Quantitation in Positron Emission Tomography: applications in Neuroscience (Research and Clinical setting)

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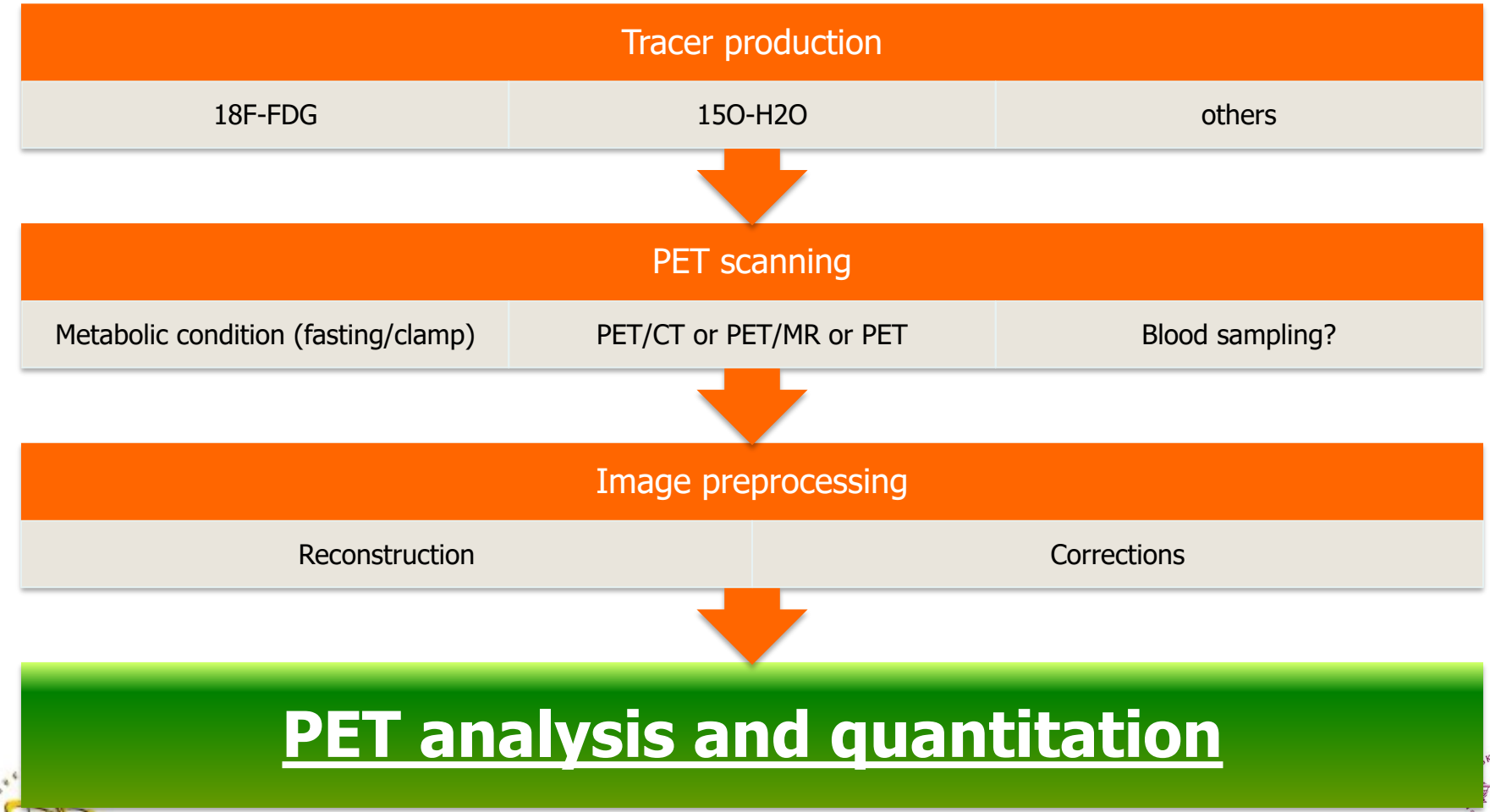
Outline / Learning objectives

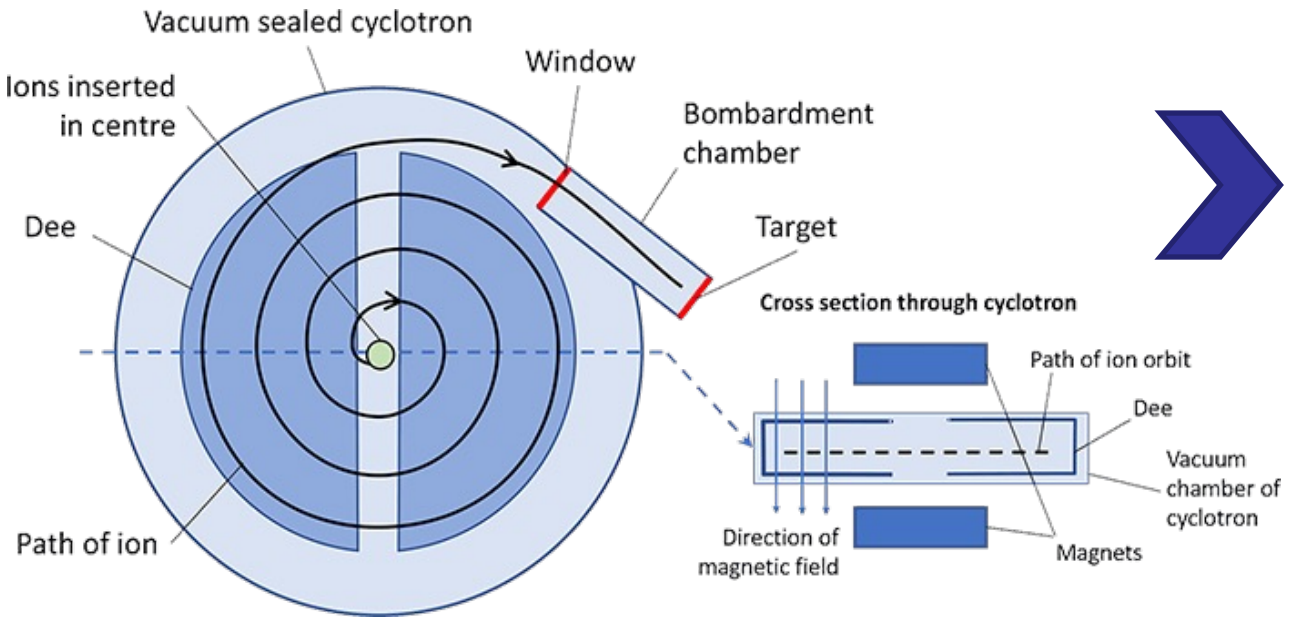
- Basics of Positron Emission Tomography
- Qualitative vs Quantitative research
- When quantitation of PET signals is recommended
- Dynamic PET
- Factors to take in consideration before analysing PET images
- Assumptions for PET tracer quantitation
- Semi-quantitative methods: SUV, SUV ratio (SUVR)
- Centiloid scale (Amyloid imaging)
- Quantitative methods: Linearizations (Logan, Gjedde-Patlak) Quantitative methods: Compartmental Models

PET research - pipeline



PET (1) – Tracer production

Cyclotron - Ion path to the target



Radiotracer

Many people involved. Very important step!
Without radiotracer, PET imaging is impossible.

PET (2) – Basic concept

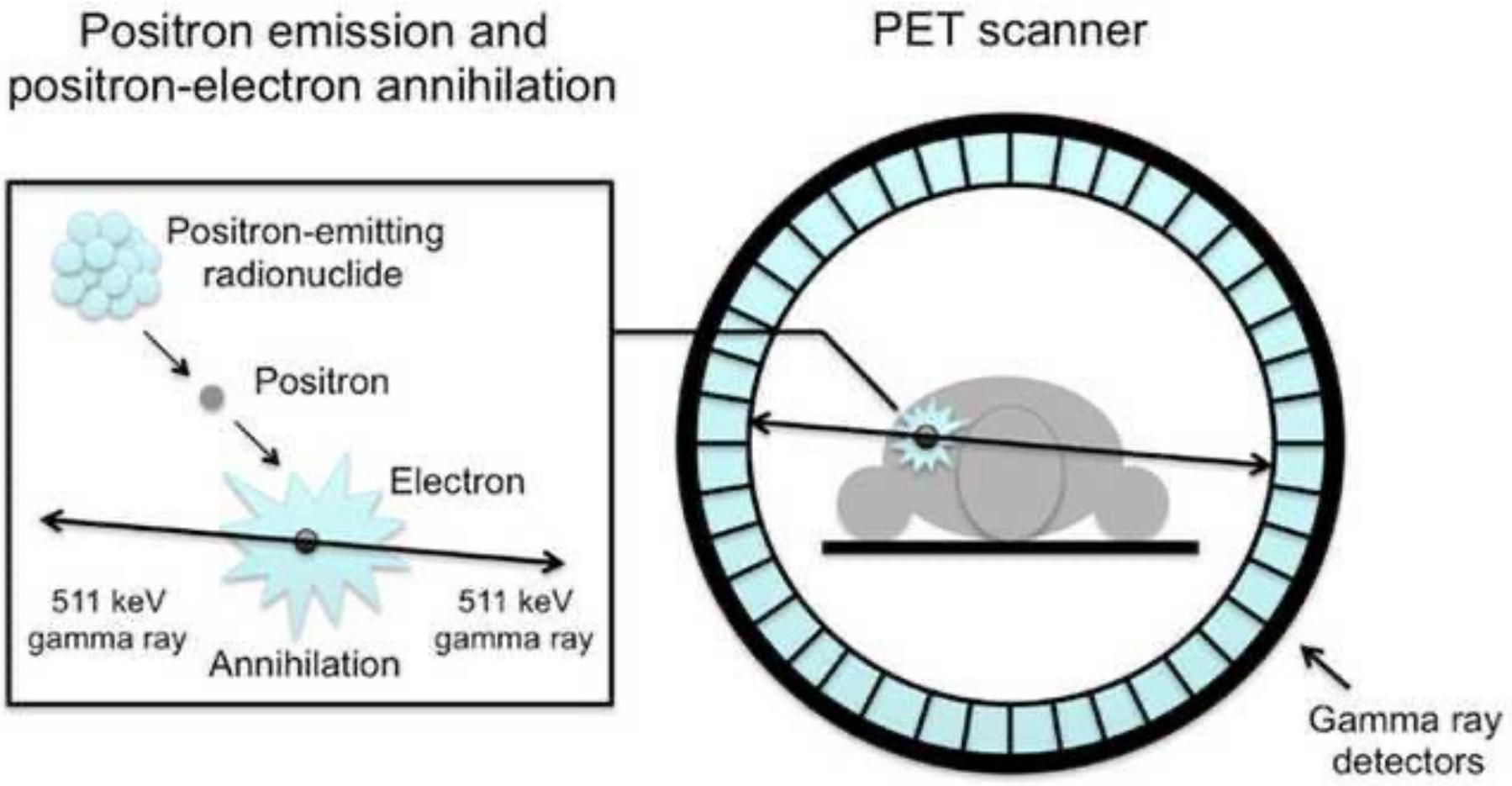
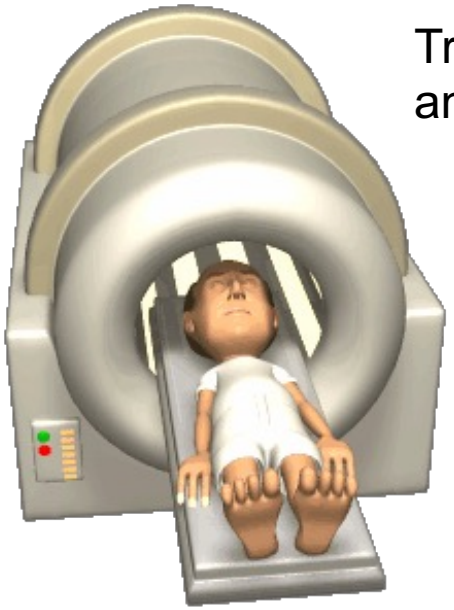
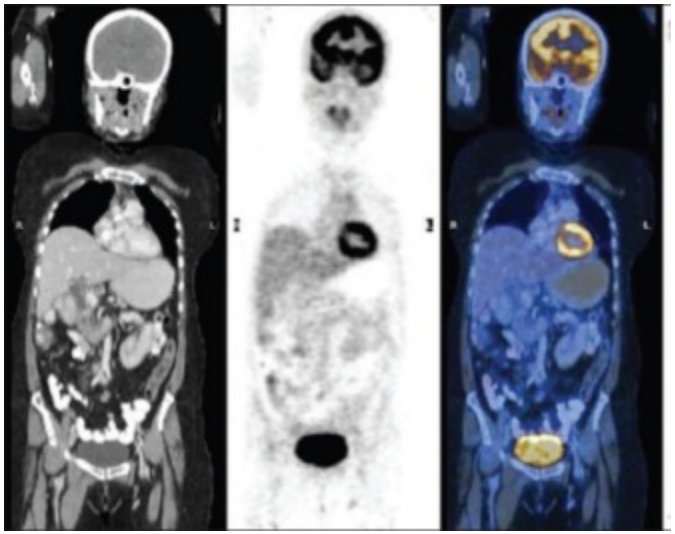


Fig. from https://www.physicsforums.com/insights/basics-positron-emission-tomography-pet/

PET (3) – PET scanning, Image pre-processing and reconstruction



Tracer administration
and Scanning



CT PET PET/CT

Image reconstruction and
corrections
(eg. decay, motion)

PET/CT figs from Tewari A. et al. 2013

Data – Qualitative vs Quantitative

Qualitative vs Quantitative research

DATA COLLECTION

- Qualitative research
  - Collecting images according to the needs of the participant
  - Collecting info from a small number of individuals
- Quantitative research
  - Collecting data using instruments with preset questions
  - Collecting info from a large number of individuals

DATA ANALYSIS and INTERPRETATION

- Qualitative research
  - A description of the quality of the image
  - Stating the larger meaning of findings
- Quantitative research
  - Data analysis tends to consist of statistical analysis
  - Describing trends, comparing group differences, relating variables
  - Interpretation tends to consist of comparing results with prior predictions and past research

Based on https://www.slideshare.net/doha07/quantitative-and-qualitative-research?next_slideshow=1

Qualitative and quantitative approaches in PET imaging

	Qualitative approach	Quantitative approach
Time consuming	Little (++)	Very much (--) (longer scan and analysis)
Dynamic scan	Not required (static) (+)	Required (-)
Time dependency	Yes (-)	No (+)
Sensitivity	Little (---) (exceptions)	Highly sensitive for comparisons (+++)
Input function	Not needed (+)	Needed (-)
Image quality	Highly dependent (--)	Less dependent (+)
Metabolic status	Assessment affected (--)	Quantitation takes into account (+++)

+ positive aspect; - negative aspect

Levels of quantification

- Looking at differences in image intensity

- Measuring radioactivity concentrations (kBq/mL)

- Normalizing radioactivity concentrations to injected activity (and for ex. body weight)

- Measuring physiological parameters

Quantitation in PET (Methods)

Qualitative — Visual assessment

Semi-quantitative — SUV, T/N ratio

Quantitative — FUR; MTGA (Patlak, Logan); Compartment model fit

Why quantitate in PET?
An example from clinical geriatrics

Amyloid imaging for the detection of abnormal accumulation in the brain of protein Aβ for the diagnosis of Alzheimer's disease

From the product information of the PET tracer approved be the European Medicines Agency

Quantitative assessment of cortical radioactive signal intensity using validated and CE marked computer software may be used to assist in the visual estimate of radioactive signal distribution. Such software provides a calculation of brain amyloid load by dividing the mean image intensity in the cortical regions associated with amyloid deposition (raised in AD subjects) with the mean image intensity in a reference region such as the pons. The measure is referred to as Standard Uptake Value ratio or SUVR. Dichotomous visual reads for flutemetamol (18F) scans were validated against the boundary between sparse and moderate neuritic plaque densities. An SUVR threshold value of 0.59 to 0.61 derived from CE marked software using the pons as a reference has been determined to give very high concordance with visual reads (see section 5.1) and may be used as an adjunct to visual reading.

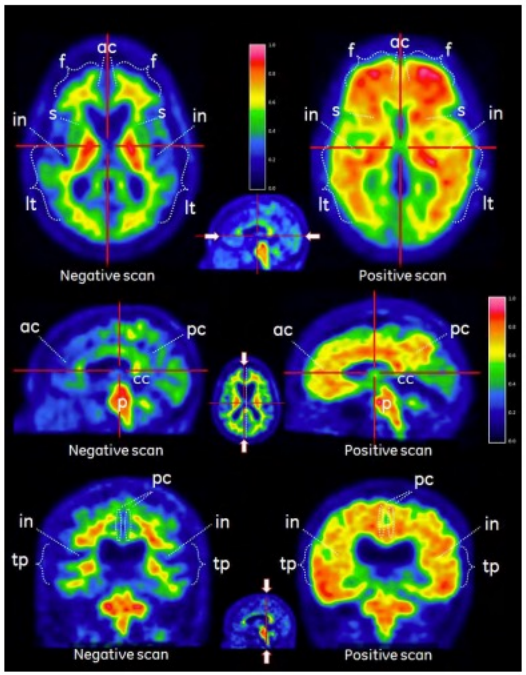


Fig and quote from: https://www.ema.europa.eu/en/documents/product-information/vizamyl-epar-product-information_en.pdf

PET - Definitions

Static / Dynamic

- Modalities of acquisition of the PET images

Frame

- A time point in a PET (dynamic) image

Time-activity curve (TAC)

- Radioactivity concentration (kBq/ml) as a function of time after tracer injection

Input function

- Authentic tracer concentration available in arterial blood circulation (most of the tracers require plasma input function)

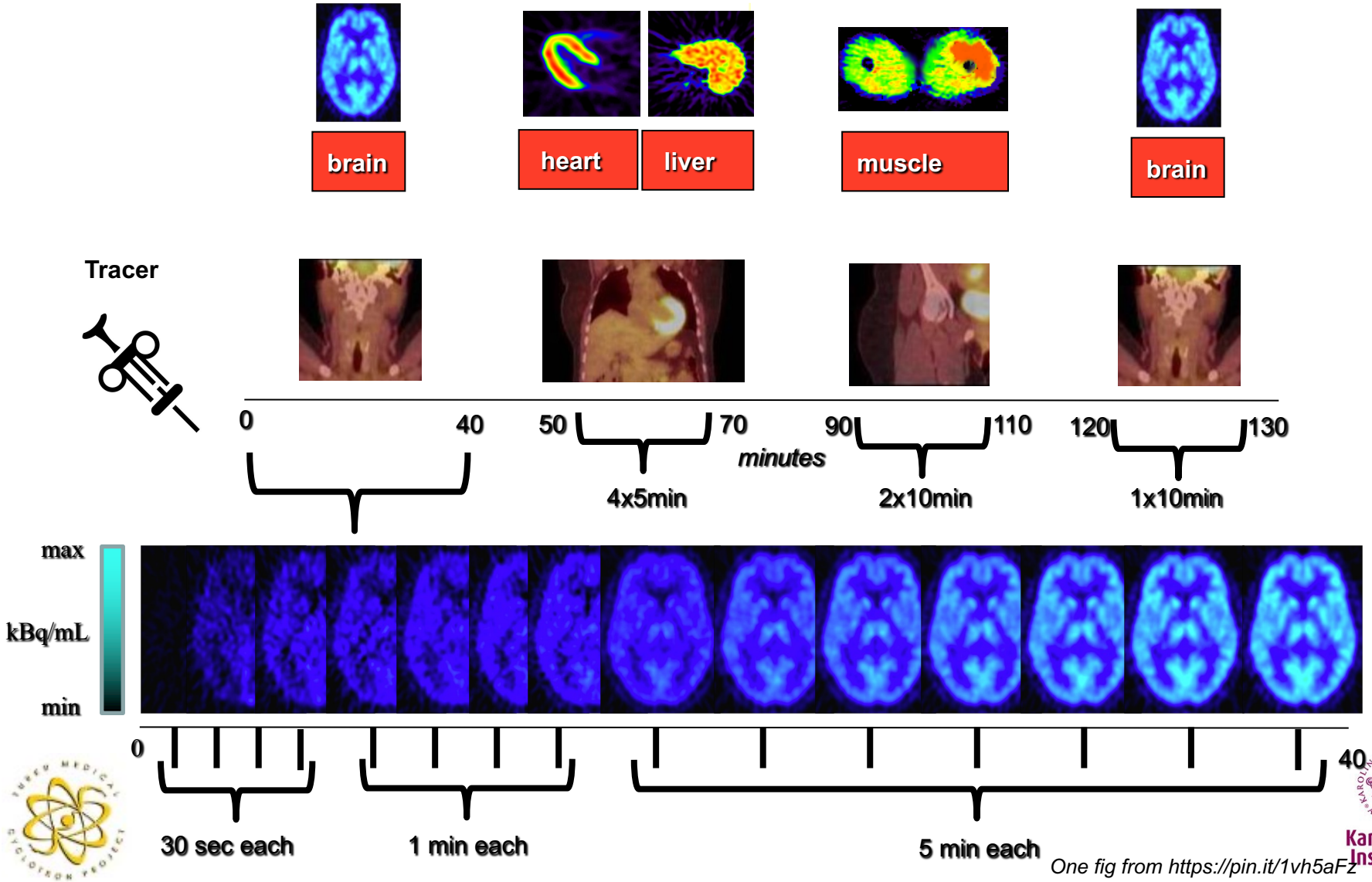
Region of Interest (ROI)/Volume of Interest (VOI)

- A region of the image from which we extract the tracer activity statistics usually as TAC

Rate Constant

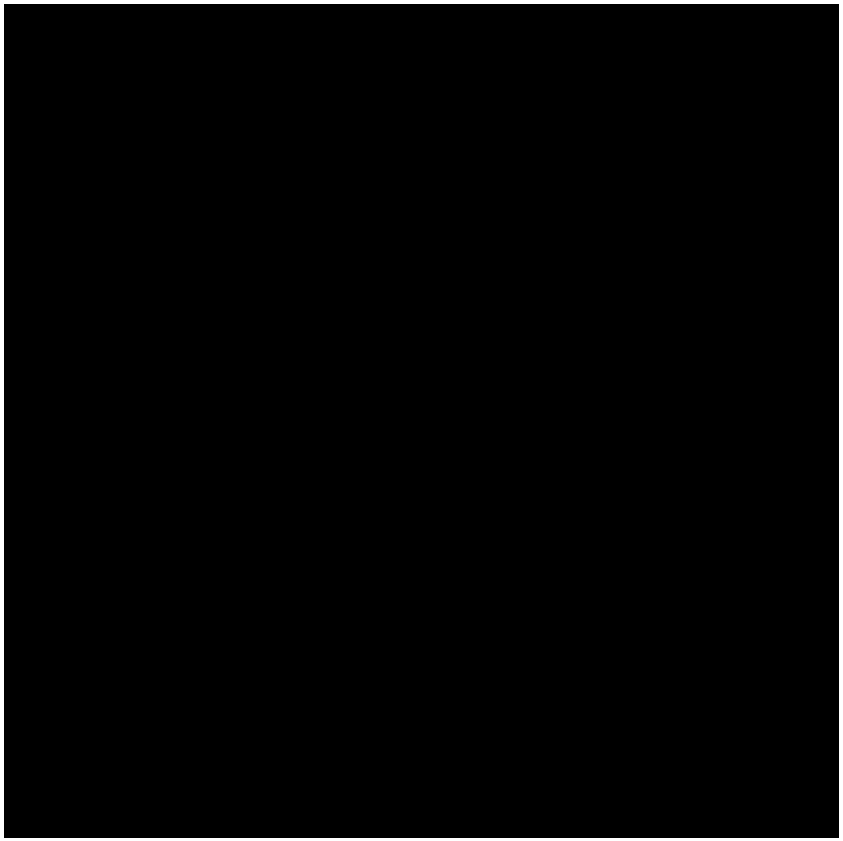
- In PET modelling, defines the rate of movement of the tracer between two compartments

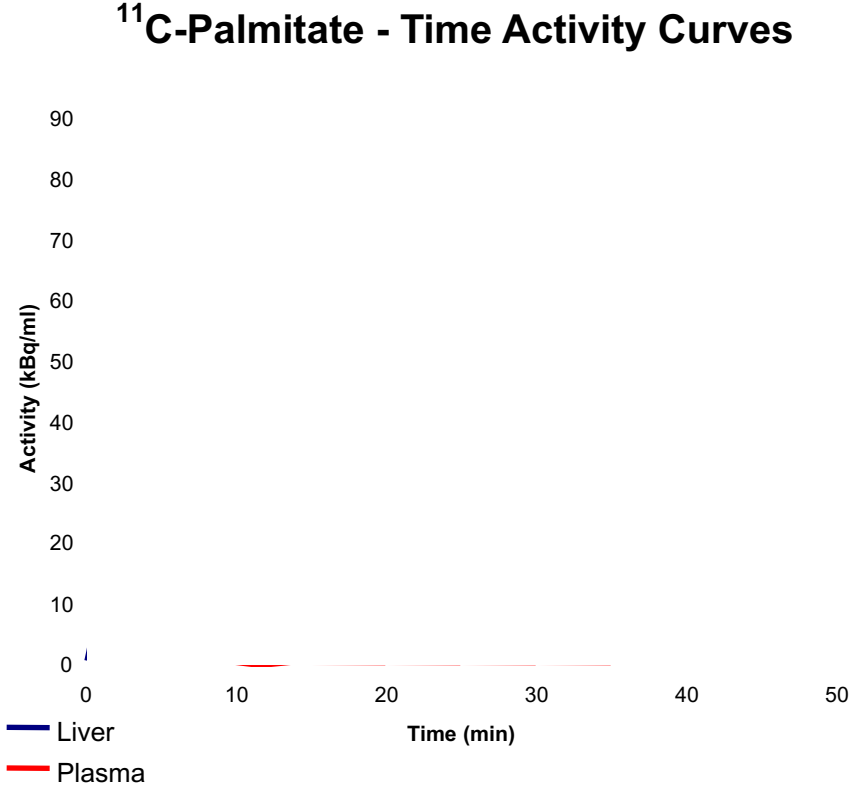
Static vs Dynamic image



One fig from https://pin.it/1vh5aF2

Example of Time Activity Curves (TACs)





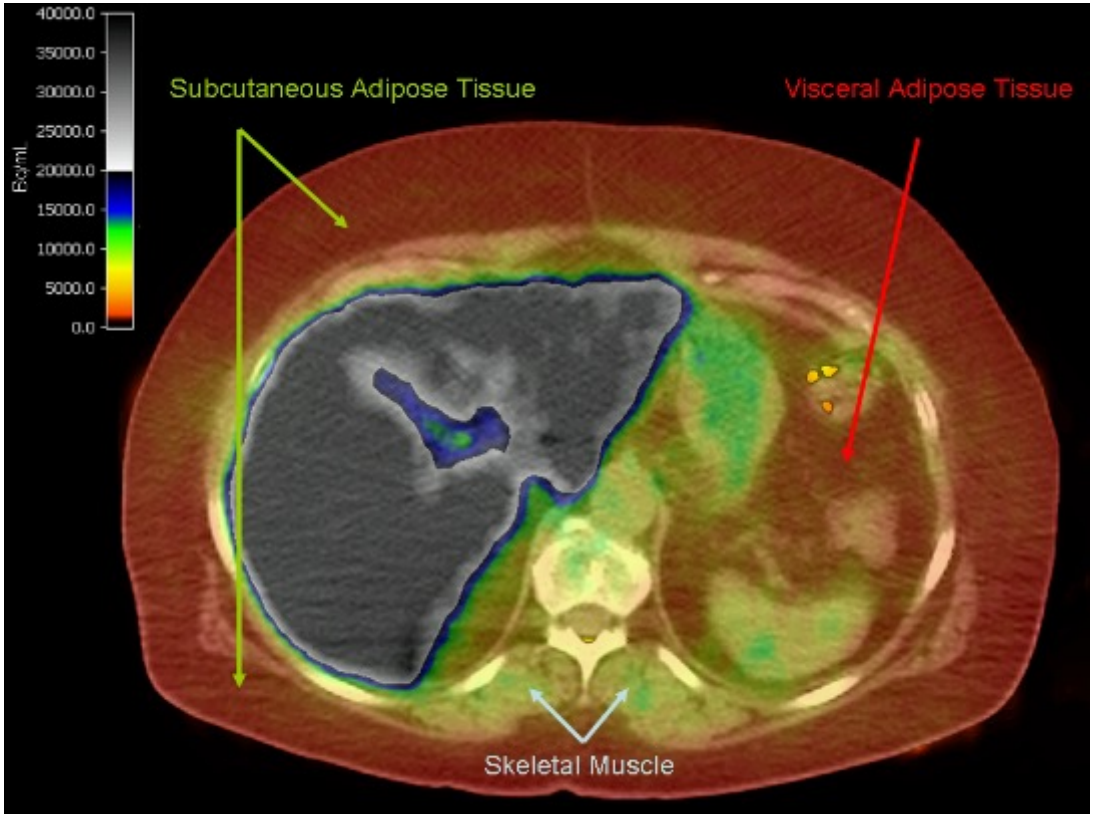
Region of Interest (ROI) in Neuroscience brain atlas examples

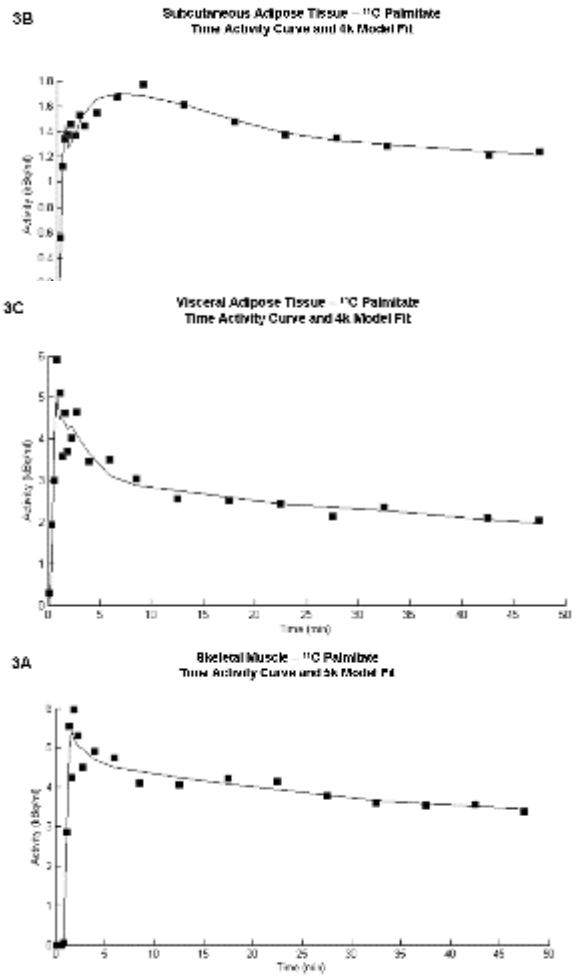
Atlas	# of regions	Horizontal	Sagittal	Coronal
Hemispheric	2			
Tissue	3			
Yeo-7	7			
Yeo-7-Lib	7			
Yeo-17	17			
Yeo-17-Lib	17			
HOS	21			
Brodmann	41			
HOC	48			
JHU	48			
PrincetonVis	49			
PP264	58			

Atlas	# of regions	Horizontal	Sagittal	Coronal
Desikan	70			
DKT	83			
AAL	116			
Glasser	360			
CPAC200	200			
Schaefer200	200			
Schaefer300	300			
Schaefer400	400			
Slab907	907			
Schaefer1000	1000			
Slab1068	1068			
Talairach	1105			

fig from Lawrence RM, 2021, Scientific Data

Tissue Activity Curves (^{11}C-Palmitate) from abdominal area





Important information to know before starting a PET image analysis

- 1) Where are the images stored? (PET-PACS/MO-disks/…)
  - In which format? (DICOM/Ecat/…)
- 2) Image preprocessing
  - Which image reconstruction? (FBP/Iterat./…)
  - Have they been corrected for decay? Important for late scans!
  - Have they been corrected for motion (rigid/ non-linear)? Were they gated? (synchronized with respiratory/cardiac phases)

Important information to know before starting a PET image analysis

- 3) Scanning conditions
  - Which scanner was used? What type of attenuation correction has been applied?
  - During which metabolic condition was the subject scanned? (fasting/clamp, warm/cold)
  - Injected dose, speed of injection?
  - Time of the PET scan from tracer injection /start of the stimulated metabolic condition

Important information to know before starting a PET image analysis

- 4) Input function
  - Was blood sampling performed? Arterialized?
  - Input from image? Mixed (peak from image, tail from sampling)? Note: Input from image derives from whole blood > it is necessary to convert it to plasma before "fusing" it to the sampled plasma TAC.
  - Metabolite correction necessary?

Semiquantitative methods

- Standardized uptake value (SUV)
  - sometimes named differential uptake ratio (DUR) or differential absorption ratio (DAR)
- Tissue-to-reference tissue ratio
  - or tumor-to-normal tissue (T/N) ratio

Standardized uptake value 1/3

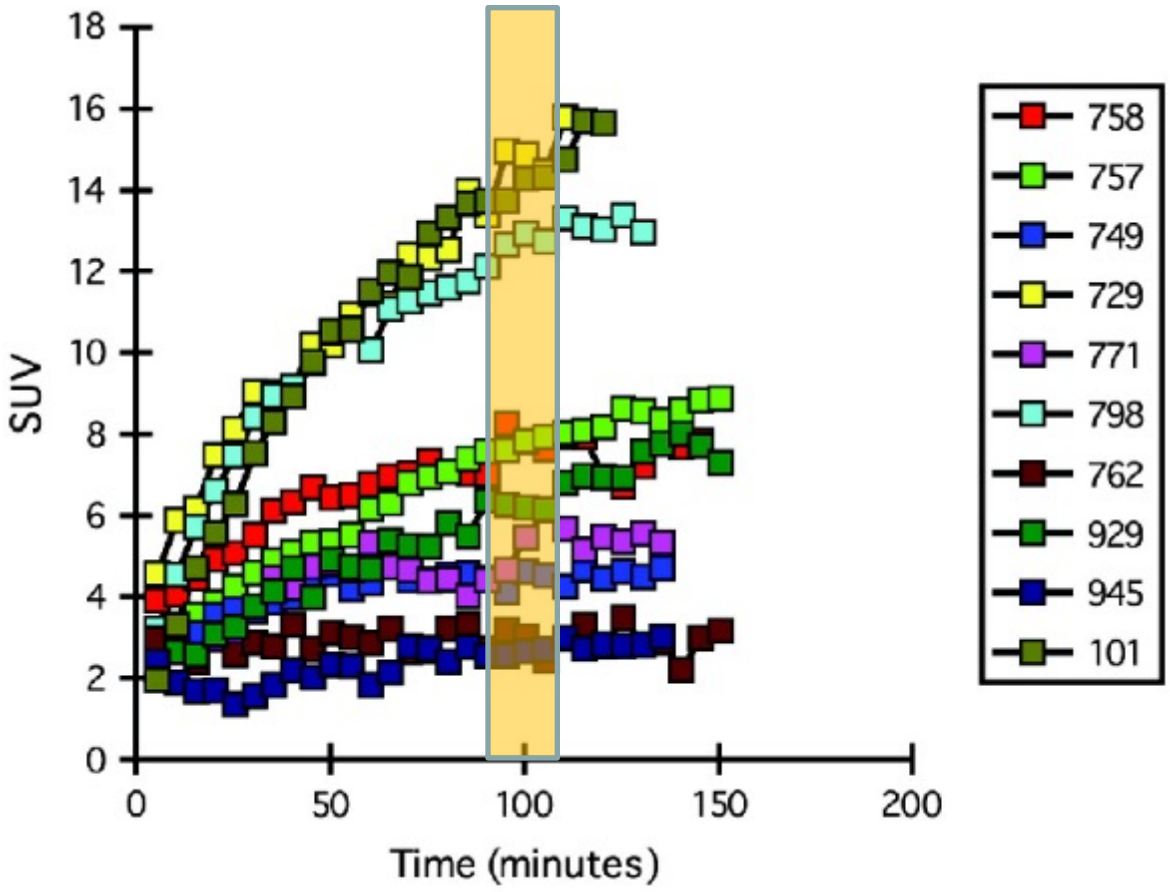
- Enables to compare patients and healthy subjects semi-quantitatively by taking into account
  - different radiotracer doses and
  - different body weight (total distribution space of injected tracer)
- Total or lean body mass, or body surface area

Standardized uptake value 2/3

$$SUV_{BW} = \frac{C_{PET}(T)}{Injected\ dose / Patient's\ weight}$$

- Tissue radioactivity and dose must be decay corrected to the same time point
- Instead of weight, body surface area (*BSA*) is recently recommended: SUV_{BSA}
- In FDG PET, correcting for plasma glucose should be considered

SUV is time-dependent 3/3



NCI PET Guidelines, 2006

SUVR

- SUVR = SUV (target region) / SUV (reference region)
- Common reference regions (examples):
  - Cerebellum (Whole, cortex)
  - Pons

SUVR and its application in AD clinical and research setting: Amyloid imaging

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2183–2199
https://doi.org/10.1007/s00259-021-05311-5

ORIGINAL ARTICLE

A multisite analysis of the concordance between visual image interpretation and quantitative analysis of [^{18}F]flutemetamol amyloid PET images

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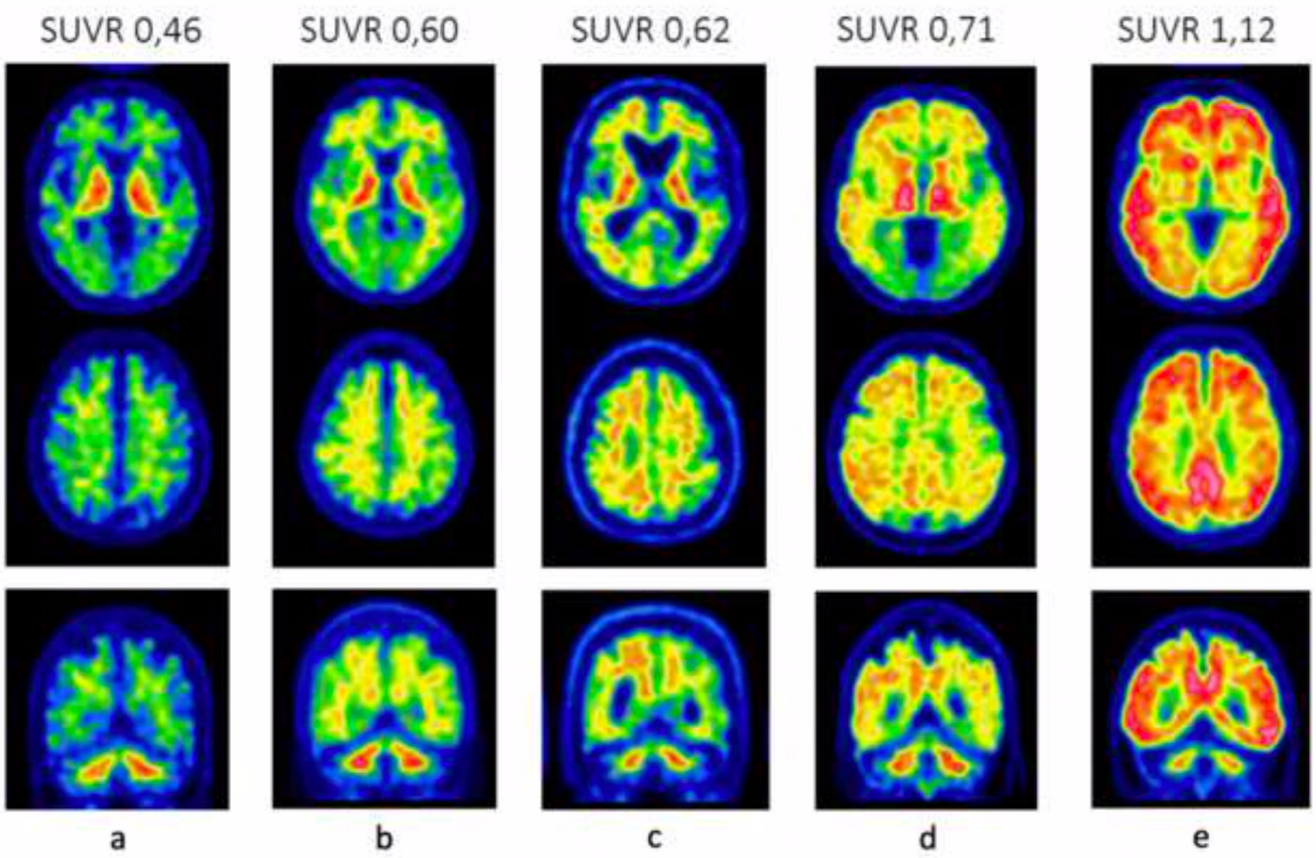

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Table 1 Summary of studies and clinical populations used for the multisite analysis

Study_Main_Institute	Study_abbr.	Type	Population	Country	Study_Reference	Ref_regions	Region_delineation	Target_regions	Software	Total_cases
GE Healthcare/Imanet (Uppsala, Sweden)	GE	Clinical research	HC: 59, MCI: 80, (p)AD: 33	Denmark, Belgium, USA, others (WW)	Thurfjell L, et al. JNM 2014 [17]	Pons, CGM, WC	PET-only adaptive template	FL,TL_lat,Cing,PL*	Cortex ID	172
Karolinska Institutet (Huddinge, Sweden)	KAROLINSKA	Clinical routine	SCD: 5, MCI: 131, AD: 41, non-AD: 10, DemNOS: 20	Sweden (Europe)	Leuzy A, et al. EJNMMI 2019 [18]	Pons	PET-only automated ROI-based	FL,TL_lat,Cing,PL	BRASS	207
Merck and Co Inc. (c/o Bioclinica) (USA)	MCK	Clinical research	(a)MCI: 928	WW (17 Countries)	Sur C, et al. Brain 2020 [19]	Pons, WC	PET-MR automated ROI-based	FL, TL, PL, Cing, Precuneus	Freesurfer	928
Saint-Luc University Hospital (Brussels, Belgium)	SLC	Clinical routine	HC: 31, SCD: 35, MCI: 94	Belgium (Europe)	Hanseeuw B, et al. EJNMMI 2020 [20]	CGM, WC	PET-MR automated template	Neocortex	PMOD	160
Amsterdam UMC (Amsterdam, The Netherlands)	AUMC	Clinical routine	Early-onset dementia (<70 yrs): 145	Netherlands (Europe)	Zwan MD, et al. Alzheimer's Research & Therapy 2017 [21]	WC	PET-MR automated ROI-based	FL, TL, PL	PVElab	145
Barcelona Brain Research Centre (BBRC) (ALFA+ Cohort) (Barcelona, Spain)	ALFA+	Clinical research	HC(ADO): 361	Spain (Europe)	Salvadó G, et al. Alzheimers Res Ther. 2019 [22]	Pons, WC	PET-only automated ROI-based	AAL Composite: FL, TL, PL, Cing, Precuneus, Angu-lar, Supram. CTX: Centiloid Global Cortical Average	SPM12	361
Lund University (BIOFINDER Cohort) (Malmö, Sweden)	BIOFINDER	Clinical research	HC: 134, SCD: 118, MCI: 149	Sweden (Europe)	Hansson O, et al. A&D 2018 [23]	Pons	PET-MR automated ROI-based	FL, TL_lat_post, Cing./Precuneus, PL	PMOD and Neuro-Mark	401
Invicro (Imaging Clinical Research) (London, UK)	INVICRO	Clinical research	Random sample from BIOFINDER: 120	Sweden (Europe)	Whittington A, et al. J Nucl Med 2019 (method) [24]	NA	ABLoad	NA	AmyloidIQ	120
AIBL (Australia)	AIBL	Clinical research	HC: 184, MCI: 60, AD: 18, non-AD: 3, unknown: 11	Australia	van der Kall LM, et al. Neurology 2020 [25]	Pons, WC	PET-only adaptive Atlas	FL, TL_lat, Cing, OL_ lat	CapAIBL	276
									Total	2770

Abbreviations: *HC*, healthy control; *MCI*, mild cognitive impairement; *(p)AD*, probable AD; *SCD*, subjective cognitive decline; *AD*, Alzheimer's disease; *non-AD*, non-AD dementia; *DemNOS*, dementia not otherwise specified; *ADO*, offspring of AD parent(s); *WC*, whole cerebellum; *CGM*, cerebellar grey matter; *WW*, worldwide; *NA*, not applicable; *Data Driven*, not derived from anatomical atlas; *FL*, frontal; *TL*, temporal; *OL*, occipital; *PL*, parietal; *lat*, lateral; *post*, posterior; *Cing*, cingulate; *Supram*, supramarginal; *Ctx*, cortex; *(minimizing spill-over from white matter, region named 'Narrow' in [17])

Karolinska Institutet

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Table 3 a Summary of discordant and concordant scans when examining visual vs SUVr (Pons, optimized cut-off). b Summary of discordant scans when examining visual vs SUVr (Pons, 0.62 cut-off)

Study	Total cases	Total concordant V+Q+	Total concordant V-Q-	Total discordant	% Disc	Total borderline/Q+	Total borderline/Q-	Agreement
a								
GE	172	71	100	1	1%	-	-	99.4%
KAROLINSKA	207	94	97	0	0%	7	9	100%
MCK	928	634	242	52	6%	-	-	94.4%
ALFA+	361	24	311	24	7%	1	1	93.3%
BIOFINDER	401	117	270	14	3%	-	-	96.5%
AIBL	276	96	160	13	5%	2	5	95.2%
Total	2345	1036	1180	104	4% (mean)	10	15	94.4% (mean)
b								
GE	172	67	101	4	2%	-	-	97.7%
KAROLINSKA	207	92	97	2	1%	5	11	99.0%
MCK	928	634	242	52	6%	-	-	94.4%
ALFA+	361	11	313	35	10%	1	1	89.4%
BIOFINDER	401	121	247	33	8%	-	-	91.8%
AIBL	276	99	155	15	5%	4	3	94.4%
Total	2345	1024	1155	141	5% (mean)	10	15	94.4% (mean)

The agreement is calculated on the total number of cases excluding borderlines

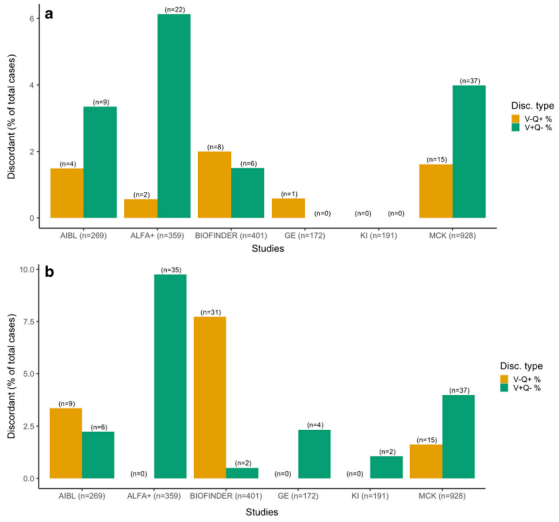
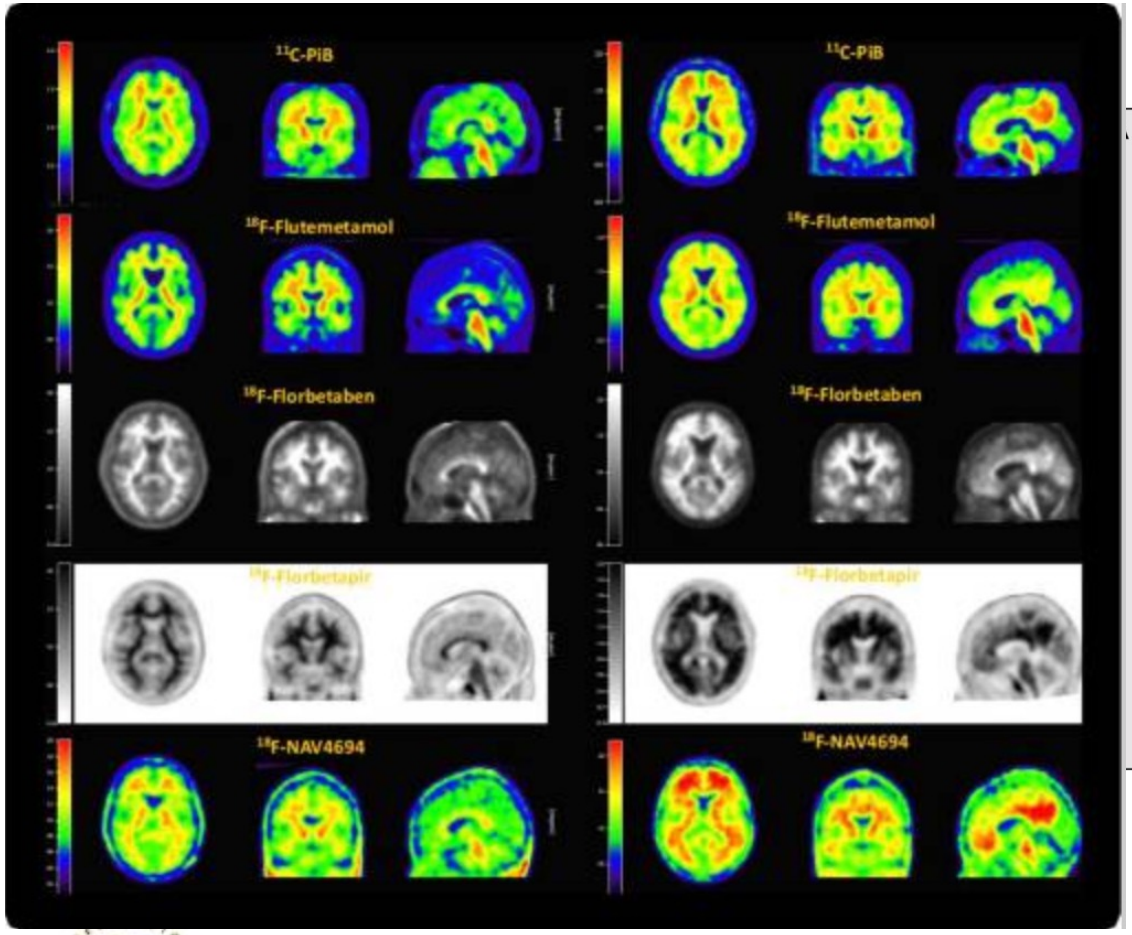
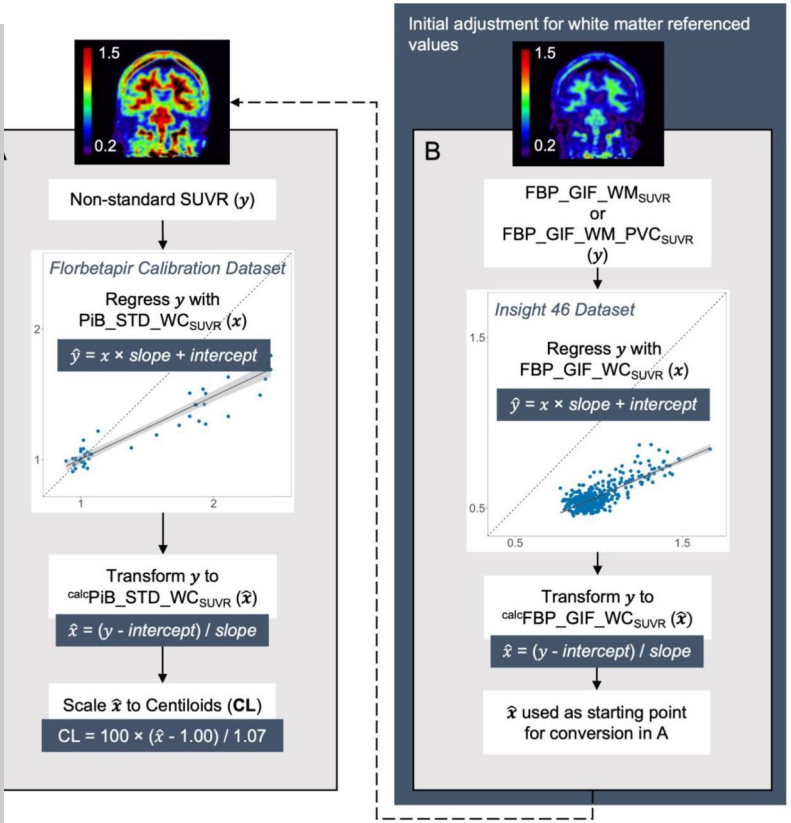


Fig. 2 Representation of number of discordant cases by study with **a**) variable (maximal performance) pons cut-off and **b**) fixed cut-off (0.62) (both with borderlines excluded). Orange bars are visual negative/quantitation positive, green bars are visual positive/quantitation negative

Nonetheless, according to competing risk regression analysis that took advantage of the full follow-up data (up to 7 years), using censoring similar to a survival analysis and discounting the contribution of the competing events (AD and OD progression), the V-Q+ discordant cases were 11% (CI 95%: 4–34%) more likely to progress to AD than V+Q- discordant cases ($p < 0.001$).

Centiloid scaling (CL) in Amyloid research





Ref original paper:
Klunk, 2015

figs from Pemberton HG, 2022, EJNMMI (left) and Coath W, 2022, preprint (https://doi.org/10.1101/2022.02.11.22270590) (right)

Centiloid scaling (CL) in Amyloid research and trials

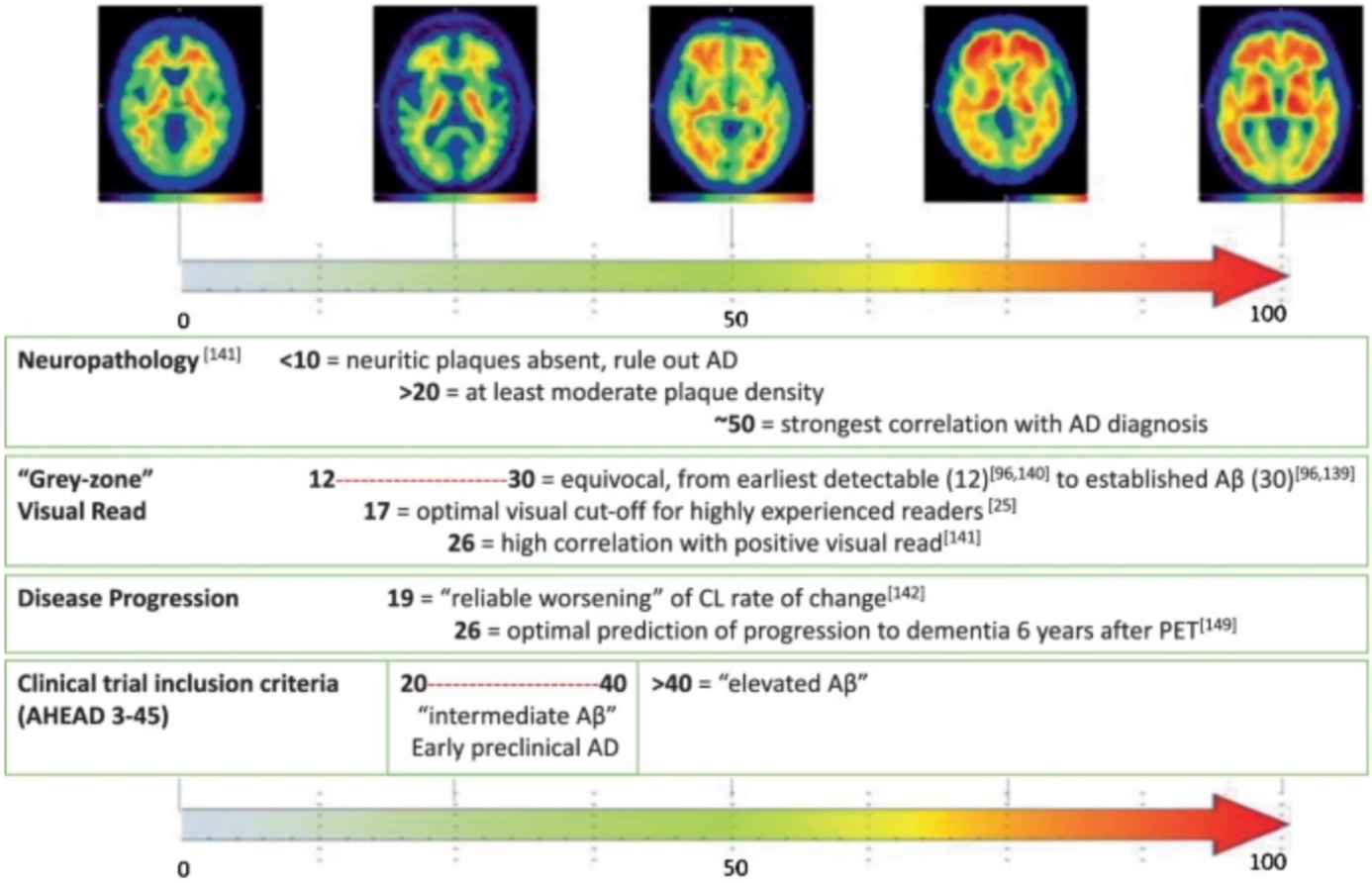


fig from Pemberton HG, 2022, EJNMMI

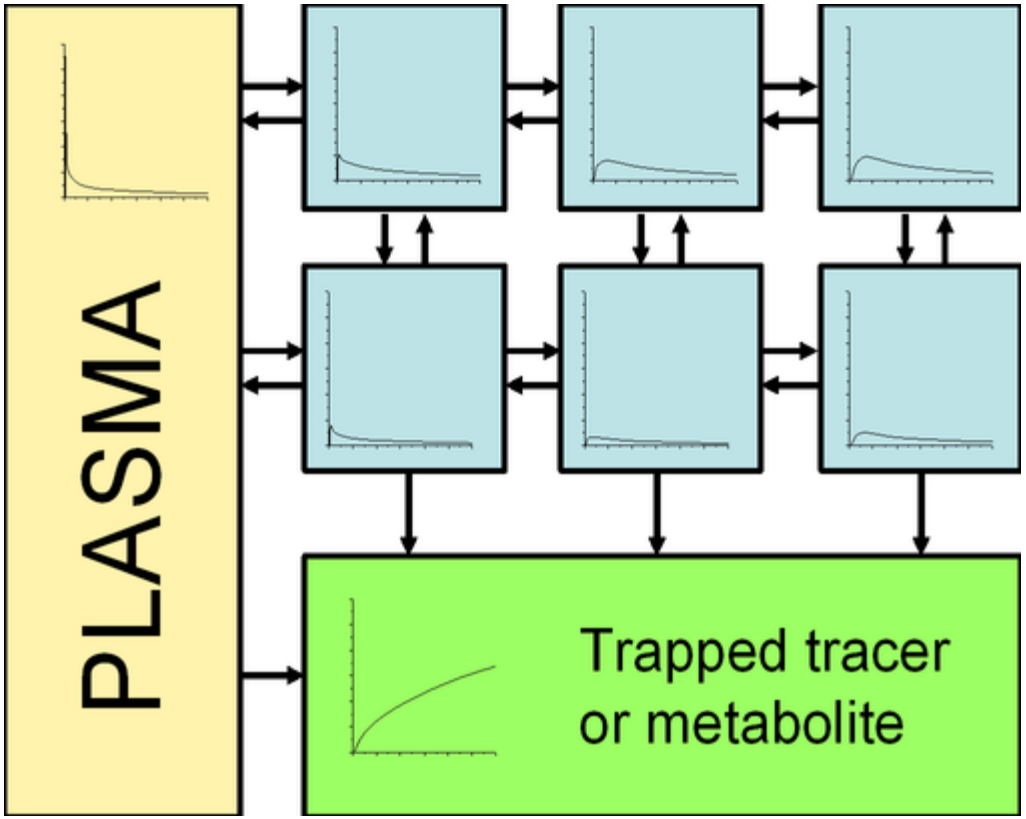
Quantitative methods

- Multiple-time graphical analysis (MTGA):
  - Gjedde-Patlak plot ("Patlak")
    - Fractional uptake rate (FUR)
  - Logan plot
- Compartment model fit
- Distributed model
- Spectral analysis

Assumptions for the tracer quantitation

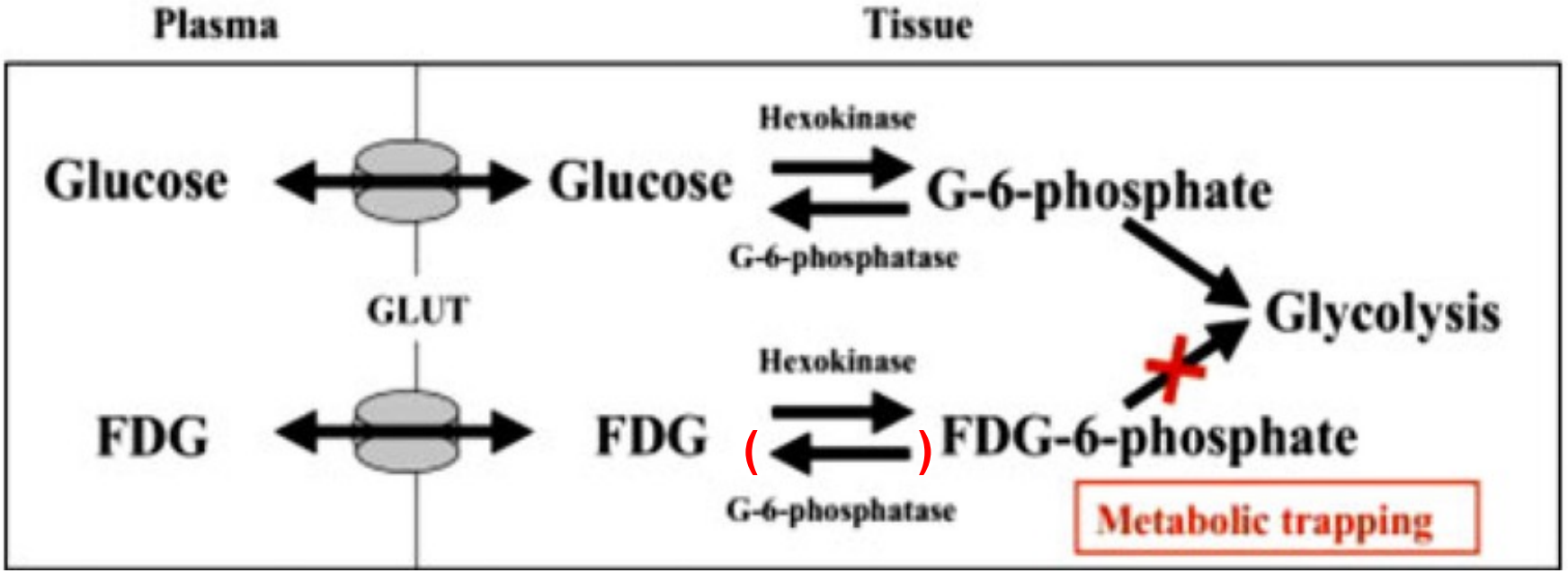
- Trace amounts > Non-interference of tracer with the process of interest
- The physiological processes and molecular interactions are in a constant state (steady state) during the PET measurement
- For kinetic models based on compartments is assumed instantaneous (and homogeneous) mixing of the tracer in each compartment

Gjedde-Patlak plot - theory



- There can be any number of reversible compartments, where the tracer can come and go.
- After some time, tracer concentrations in these compartments start to follow the tracer concentration changes in plasma (ratio does not change).
- Then, any change in the total tissue concentration (measured by PET) per plasma concentration, represents the change in irreversible compartments.

^{18}F-FDG metabolism

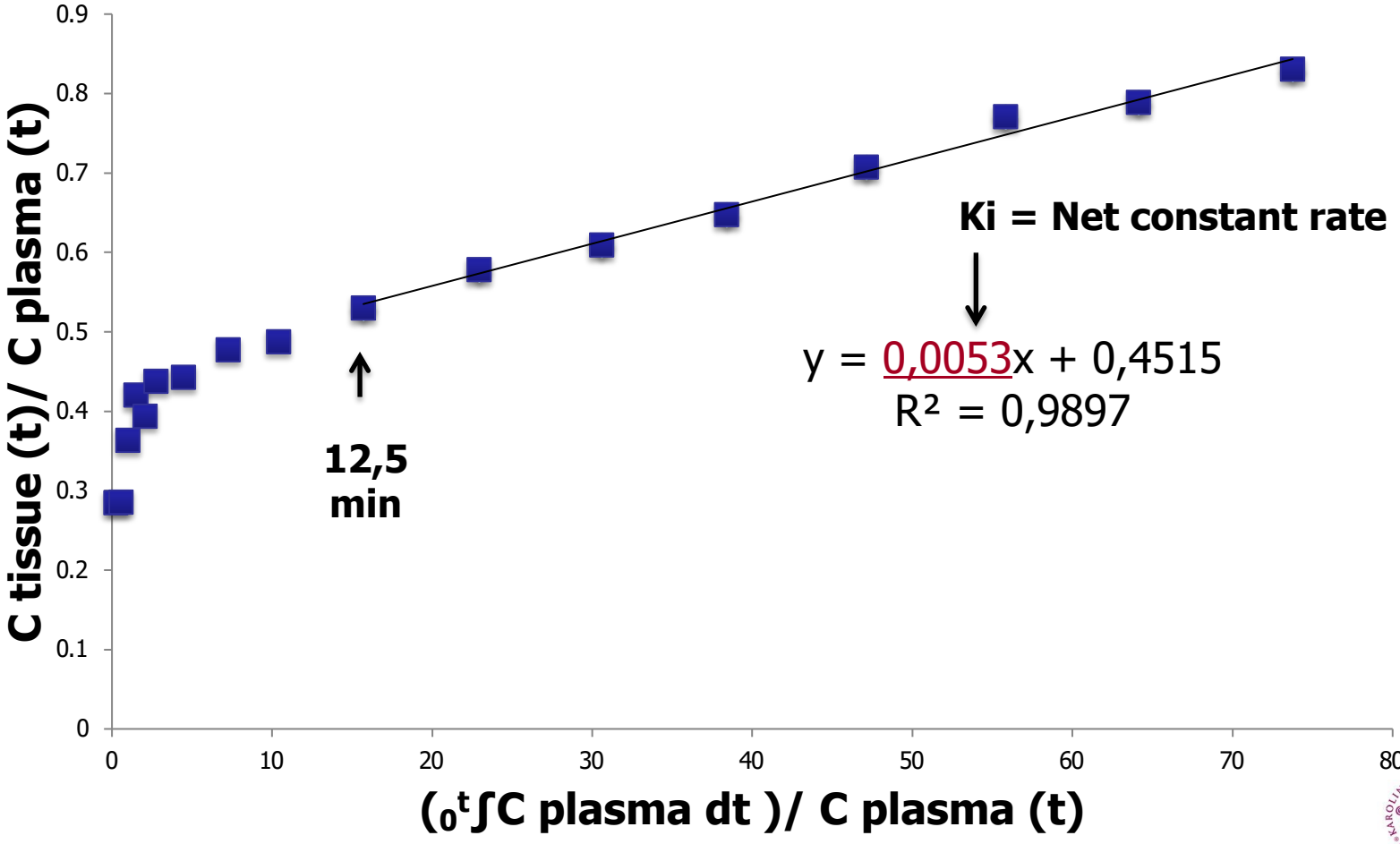


Figs from Abdelbaky et al, Current Cardiovascular Imaging Reports 2011

Gjedde-Patlak plot for the assessment of tissue glucose uptake

- Dynamic PET scan (18F-FDG, tracer)
- Input function (plasma)
- Average blood glucose concentration during the scan
- Lumped constant (LC) of the target tissue
  - LC is a correction factor that takes in consideration that the tracer and tracee might have different affinity for receptors or slightly different behavior. It could vary among different tissues and metabolic conditions.

Example of Patlak plot from real data (fasting myocardium FDG)



REMEMBER!!

- Choice of the interval – Discard the beginning, no time dependency unless at very late times (>100 min*) when FDG starts to become de-phosphorylated.
- Always check the plot for anomalies, investigate outliers: Motion? Artifacts frame dependent? Input function anomaly?

* debatable, depends on the tissue

K_i and metabolic rate

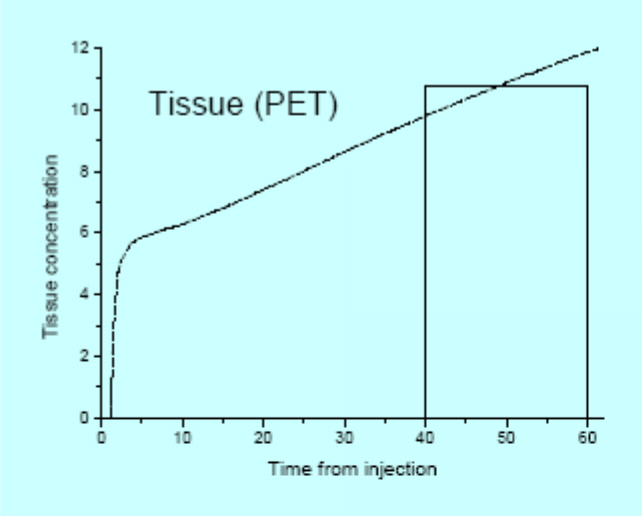
- If PET tracer is an analogue of glucose (e.g. [F-18]FDG) or fatty acids (e.g. [F-18]FTHA) or other native substrate, then
- Ki can be used to calculate the metabolic rate of the native substrate
- For example; [F-18]FDG PET study:

$$MR_{Gluc} = K_i \times \frac{C_{Gluc}^{Plasma}}{LC}$$

All good but…

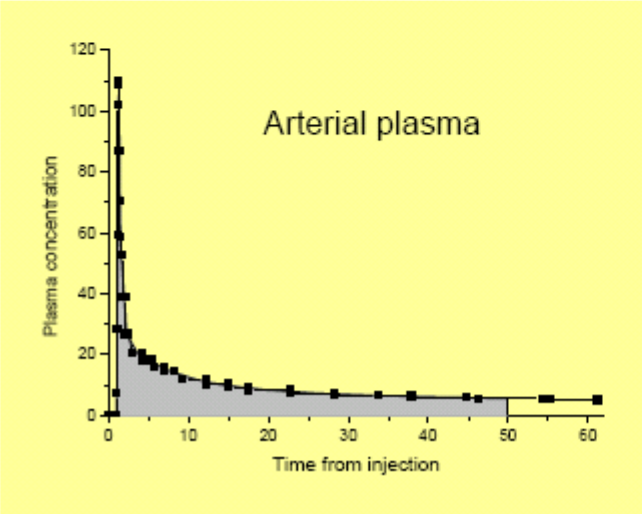
- Patlak plot works fine when the target tissue has high uptake (high signal to noise ratio) or with many frames.
- But with late scans and short acquisition times and maybe a low uptake, the plot might result in high intercept on the y axis, underestimation of ki, sometimes even negative ki.
- What to do? There's a solution …

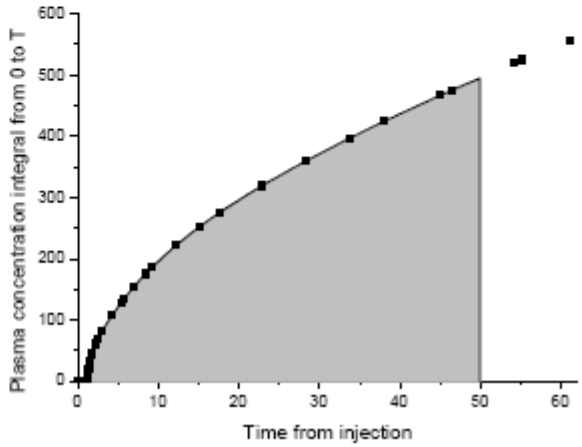
Fractional uptake rate (FUR)



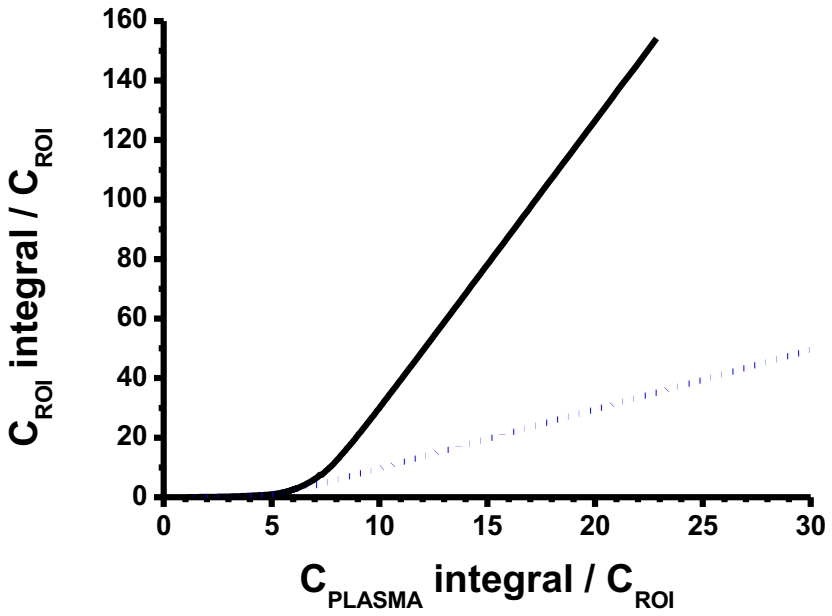
Fractional Uptake Rate

$$FUR = \frac{C_{TISSUE}(T)}{\int_0^T C_{PLASMA}(t)dt}$$





Logan plot (for reversible tracers)



- Y-axis: Integral of tissue curve divided by tissue concentration
- X-axis: Integral of plasma curve divided by tissue concentration
- Slope equals volume of distribution, V_T

Irreversible or reversible uptake? (stepwise method)

- Gjedde-Patlak plot (MTGA for irreversible tracers)
- If the plot becomes linear, then uptake is irreversible (during PET scanning)
- If the plot turns down, try Logan plot (MTGA for reversible tracers)
- If Logan plot becomes linear, then uptake is reversible
- If both Gjedde-Patlak and Logan plots are linear, it may be possible that the tracer distribution in the tissue is characterized by both components (reversible and irreversible)

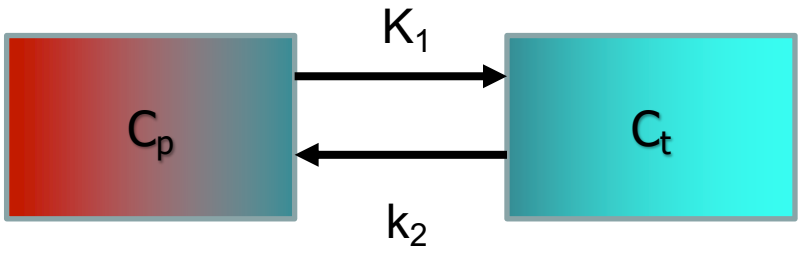
MTGA (Multiple-time graphical analysis) Summary

- Gjedde-Patlak plot for irreversible uptake, Logan plot for reversible
- Linearity of plots and influential points must be checked
- Plasma or reference region input can be used, depending on the tracer
- Outcome from Gjedde-Patlak plot is net influx constant K_i which may be used further to calculate metabolic rate
- Outcome from Logan plot is distribution volume V_T
- Easy and fast way to calculate voxel-by-voxel from dynamic PET images is by producing K_i or V_T parametric images

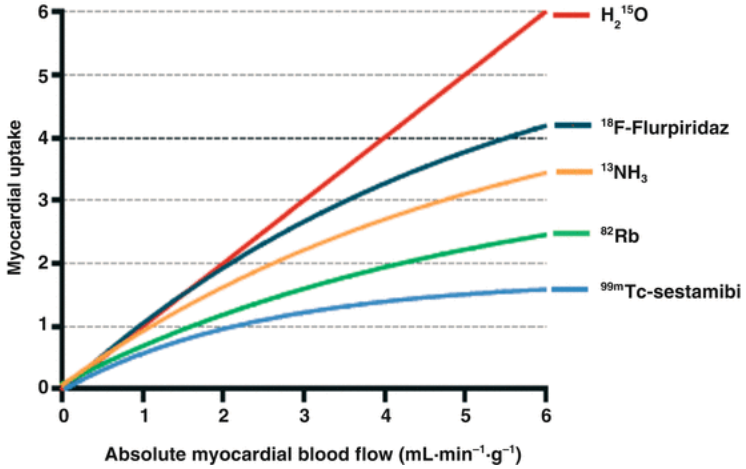
Compartmental Modeling

- Gold standard of PET quantitation
- Examples:
  - Flow measurements (^{15}O-H_2O) based on 1-TC model with 2k (rate constants)
  - FDG kinetic can be studied with a 2-TC with 3k and Gjedde-Patlak plot approximate this model

Single compartimental model



C_p = Tracer in blood
C_t = Tracer in tissue
Ks = rate constants



V_T (Distribution Volume) = K_1/k_2
K_1 = extraction x flow -> Flow = K_1/extraction

Perfusion/Blood flow measured with ^{15}O-water = K_1

Fig from Danad et al, 2013
PMID: 23842709

Why quantitate in PET?
An example from cardiology

"Absolute quantification of myocardial blood flow has potential to improve diagnostic accuracy of perfusion imaging and stratification of patient's risk when compared with conventional, qualitative analysis." (Saraste A, Knuuti J; 2015)

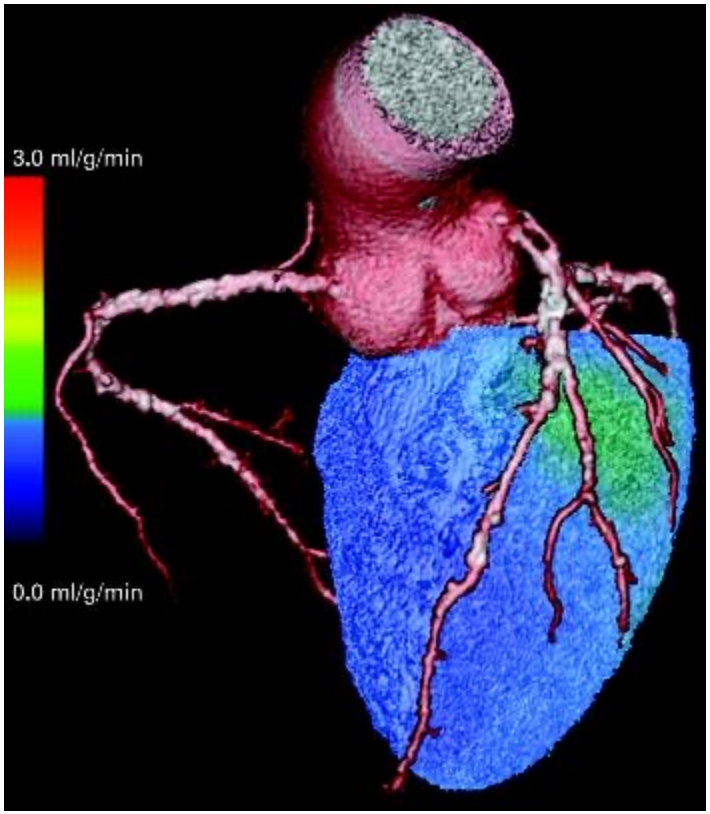
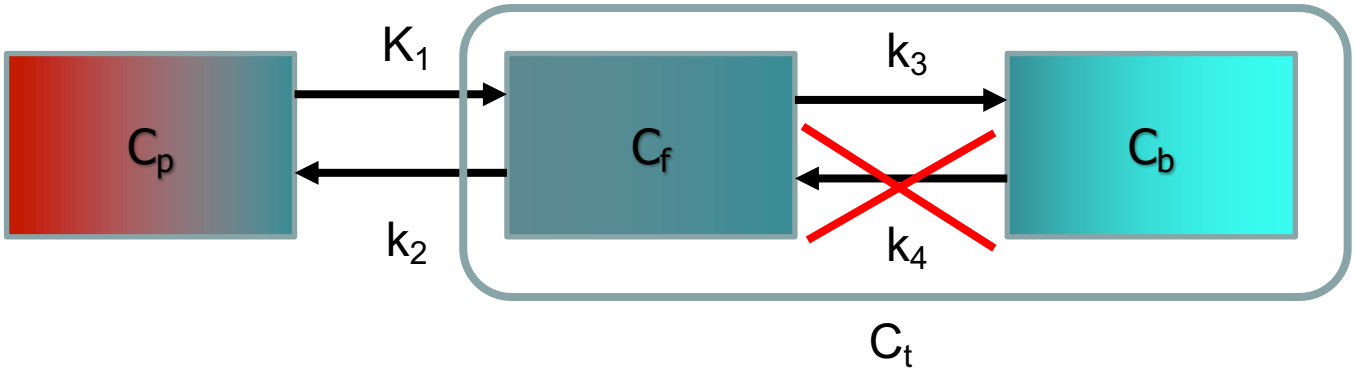


Fig from Knuuti J. and Bengel FM 2008

Two tissue compartiment irreversible model



C_p = Tracer in blood
C_f = Free component of the tracer in the tissue
C_b = Tracer bound in the tissue
C_t = Tracer in tissue
Ks = rate constants

Ki (net influx rate constant) = k3*K1/(k2+k3)

Approximated by Gjedde-Patlak plot Ki (slope)

Input function shape is essential for proper modelling!

- It might be necessary to correct input curves derived from arterialized samples that are not frequent enough to resolve the initial peak.
- K_1 is highly influenced by the shape of the early part of the input curve.
- Especially compartmental models results highly depend on it.

Take home messages

- When planning a PET study, optimize the protocol according to the research question and the necessary quantitation of the PET data
- Remember pros and cons of the different methods, evaluate time and costs
- Evaluate the necessity to take blood samples according to the final quantification
- Quantitative methods are versatile tools essential in the research setting and useful also in the clinical setting

Thank you for the attention

Further information

- **Contact at Karolinska Institutet/Turku PET Centre**
  Modeller/Biotechnologist, PhD, Docent, Marco Bucci
  (marco.bucci(at)utu.fi)
- **Contact at Turku PET Centre**
  Modeller/Biochemist, MSc, Vesa Oikonen
  (vesa.oikonen(at)utu.fi)

- **Quantification of PET Data**
  http://www.turkupetcentre.net/petanalysis/quantification.html

- **PET data analysis process**
  http://www.turkupetcentre.net/petanalysis/analysis_process.html

- **Free Medical Imaging Software**
  https://idoimaging.com