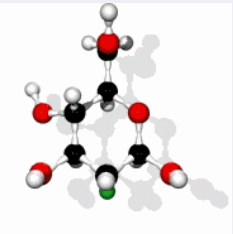
電気通信大学　2012年11月28日（水）



PETで見る脳の働き

菅野巌

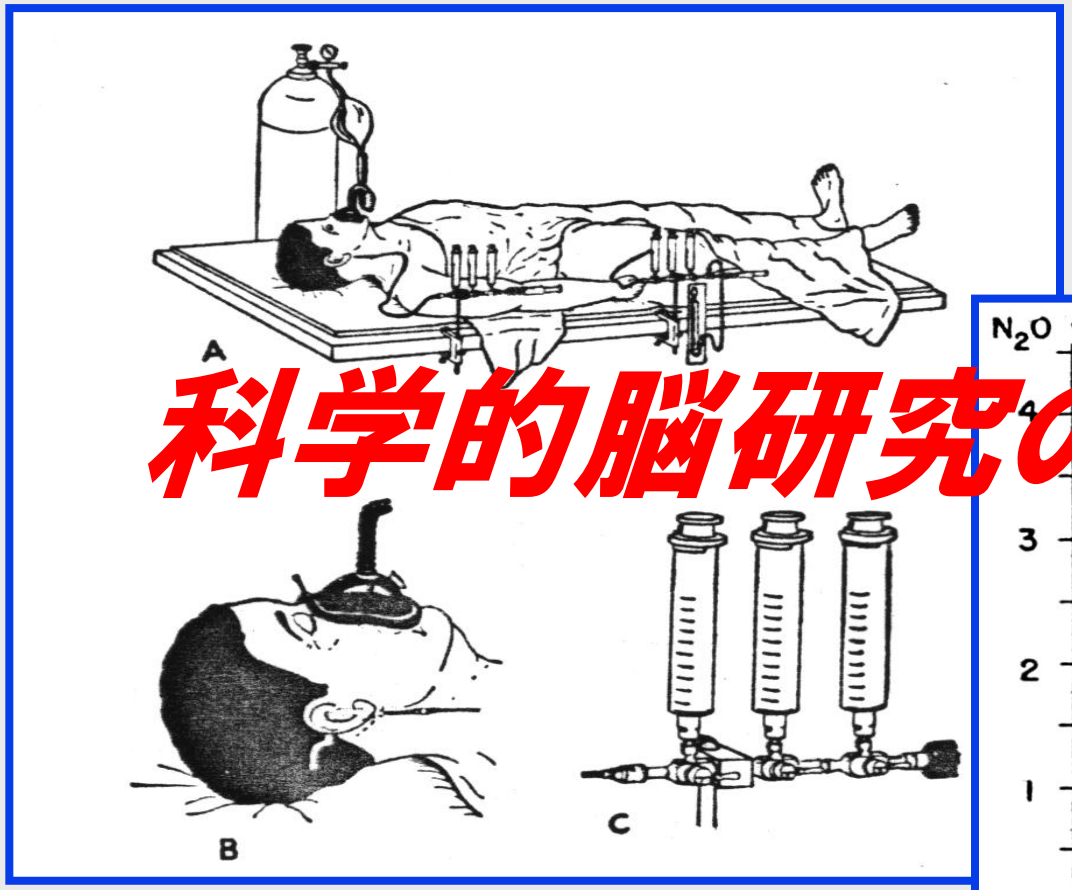
放射線医学総合研究所

分子イメージング研究センター

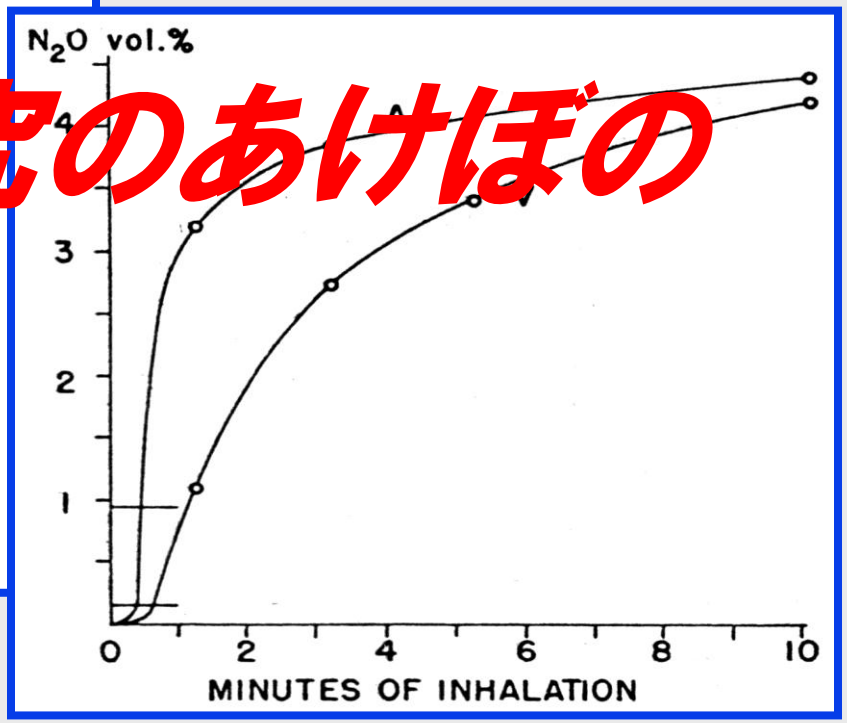
今日の内容

1. 定量的脳機能測定のあけぼの
2. PET原理と循環代謝測定
3. 脳活動と脳血流調節
4. 分子イメージングへの開眼
5. 脳の研究手段

最初の脳血流量の定量測定法



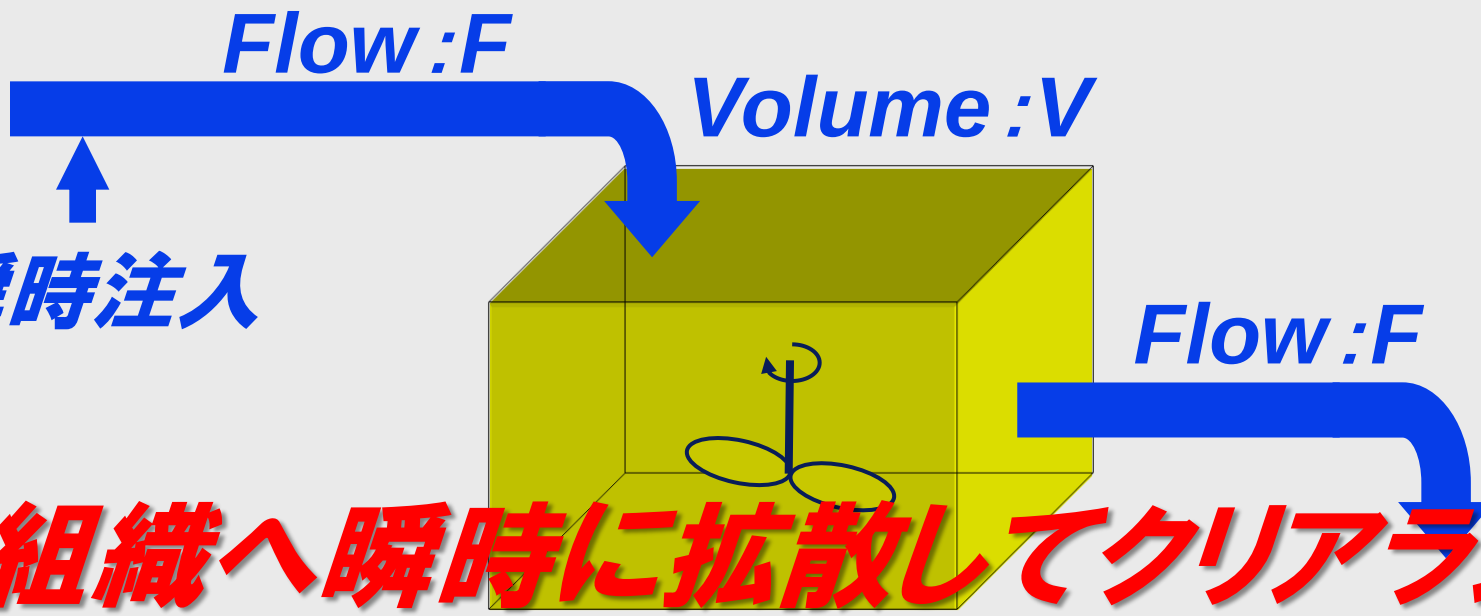
不活性ガスN_2O飽和法



科学的脳研究のあけぼの

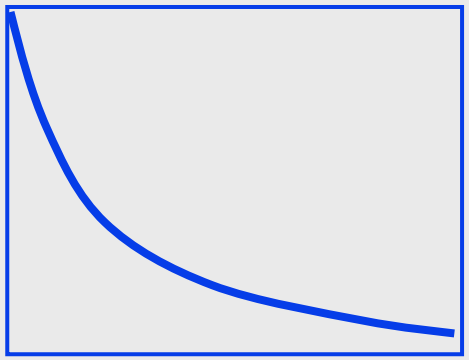
Kety-Schmidt 1940

不活性ガスクリアランス法原理



脳組織へ瞬時に拡散してクリアランス

Tracer Concen.



time

Clear. Curve

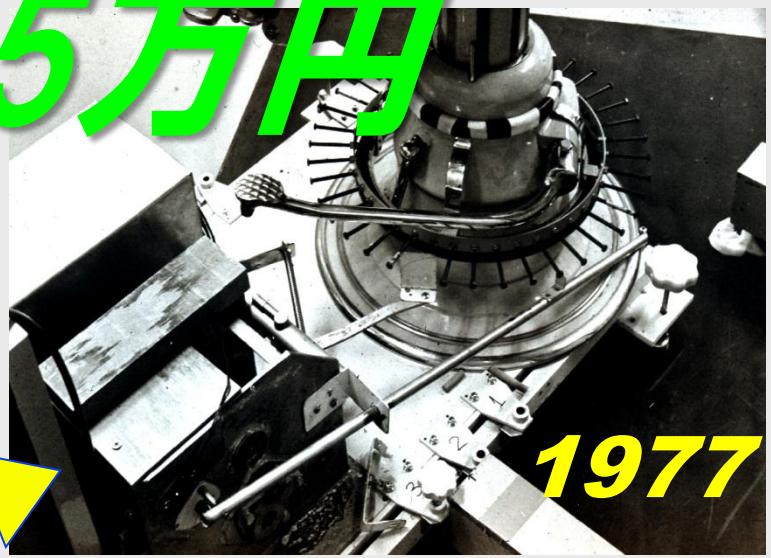
[$Ci = e^{-F/V}$]

Autofluoroscope (Gamma Camera)

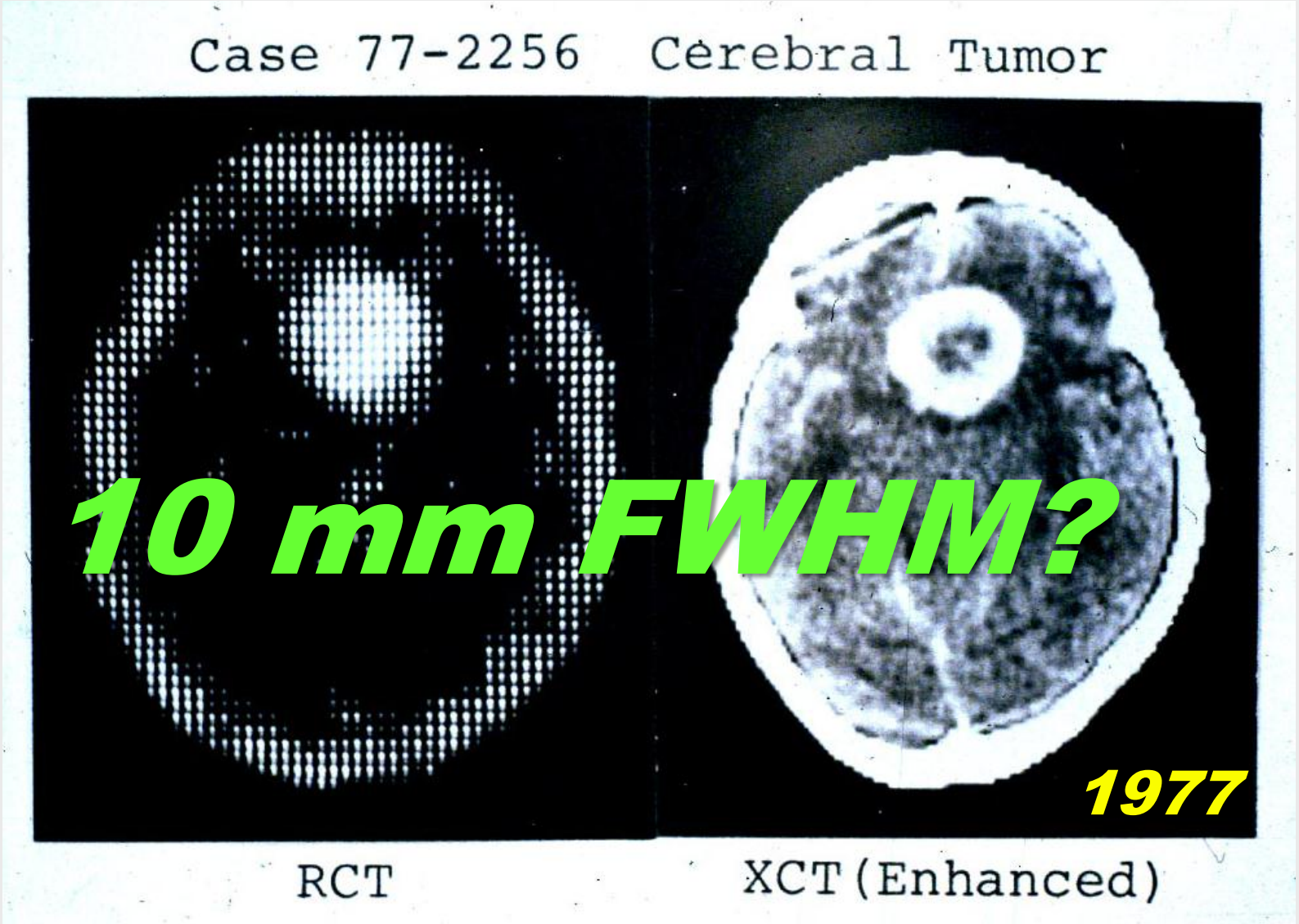
患者が回転する断層装置の開発
Patient rotates in front of Autofluoroscope

廃品利用の回転いす
Rotating chair made from scrap

総費用15万円

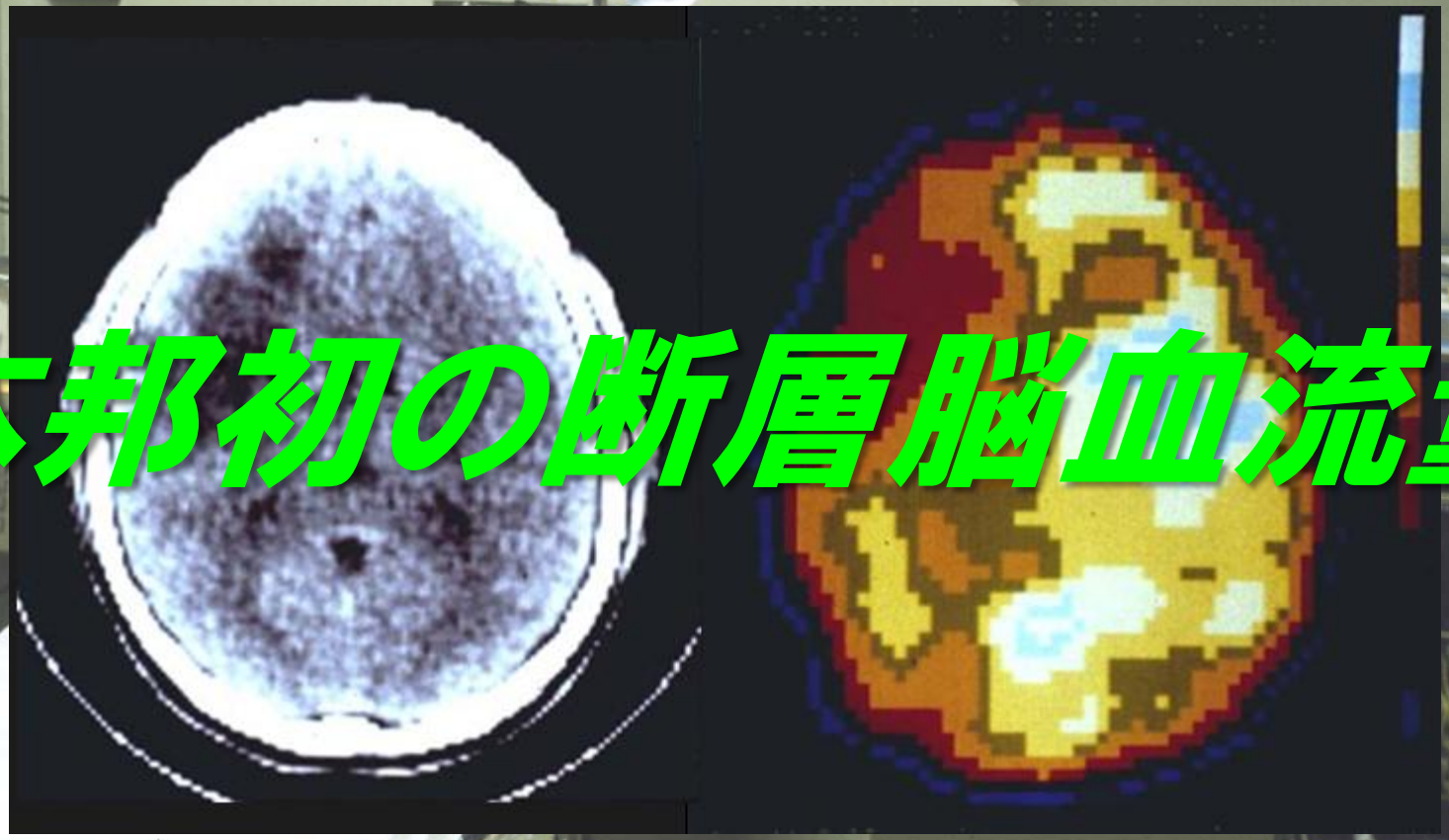


本邦初のヒト脳RI断層画像
First Human Radioisotope Tomogram



HEADTOME for Clinical Application

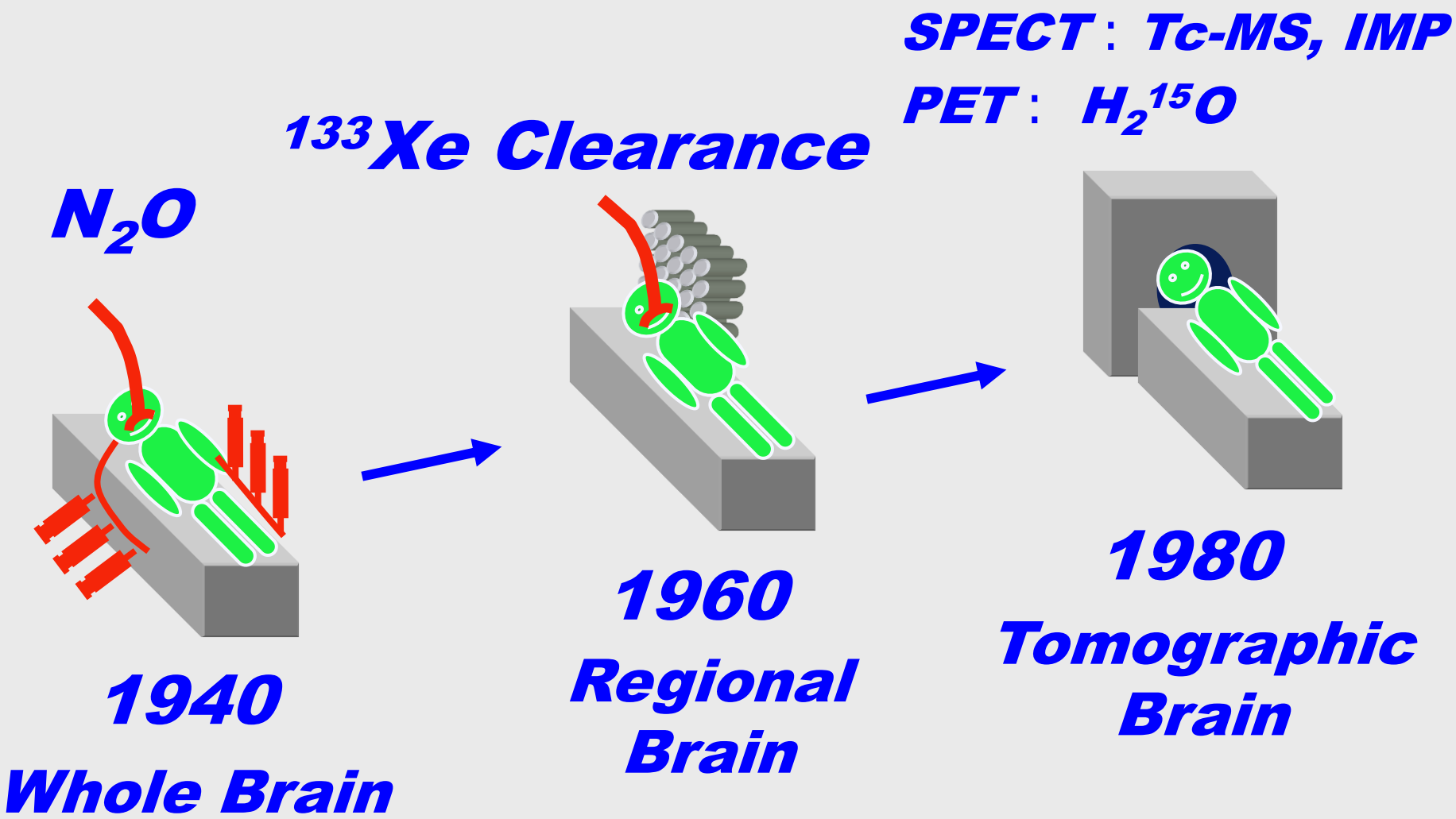
Headtome ^{133}Xe measurement



本邦初の断層脳血流量

1980

定量的脳血流量測定法の歩み



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秋田脳研へ超小型サイクロトロンの導入

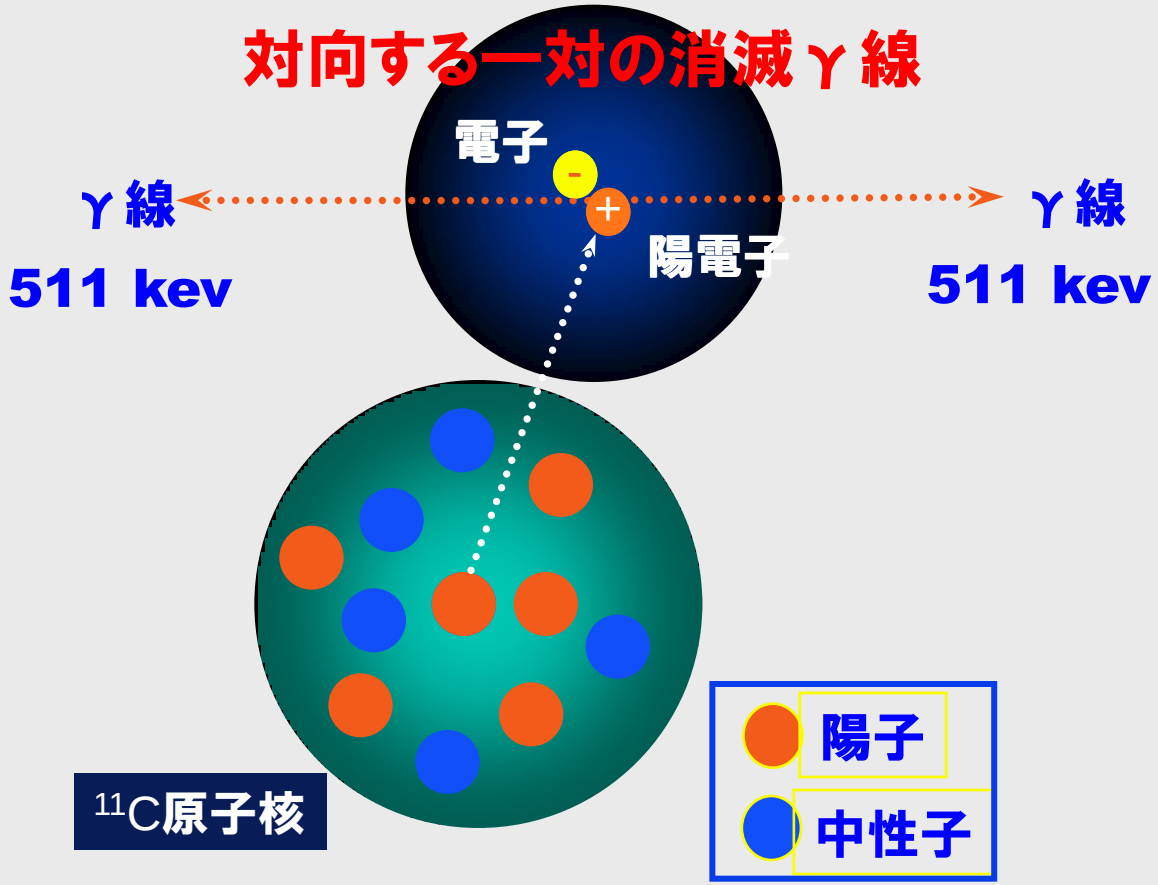
1983

PETの原理

ポジトロン（Positron）＝陽電子

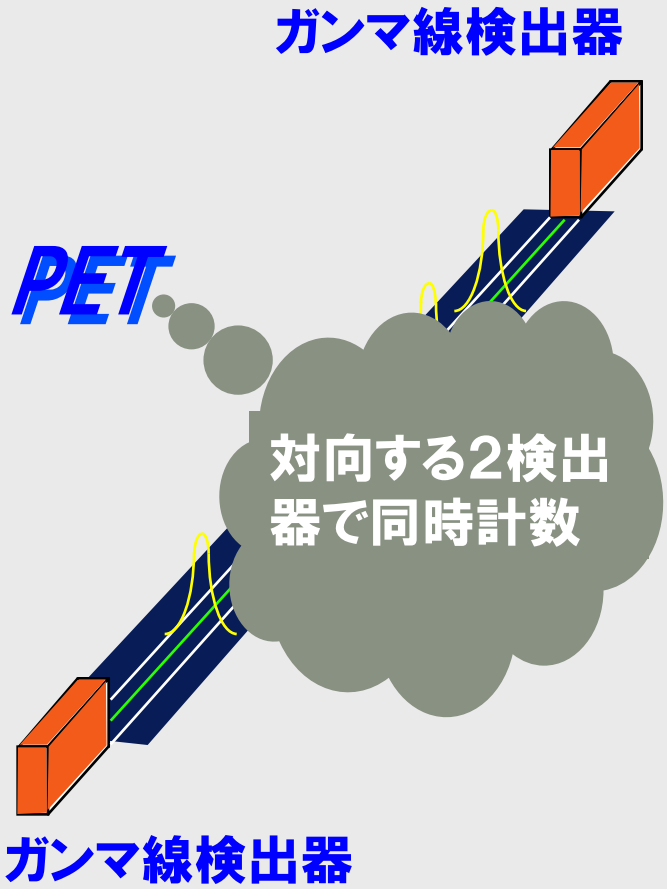
ポジトロンを放出する主要核種と半減期

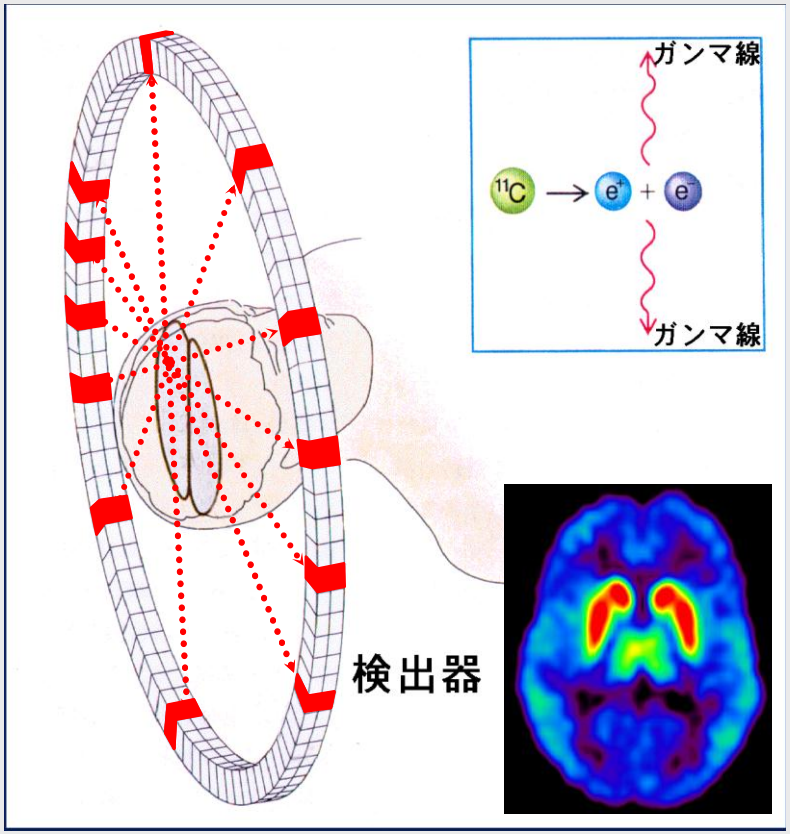
^{18}F	110分
^{11}C	20分
^{13}N	10分
^{15}O	2分



同時計数による高感度と高分解能

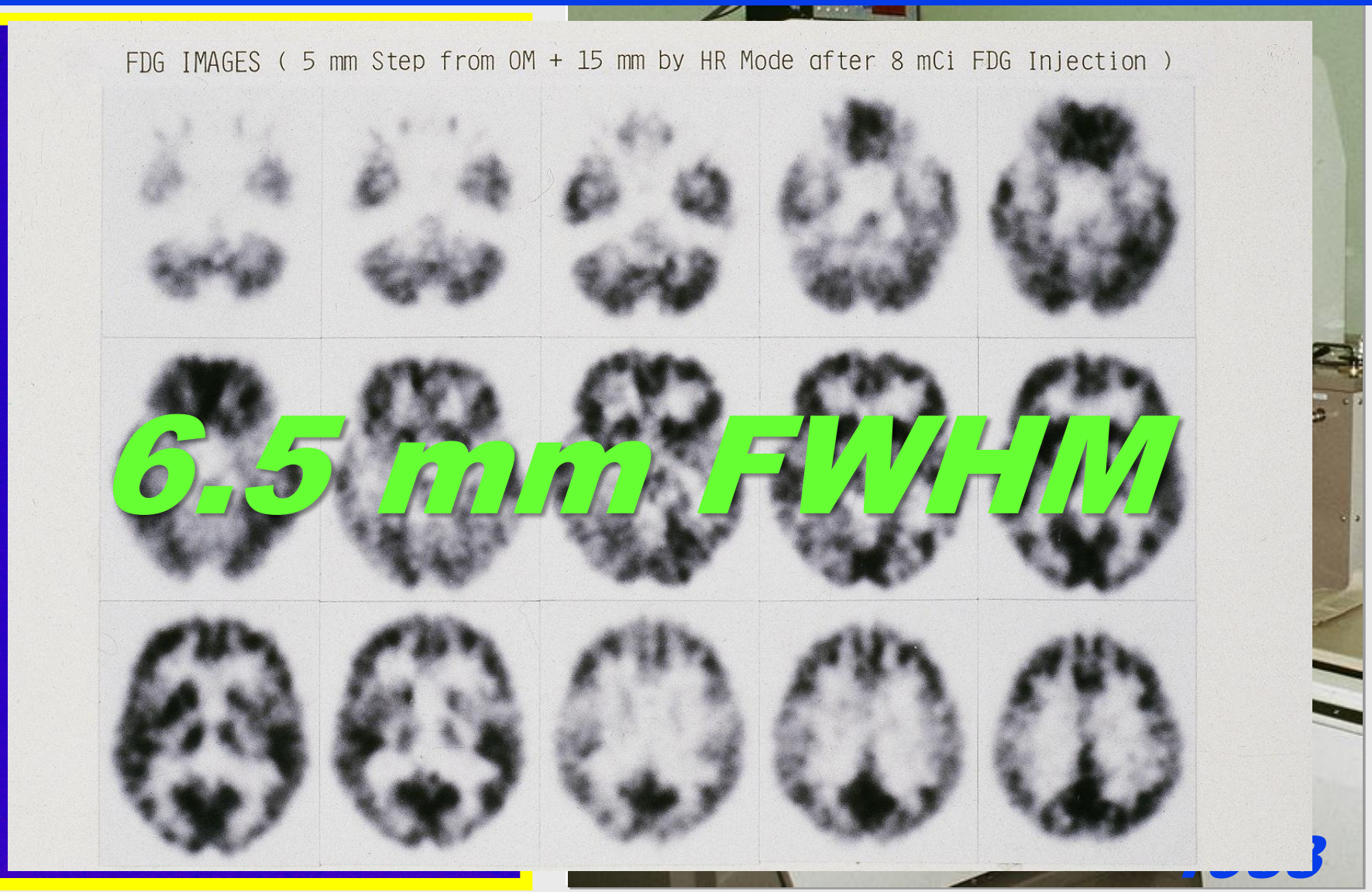
高感度、高分解能、精度(定量性)測定





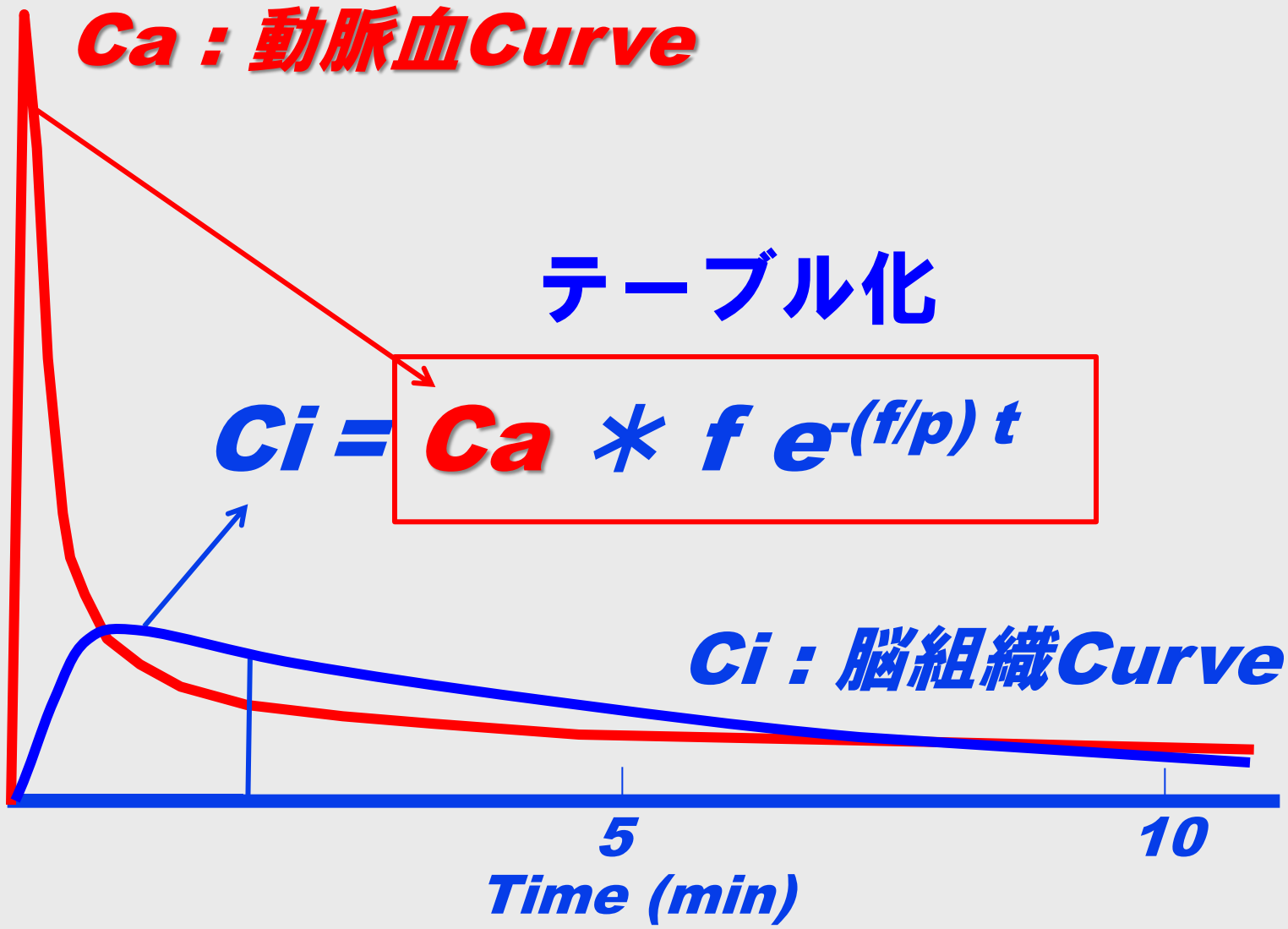
測定感度 ～ 10^{-9}（MRI~10^{-5}）

HEADTOME III PET専用装置

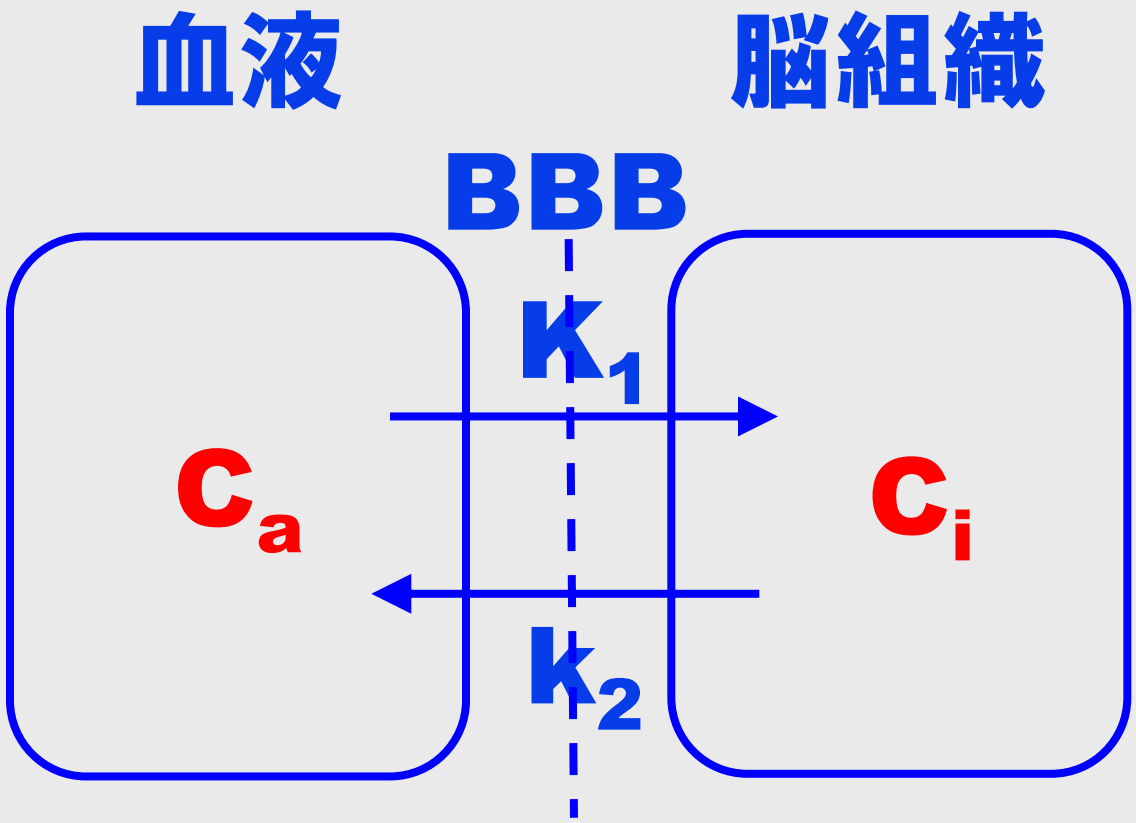


(Kanno et al, JCAT 9: 931-9, 1985)

動脈血Curveと脳組織Curve



^{15}Oモデル：$H_2{}^{15}O$

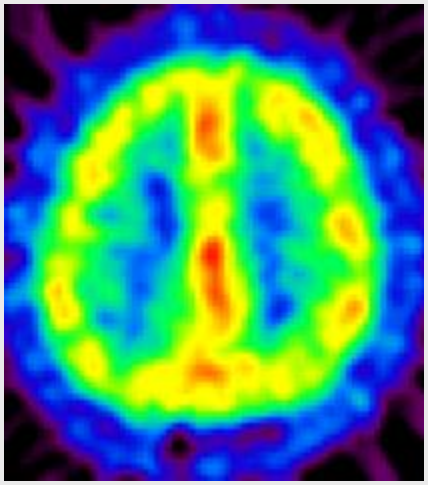


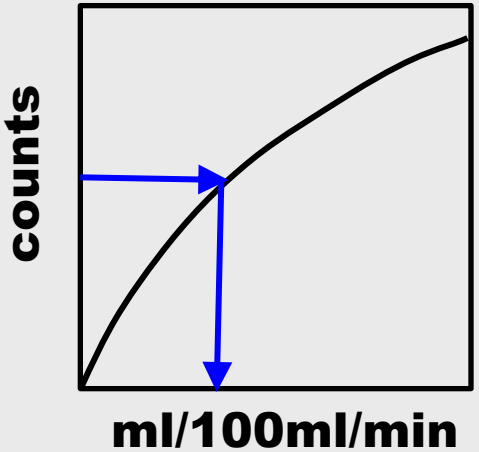
$$dC_i / dt = K_1 C_a - k_2 C_i$$

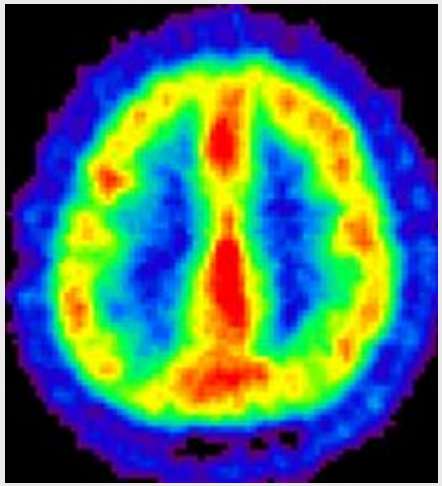
テーブルルックアップ法

Counts **Function**

Raw Image **Nomogram** **CBF**

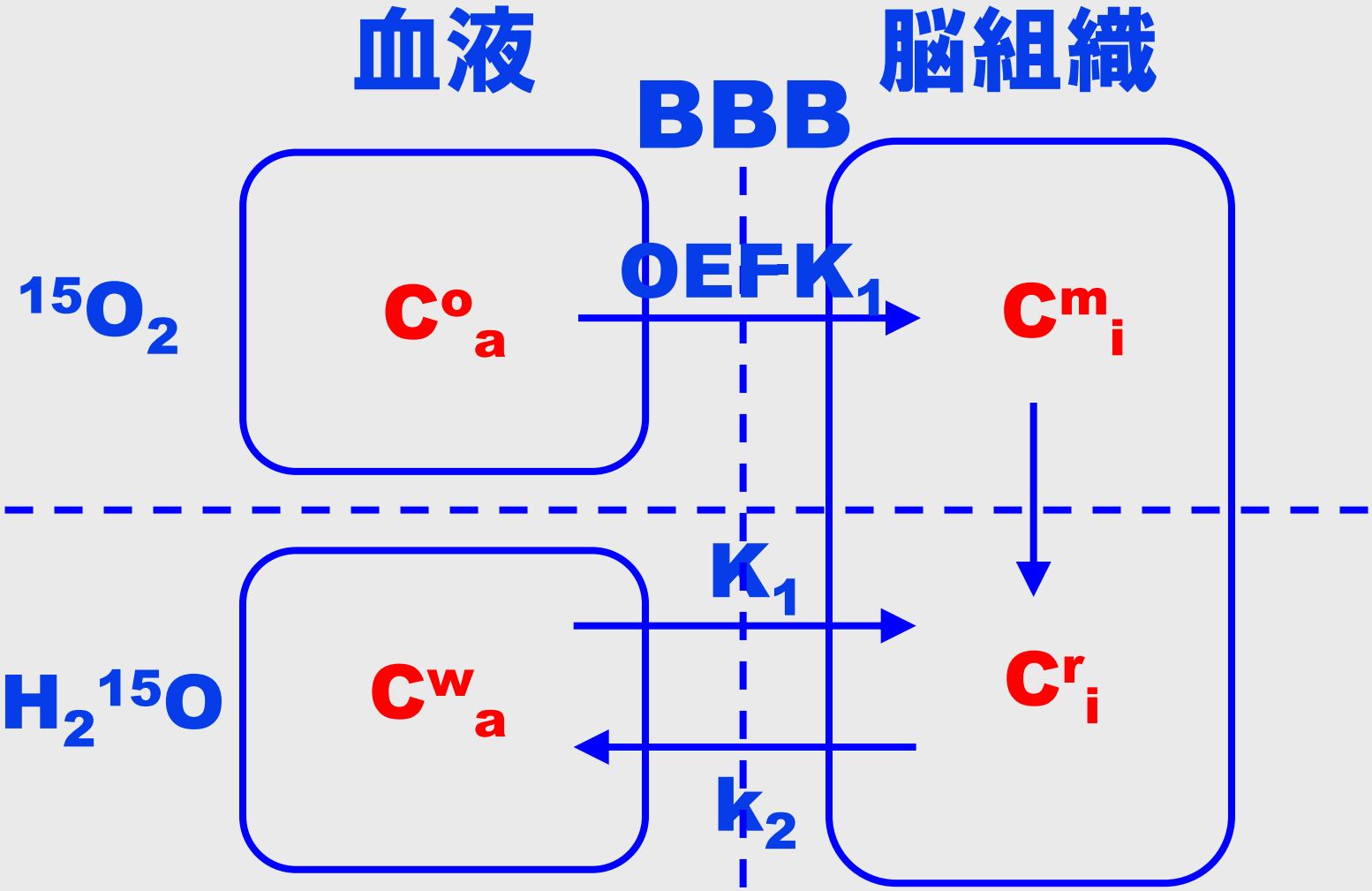






Kanno and Lassen JCAT:3, 71-76, 1979

^{15}Oモデル：$^{15}O_2$



脳における^{15}O-PETの特長

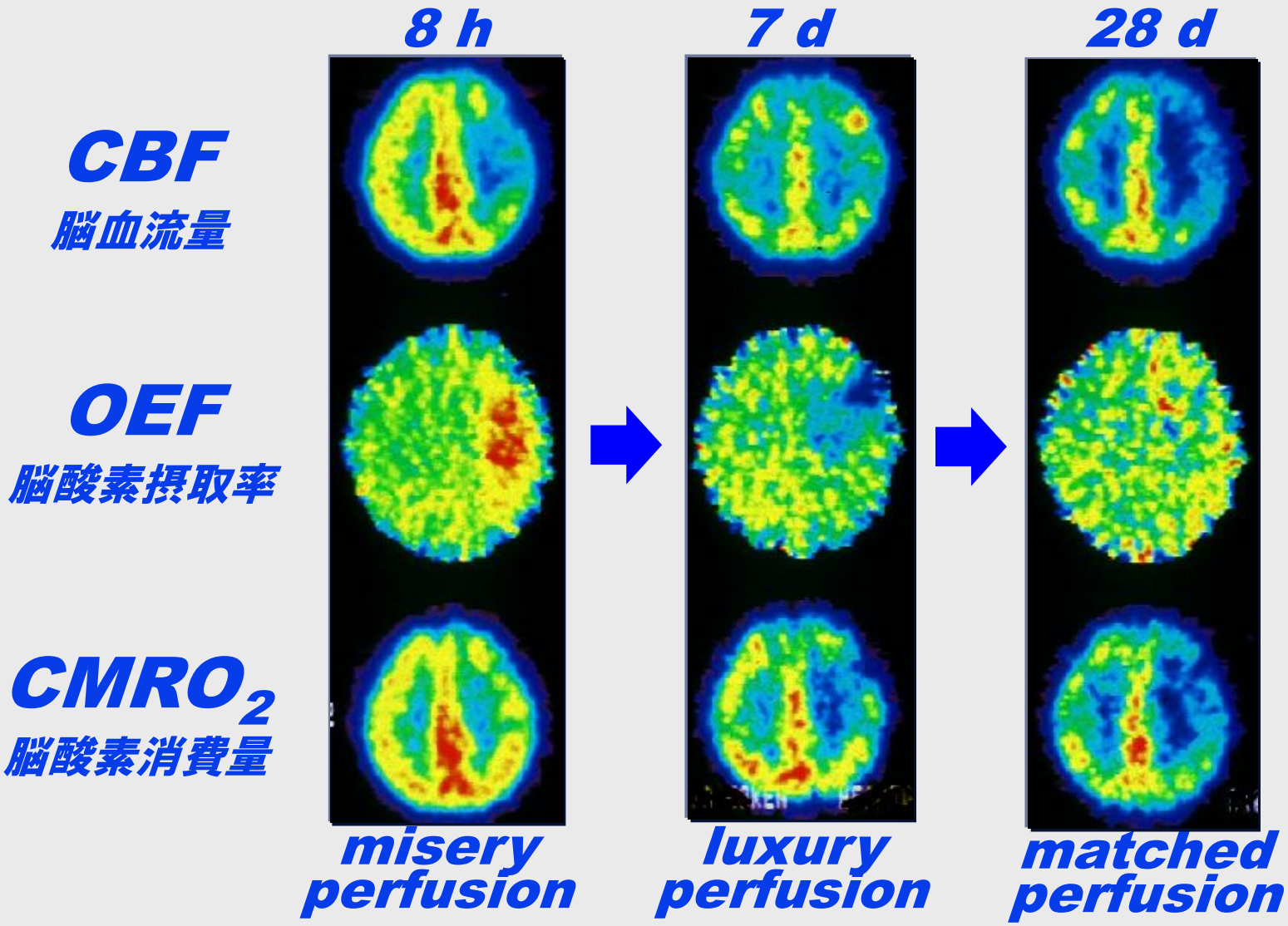
1. 酸素の供給と消費の同時測定が可能

脳循環代謝の評価に最適

2. 脳血流の短時間反復測定が可能

負荷反応測定に最適

Time Course after Stroke



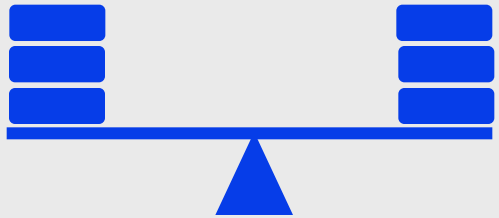
Akita Research Institute of Brain & Blood Vessels

乏血灌流と贅沢灌流
Misery perfusion and Luxury perfusion

血流=酸素供給　酸素消費
supply　consumption

正常
control

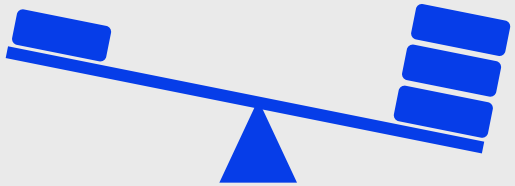
OEF→



正常灌流
normal

急性期
acute

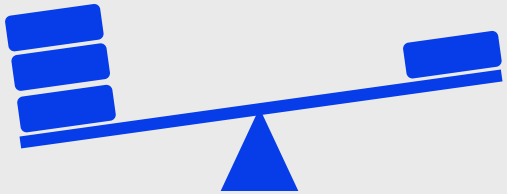
OEF↑



乏血灌流
misery

亜急性期
subacute

OEF↓



贅沢灌流
luxury

慢性期
chronic

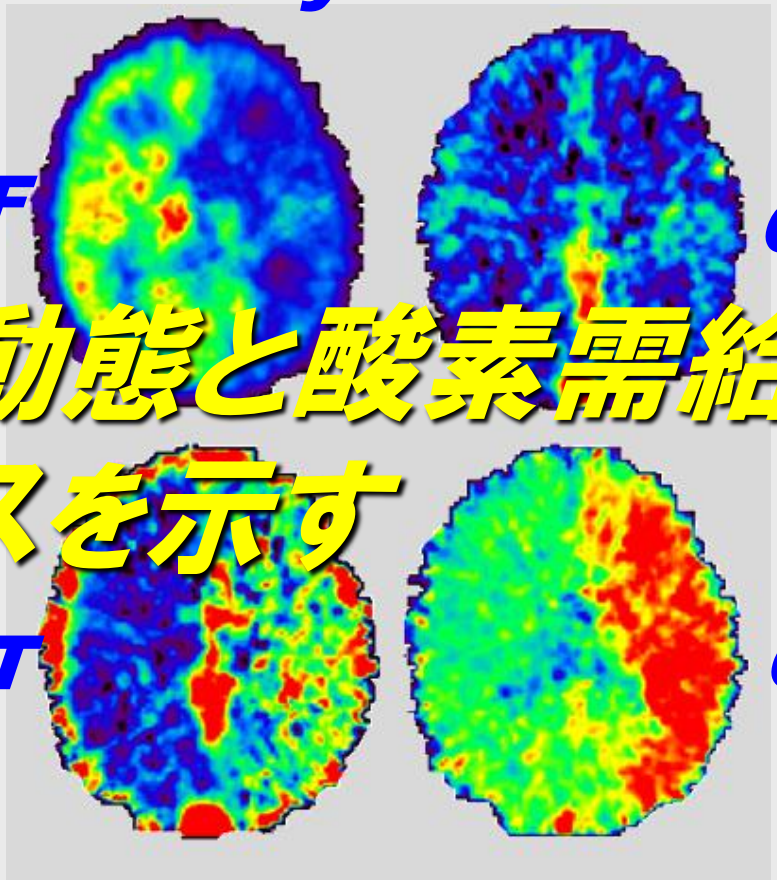
OEF→

平衡灌流
matched

循環予備能と代謝予備能の可視化

HEADTOME III

^{15}O gas steady-state method



O_2 PETは血行動態と酸素需給バランスを示す

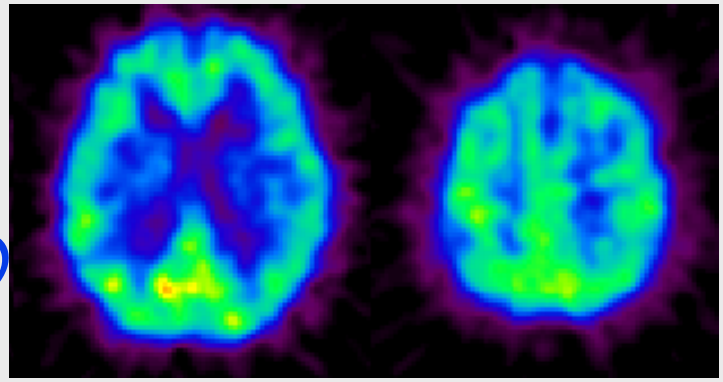
Left ICA Occlusion

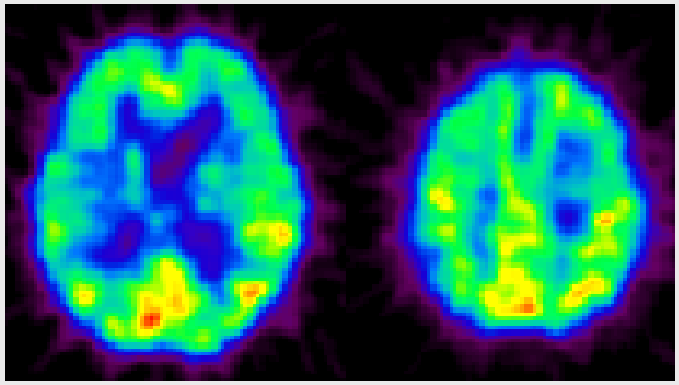
1983

ステント術の評価

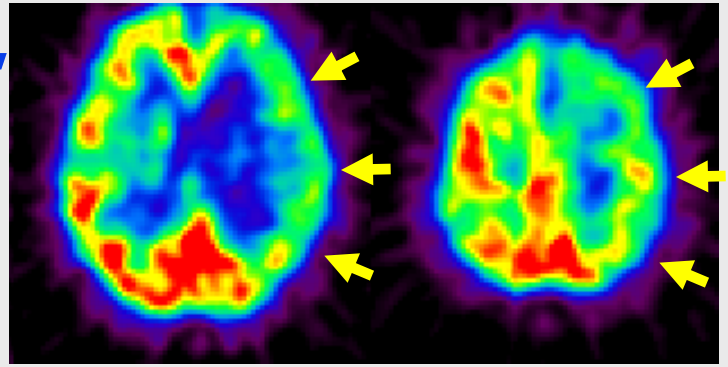
術前　　術後

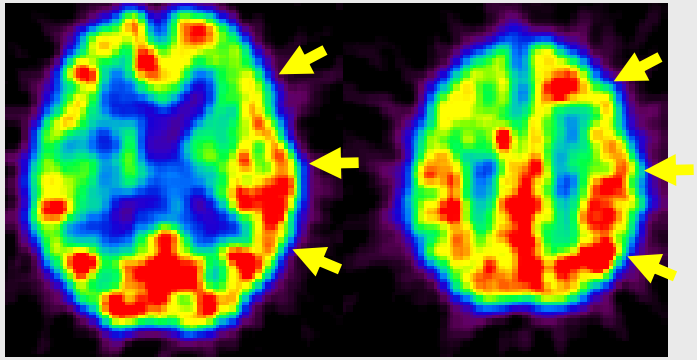
CBF（安静時）





CBF（CO_2）





03/01/08　　03/01/17

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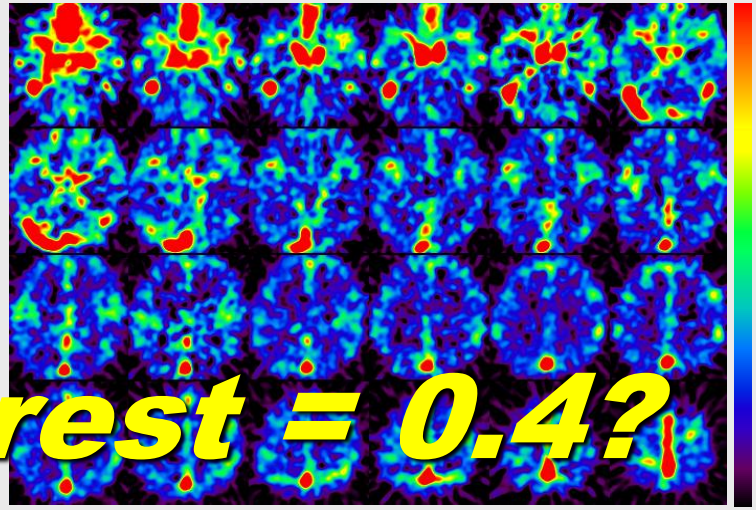
安静時の脳血流代謝
CBF & Metabolism at rest

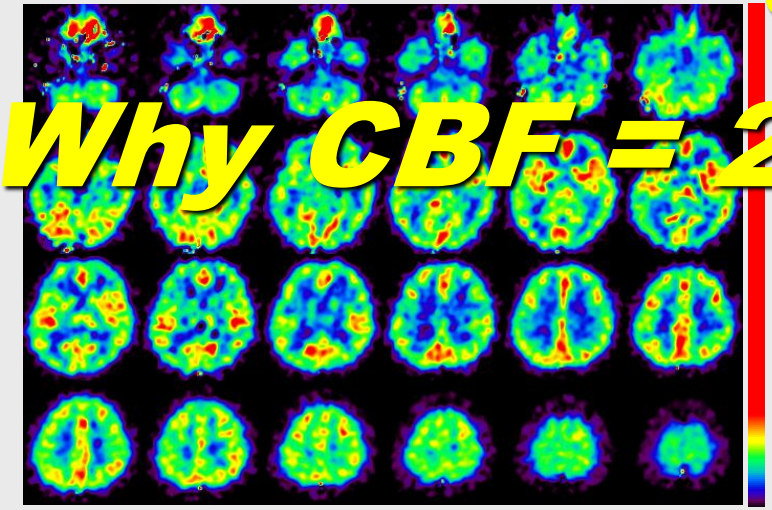
CBF

CBV



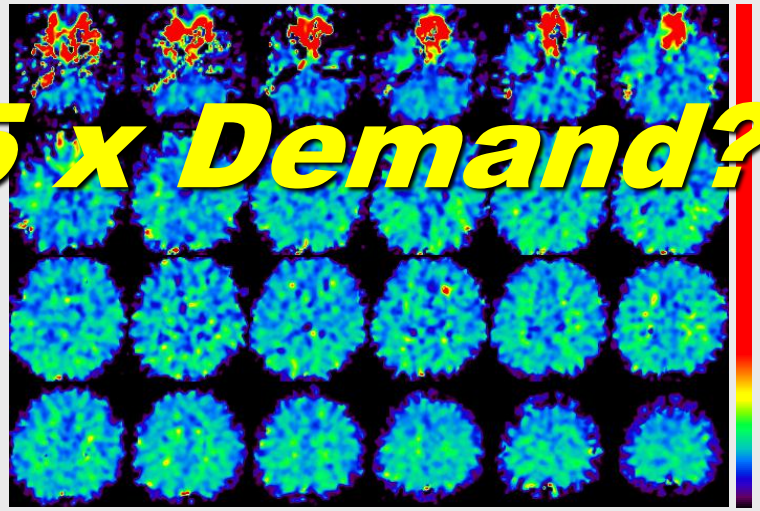
Why OEF at rest = 0.4?

CMRO2



or

OEF



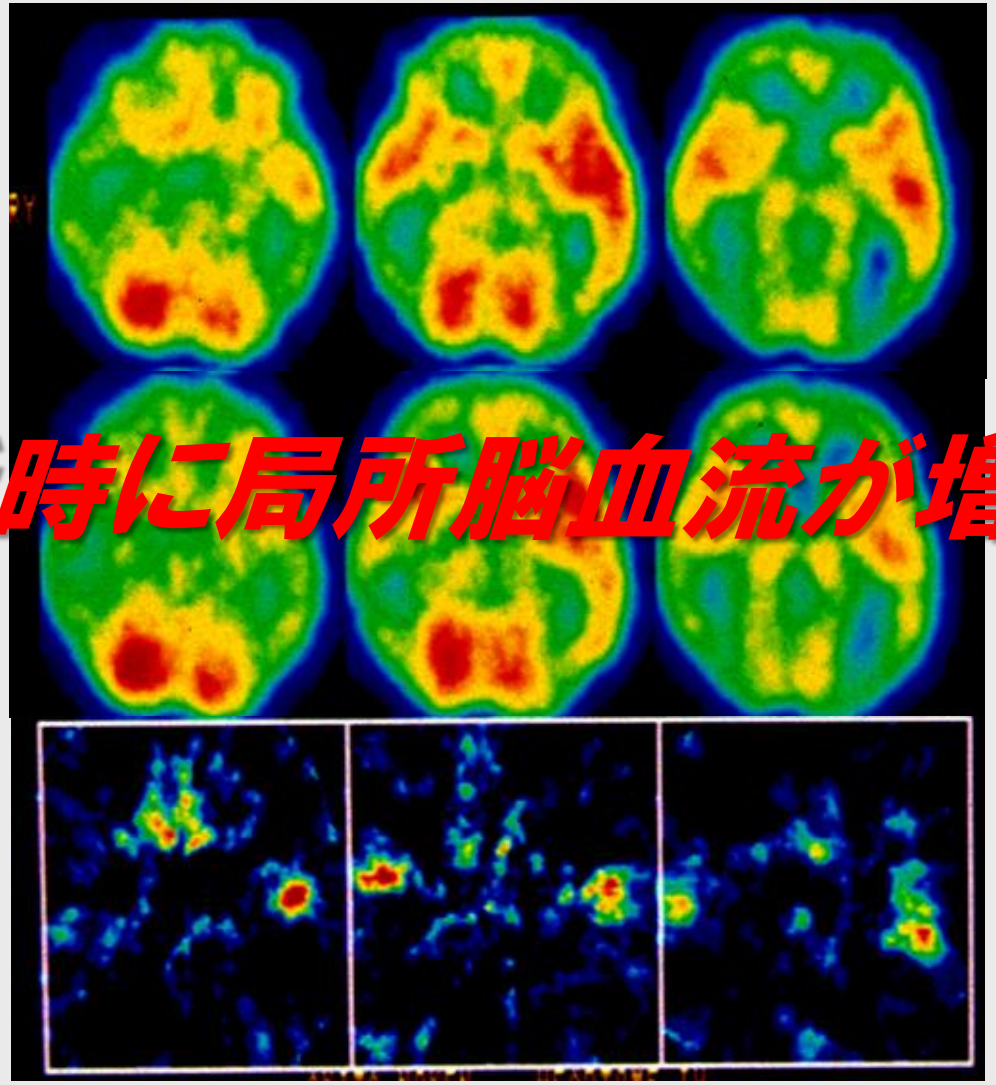
Why CBF = 2.5 x Demand?

賦活時の局所脳血流量
Local CBF during activation

物語
Story

雑音
Noise

差分
Subtr



なぜ賦活時に局所脳血流が増える？

1985

古典的：神経血管カプリング
Theory : Neurovascular Coupling

神経活動 ↑

↓

エネルギ代謝 ↑

↓

代謝基質需要 ↑

↓

脳血流量 ↑↑↑

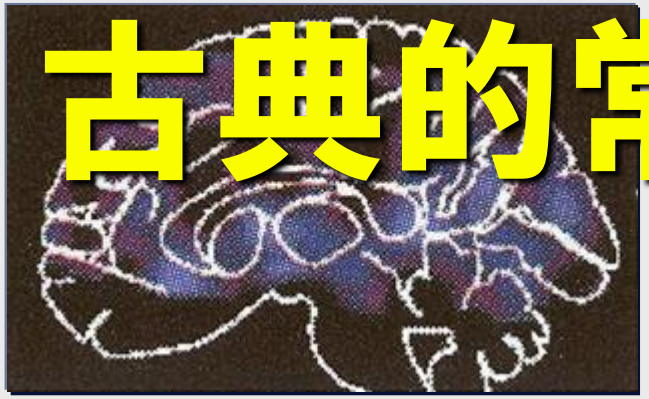
脳賦活時の血流酸素代謝糖代謝
CBF, CMRO2, CMRGlc, AVO2

CBF

CMRG

賦活時にCMRO$_2$が増加しない

古典的常識の崩壊



CMRO$_2$

AVO$_2$

Fox et al, 1984; Raichle ME, in Neuroenergetics:HFSP, 2001

神経血管カプリング駆動源
Driving Source of Neurovascular Coupling

1. 酸素欠乏 (O_2 lack)
2. 代謝産物 (metabolites)
3. 発熱現象 (heat production)
4. メディエータ (mediators)

神経血管カプリング駆動源
Driving Source of Neurovascular Coupling

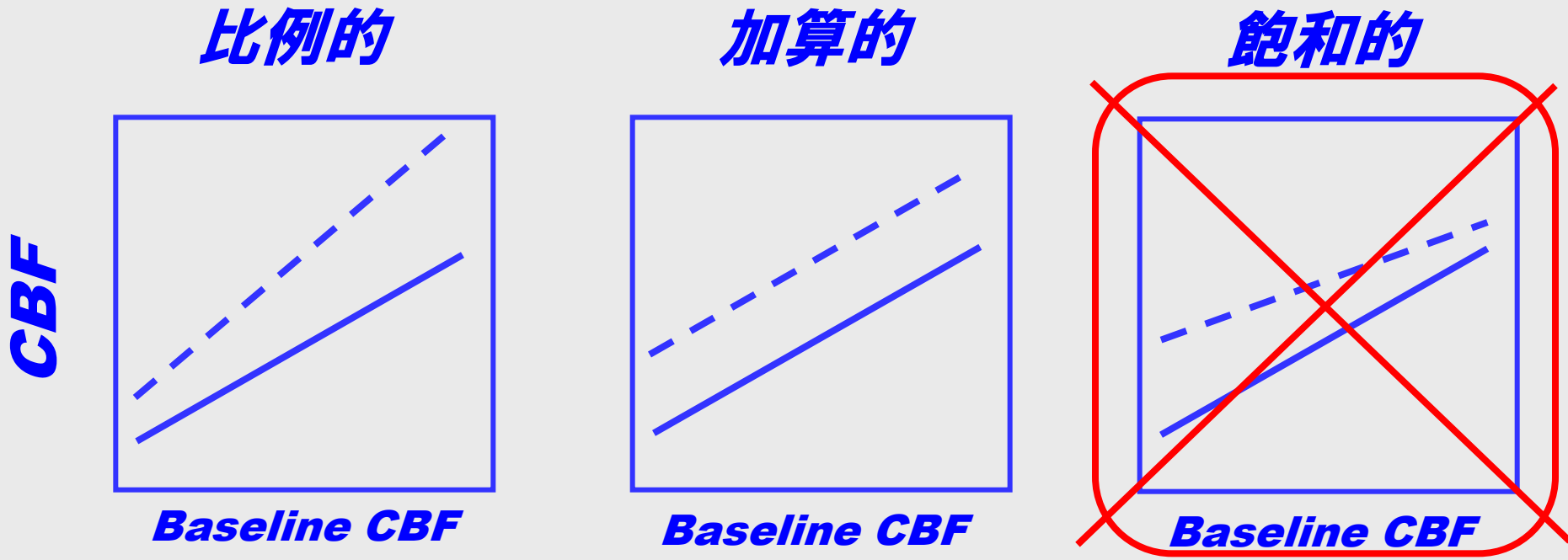
~~1．酸素欠乏 (O_2 lack)~~

2．代謝産物 (metabolites)

3．発熱現象 (heat production)

4．メディエータ (mediators)

Activation CBF vs Baseline CBF



—— Baseline CBF - - - - Activation CBF

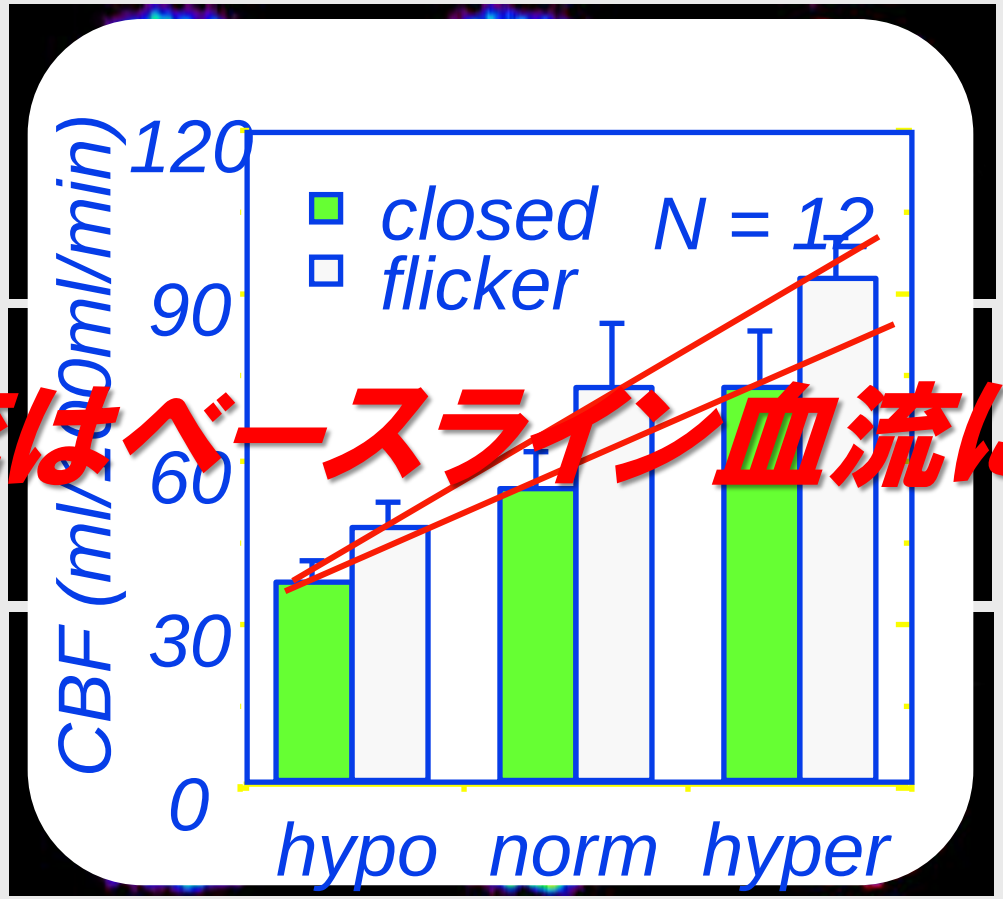
Baseline CBF vs Activation CBF

Baseline Activation Subtraction

Hypo-capnia

Normo-capnia

Hyper-capnia

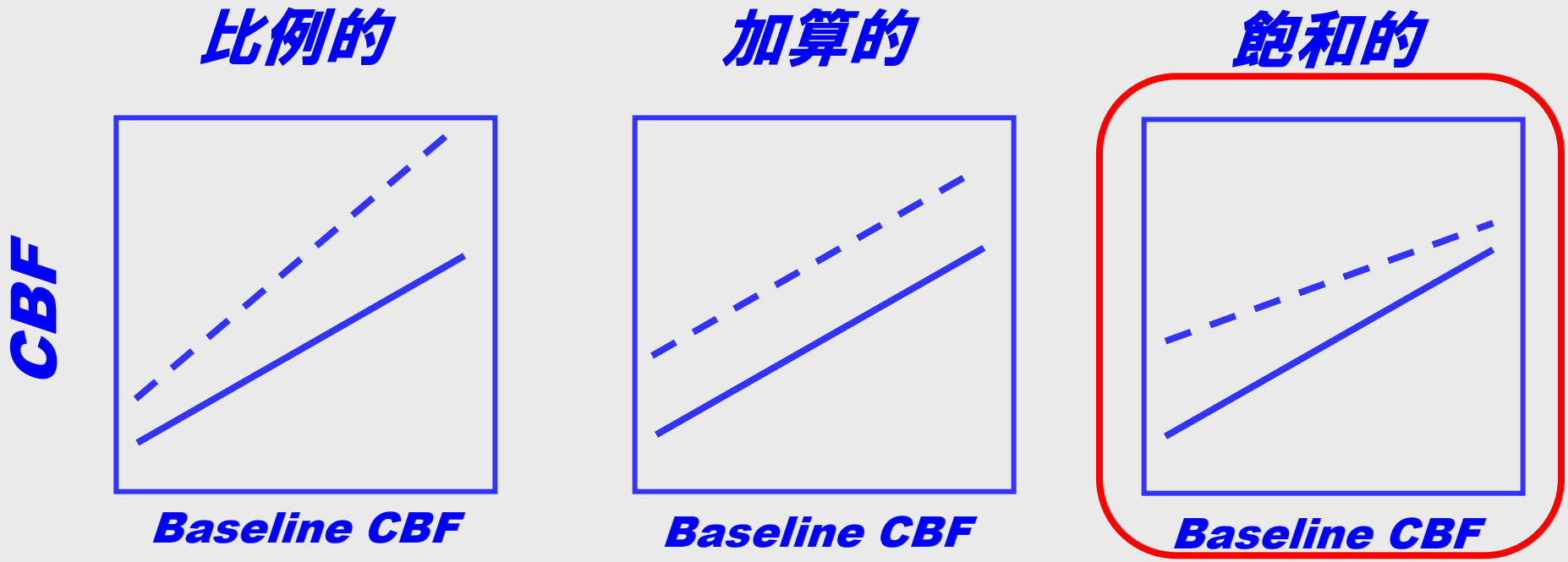


賦活血流はベースライン血流に比例

Eye Closed (C) 8Hz Flicker (F) F-C

(Shimosegawa, et al. JCBFM 15:111-114, 1995)

Activation CBF vs Baseline CBF



—— Baseline CBF - - - - Activation CBF

神経血管カプリング駆動源
Driving Source of Neurovascular Coupling

~~1．酸素欠乏 (O_2 lack)~~

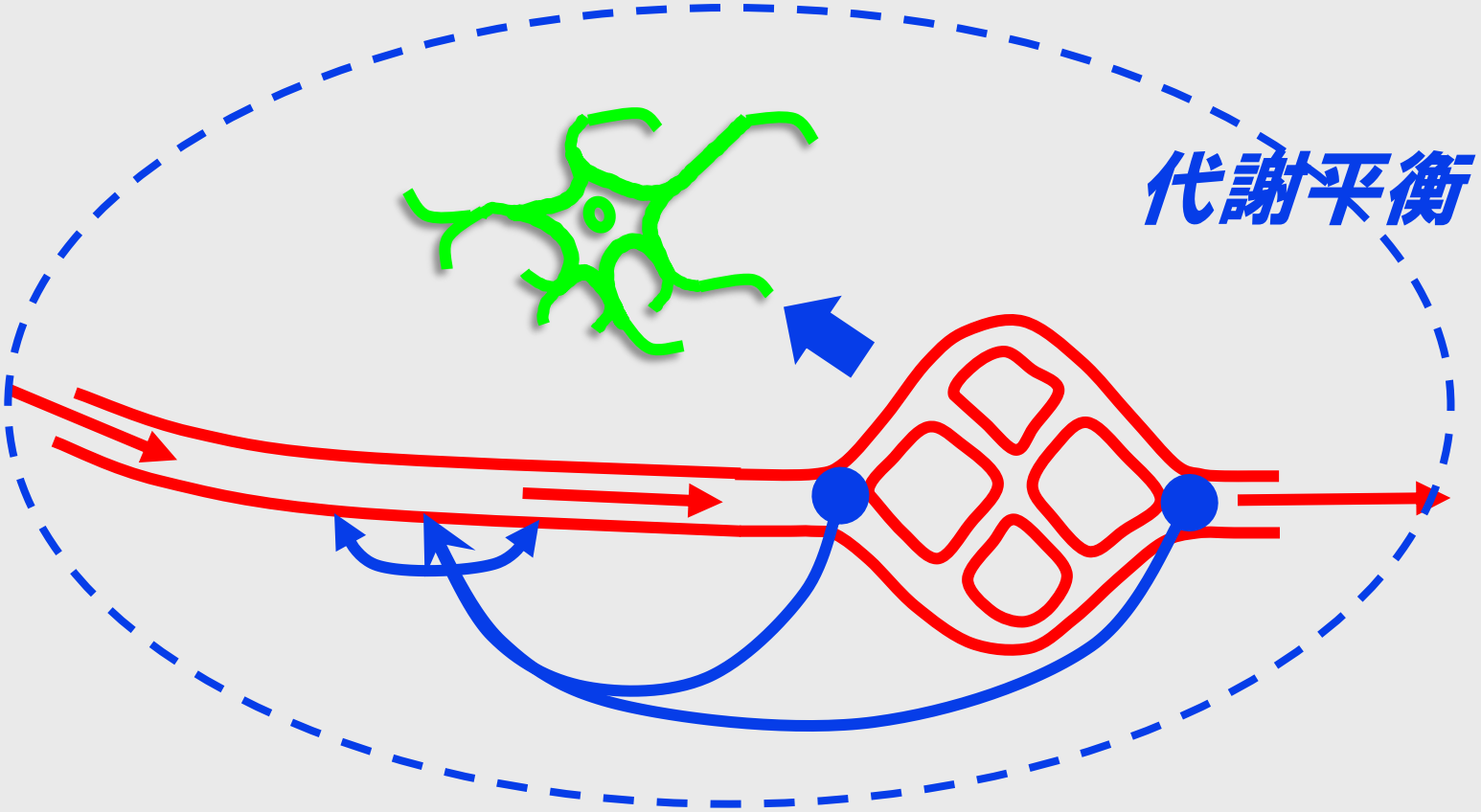
~~2．代謝産物 (metabolites)~~

~~3．発熱現象 (heat production)~~

4．メディエータ (mediators)

フィードバック仮説
Feedback Hypothesis

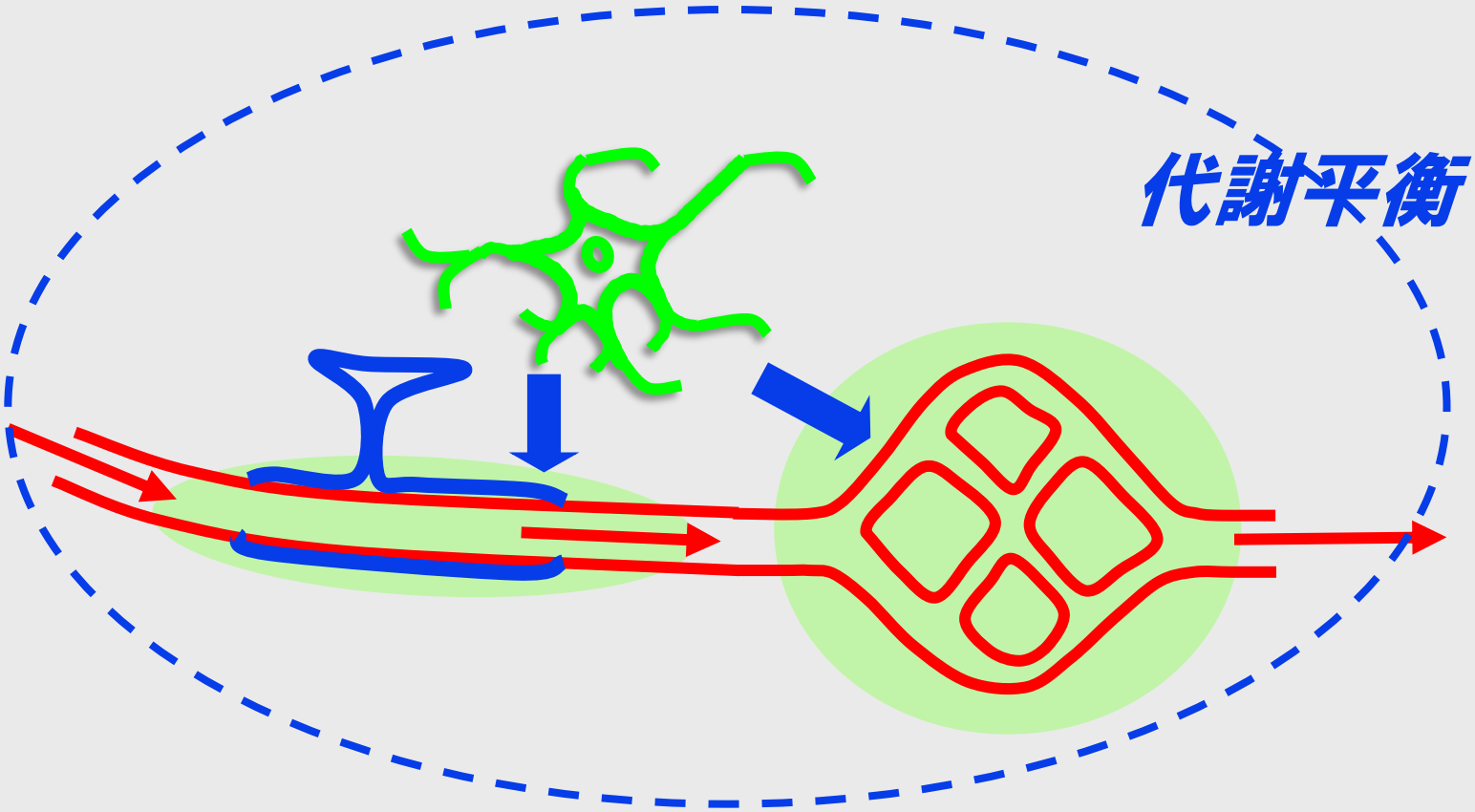
血流変化量を感知して定量的に血流量を制御



神経賦活→代謝増加 ⇄ 血流変化→血流制御

フィードフォワード仮説
Feed Forward Hypothesis

メディエータの発現量に応じて血流量を制御



神経活動→メディエータ発現→血流制御

ミクロ計測によるマクロ計測の疑問の解明

マクロ計測（SPECT, PET, MRI）

測定サイズ >> 血管径

→ 血管内と脳組織の平均の測定

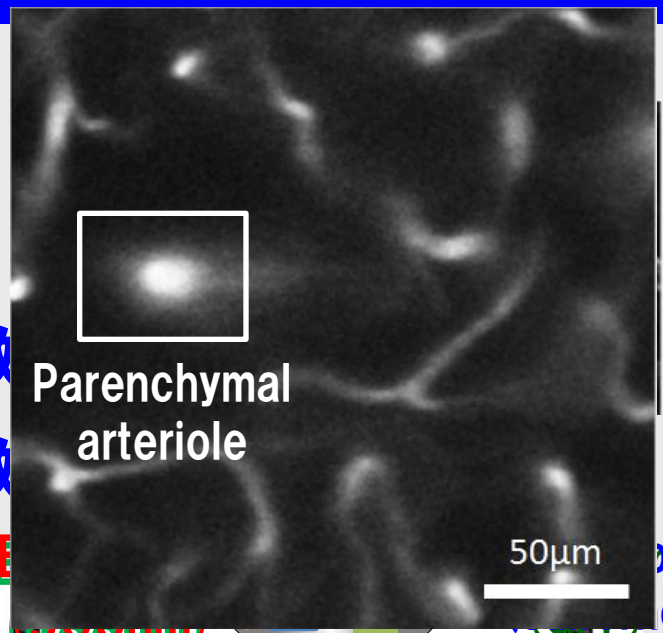
ミクロ計測（二光子, 共焦点）

測定サイズ << 血管径

→ 血管ネットワークを独立に測定

→ メディエータの直接測定

二光子顕微鏡による大脳皮質の測定



脳表動脈

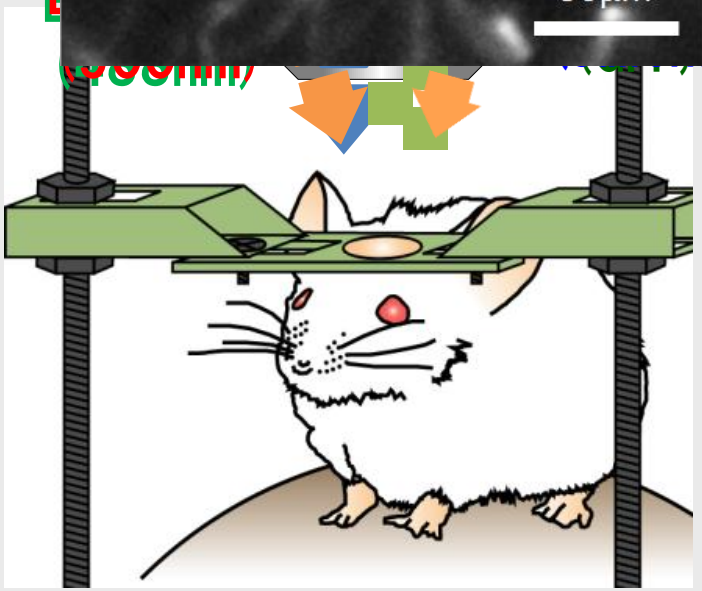
共焦点顕微

二光子顕微

共焦点顕微鏡:Tie2-GFP

rescence

odamine101)



穿通動脈

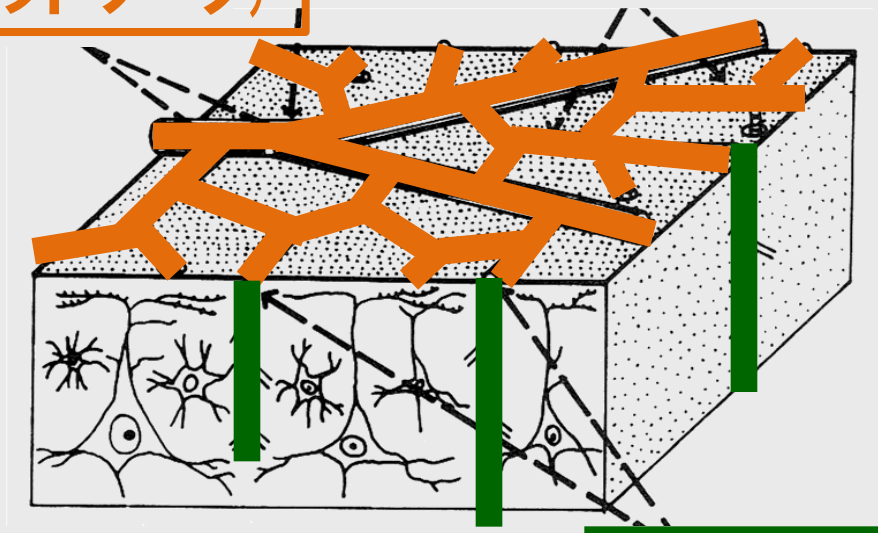
覚醒下　自由歩行

二光子顕微鏡:SR101

二光子顕微鏡による大脳皮質の測定

脳表動脈と穿通動脈の役割

脳表動脈
（血流配分ネットワーク）

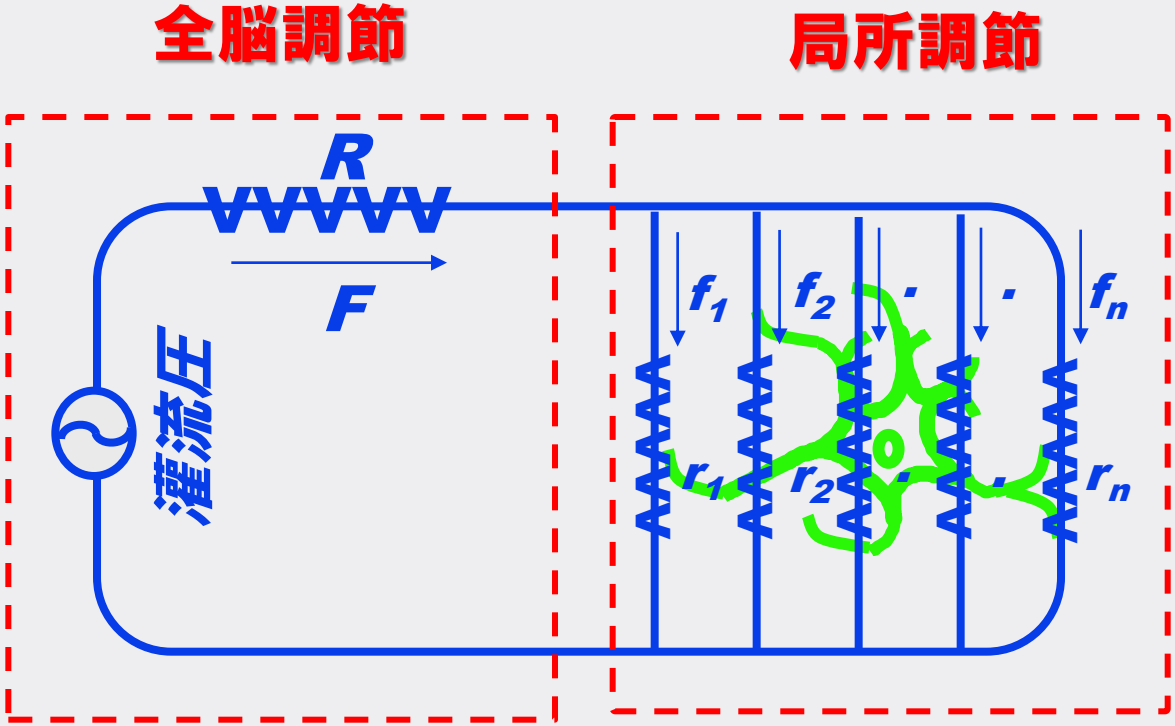


穿通動脈
（組織への血流供給）

The diagram of vascular network in cerebral tissue (Mchedlichvili, 1984)

全脳と局所の血流調節

相対値CBFが神経活動と直線的



$F = f_1 + f_2 + \ldots + f_n$;　　$f_1 r_1 = f_2 r_2 = \ldots = f_n r_n$

局所血流　∝　局所抵抗

脳血流、たかが血流、されど脳血流

脳血流は

脳機能維持のための単純なインフラ機能

しかし

脳機能賦活時の精緻な局所調節機構

ゆえに

脳機能マッピングの手段として君臨

なお

MRI-BOLDは脳血流等価

今日の内容

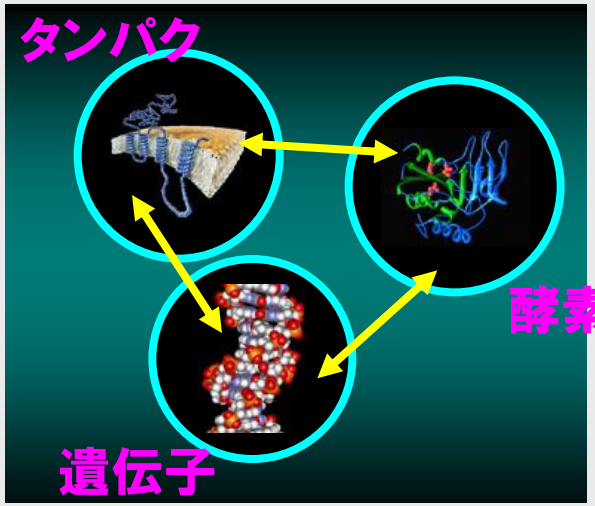
1. 定量的脳機能測定のあけぼの
2. PET原理と循環代謝測定
3. 脳活動と脳血流調節
4. 分子イメージングへの開眼
5. 脳の研究手段

秋田脳研から放医研へ

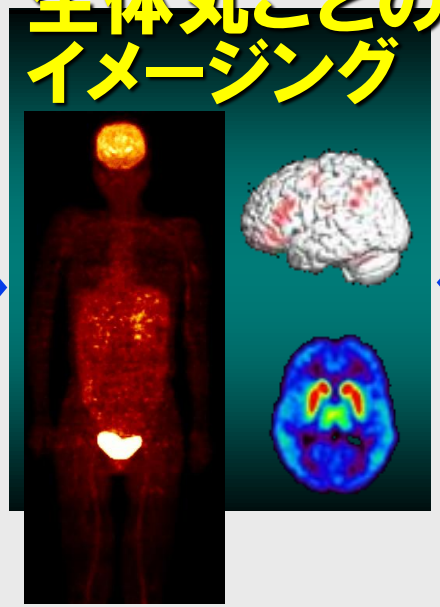
2006

分子イメージングとは

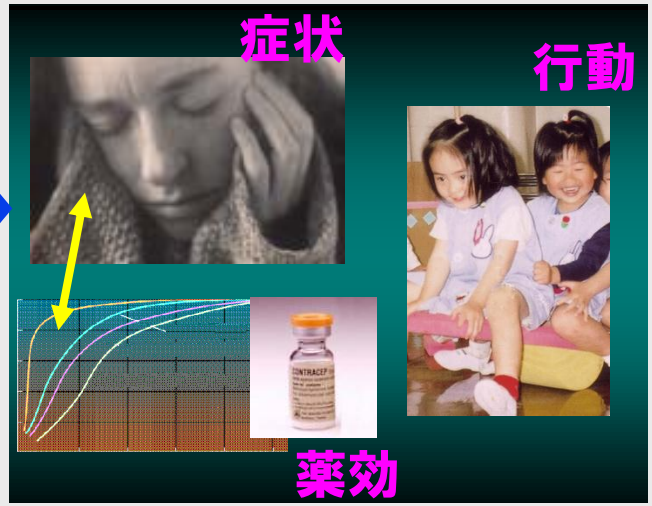
生体内分子



生体丸ごとのイメージング



生体の機能



分子の生体における機能を見る

ライフサイエンスの基盤技術の一つ

磁気共鳴技術　放射線測定技術　蛍光測定技術　化学合成技術

Large Library of Probes

PET probes available for human use at NIRS

Brain

Neuroreceptor

D1
- ^{11}C-SCH23390
- ^{11}C-NNC 112

D2
- ^{11}C-Raclopride
- ^{11}C-FLB 457

PBR
- ^{11}C-DAA1106
- ^{18}F-FEtDAA1106

5-HT$_{1a}$
- ^{11}C-WAY 100635

mAch
- ^{11}C-NMPB

BZR
- ^{11}C-Ro 15-4513
- ^{11}C-Flumazenil

NMDA
- ^{11}C- Ac- L703,717

Transporter

Dopamine
- ^{11}C-PE2I

5-HT
- ^{11}C-DASB
- ^{11}C-McN5652

MDR
- ^{11}C-Verapamil

Neurotransmitter Enzyme

AchE
- ^{11}C-MP4A
- ^{11}C-MP4P

BuChE
- ^{11}C-5R3B
- ^{11}C-MP3B

Dopamine Metabolism
- ^{11}C,^{18}F-DOPA

Circulation

MGlc
- ^{18}F-FDG

BF
- ^{82}Rb/^{82}Sr
- $^{13}NH_3$ $H_2{}^{15}O$ $^{38}K^+$

Cancer

Protein Synthesis
- ^{11}C-Methionine
- ^{11}C,^{18}F-Tyrosine

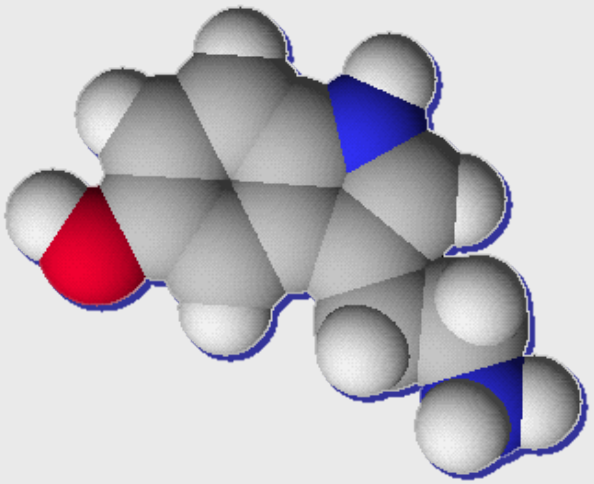
Nuclei Synthesis
- ^{18}F-FLT, ^{34m}Cl-U
- ^{34m}Cl-dUr

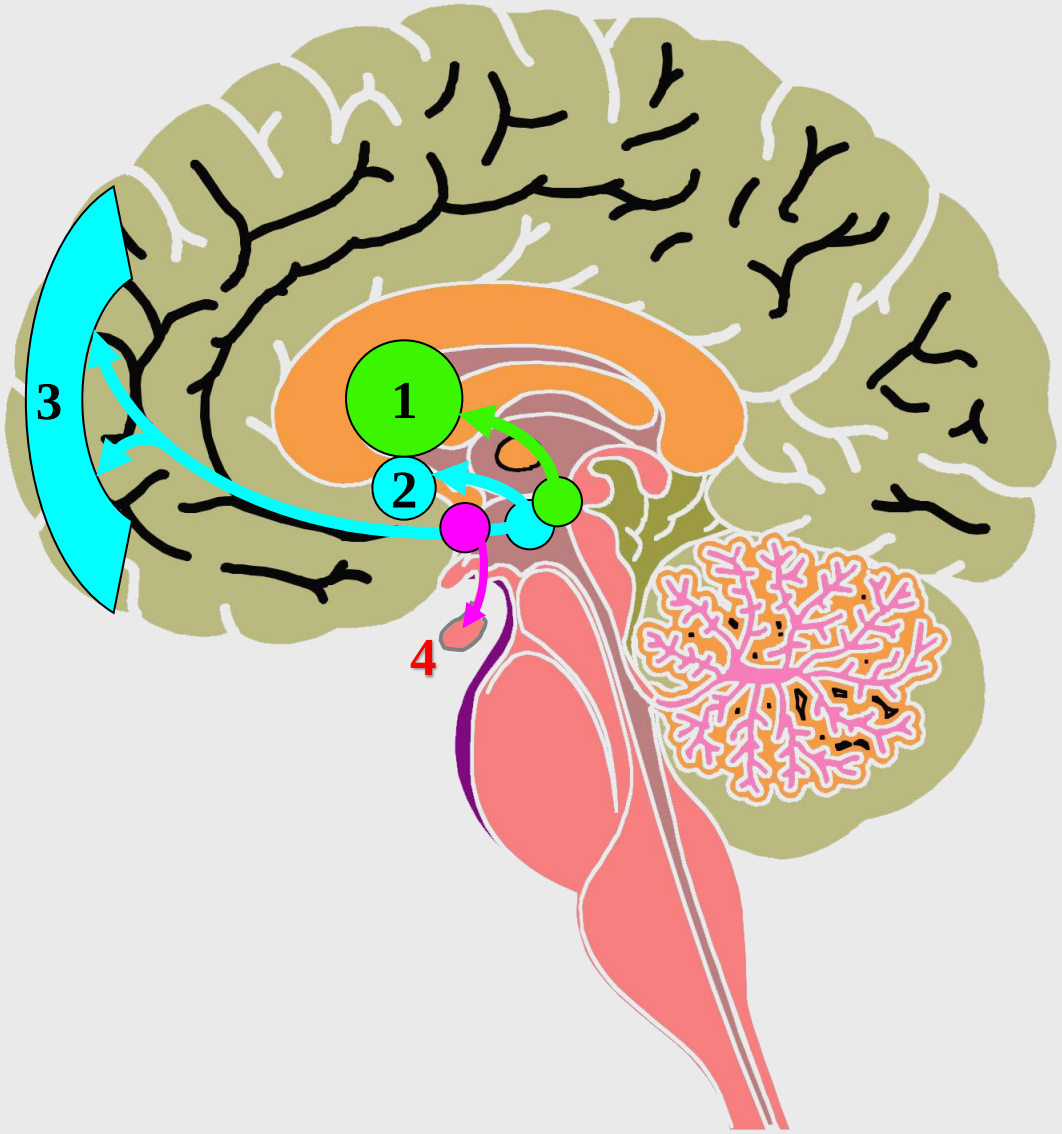
Receptor
- ^{11}C-Iressa
- ^{18}F-estradiol

Hypoxia
- ^{61,62}Cu-ATSM
- ^{18}F-Misonidazole

GLipo
- ^{11}C-acetate

中枢ドーパミン投射経路





1 黒質線条体系 (A9)
黒質 → 基底核

2 中脳辺縁系 (A10)
腹側被蓋野 → 側坐核

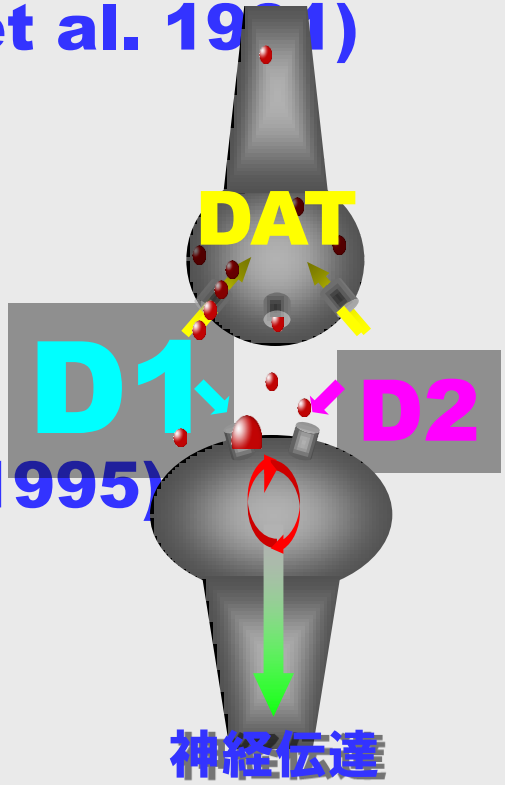
3 中脳皮質系 (A10)
VTA → 前頭皮質

4 隆起脳下垂体系 (A12)
視床下部 → 下垂体

大脳皮質ドーパミンD1受容体機能

認知機能

記憶や予期の機能: ワーキングメモリー
(Sawaguchi et al. 19[illegible])

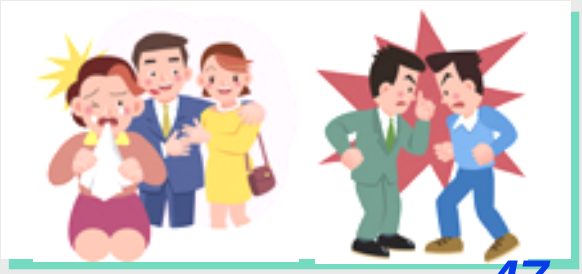


動機付け

行動を強化する
(Weed et al. 1995)

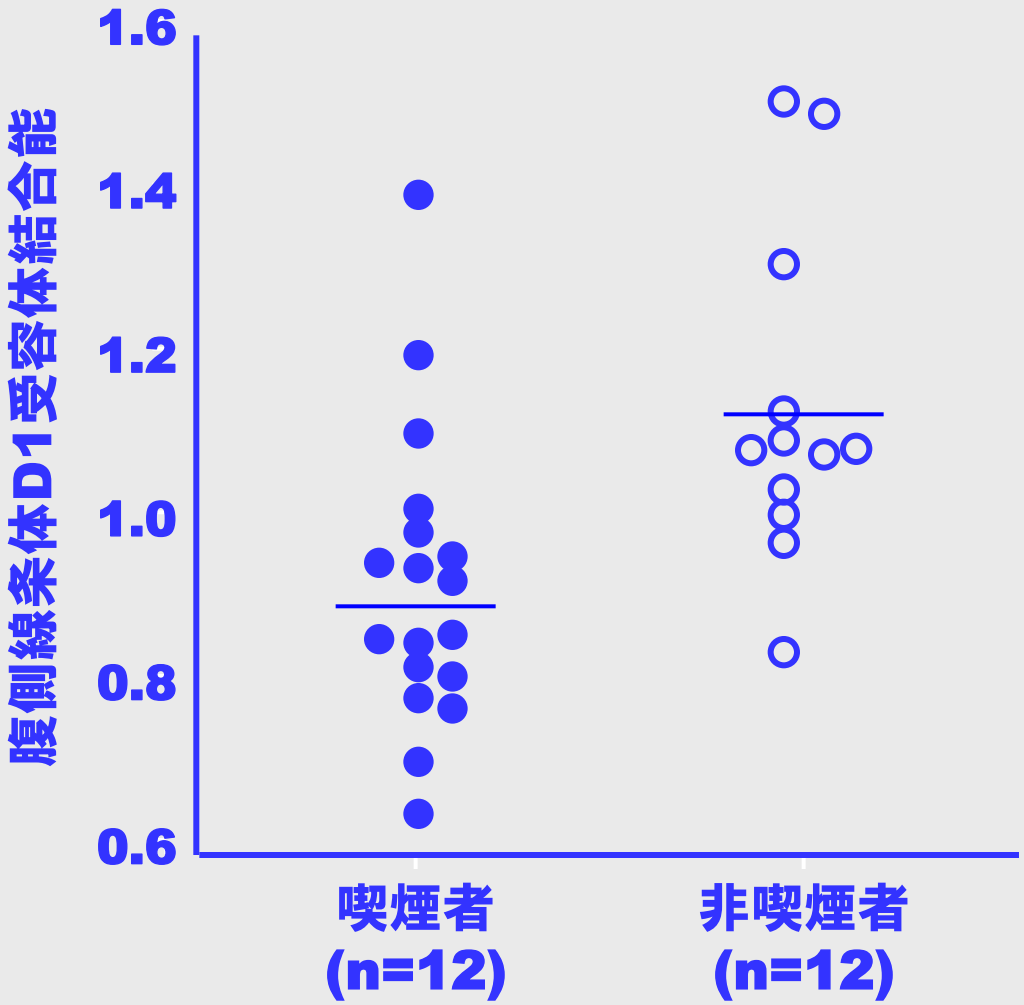
情動反応

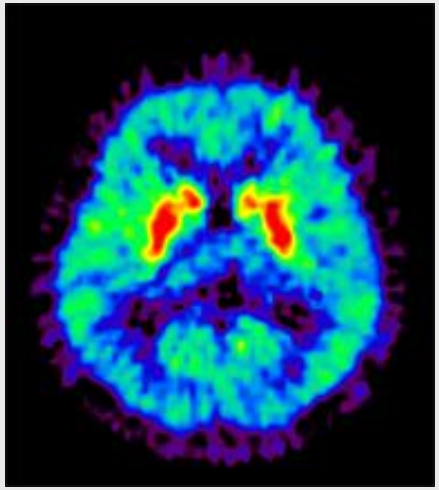
感情的な行動をコントロールする
(Lewis et al. 1994)



喫煙習慣による腹側線条体D1受容体の差異

喫煙者の腹側線条体におけるD1結合能は非喫煙者よりも有意に低い

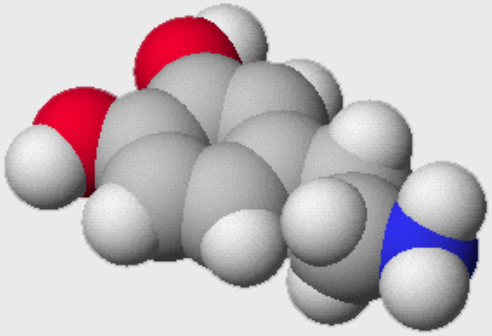




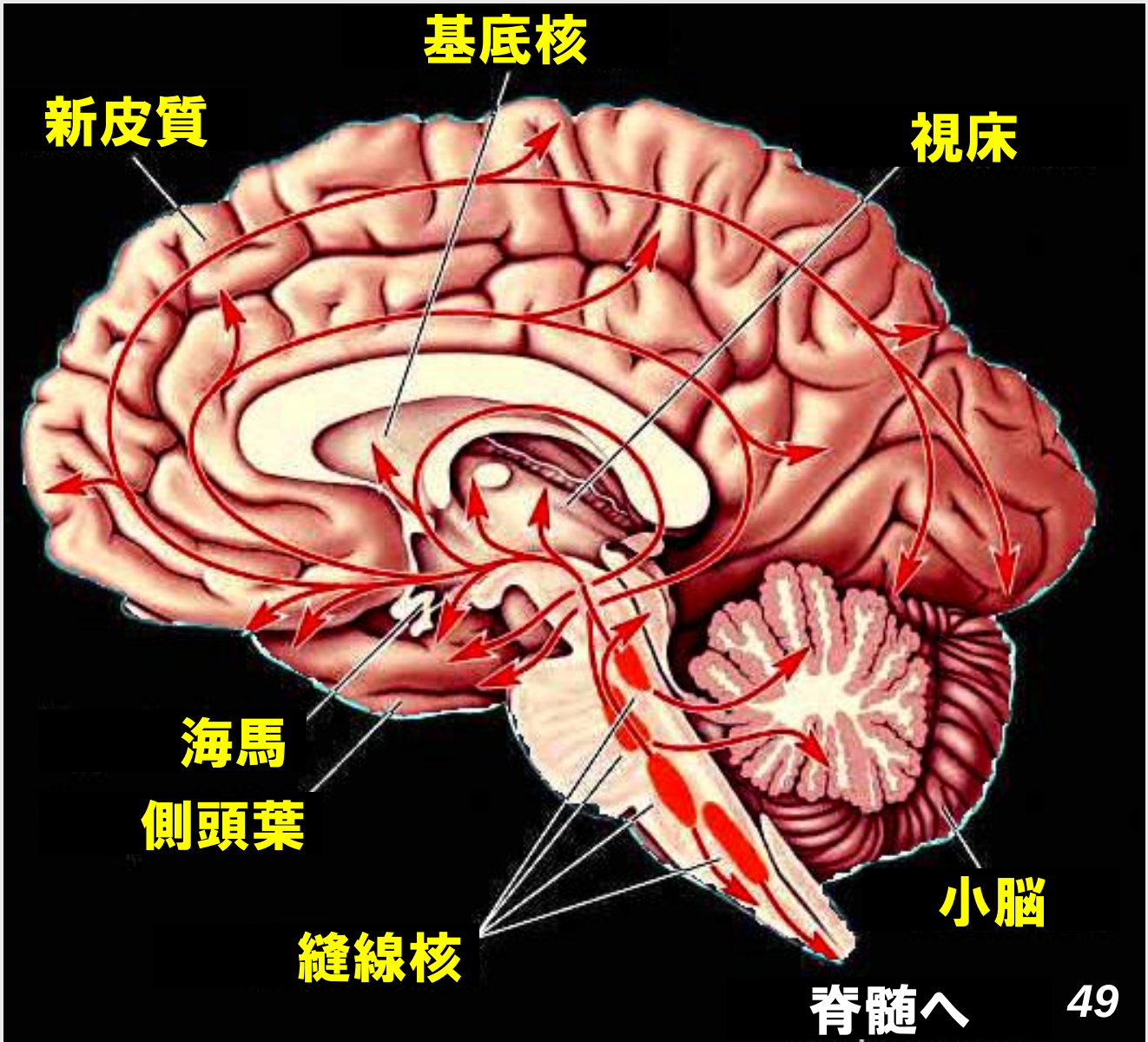
[^{11}C]SCH23390

(Biol Psychiatry 2006)

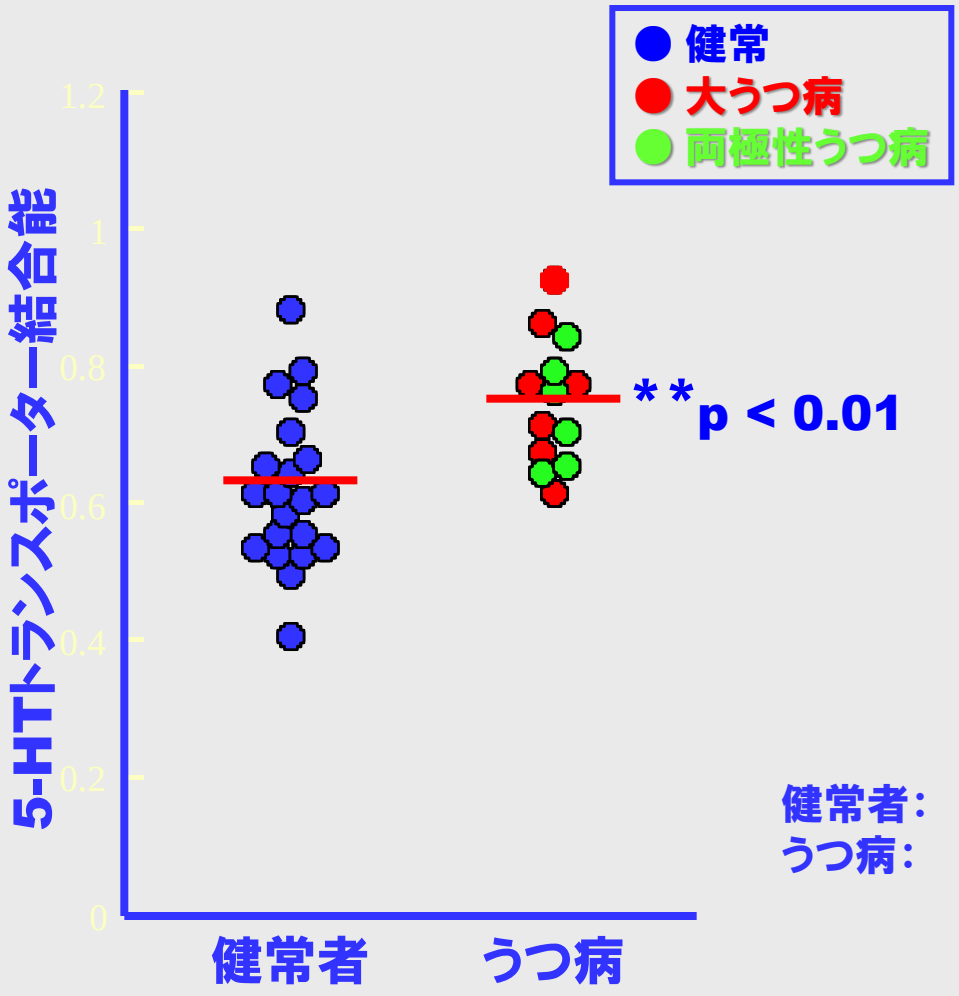
セロトニン神経系



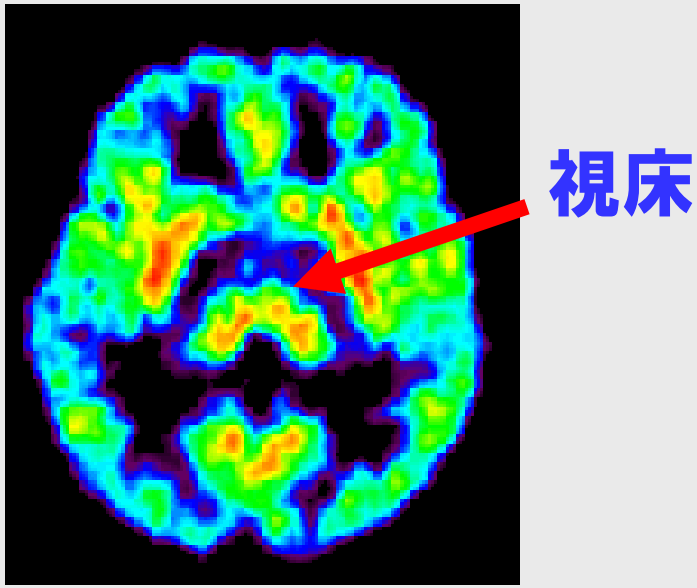
セロトニン



うつ病のセロトニン トランスポーター



[^{11}C] (+) McN5652



年齢補正

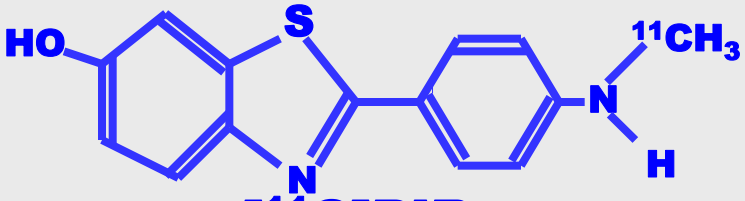
健常者: Adjusted BP = BP + 0.0074 × (Age − 42.3)

うつ病: Adjusted BP = BP + 0.0071 × (Age − 43.0)

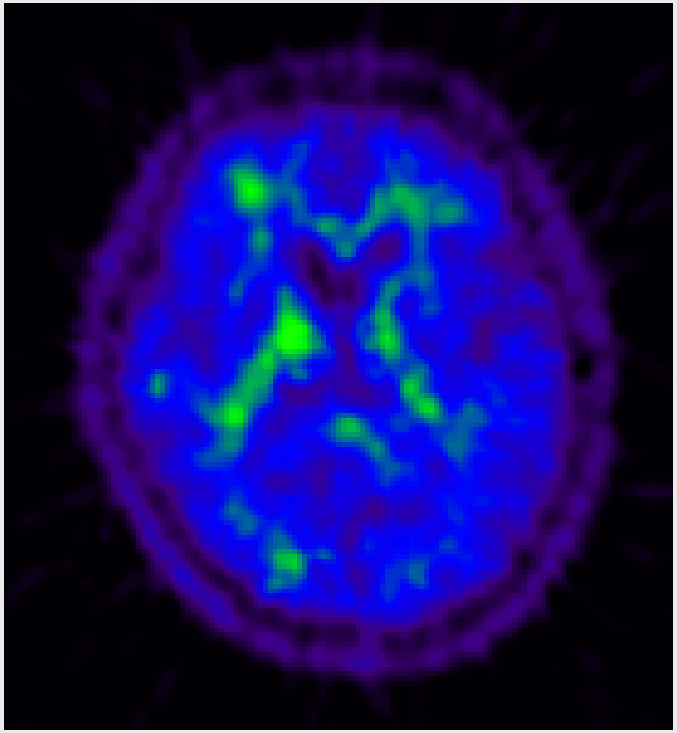
(BP: binding potential)

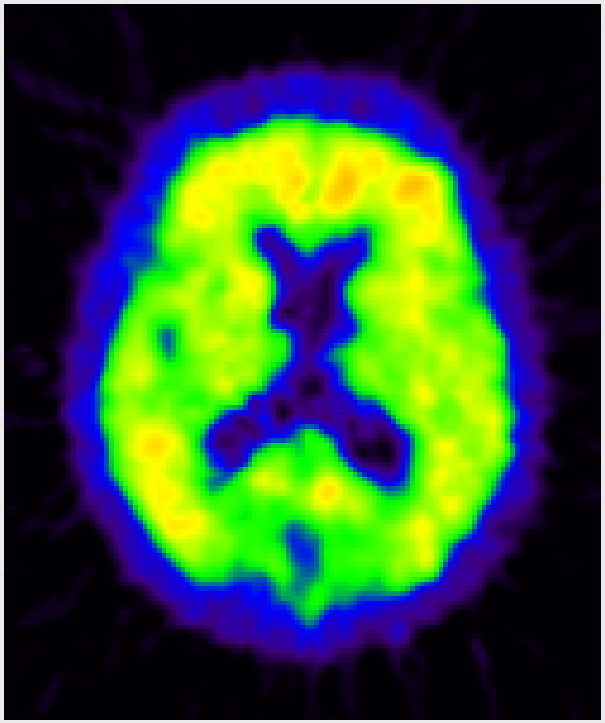
(Biol Psychiatry, 2002)

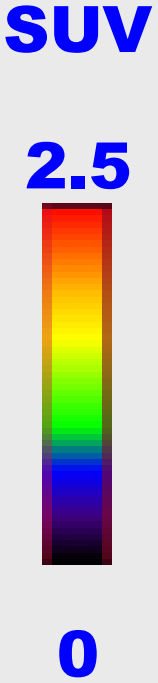
アミロイドのPET画像



[^{11}C]PIB





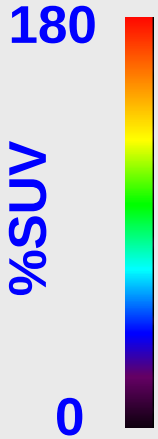


正常者
(50歳女性)

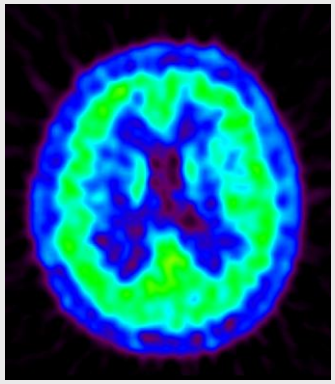
アルツハイマー病患者
(70歳女性)

TSPO Imaging in Alzheimer's Disease

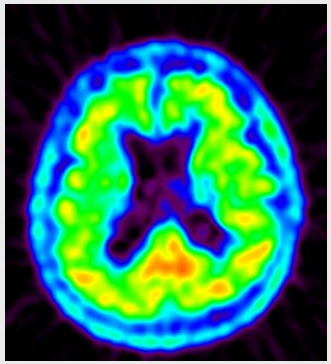
[^{11}C]DAA1106

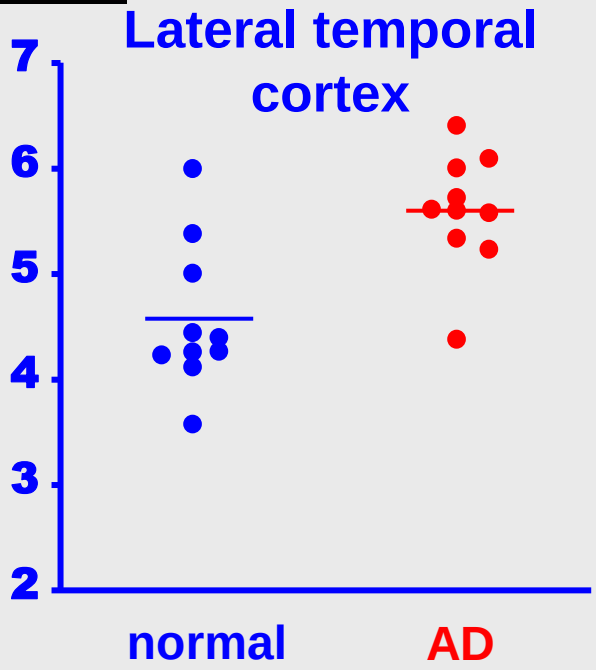


Aged Normal



Alzheimer's Disease

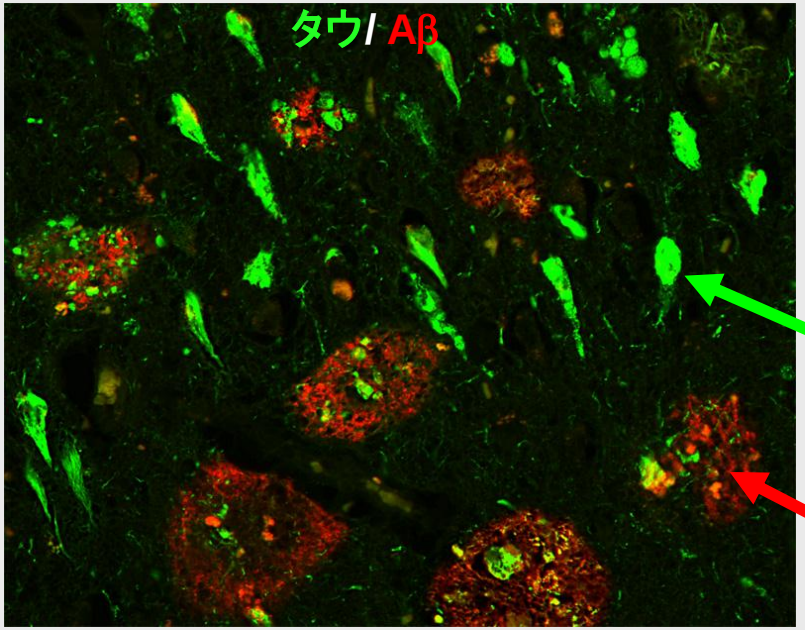


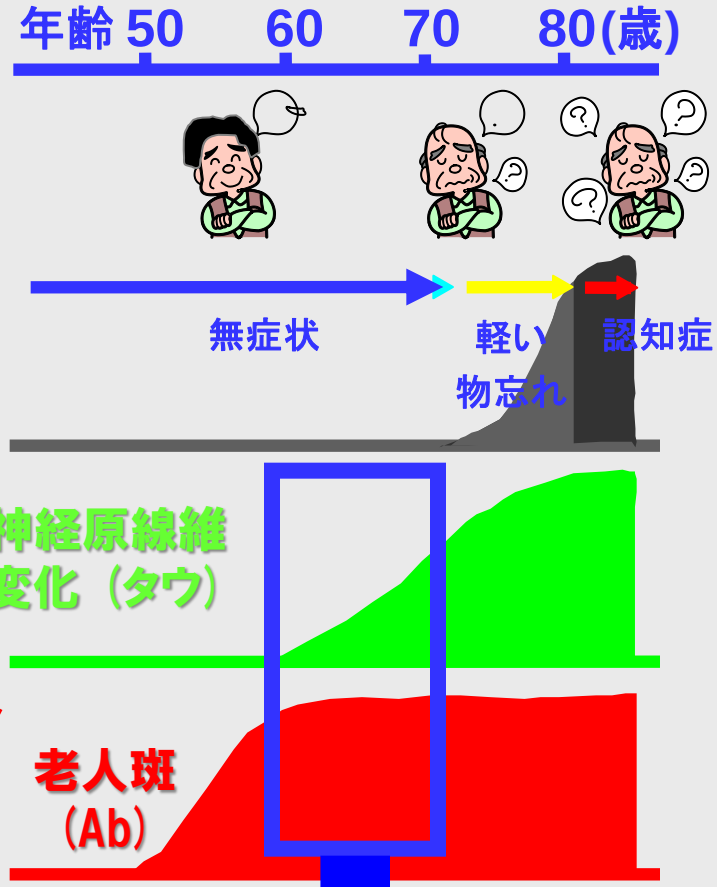


(Biol Psychiatry 2008)

脳老化の早期診断を目指した画像技術

アルツハイマー病患者の脳

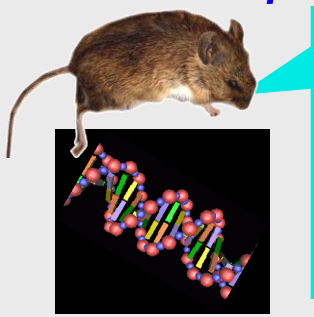




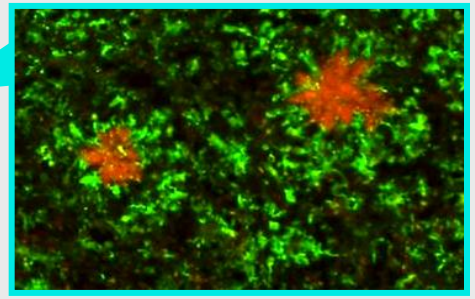
超早期診断が実現
脳年齢判定？

生きた脳でゴミ蓄積を検出

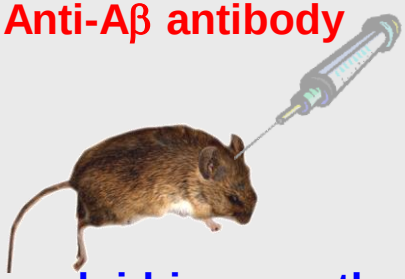
Aβ Immunization in Tg Mice



β amyloid deposition

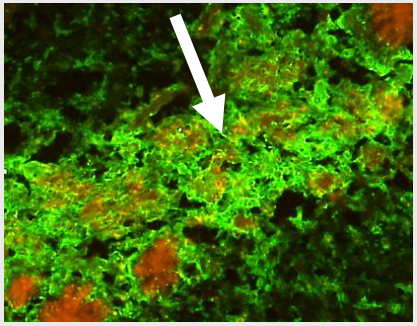


Anti-Aβ antibody



Anti-amyloid immunotherapy

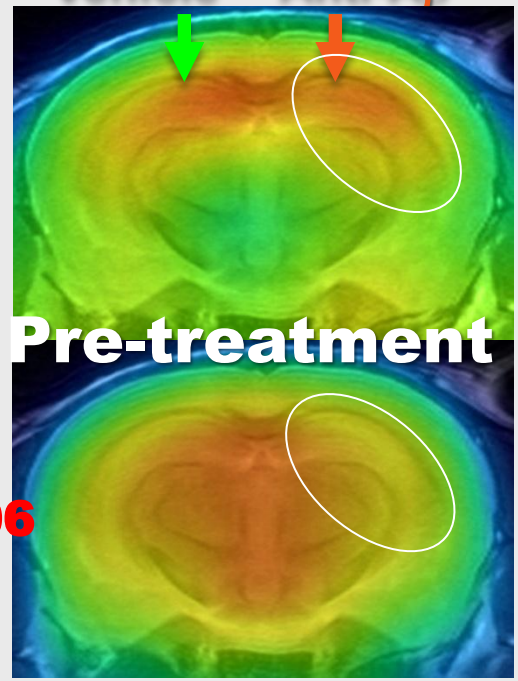
Activated microglia phagocytosis of amyloid



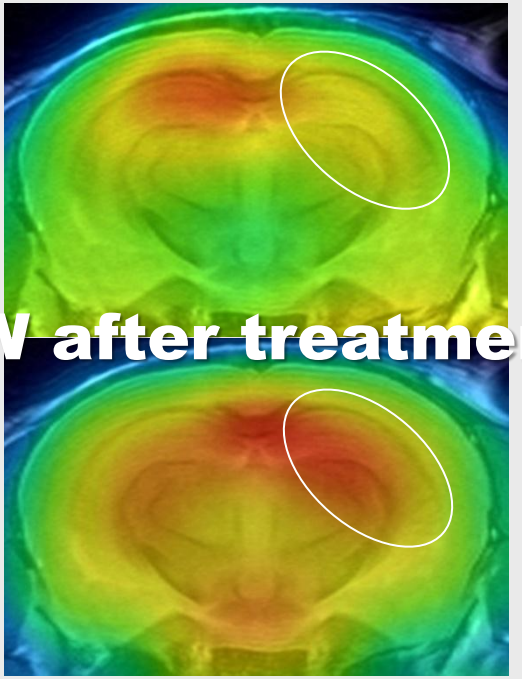
Vehicle Anti-Aβ

Amyloid ([^{11}C]PIB)

TSPO [^{18}F]FE-DAA1106



Pre-treatment



2W after treatment

(J Neurosci 2007)

PET enables in vivo monitoring of anti-amyloid treatment

今日の内容

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3. 脳活動と脳血流調節
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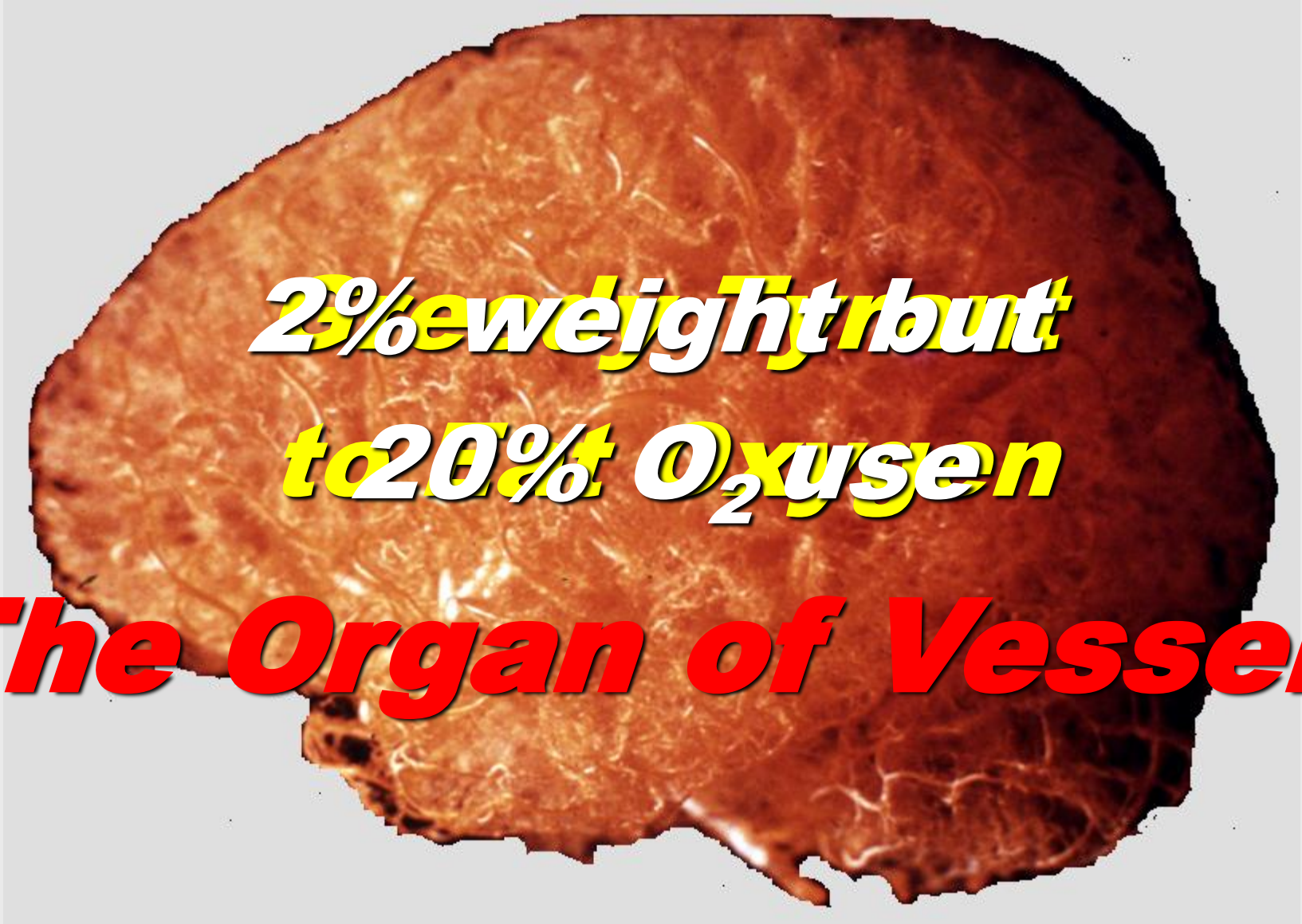
5. 脳の研究手段

What is Brain?



2% weight but

to 20% O_2 use

The Organ of Vessels

神経科学者との出会い

JST地域結集事業（1996－2000）

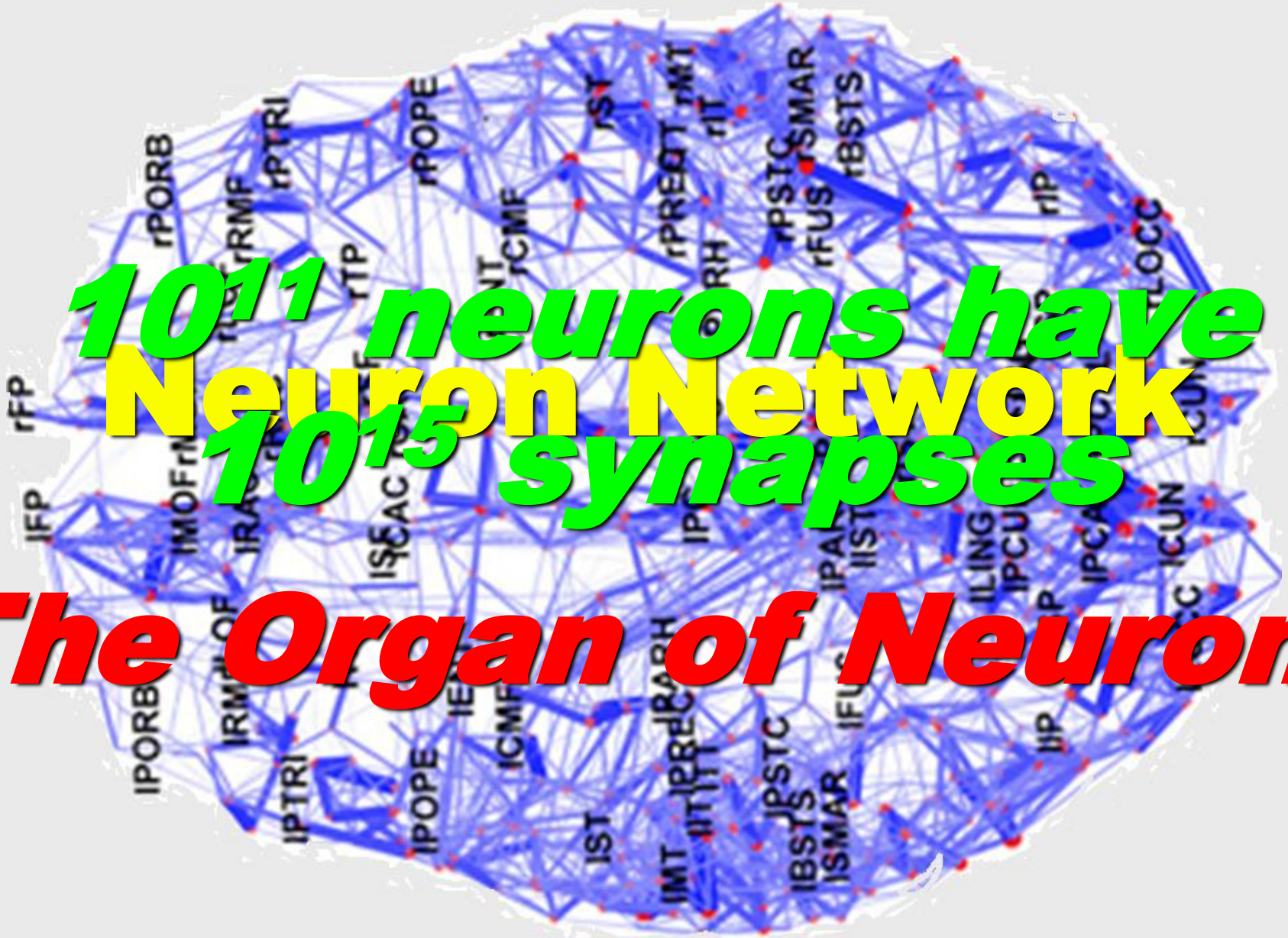
脳賦活に伴う二次信号の計測とその発生機序に関する研究

Measurement and mechanism of the secondary signal during neuronal activation

脳科学者は脳に血管があることを無視していた！

Tanaka (RIKEN) *Iijima (ETL)* *Kanno (Akita-Noken)*

What is Brain?



10^{11} neurons have

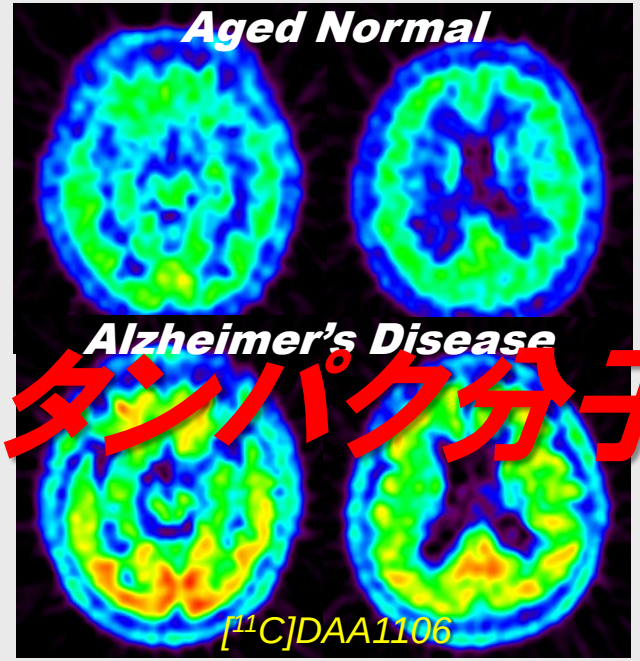
Neuron Network

10^{15} synapses

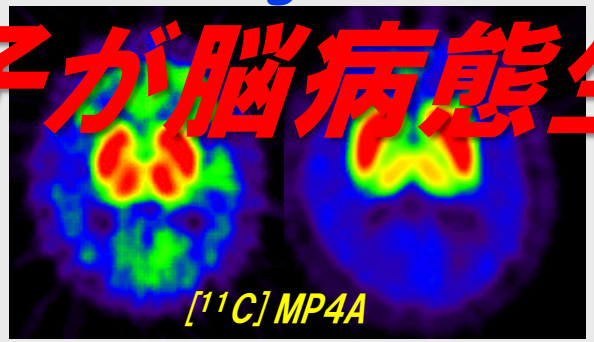
The Organ of Neurons

放医研における脳

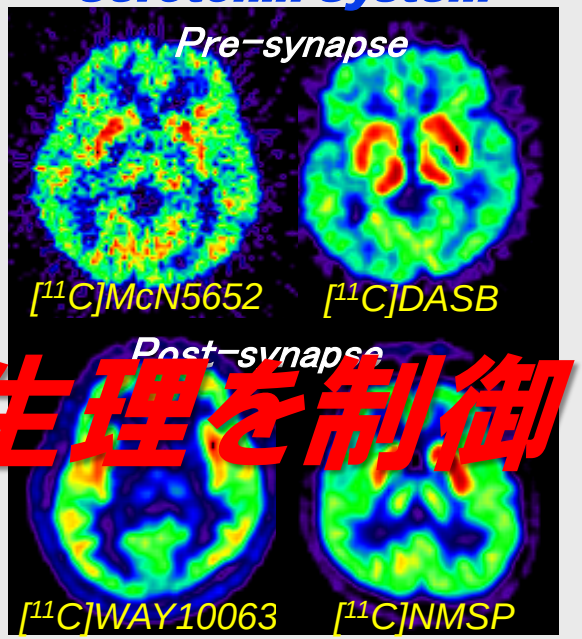
Brain Inflammation



Monitoring treatment

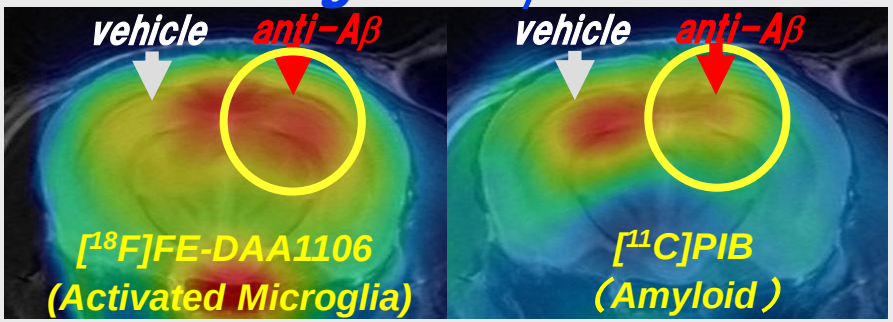


Serotonin System

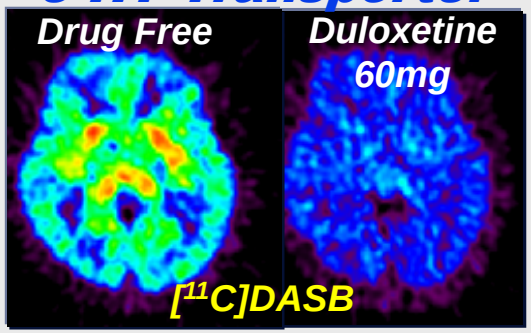


タンパク分子が脳病態生理を制御

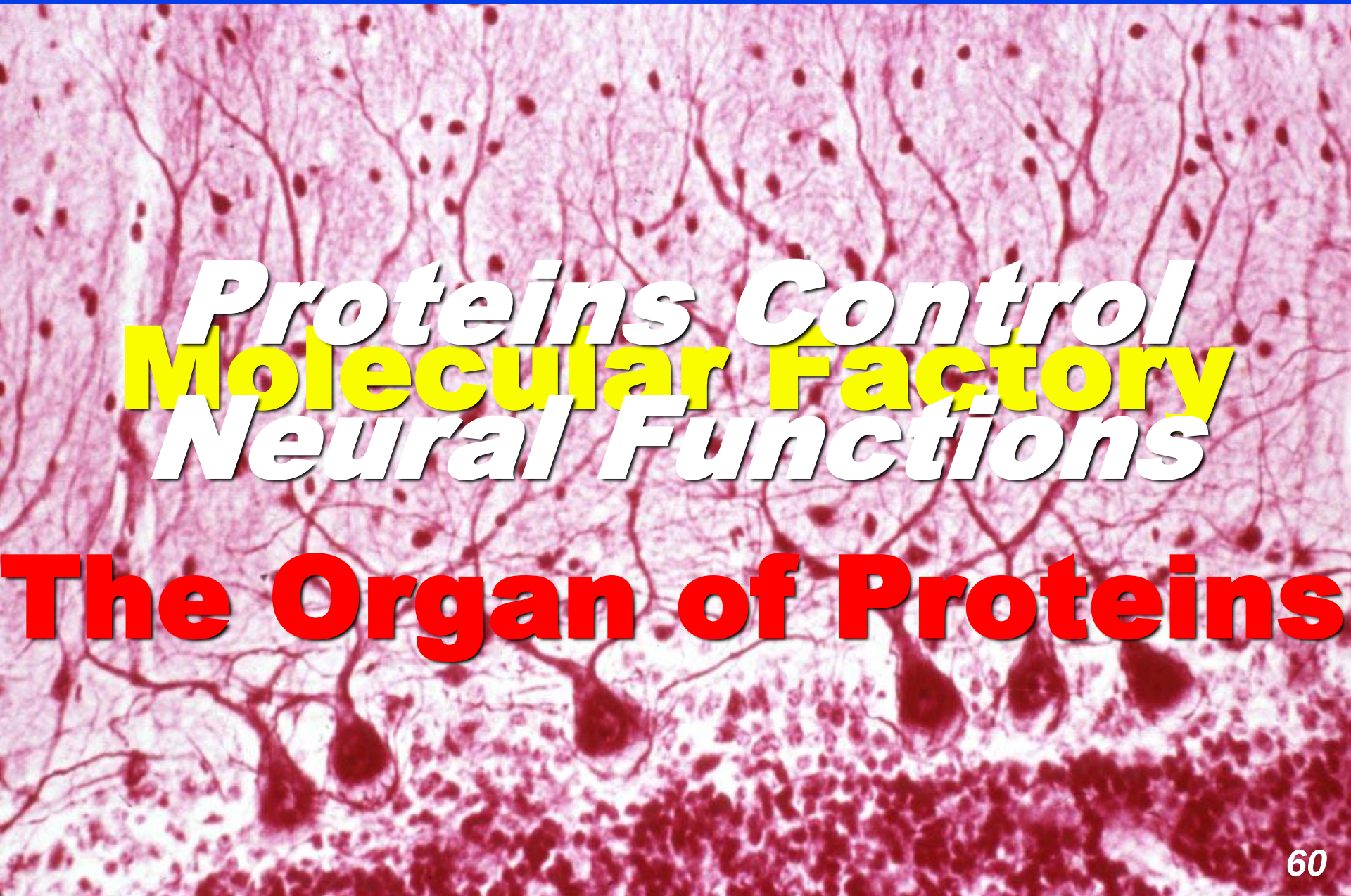
Monitoring anti-Aβ treatment



5-HT Transporter



What is Brain?



Proteins Control
Molecular Factory
Neural Functions

The Organ of Proteins

What is Brain?

1. 秋田脳研・・・・・ Organ of Vessels

2. 神経科学者・・・ Organ of Neuron

3. 放医研 ・・・・・・ Organ of Protein

Brain is never solved puzzle!

群盲象を撫でる

A blind man touches an elephant body.

謝辞

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