Different patterns of PIB uptake in AD patients

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Introduction

Recently the Pittsburgh Compound-B "PIB" labelled with ^{11}C has been demonstrated to image brain β-amyloid in Alzheimer's disease (AD) (1)

Here we report results for healthy controls (HC) and AD-patients using kinetic modelling providing the PIB net accumulation (K_{acc}) and unidirectional influx (K_1) across the BBB, and compared this information with a reference tissue method.

The effect on K_1 and K_{acc} of CBF-changes were investigated in a monkey.

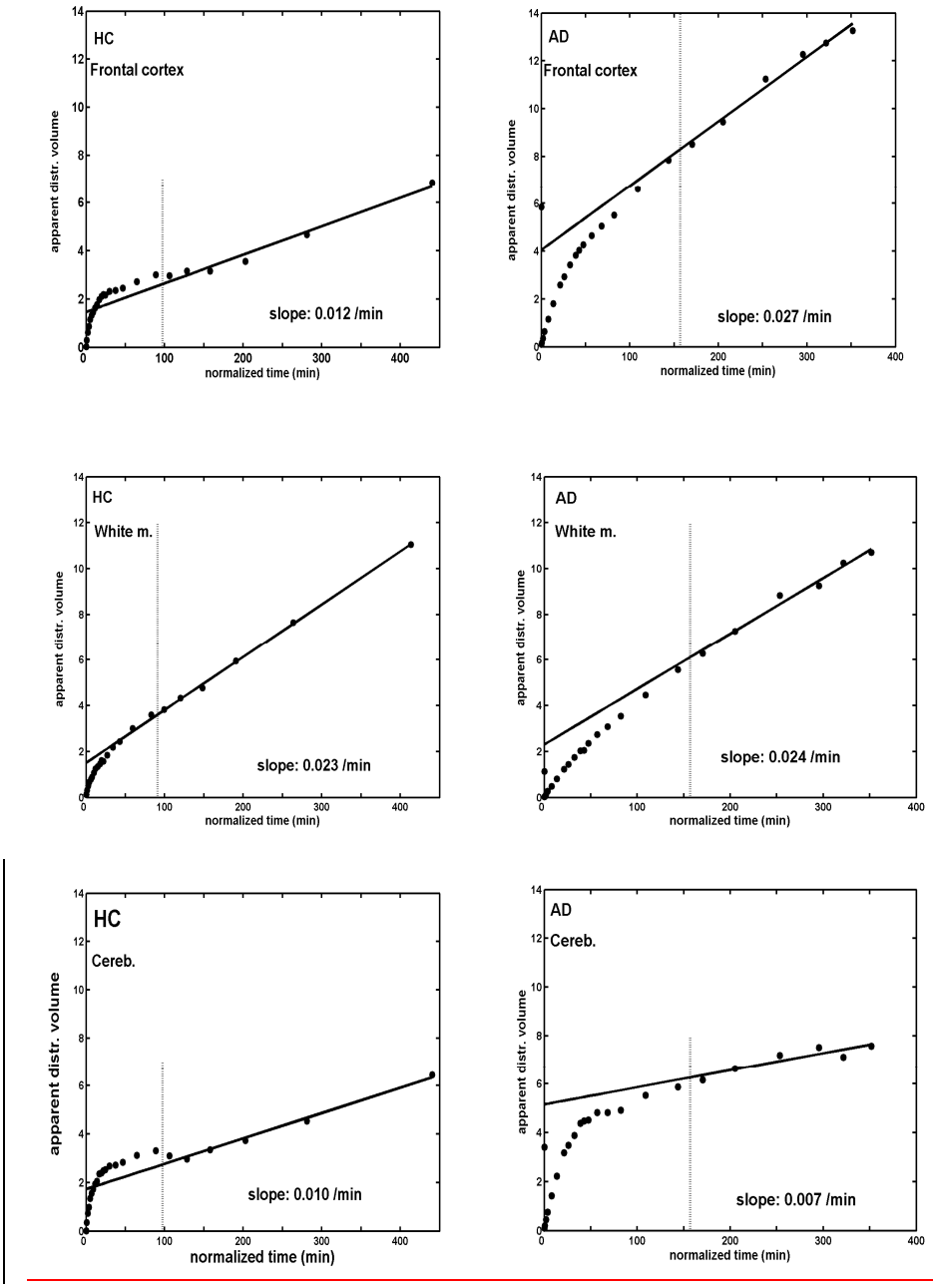
Materials and Methods

9 healthy controls (HC), and 17 AD-patients participated in the study. Data were acquired in 3D mode on an ECAT HR+ camera. After a bolus administration of approximately 300 MBq of PIB the time course of the tracer in the brain was followed during 60 min.

The input function was determined with arterial sampling in a sub-sample of 4 HC-subjects and 4 AD-patients.

Double scans with [^{15}O]H_2O and PIB were performed repeatedly on one monkey, at baseline conditions and after increase of $PaCO_2$ with the aid of respiratory control.

Results

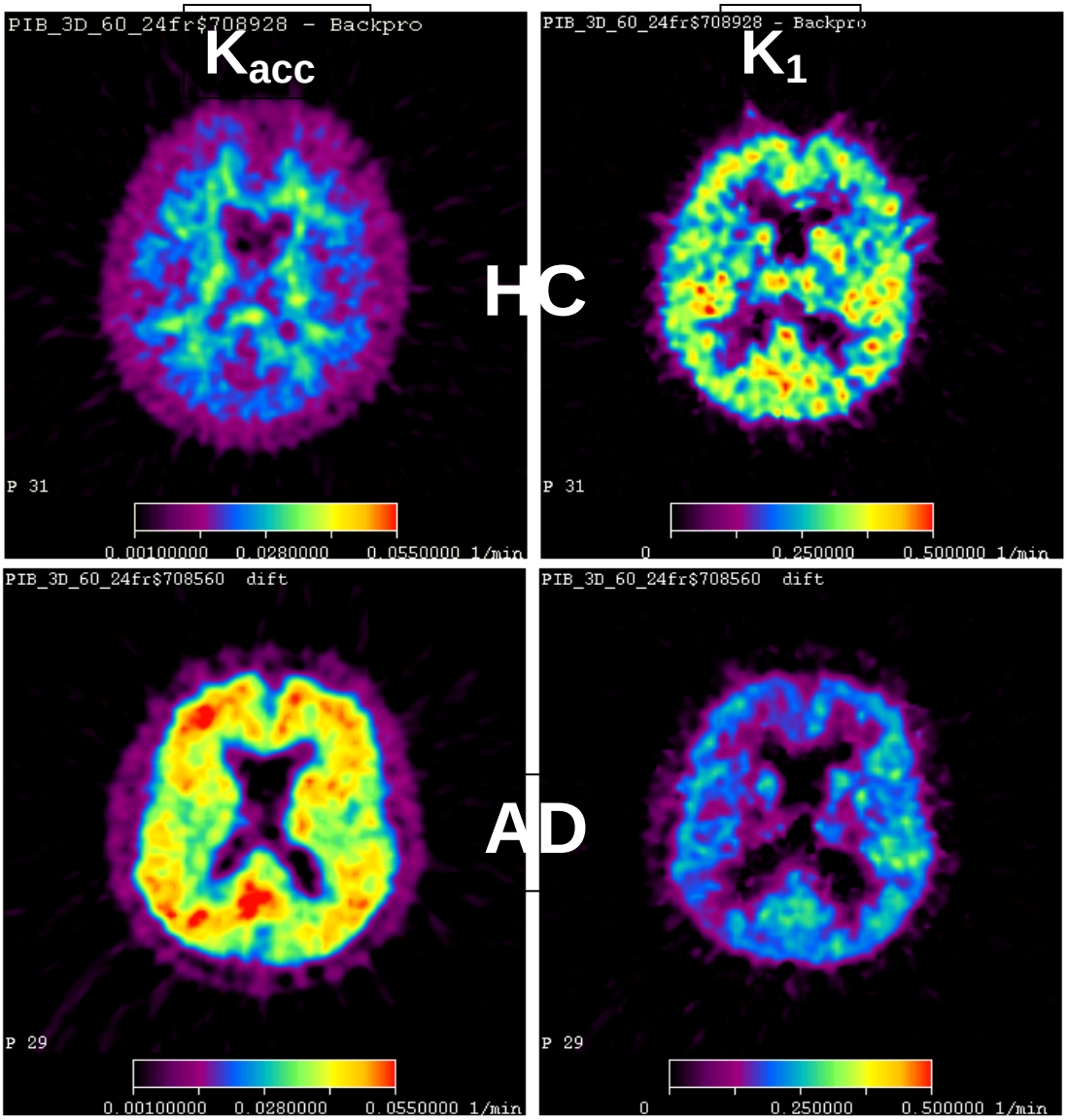


Gjedde-Patlak plots for one HC subject (left) and one AD patient (right). Top: frontal cortex, middle: white matter, bottom: cerebellum

The Gjedde-Patlak plots show that PIB is far from equilibrium in the brain.

Consequently, for the scans with arterial sampling we have applied the model with one reversible and one irreversible tissue compartment and three rate constants. Parametric maps of $K_{acc} = K_1k_3/(k_2+k_3)$ and K_1 were created using a linear algorithm [2].

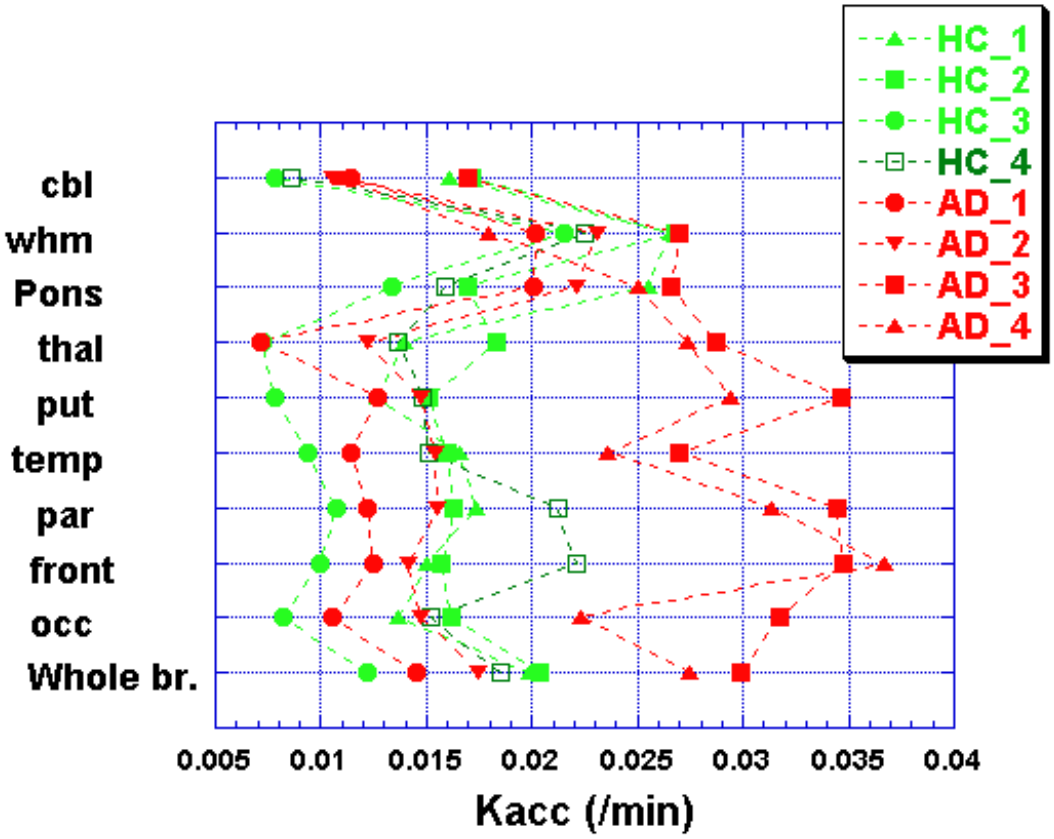
In the extended sample with 9 HC subjects and 17 AD patients, the ratio between the uptakes in the target- and reference regions in a late time interval (40-60 min) was used as a simple measure of PIB accumulation. This measure was found to correlate well with K_{acc}.



Maps of
the net accumulation rate constant K_{acc}
and
the unidirectional influx rate constant K_1

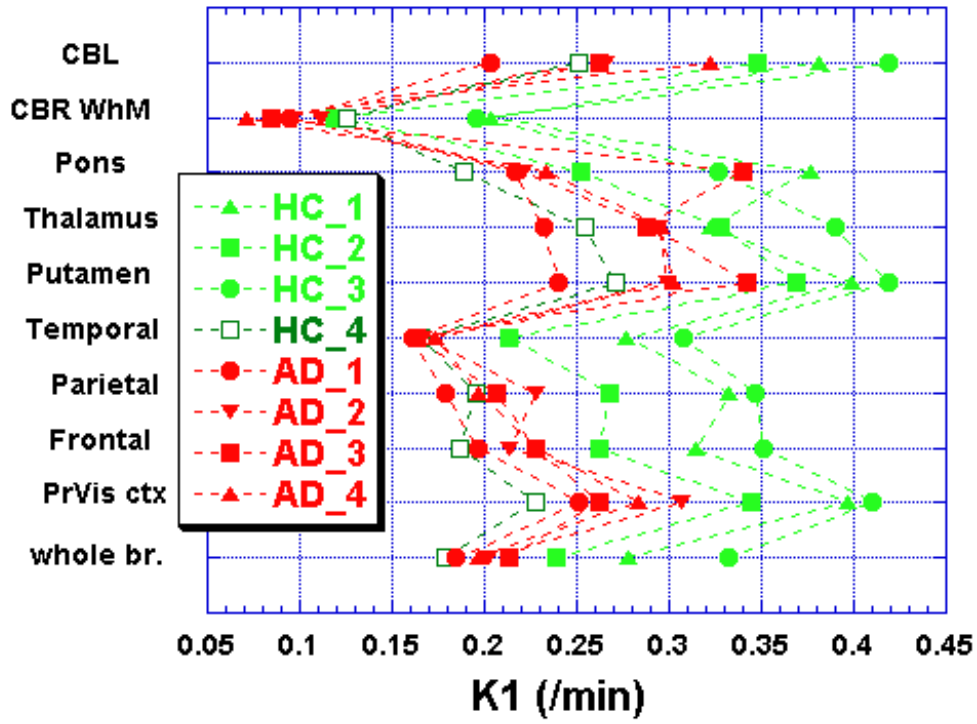
upper row: HC subject
lower row: AD-patient

K_{acc}: scale between 0.001 and 0.055 min^{-1}
K_1 : scale between 0 and 0.5 ml g^{-1} min^{-1}



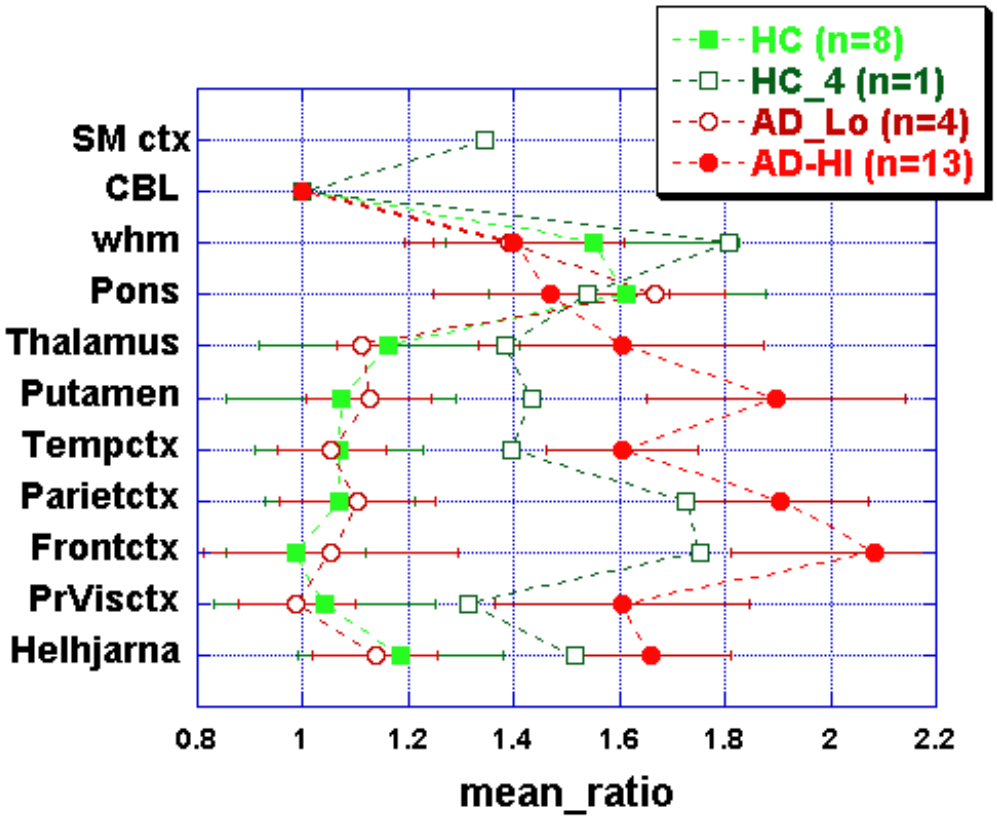
Regional values of the net accumulation rate constant K_{acc} for each subject in the HC- and AD- samples with measured input function.

Subject HC_4 (the oldest control) had somewhat enhanced accumulation in frontal and parietal cortex, compared to the other controls.



Regional values of the unidirectional influx constant K_1 for each subject in the HC- and AD- samples with measured input function

Note subject HC_4 who had lower K_1 values than the other controls, in the range of the AD-patients (cf. the K_{acc}-values on p.6).



The target-to-cerebellum ratio for subjects in the extended sample (9 HC, 17 AD)

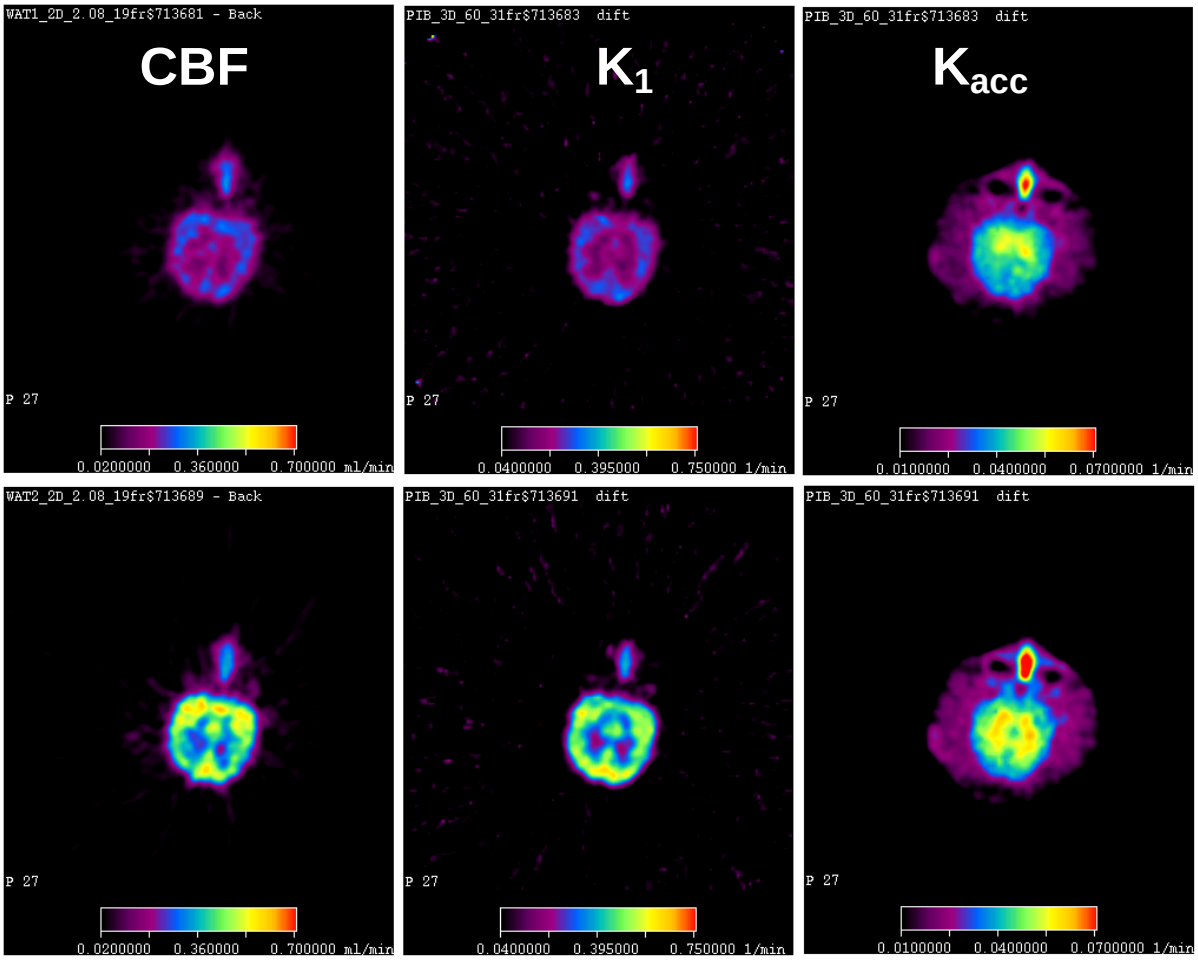
The AD sample was found to have two main groups, one with high accumulation in cortical regions, and another with low accumulation, close to the one found for the HC subjects (except HC_4).

Comments to the results on p. 5-8:

Two of the AD patients had high accumulation rate (K_{acc}) of PIB in cortical areas, whereas two patients had low accumulation, comparable with the values found for the HC subjects.

All 4 AD patients had low K_1-values in the cortical regions.

In the extended sample, using target-to reference ratio as measure, all HC subjects (except HC_4), and four AD patient had small PIB accumulation, whereas the remaining patients (13) had high accumulation.



Parametric maps from the monkey experiment.

Left: CBF (scale from 0.02 to 0.7 ml g^{-1} min^{-1})

Middle: K_1 (scale from 0.04 to 0.75 ml g^{-1} min^{-1})

Right: K_{acc} (scale from 0.01 to 0.07 min^{-1})

Upper row: baseline

Lower row: after increase of $PaCO_2$ by respiratory control

As an effect of the respiratory control, $PaCO_2$ changed from 5.0 ± 0.2 kPa during the baseline scans into on the average 7.2 ± 0.1 kPa during the two later scans.

Results from the monkey experiment.

Region	CBF (ml g^{-1} min^{-1})		K_1 (ml g^{-1} min^{-1})		K_{acc} (min^{-1})	
	Base	CO_2	Base	CO_2	Base	CO_2
Cereb. cortex	0.38	0.68	0.29	0.55	0.029	0.034
Frontal cortex	0.30	0.46	0.24	0.37	0.021	0.027
Occipital cortex	0.36	0.66	0.29	0.58	0.026	0.034
Thalamus	0.38	0.68	0.18	0.35	0.026	0.032

Base: baseline experiment, CO_2: experiment with increased CBF caused by increasing $PaCO_2$ with the aid of respiratory control.

The increases in K_1 were close to the increases in CBF (see parametric maps and table), indicating that K_1 for PIB is a good index for CBF. The increases in K_{acc} were smaller: in the range 20 to 30%.

Conclusions

Irreversible models describe the kinetics of PIB in the time interval 0-60 min, and the net accumulation K_{acc} is a suitable measure of the PIB accumulation rate.

Among the patients with diagnosis AD there was a sub-group with low PIB accumulation in cortical areas.

Compared to the controls, all patients with diagnosis AD had decreased unidirectional influx of PIB into the brain.

References

(1) Klunk W, MD, Engler H, Nordberg A, Wang Y, Blomquist G, Holt D P, Bergström M, Savitcheva I, Huang G, Estrada S, Ausén B, Debnath M, Barletta J, Price J C, Sandell J, J. Lopresti B J, Wall A, Koivisto P, Gunnar Antoni G, Mathis C A, Långström B. Imaging Brain Amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 55:306-319, 2004

(2) Blomqvist G. On the construction of functional maps in positron emission tomography. J cereb Blood Flow Metab 4:629-632, 1984