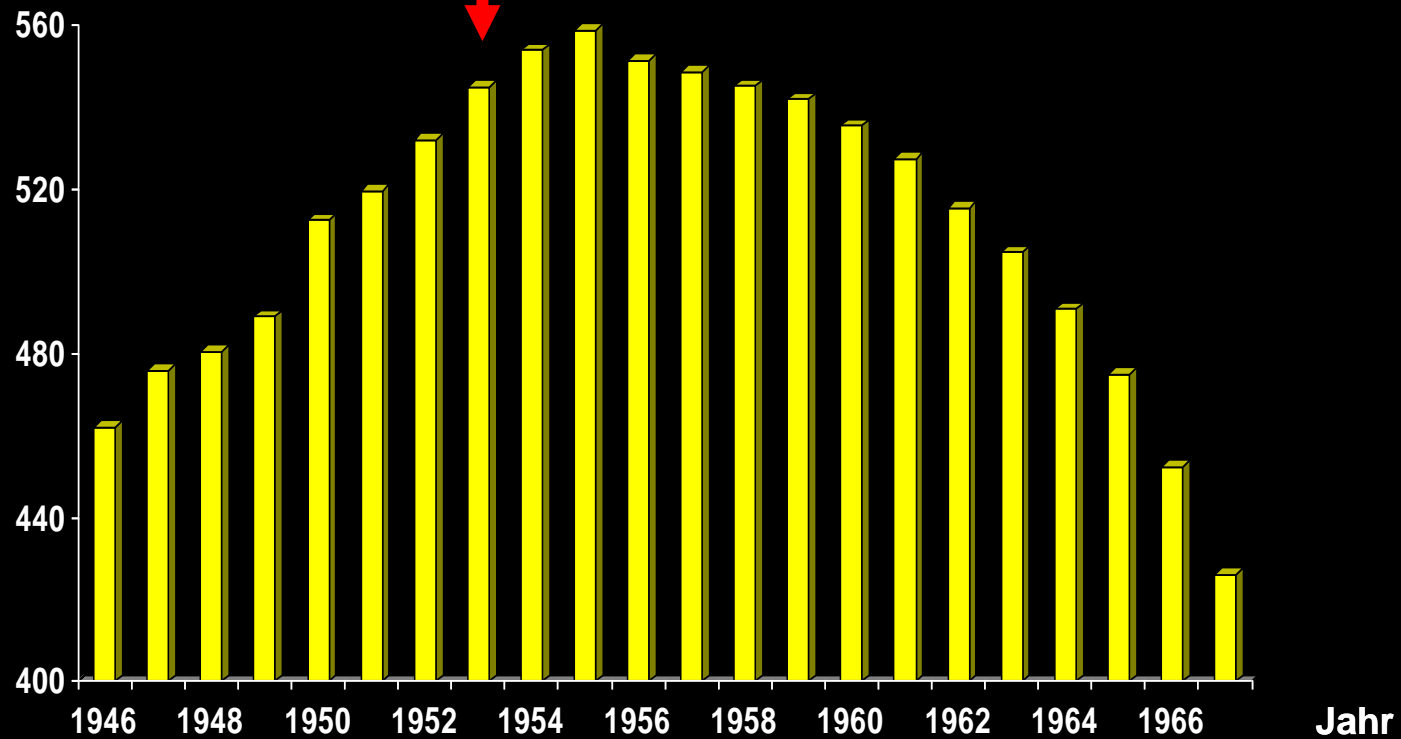
## Psychiatrische Langzeitpatienten

Zunahme der Patientenzahl  
vor der Psychopharmaka-Ära

Abnahme der Patientenzahl  
in der Psychopharmaka-Ära

Zahl der Patienten  
[Tausend]

Einführung von Reserpin und Chlorpromazin



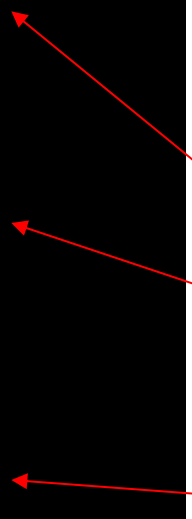
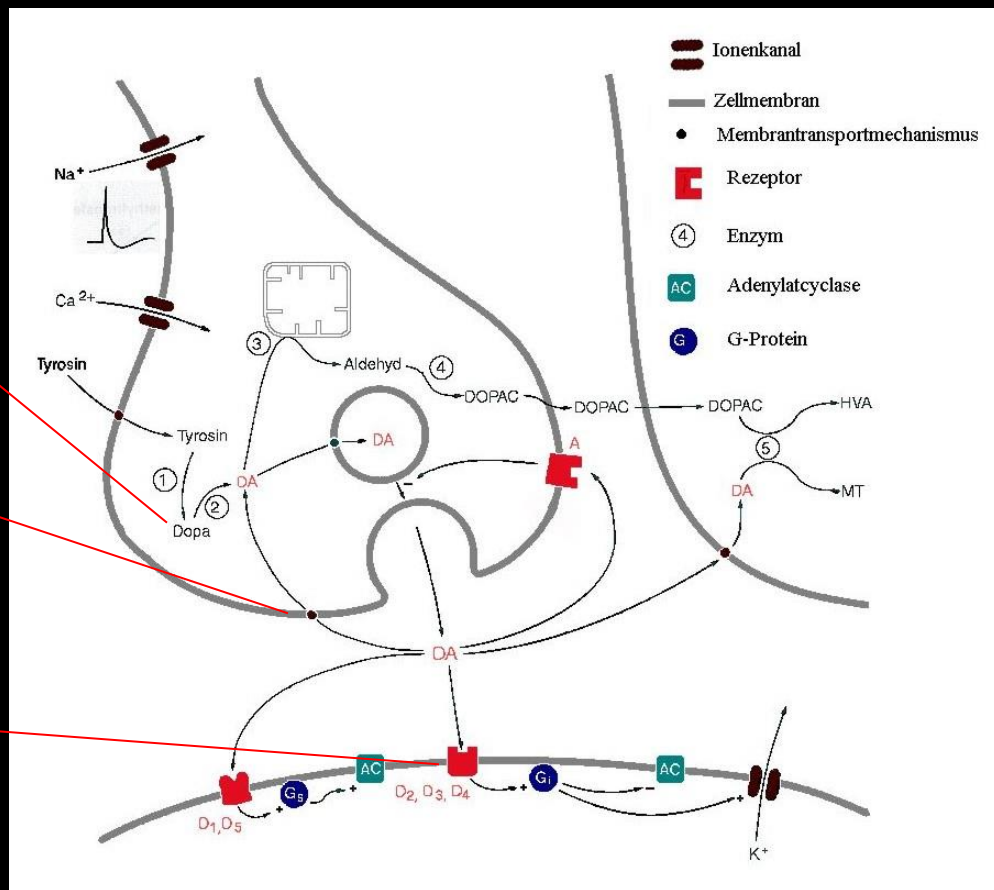
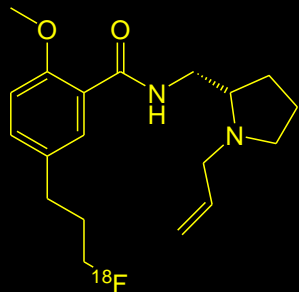
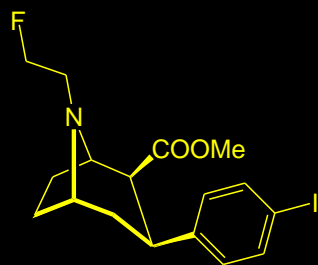
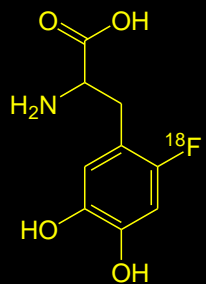


## Neuroleptika

- Wie und wo wirken Neuroleptika ?
- Wie bestimme ich die effiziente Dosis  
(der Patient als „black box“)
- Minimierung von Nebenwirkungen!



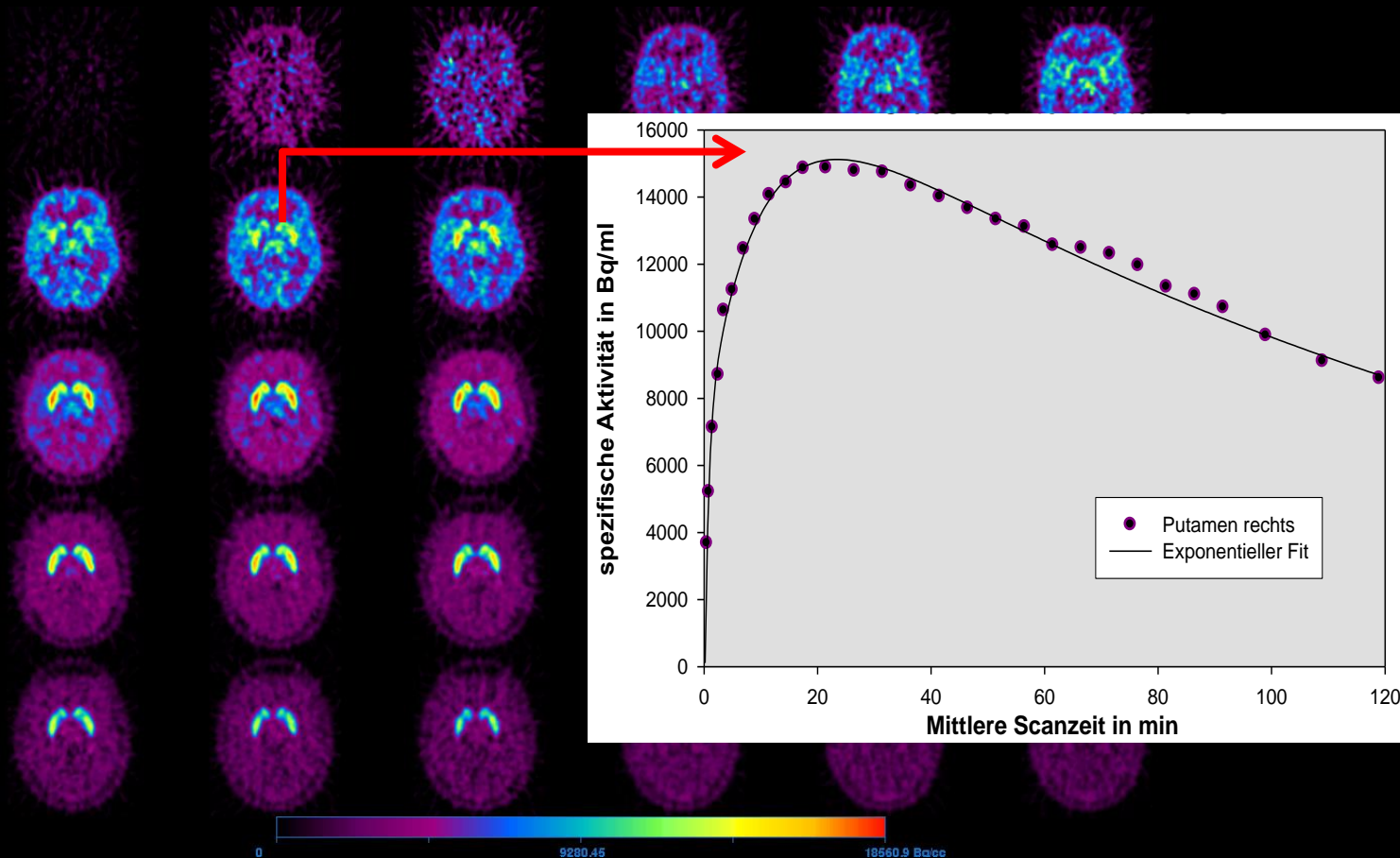
# Das dopaminerge System





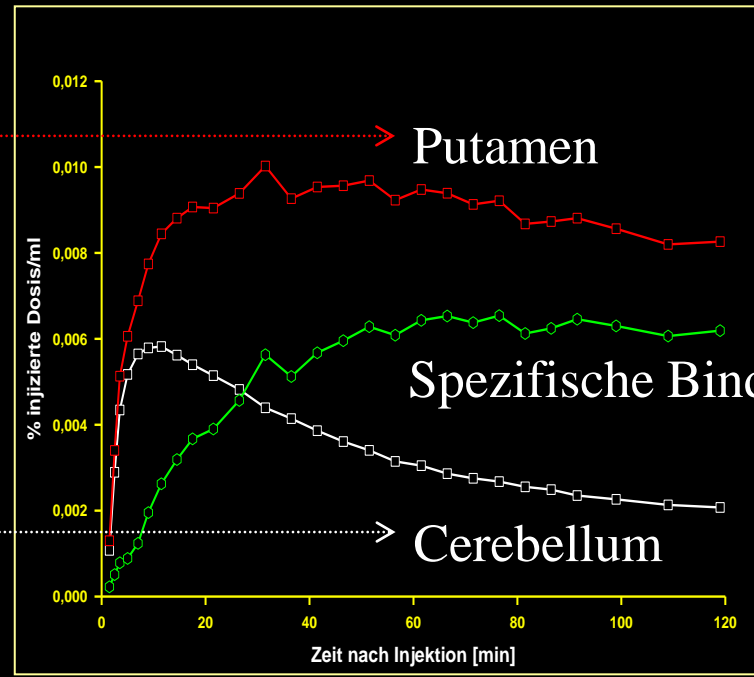
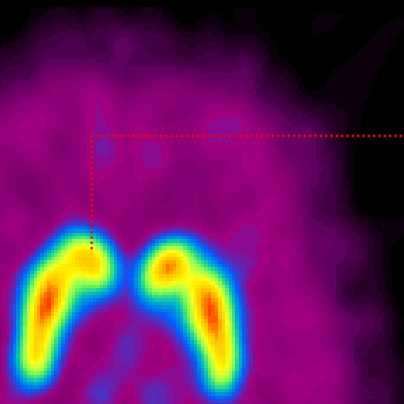


# Dynamisches PET am Beispiel $[^{18}\text{F}]\text{DMFP}$





# Spezifische Bindung von $[^{18}\text{F}]\text{DMFP}$

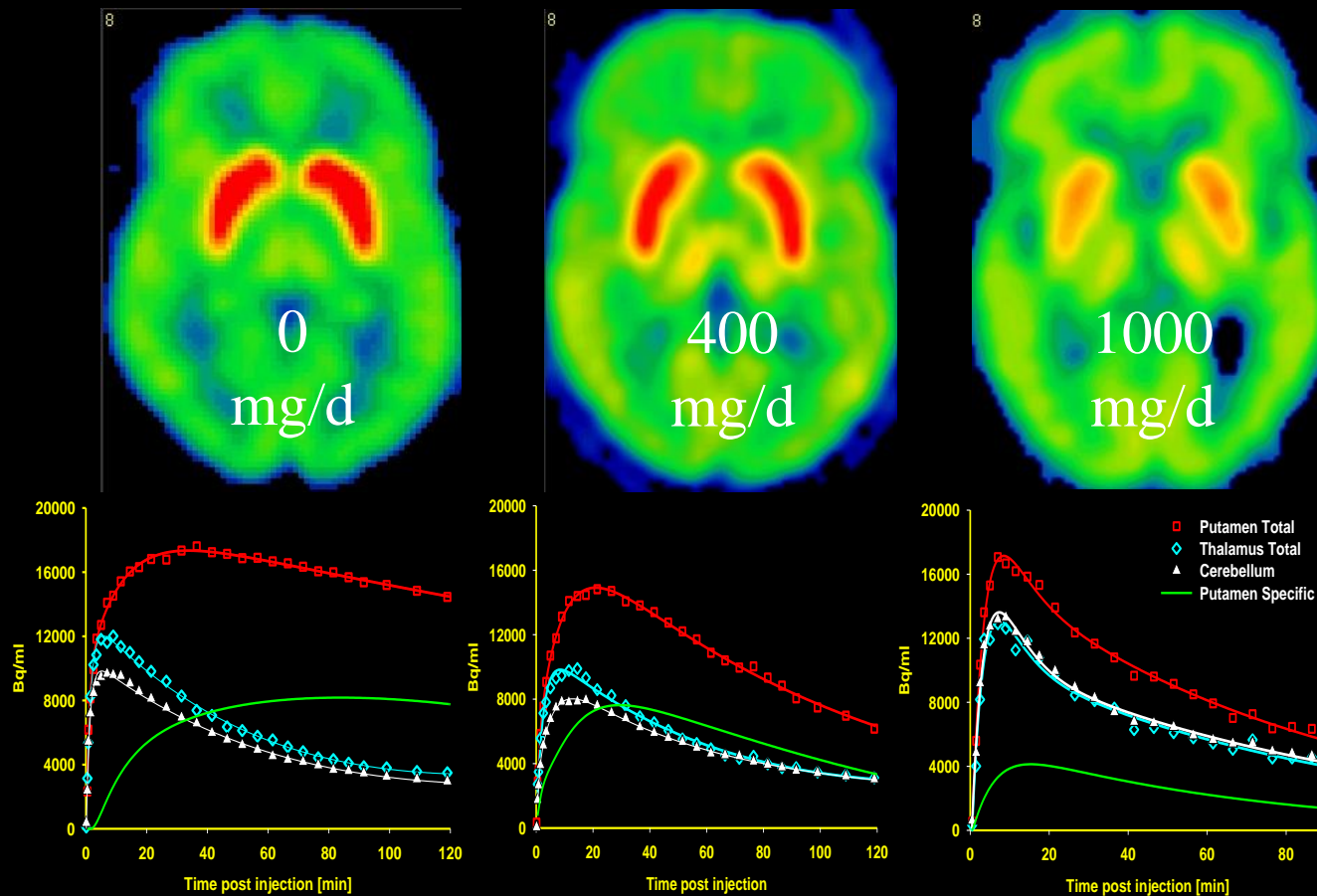


- ➔ Verteilungsvolumina
- ➔ Rezeptordichte
- ➔ Bindungspotential



# DDD: Determination of Dosages of Drugs

[<sup>18</sup>F]DMFP: D<sub>2</sub>-Rezeptorbelegung durch Amisulpride





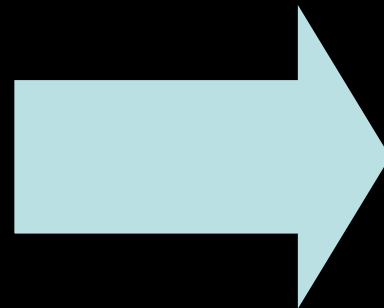
**ZNS-Diagnostik**

**Tumordiagnostik**



## Rezeptorligand-Rezeptor-Interaktion

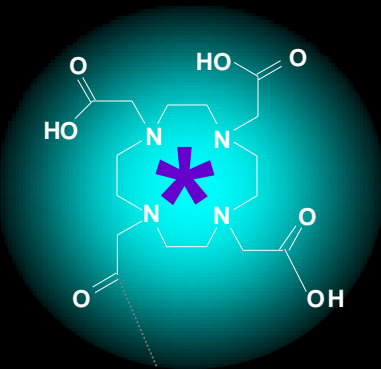
Neuro-  
Rezeptoren



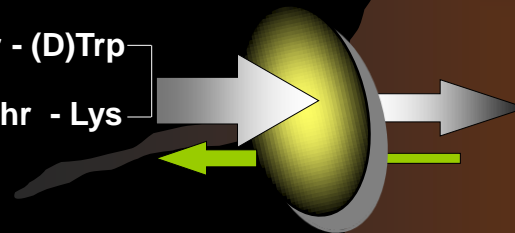
Tumor-  
Rezeptoren



# Tumor-Rezeptoren



(D)Phe - Cys - Tyr - (D)Trp  
 Thr(ol) - Cys - Thr - Lys



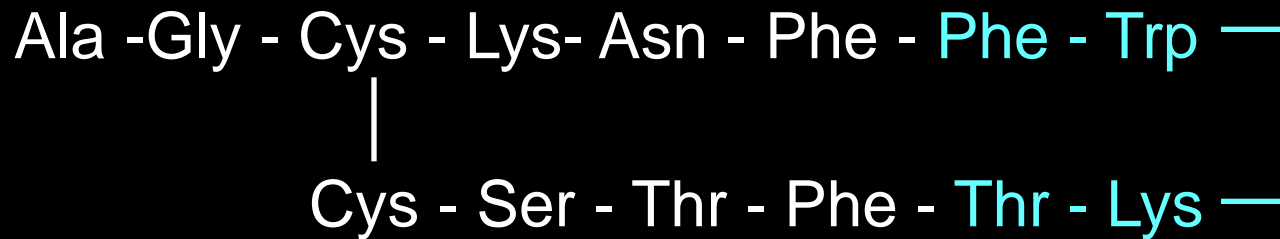
**Somatostatin-Rezeptor**  
**Octreotid (SMS 201-995) an**  
**humane SRIF-Rezeptorsubtypen**

hSSTR1	> 1000 nmol / L
hSSTR2	0.32 nmol / L
hSSTR3	31.6 nmol / L
hSSTR4	> 1000 nmol / L
hSSTR5	7.3 nmol / L



## Liganden für den Somatostatinrezeptor

### Somatostatin



### Octreotid









1. Messprinzip und Messung der Signale
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3. Biochemische Konzepte
4. **Synthese geeigneter Moleküle**
5. Medizinische Bewertung (Diagnostik)

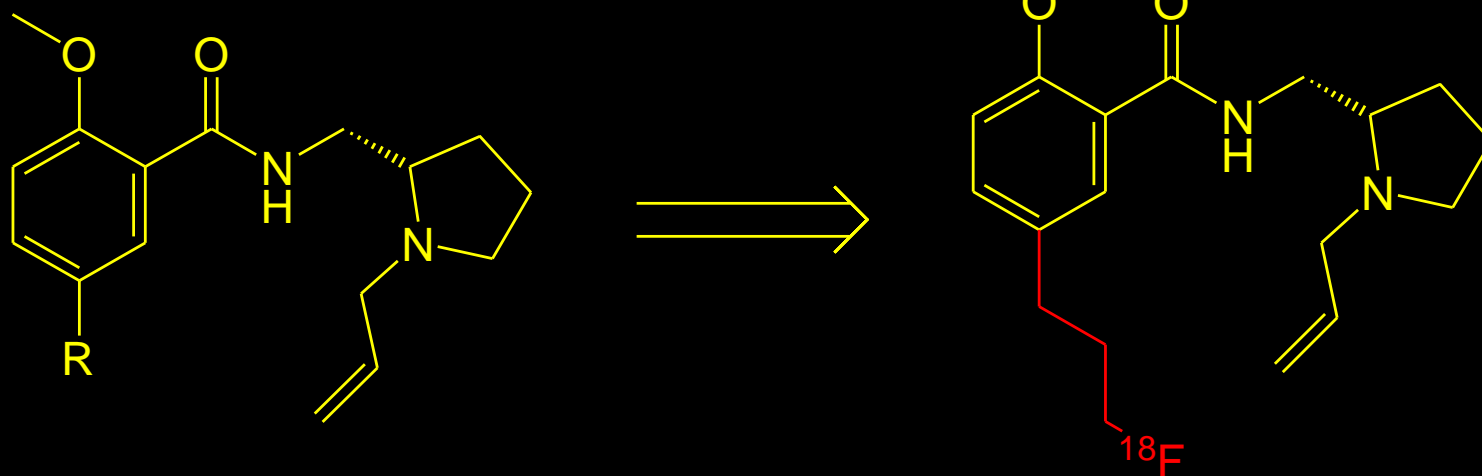


## Arbeitsplan zur Darstellung eines Radioliganden

- Identifizierung geeigneter Leitstrukturen
- Modifikation des Liganden bezüglich der Markierung
- Synthese der Referenzverbindung
- In vitro-Evaluierung  
(Bestimmung der Affinität, Lipophilie, etc.)
- Synthese des Markierungsvorläufers
- Optimierung der Markierungsreaktion
- Tierversuche

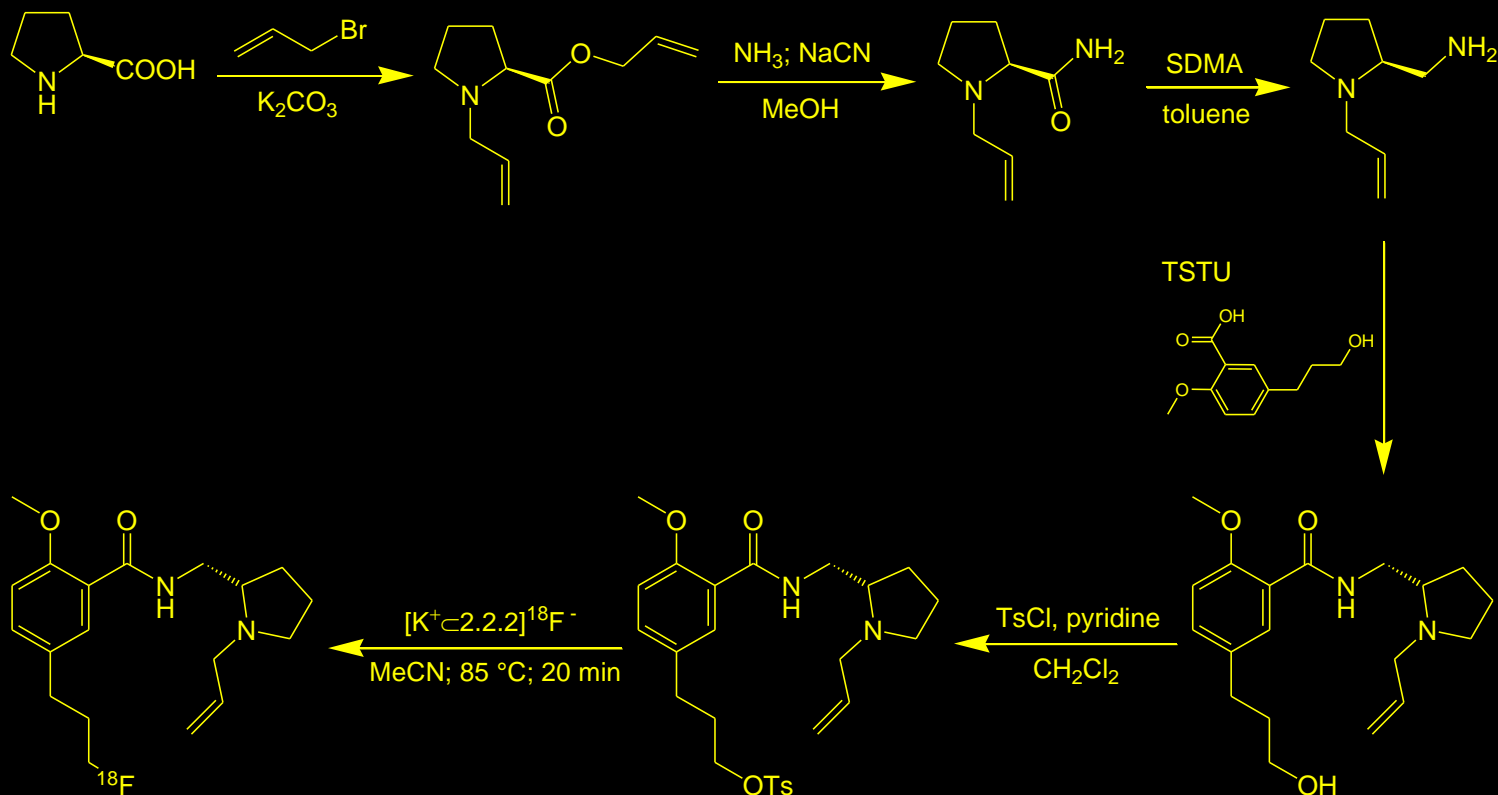


## Leitstruktur für D<sub>2</sub>-Liganden





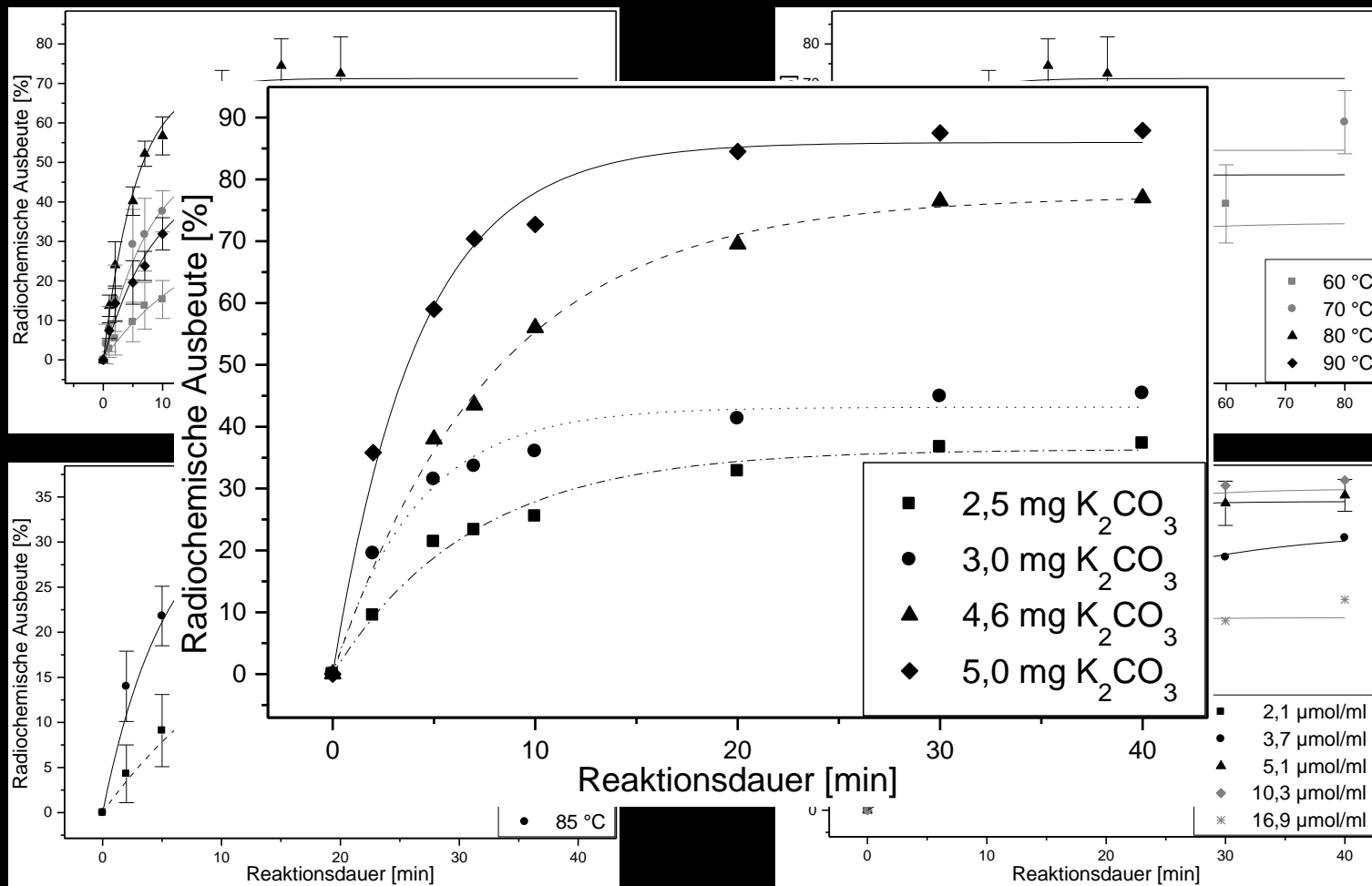
## Syntheschema [<sup>18</sup>F]DMFP



Anschließend: in vitro-Evaluierung (logP = 2,07 ± 0,08; K<sub>i</sub> = 15 ± 9 nmol)

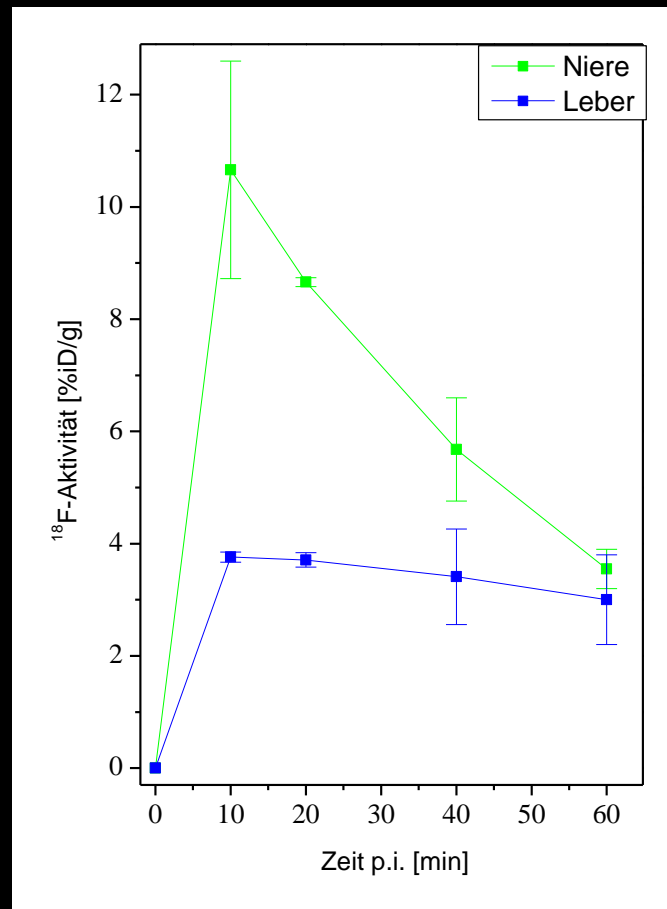
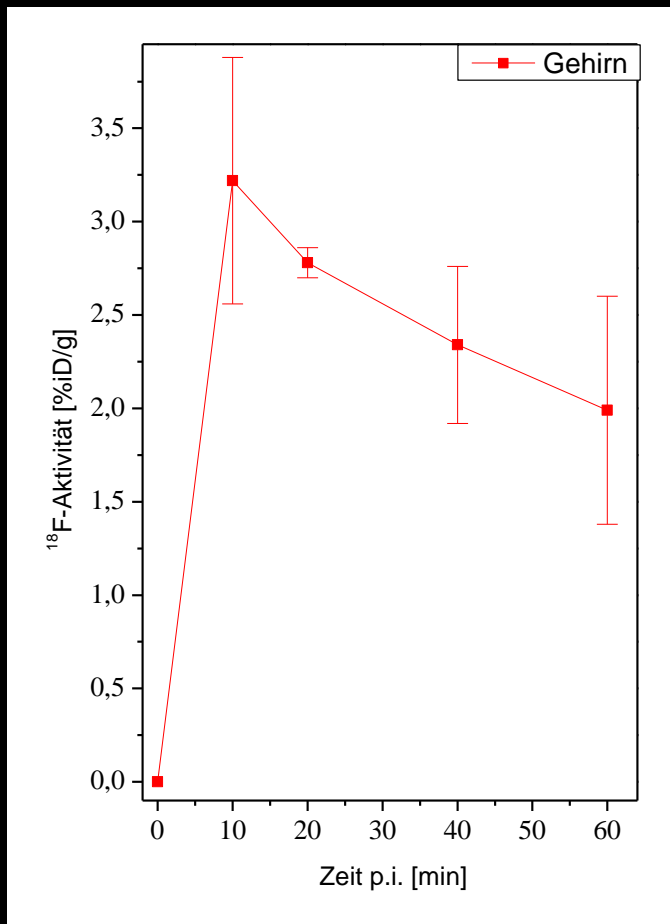


# Optimierung der Markierung



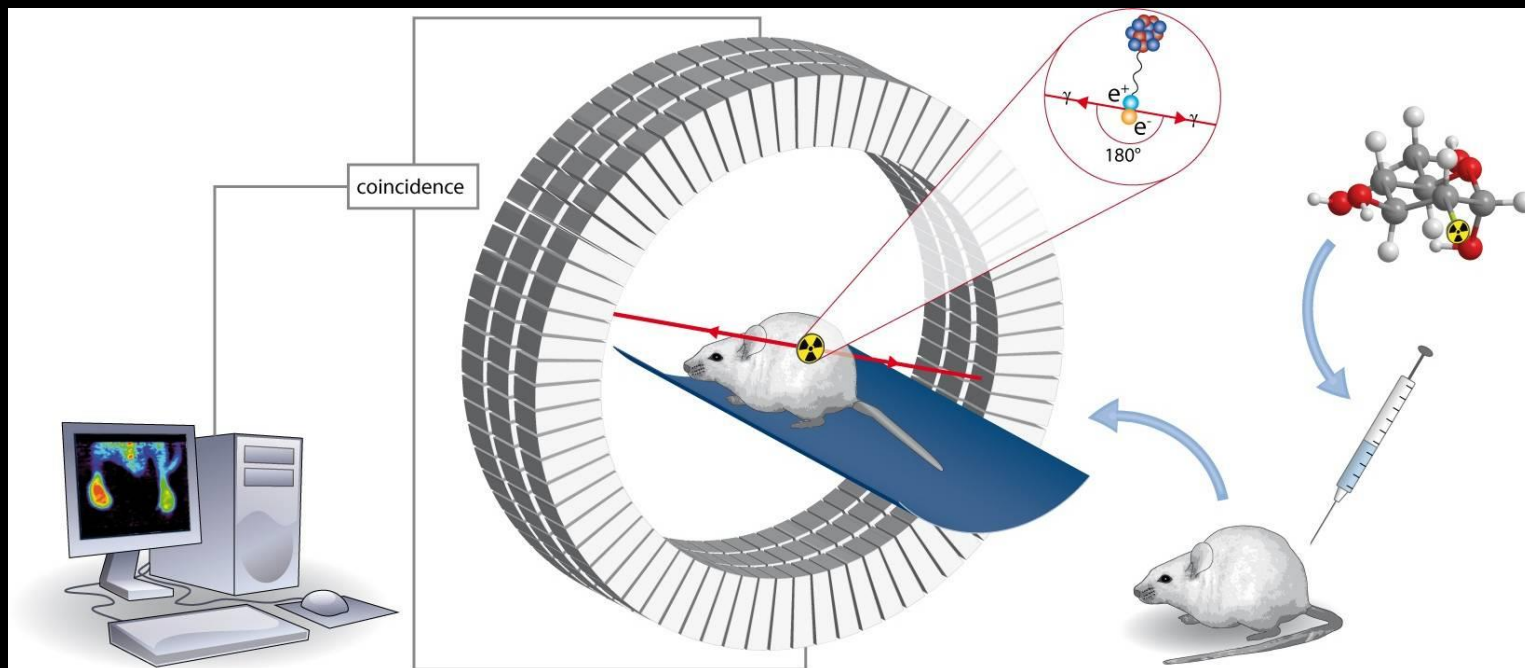


## Ex vivo-Biodistributionen



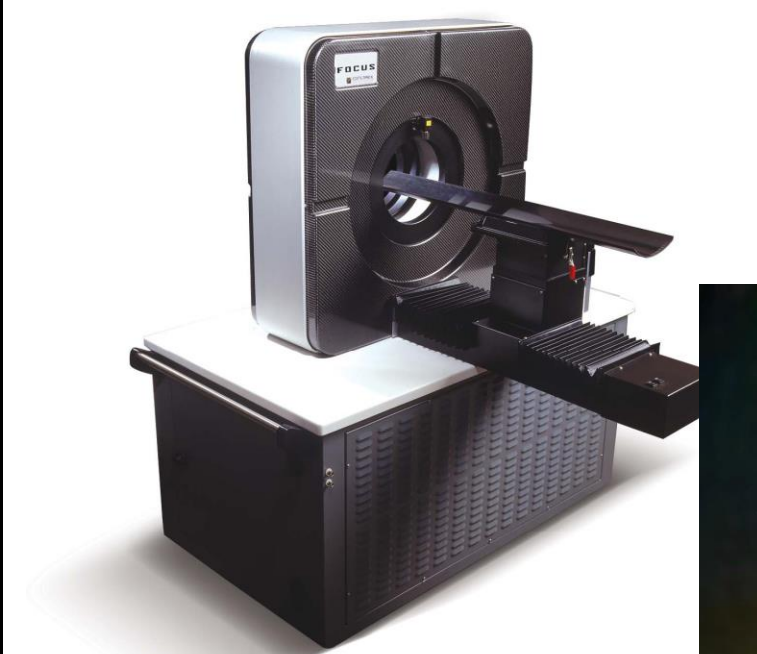


# Studien am Tier PET-Scanner





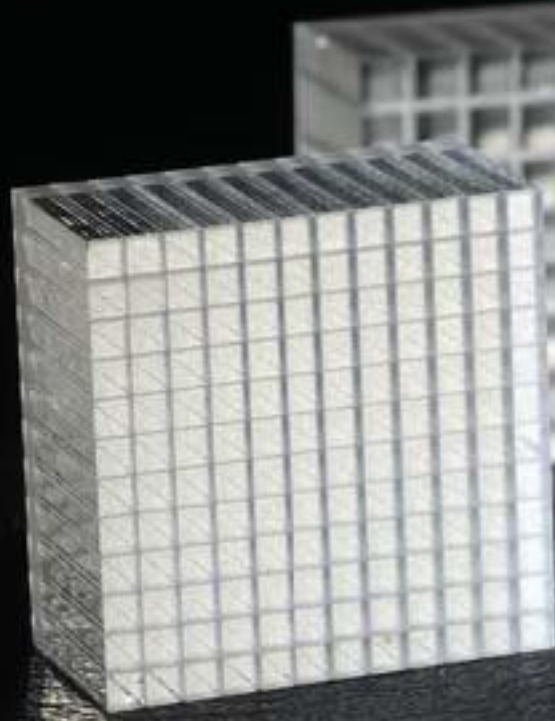
## Studien am Tier PET-Scanner







## Studien am Tier PET-Scanner

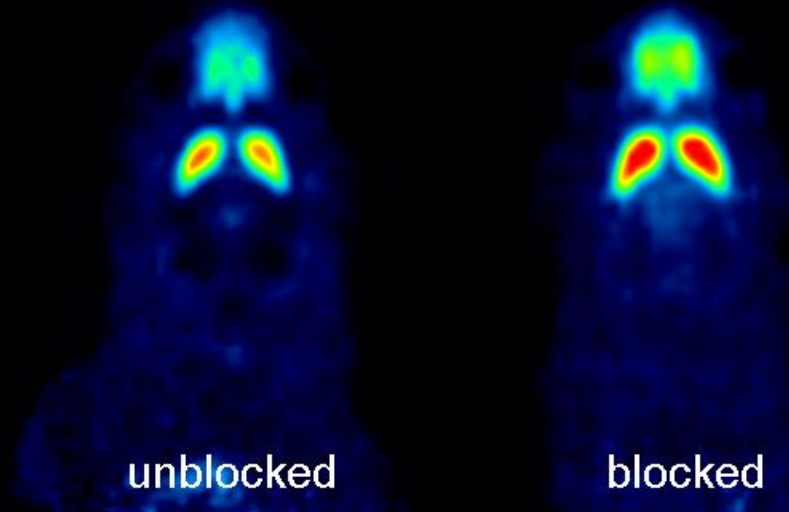


PARAMETER	NaI	BGO	LSO
Dichte [g/mL]	3,67	7,13	7,4
Ordnungszahl [ $Z_{\text{eff}}$ ]	50	73	65
Mittlerer freier Weg [cm]	2,88	1,05	1,16
Hygroskopisch	Ja	Nein	Nein
Robust	Nein	Ja	Ja

PARAMETER	NaI	BGO	LSO
Zerfallszeit [ns]	230	300	40
Spitzenemissionswellenlänge [nm]	410	480	420
Lichtleistung relativ zu NaI	1	0,15	0,75
Energieauflösung bei 511 keV	7,8%	10,1%	10%

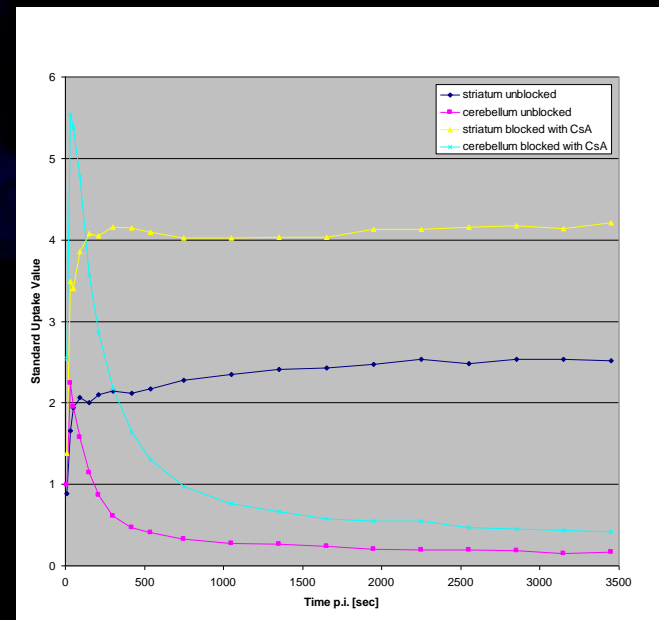


## Studien am Tier PET-Scanner



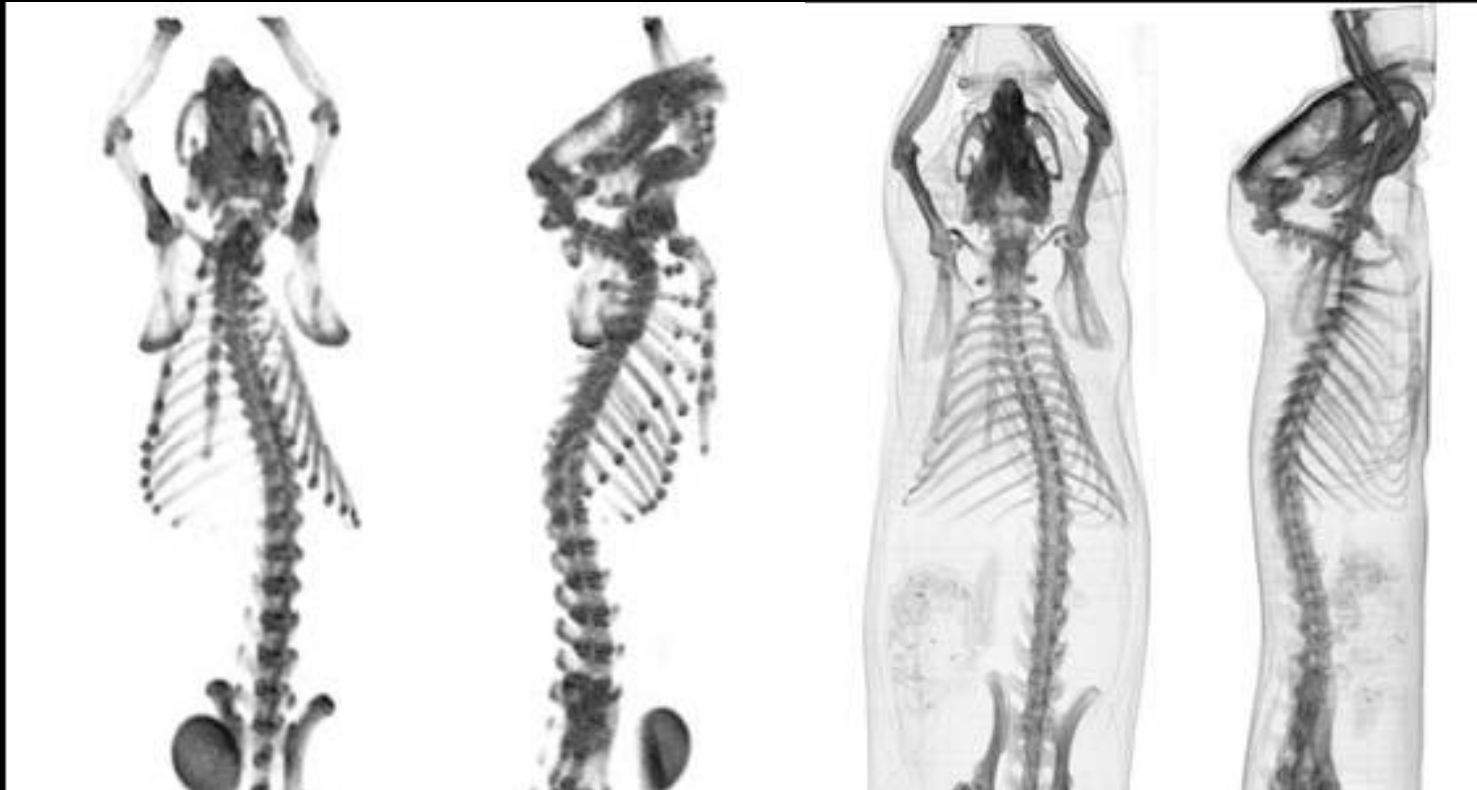
[<sup>18</sup>F]Fallypride sum images (0-60 min p.i.) of untreated (left) and with Cyclosporine A treated (right) Sprague Dawley rats

Plot of striatal and cerebellar [<sup>18</sup>F]Fallypride uptake for blocked and unblocked Sprague Dawley rats





## Studien am Tier PET-Scanner



*(left) Bone images acquired on a microPET; bone images (right) acquired on a microCAT. Images courtesy of Crump Institute for Molecular Imaging, Los Angeles, CA.*

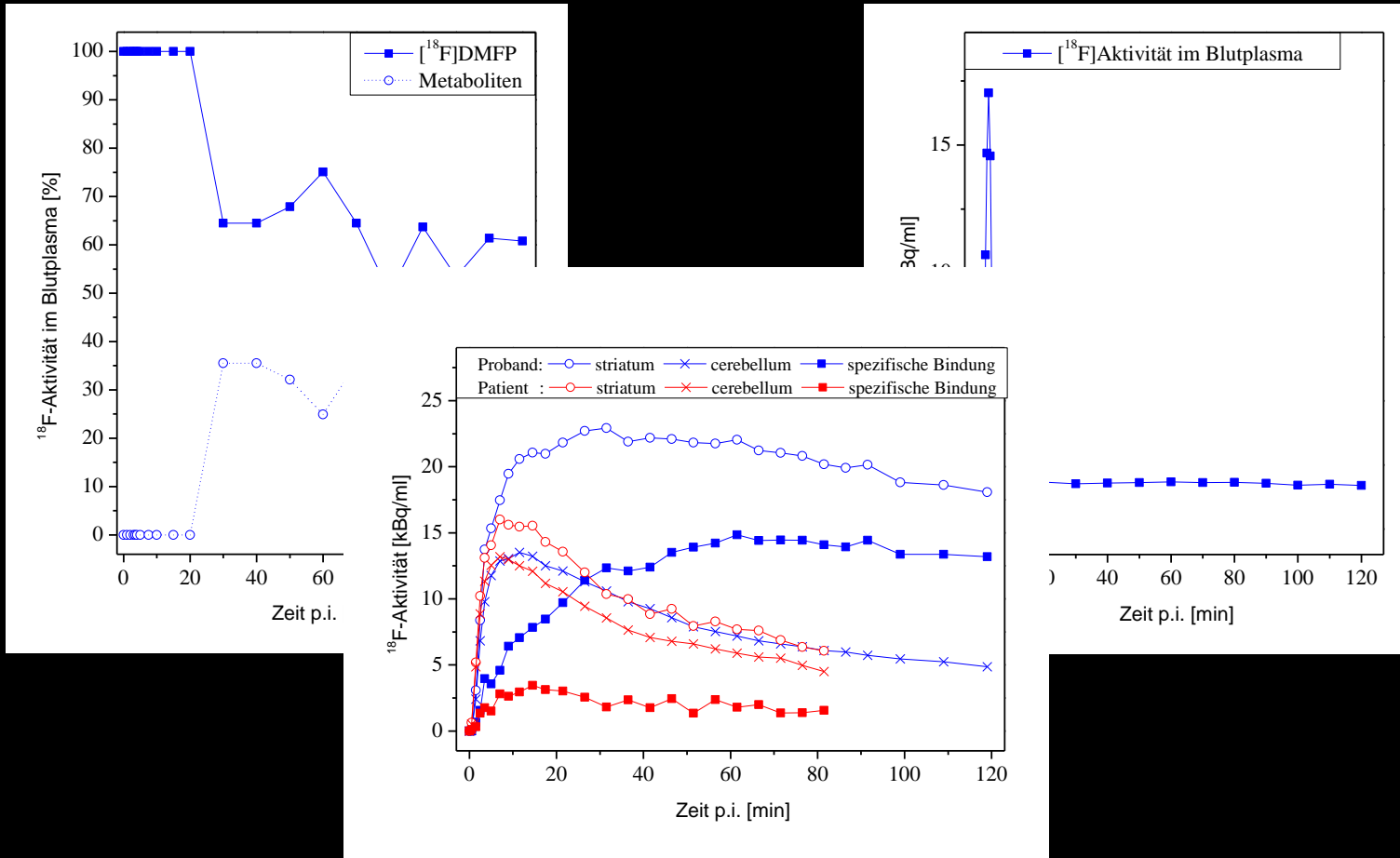


## Studien am Tier PET-Scanner



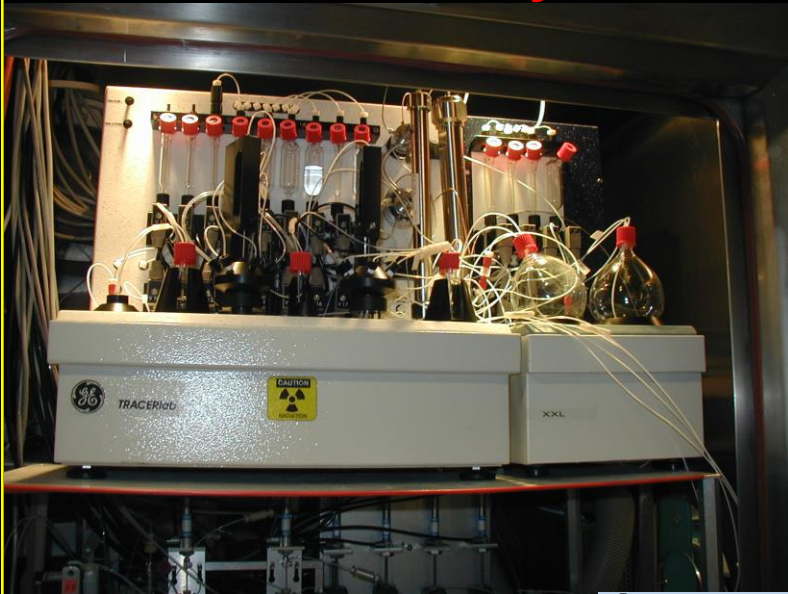


# Probandenstudien



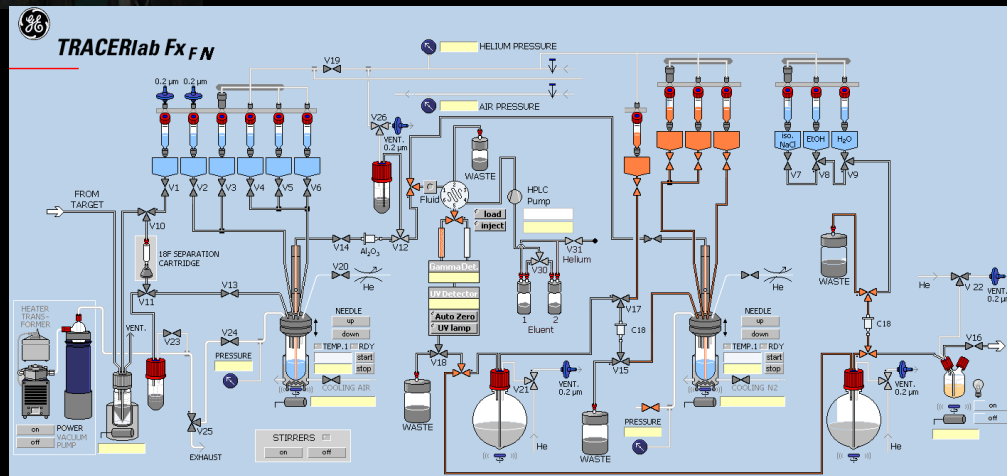


# Synthesen der Tracer



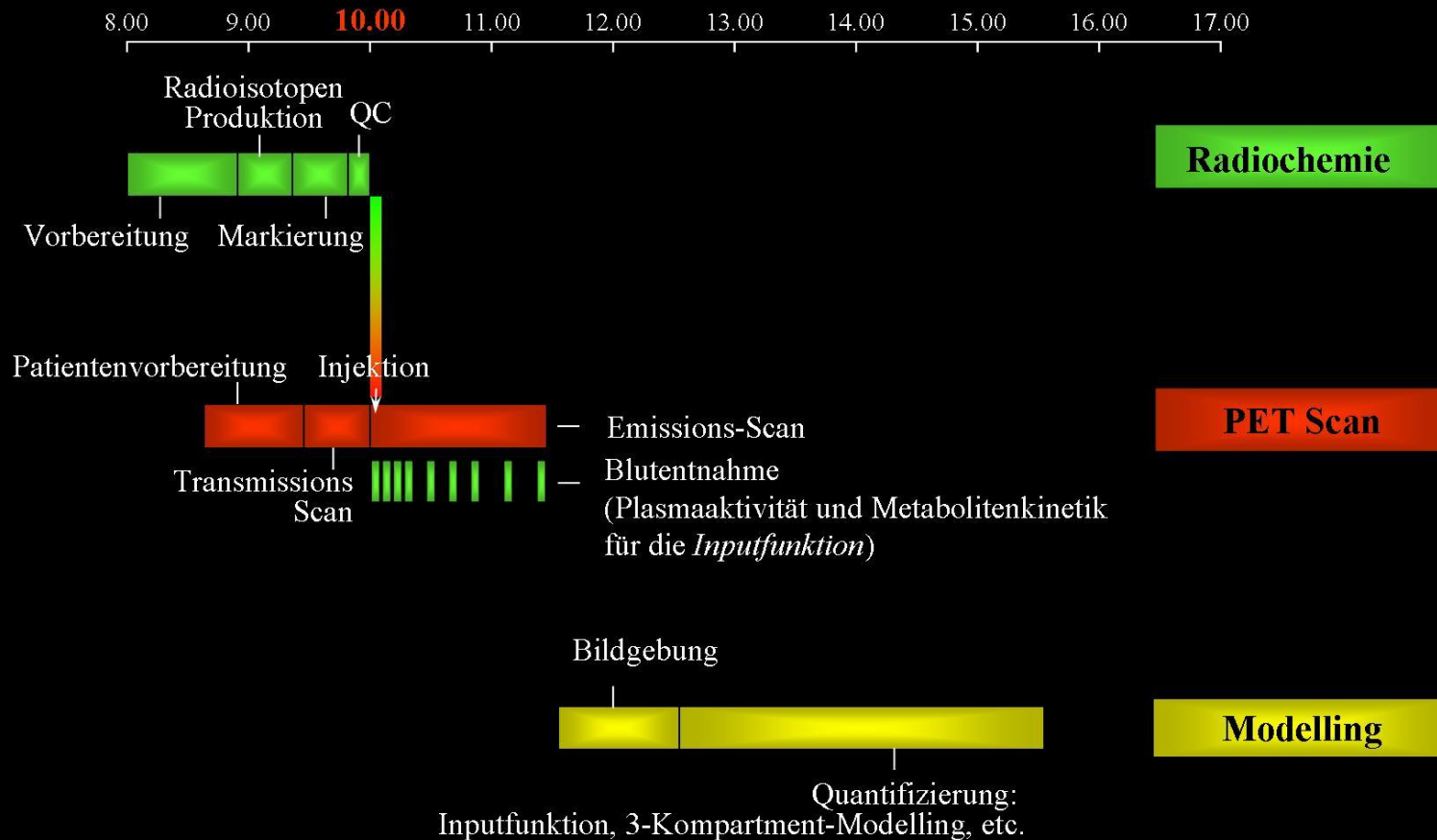
## Vollautomatisierte Module:

- Geringe Strahlenbelastung des Personals
- Bessere Reproduzierbarkeit der Synthesen
- GMP leichter umsetzbar





# PET-Tagesplan





- 1. Messprinzip und Messung der Signale**
- 2. Herstellung geeigneter Radioisotope**
- 3. Biochemische Konzepte**
- 4. Synthese geeigneter Moleküle**
- 5. Medizinische Bewertung (Diagnostik)**



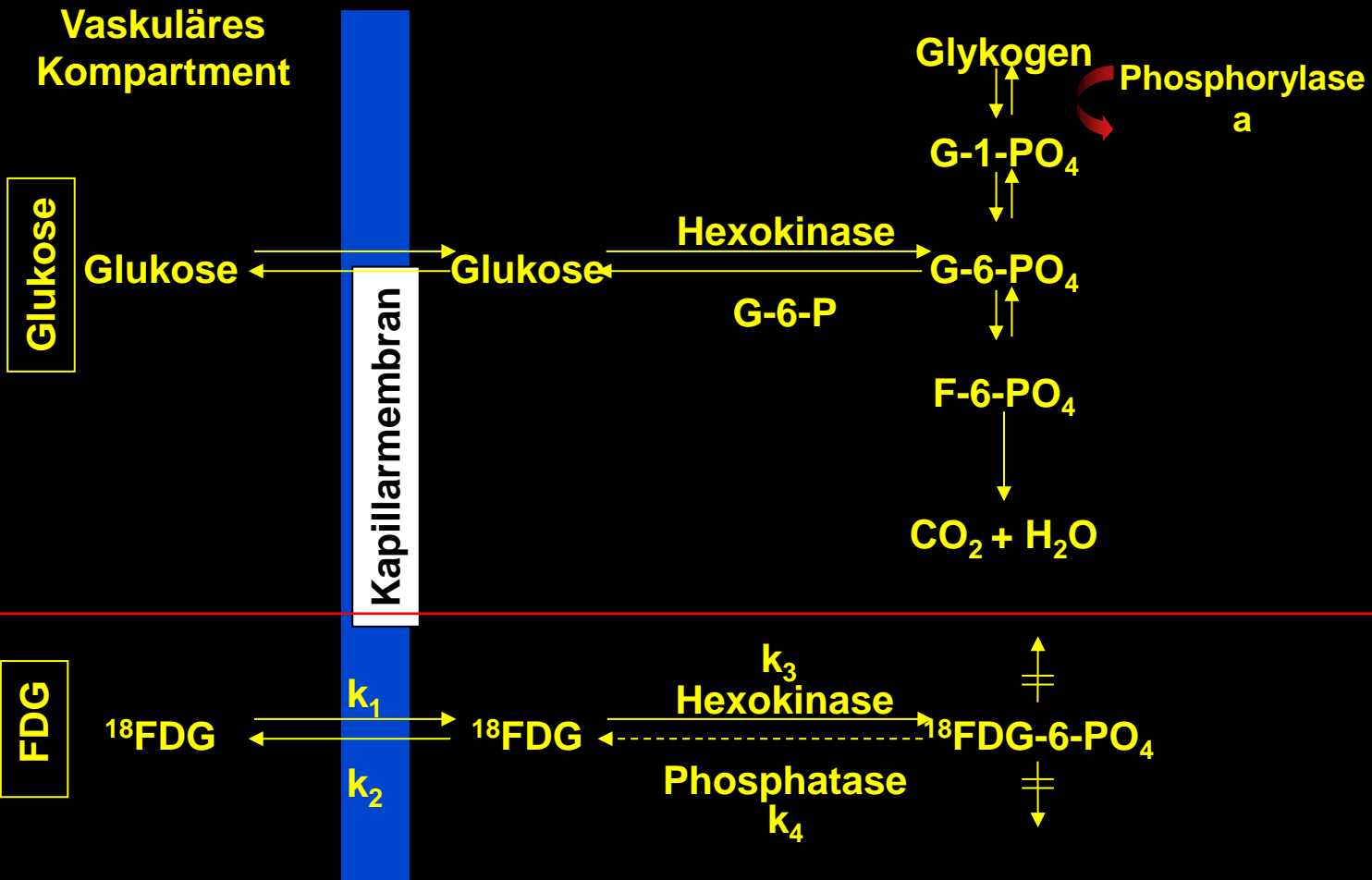


**ZNS-Diagnostik**

**Tumordiagnostik**

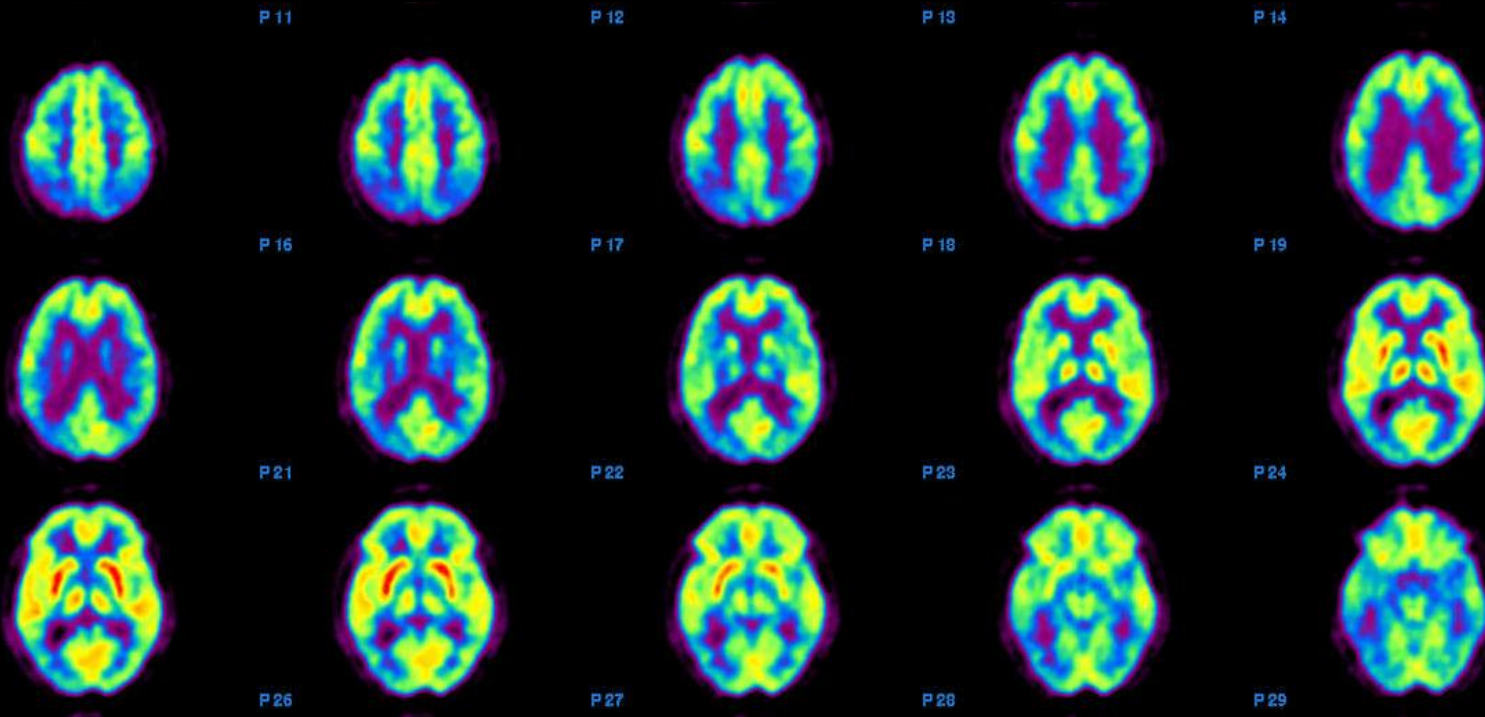


# [<sup>18</sup>F]FDG





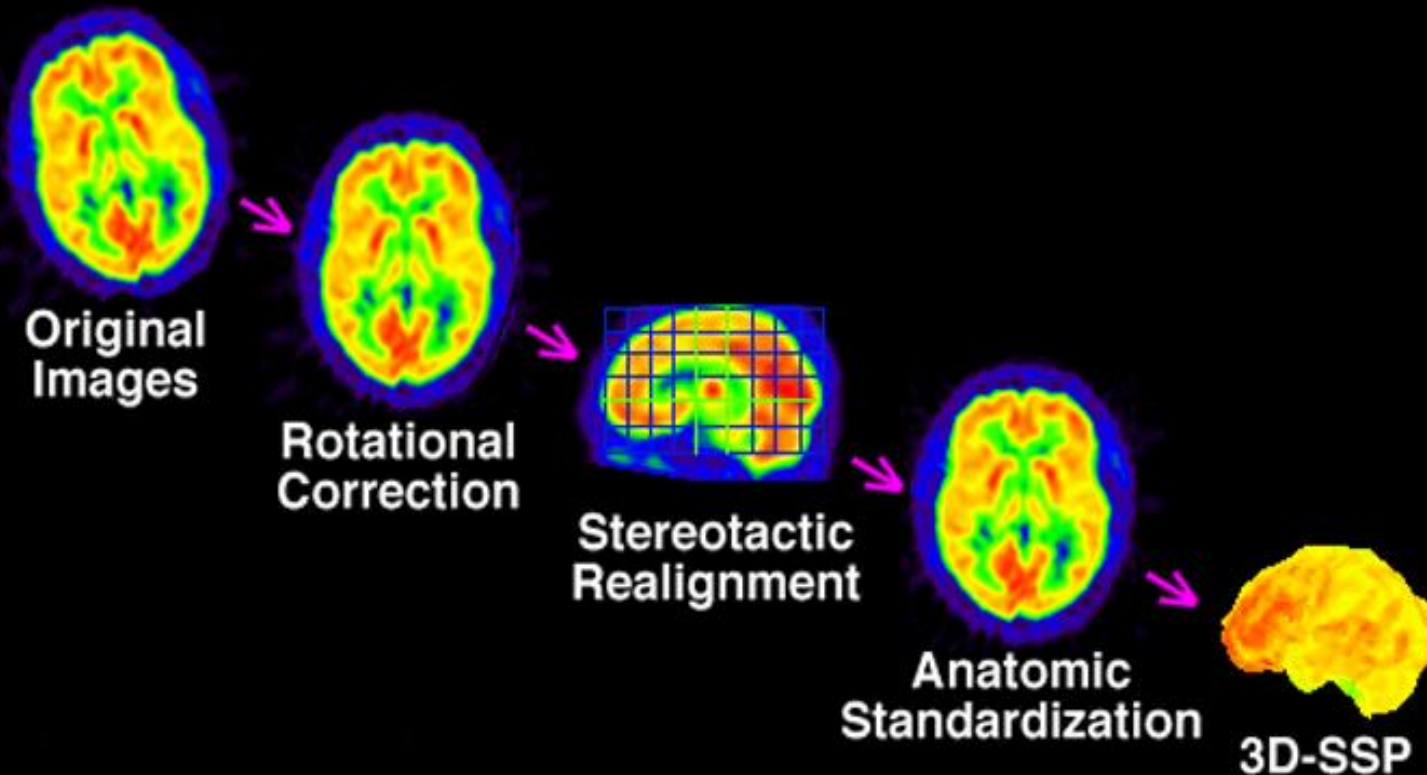
# [<sup>18</sup>F]FDG (Alzheimer)





# [<sup>18</sup>F]FDG (Alzheimer – mittels Neuro-Stat))

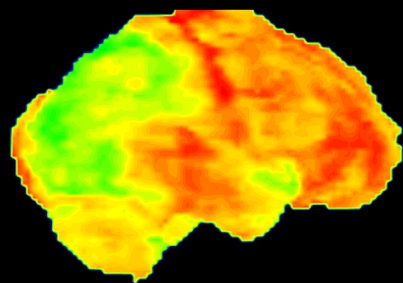
## AUTOMATED PET 3D-SSP ANALYSIS



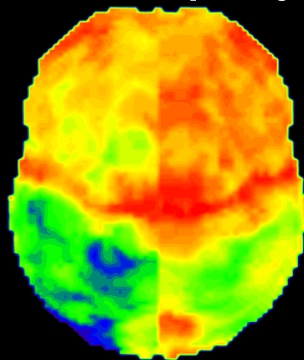


# [<sup>18</sup>F]FDG (Alzheimer – mittels Neuro-Stat)

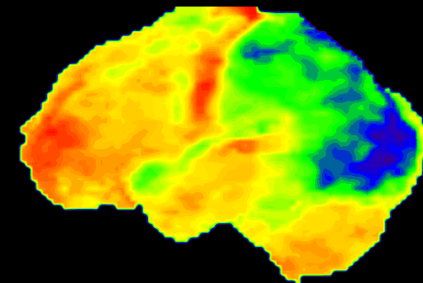
## Oberflächenprojektion



rechts lateral

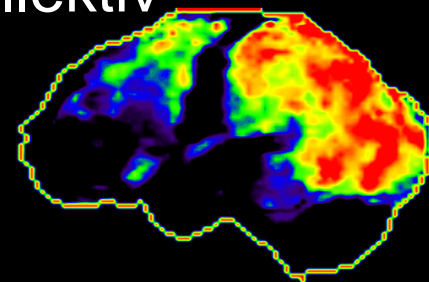
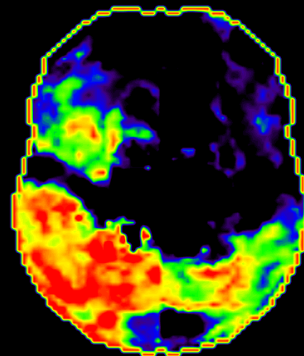
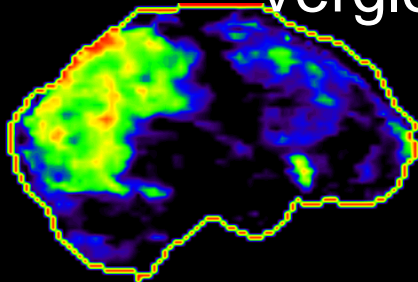


oben



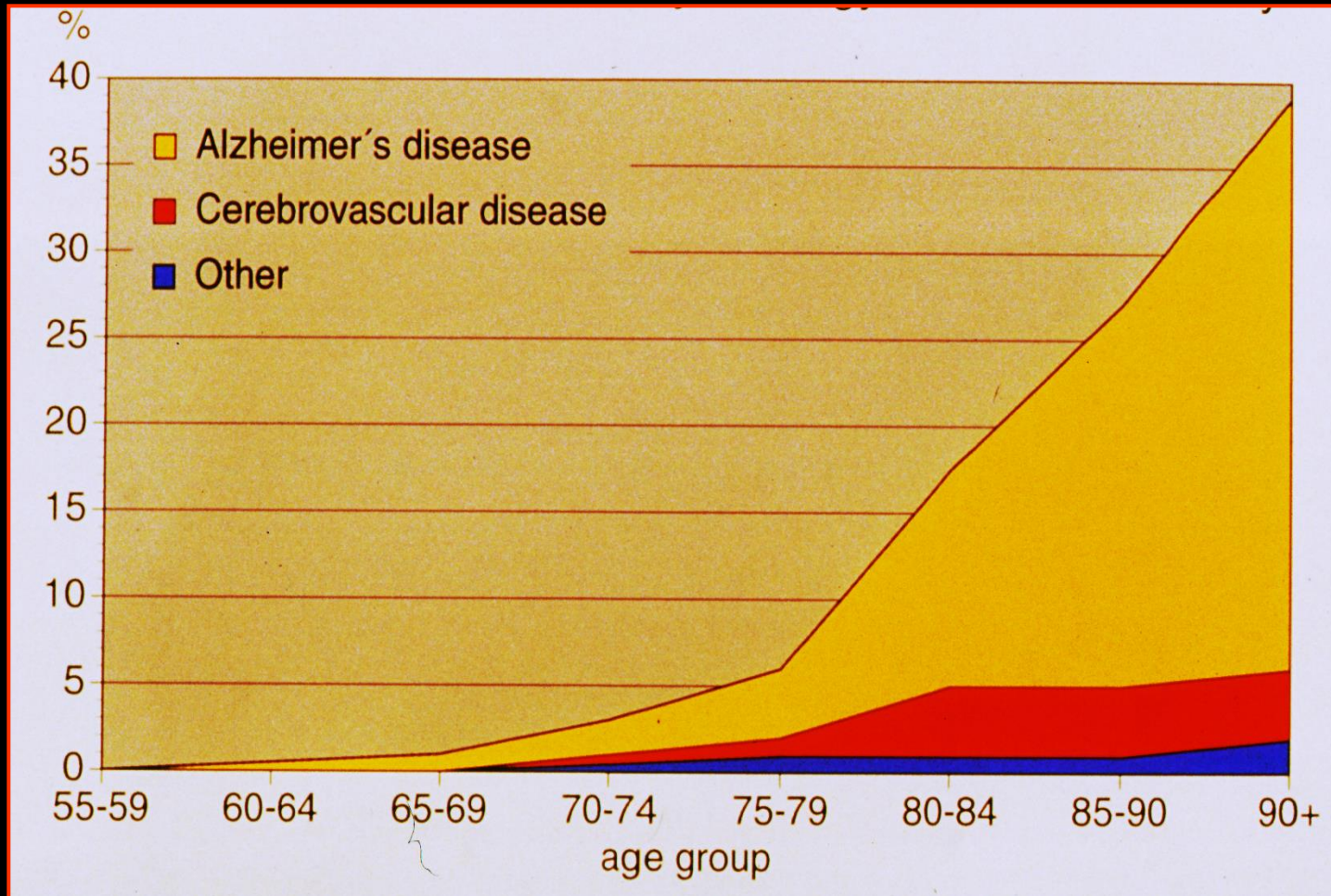
links lateral

## Vergleich zu einem Normkollektiv





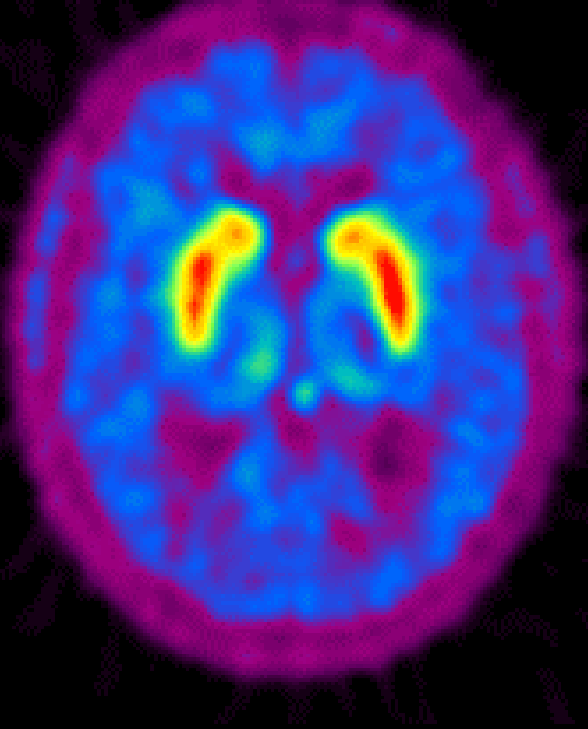
## Demenz-Risiko (Rotterdam-Studie)



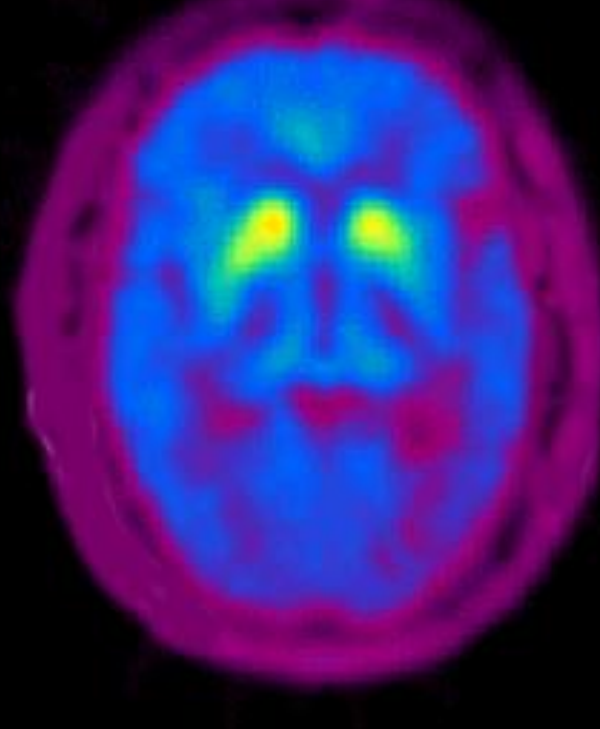


## [<sup>18</sup>F]Fluordopa

Normalbefund



M. Parkinson



Dopamin-Rezeptorsystem: Parkinson, ...



## [<sup>18</sup>F]Fluordopa (Differentialdiagnostik)

Patient A



Patient B

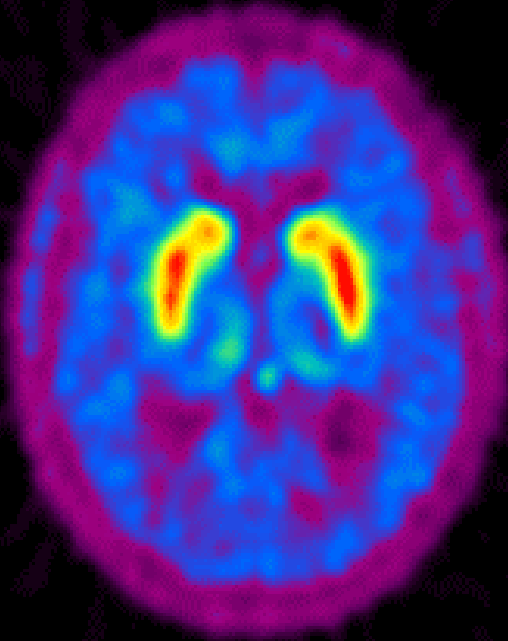






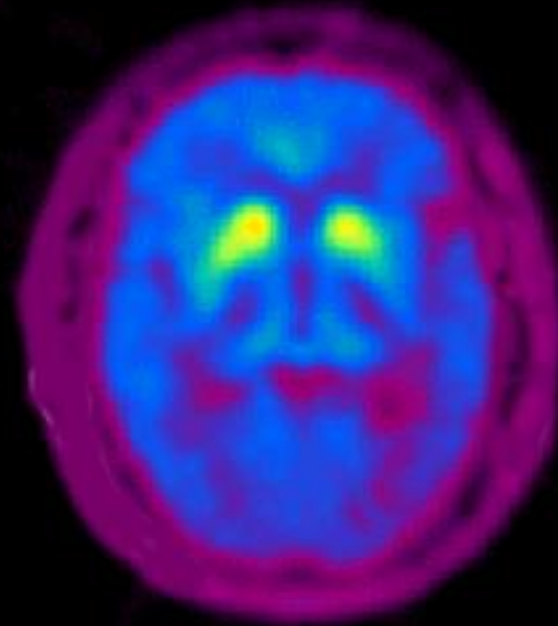
## [<sup>18</sup>F]Fluordopa (Differentialdiagnostik)

Patient A



Essentieller Tremor

Patient B



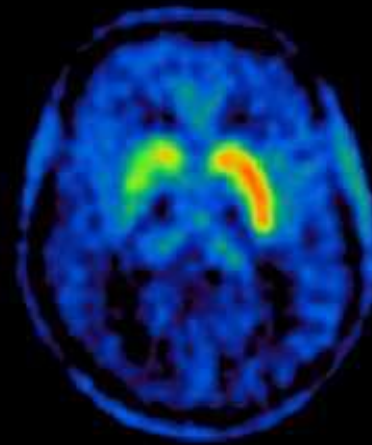
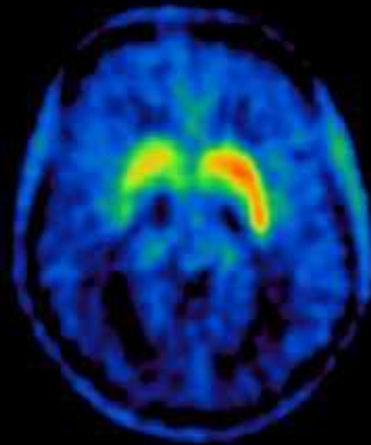
M. Parkinson



# [<sup>18</sup>F]Fluordopa

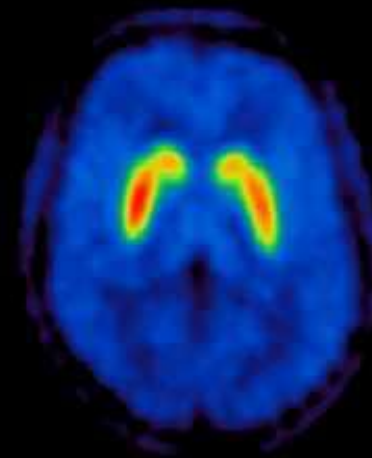
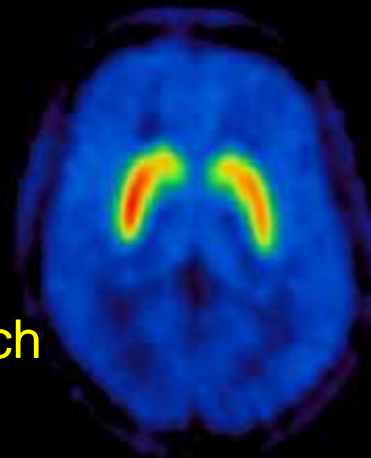
F18-Dopa

präsynaptisch



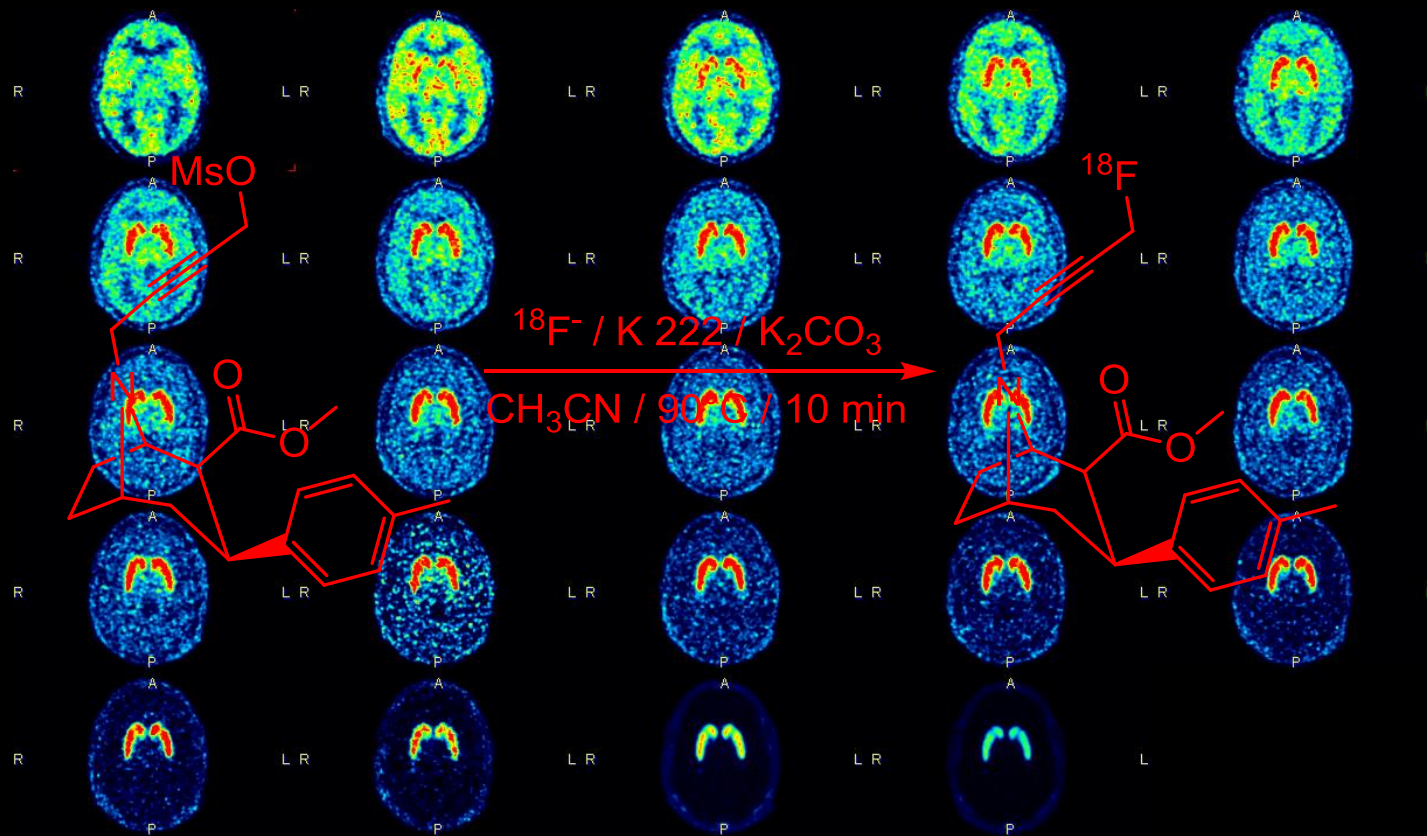
F18-DMFP

postsynaptisch





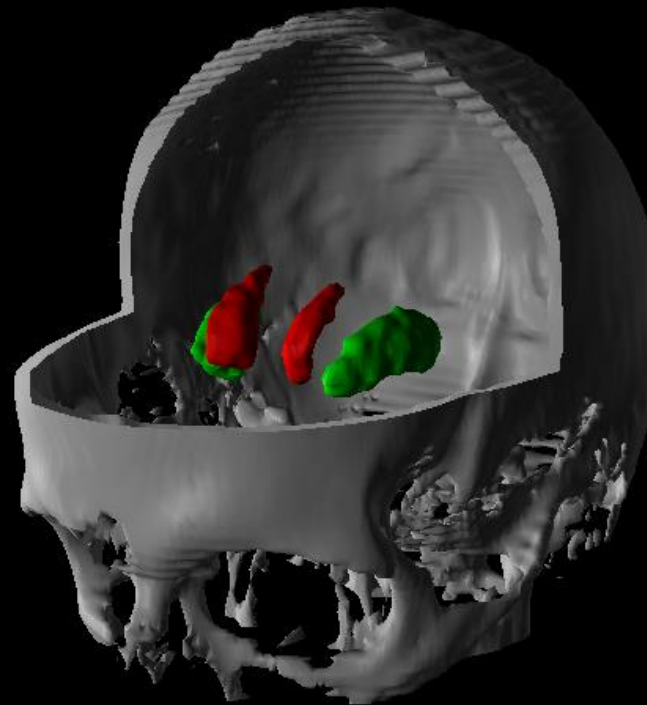
# [<sup>18</sup>F]PR04.MZ



**DAT: Parkinson...**



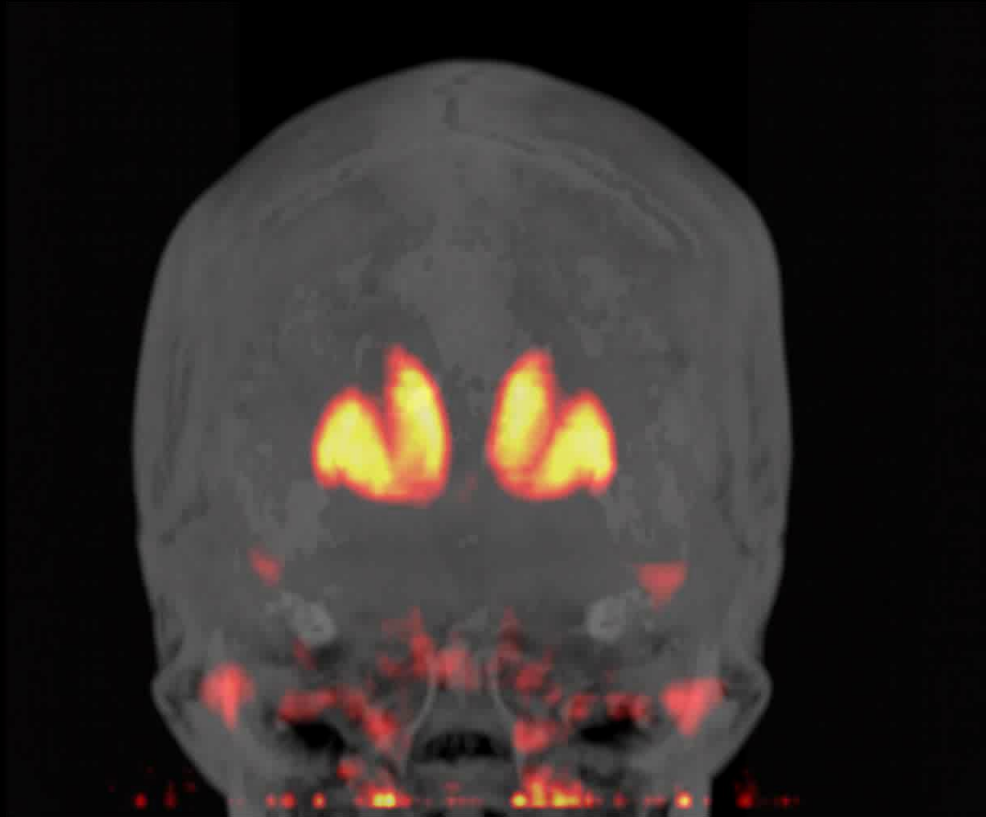
[<sup>18</sup>F]PR04.MZ



**DAT: Parkinson...**



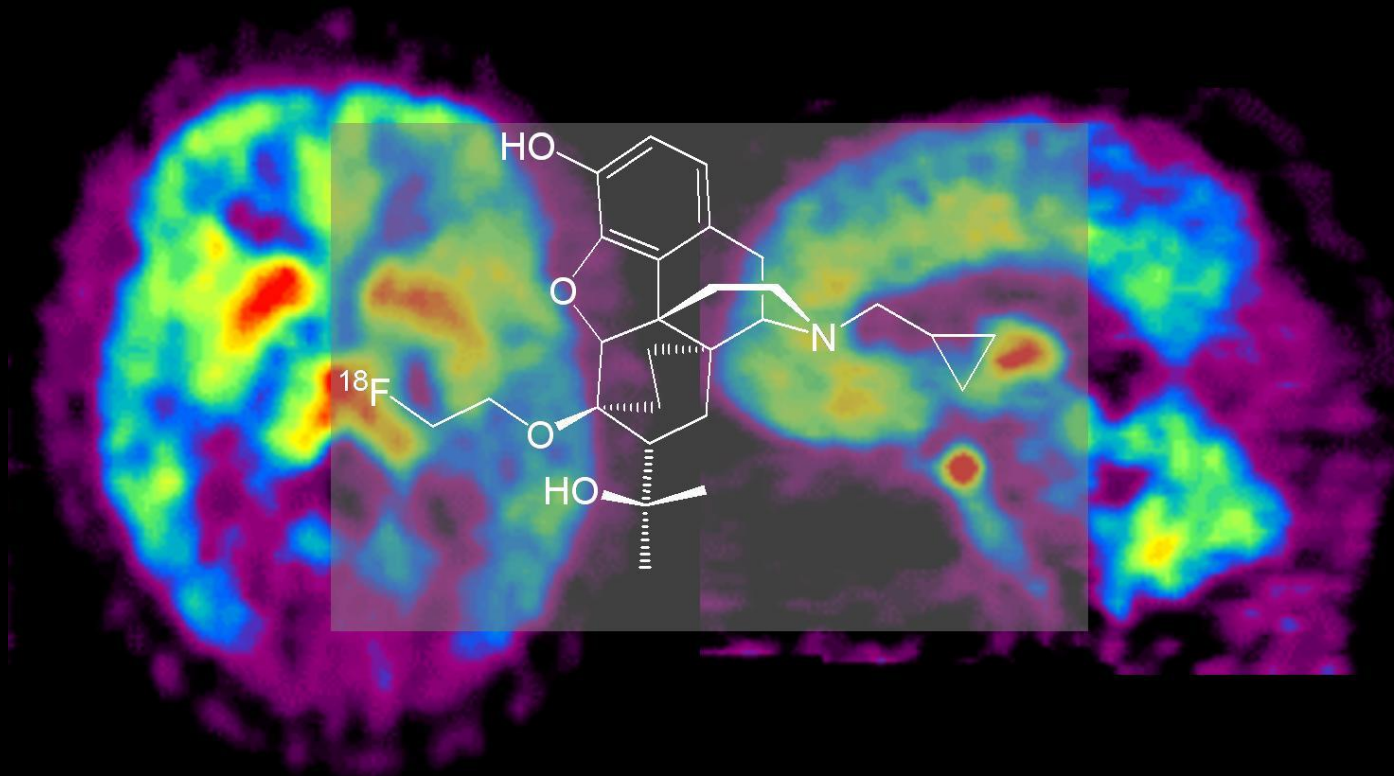
[<sup>18</sup>F]PR04.MZ



**DAT: Parkinson...**



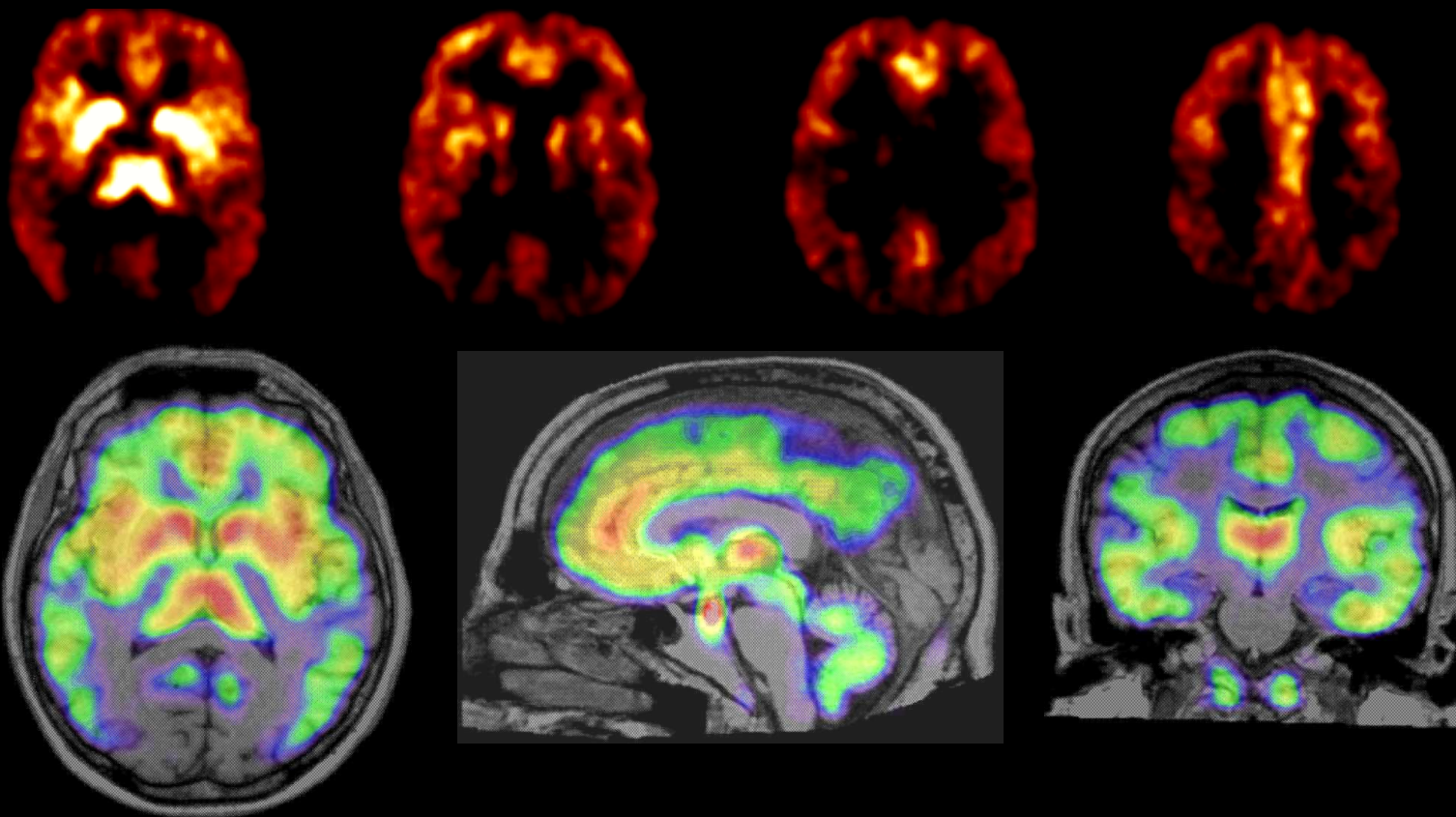
## [18F]Fluorethyl-diprenorphin



Opiat-Rezeptorsystem: Schmerz, Sucht, ...



# [18F]Fluorethyl-diprenorphin

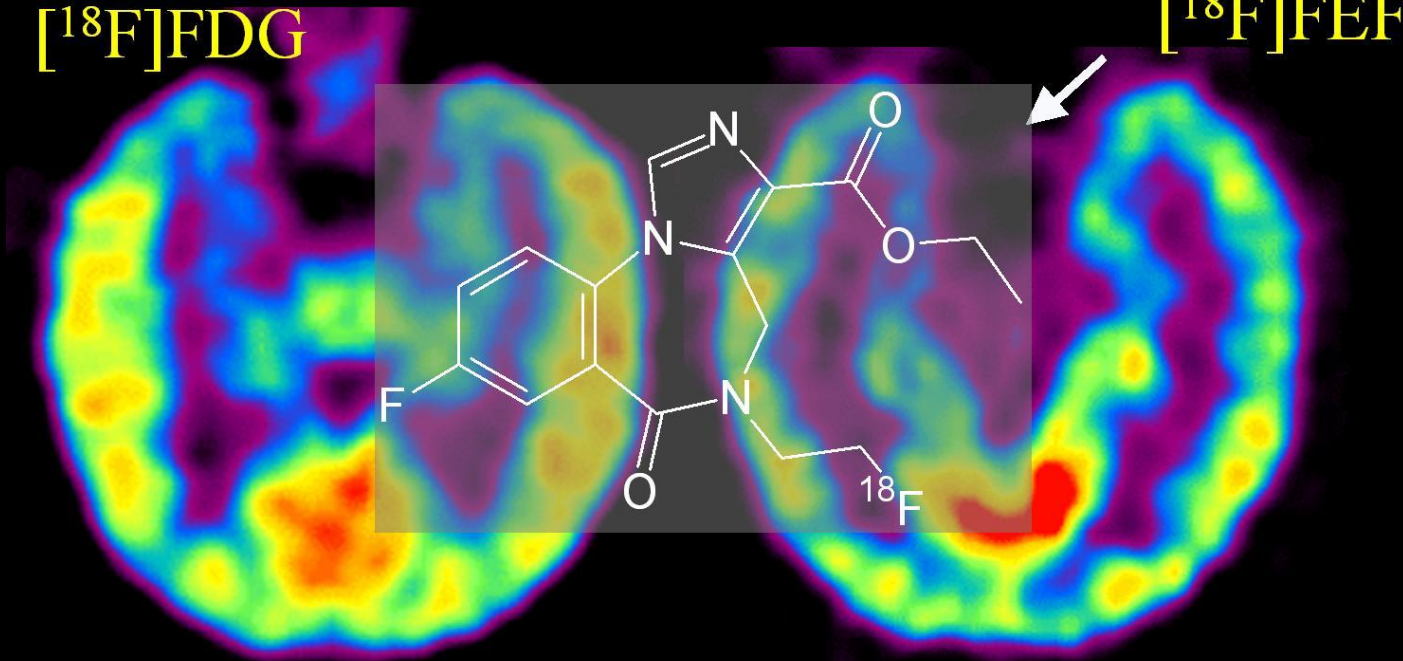




## [<sup>18</sup>F]Fluorethyl-flumazenil

[<sup>18</sup>F]FDG

[<sup>18</sup>F]FEF

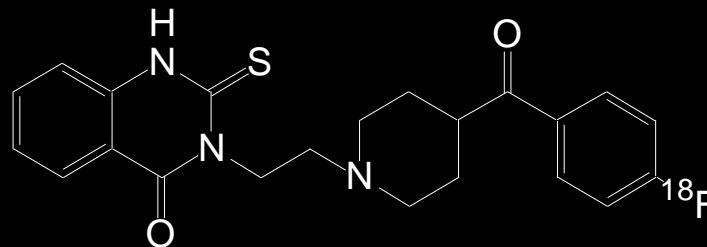
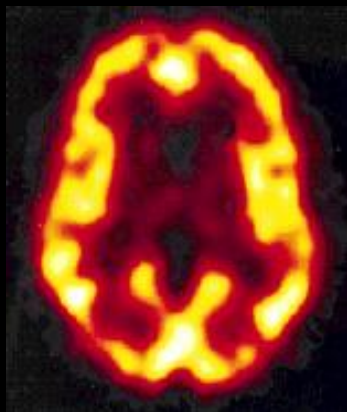


**GABA-Rezeptorsystem:** Alkoholabhängigkeit, Angst, ...



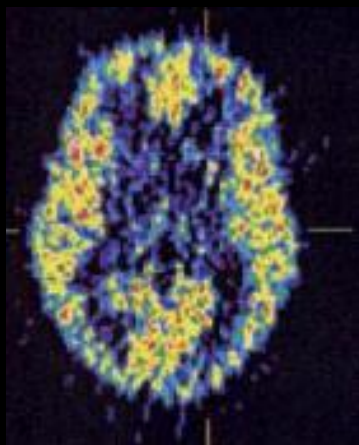


## Das serotonerge System



[<sup>18</sup>F]Altanserin

$K_i = 0.13 \text{ nM}$



[<sup>11</sup>C]MDL 100907

$K_i = 0.36 \text{ nM}$



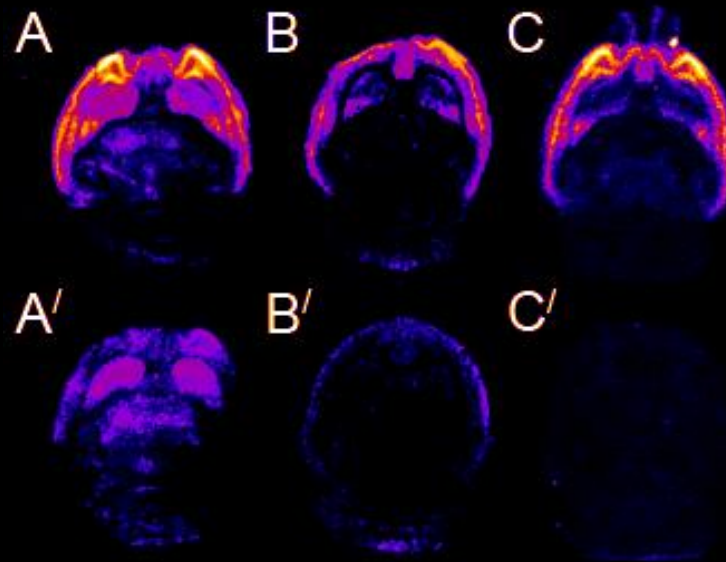
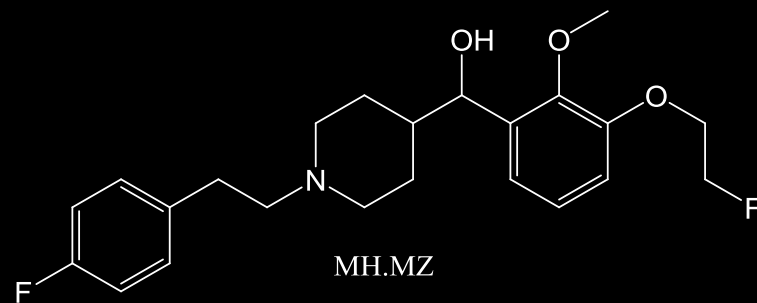
## Das serotonerge System

### [<sup>18</sup>F]Altanserin

- Fluorierung erlaubt "Satellienkonzept"
- Langer Gleichgewichtszustand
- Schnelle Metabolisierung
- Hohe MV-Konzentration => Teuer!!
- Lange Syntheszeit

### [<sup>11</sup>C]MDL 100907

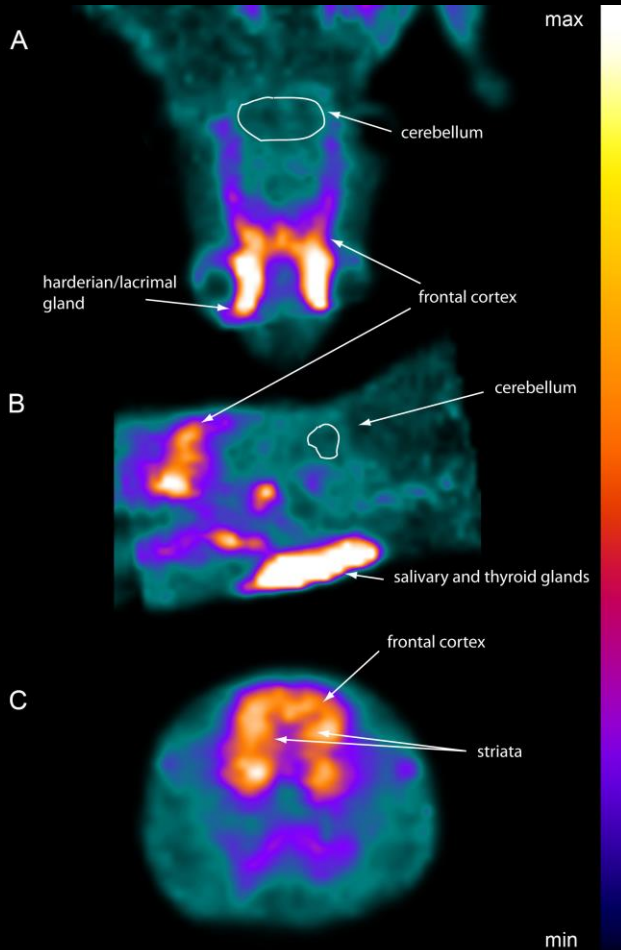
- Metaboliten passieren BHS nur geringfügig
- Höhere Selektivität als Altanserin



A [<sup>18</sup>F]Altanserin B [<sup>3</sup>H]MDL 100907 C [<sup>18</sup>F]MH.MZ



# Das serotonerge System

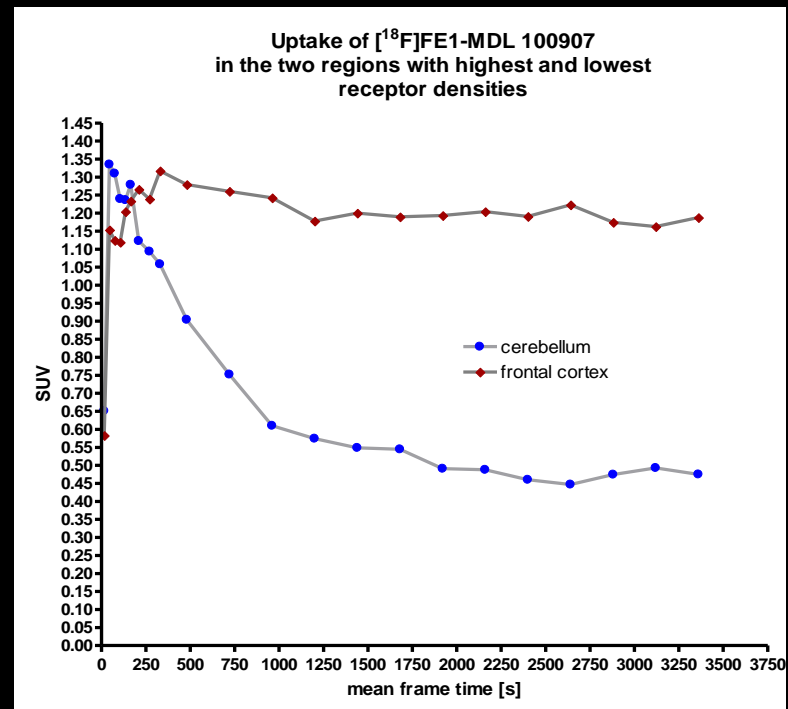


## Links:

Repräsentative  $\mu$ PET Bilder von  $[^{18}\text{F}]\text{MH.MZ}$  (n=1) with  
A) transversaler, B) sagittaler and C) coronarer Orientierung

## Rechts:

SUV von  $[^{18}\text{F}]\text{MH.MZ}$  im Cerebellum und frontalen Cortex



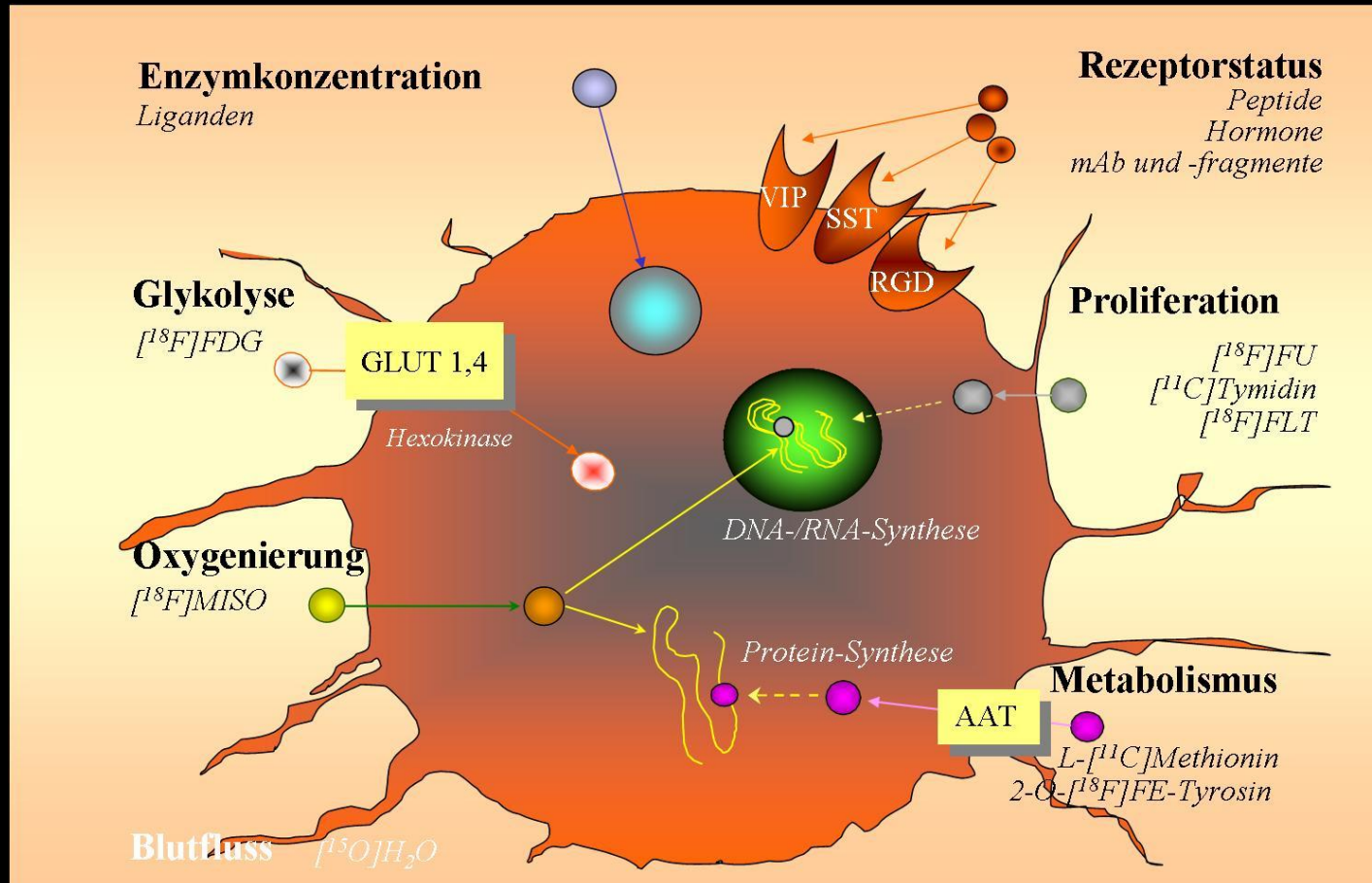


**ZNS-Diagnostik**

**Tumordiagnostik**



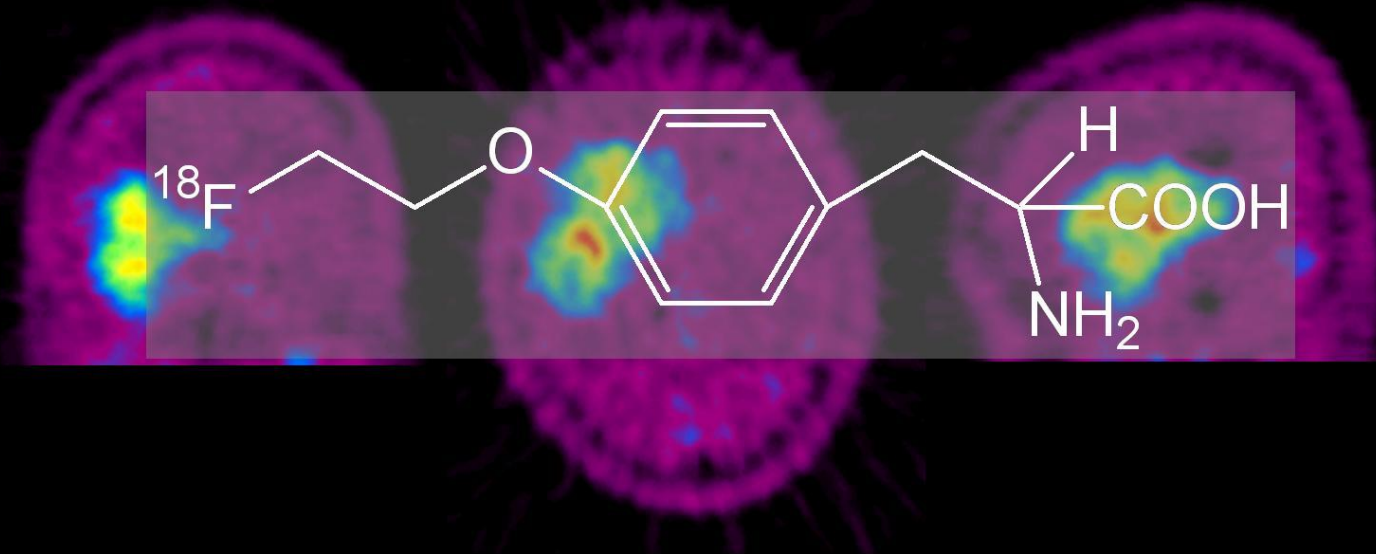
# Onkologische PET-Tracer





## [<sup>18</sup>F]Fluorethyl-tyrosin

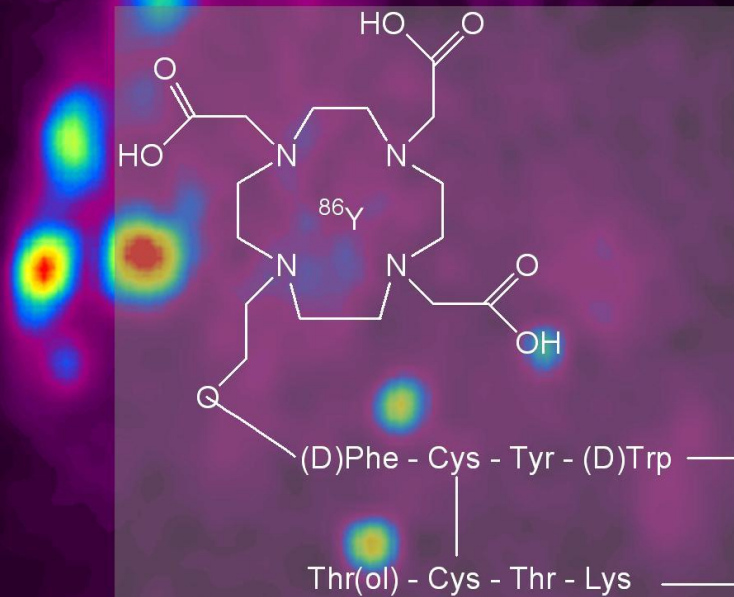
<sup>18</sup>F-Fluorethyl-Tyrosin PET Rezidiv Astrocytom III



Proteinsyntheserate: Zellproliferation



## Somatostatin-Liganden



**Somatostatin-Rezeptoren:** neuroendokrine Tumore



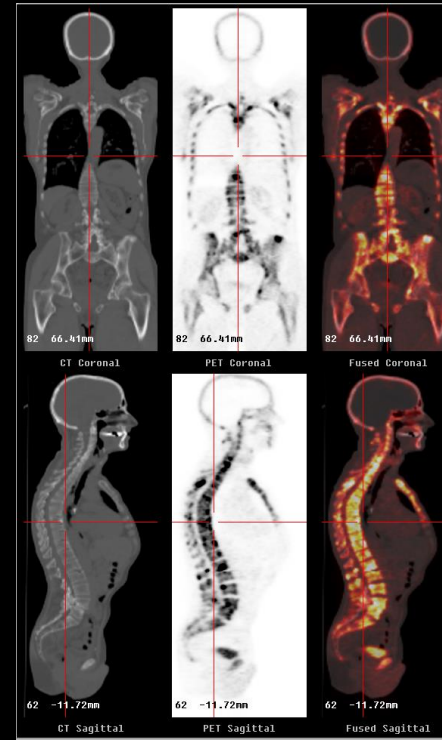
# [<sup>68</sup>Ga]DOTATOC



[<sup>18</sup>F]FDG



[<sup>68</sup>Ga]DOTATOC



PET-CT



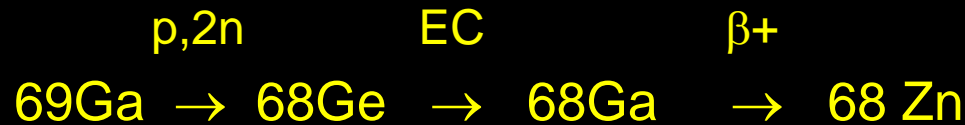


## Der Praktikumsversuch

- Elution des Ga-Generators
- Untersuchung der Reaktionskinetiken  
(Abhängigkeit der RCA von der Temperatur)
- Auswertung der RCA mittels Radio-DC

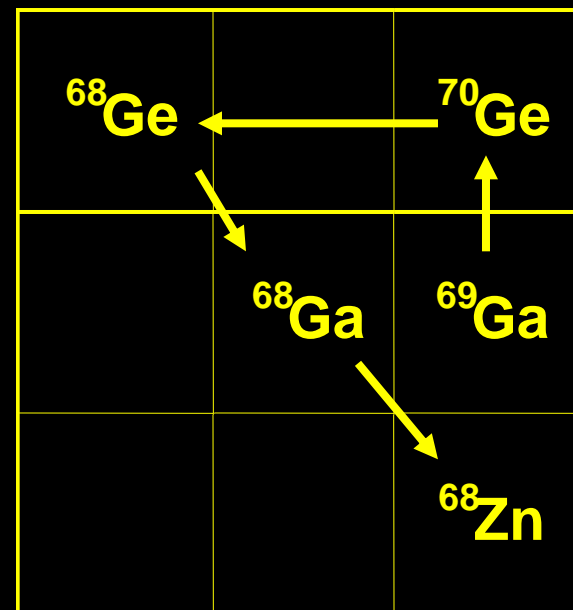


## Der Positronenemitter $^{68}\text{Ga}$



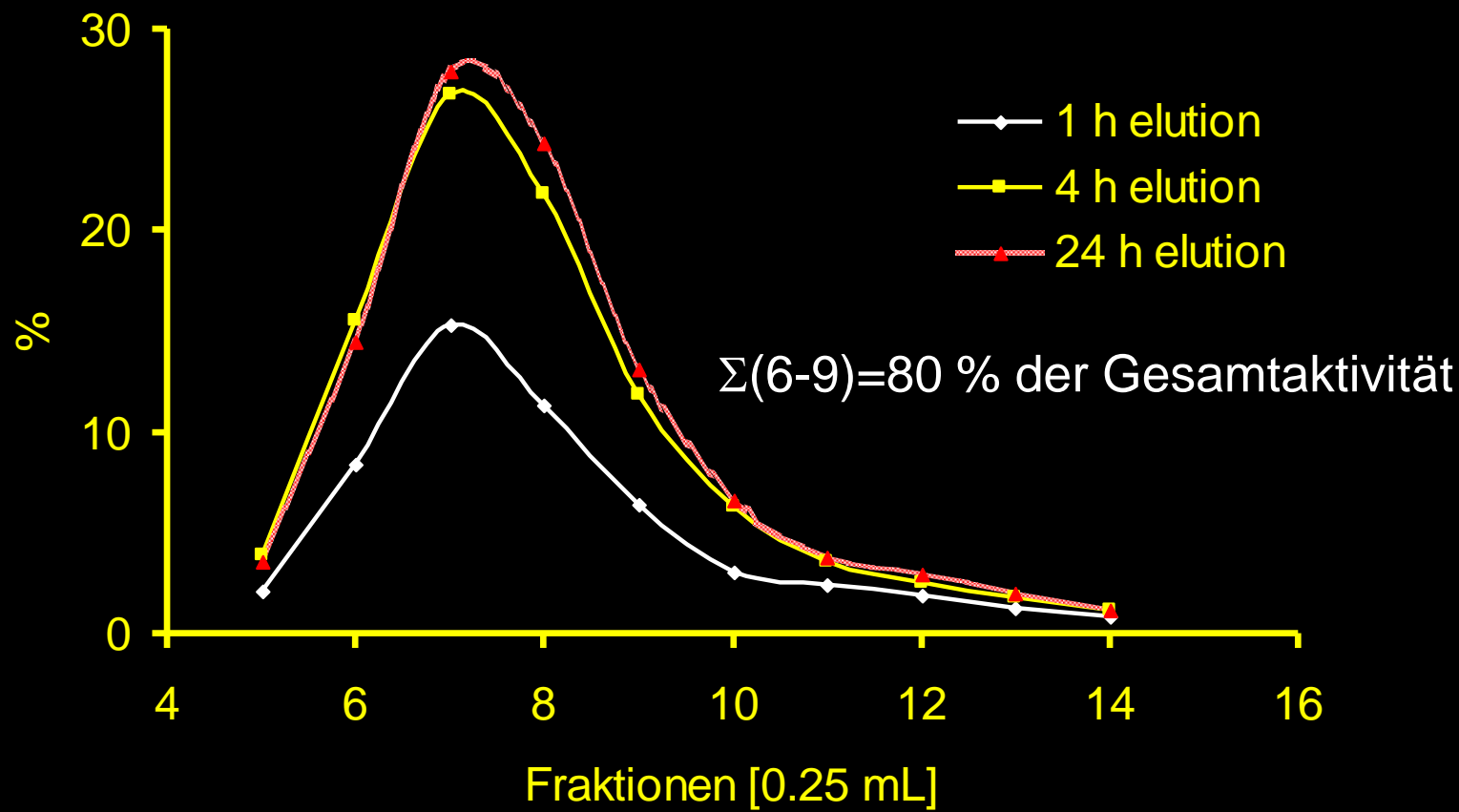
- $t_{1/2}$  :  $^{69}\text{Ga}$  : stabil
- $t_{1/2}$  :  $^{68}\text{Ge}$  : 270 d
- $t_{1/2}$  :  $^{68}\text{Ga}$  : 68 min\*
- $t_{1/2}$  :  $^{68}\text{Zn}$  : stabil

* MeV	[%]	
0.511	178	$\gamma$
1.077	3	$\gamma$
1.8	88	$\beta^+$



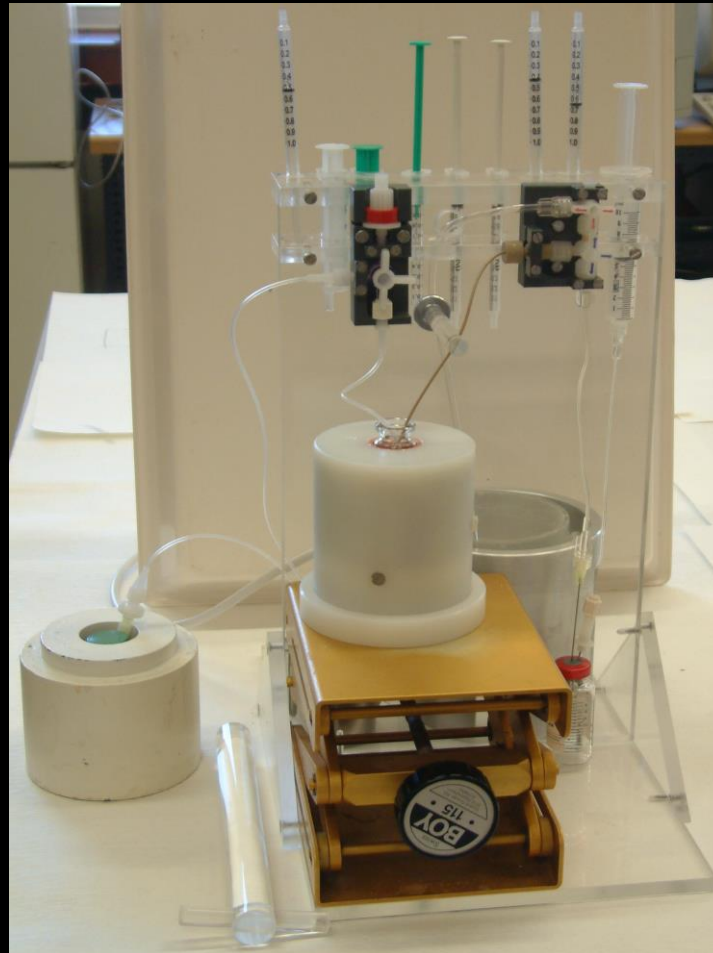


## Nachbildung des $^{68}\text{Ga}$ aus einem Ga/Ge-Generator



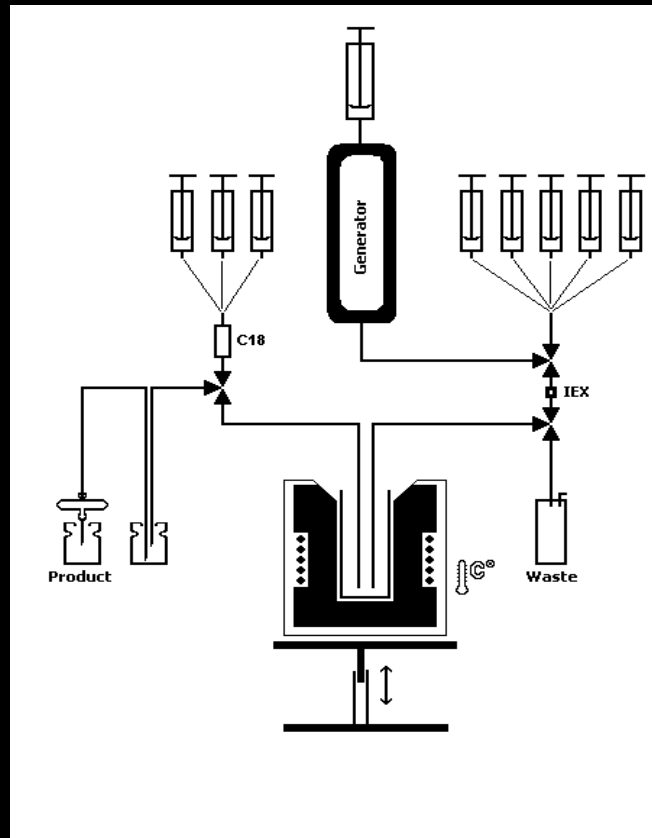


## Aufbau des Ga-Generators





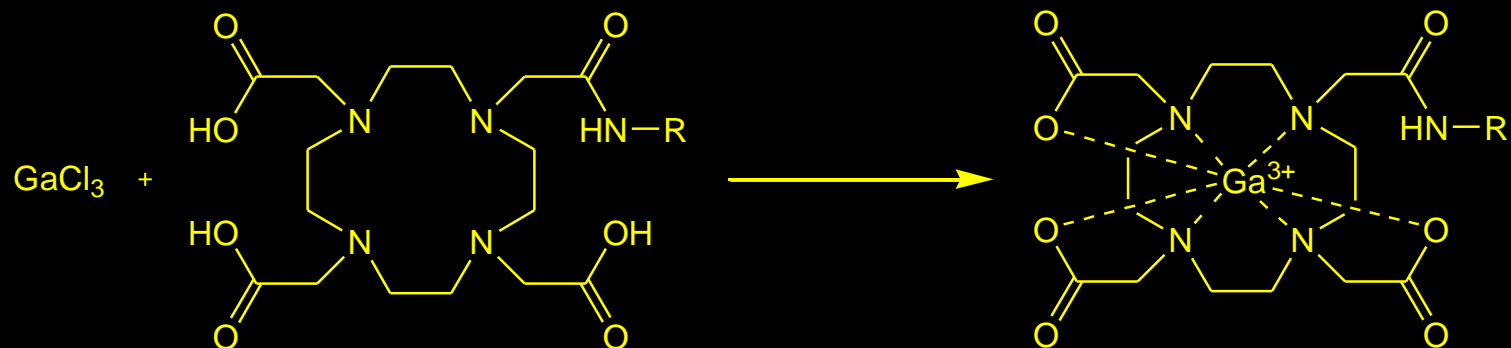
## Elution des Ga-Generators



	Schritte	Verwendete Lösungen		Temp.	Zeit
		Typ	Volumen		
1	<b>Generator-Elution</b>	0.1N HCl	6 mL	RT	2
2	<b>Konditionierung der KX</b>	80% Aceton / 0.15 N HCl	5 mL	RT	0.5
3	<b><sup>68</sup>Ga-Elution vom Harz</b>	97% Aceton / 0.05 N HCl	400 µL	RT	3
4	<b>KX Reinigung</b>	4 N HCl / H <sub>2</sub> O	1 mL / 1 mL	RT	
5	<b>Markierung</b>	5 mL H <sub>2</sub> O + 10 µg DOTA + 3	6 mL	95°C	10
6	<b>Konditionierung der C-18</b>	Ethanol/ H <sub>2</sub> O	2 mL / 2 mL	RT	
7	<b>Beladung C-18</b>	5		95°C	4
8	<b>Waschen der C-18</b>	H <sub>2</sub> O	2 mL	RT	0.5
9	<b>Elution des <sup>68</sup>Ga-DOTA</b>	Ethanol	0.5 mL	RT	1.5
10	<b>Verdünnung</b>	0.15 M NaCl + 9	5 mL	RT	1
11	<b>Filtration</b>	10		RT	5
12	<b>Radio-DC</b>	0.1 M Na <sub>3</sub> Citrat		RT	



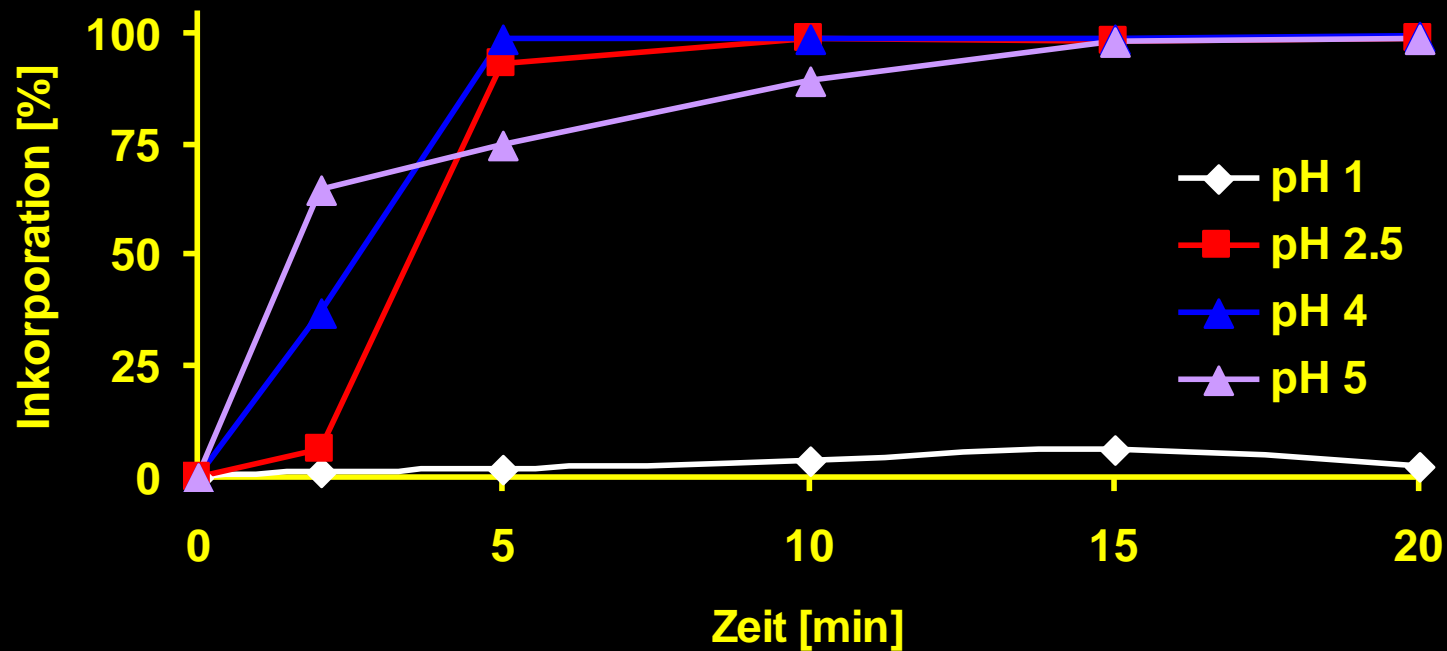
## Reaktion des $^{68}\text{Ga}$ mit DOTA-Derivaten





## Synthese von $^{68}\text{Ga}$ -DOTA-Derivaten

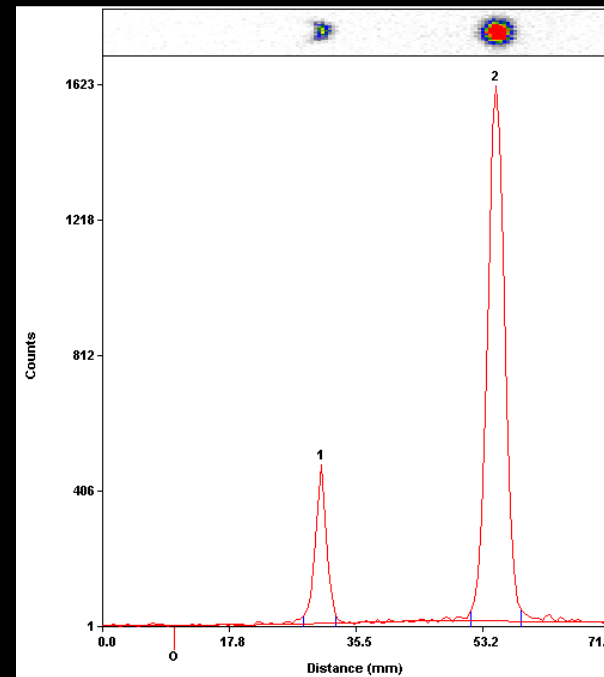
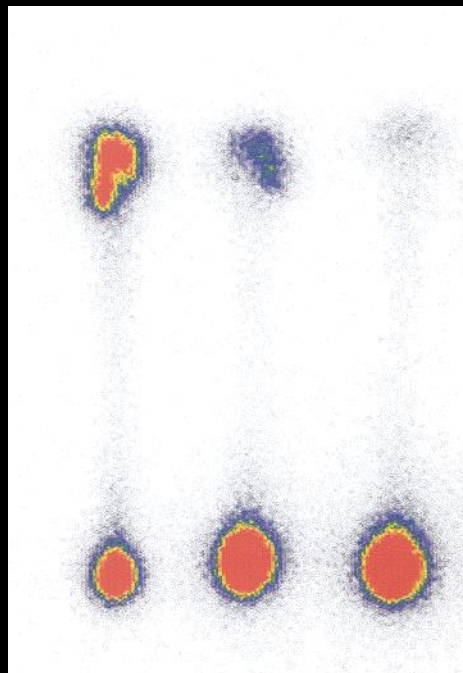
Reaktionskinetiken der Darstellung von  $^{68}\text{Ga}$ -DOTA-Derivaten hängen von verschiedenen Reaktionsparametern ab (t, T, pH,...)





# Auswertung der $^{68}\text{Ga}$ -Reaktionskinetiken

1min    5 min    10min



51%    85%    94%