Details of recruitment, demography and MRI scans.

This study was approved by the local and regional regulatory Ethics committee (Riverside Research Ethics Committee-National Health Research Services, Health Research Authority, UK), and the approval for administration of radioactivity was given by ARSAC (Administration of Radioactive Substances Advisory Committee).

Subjects were recruited from teaching hospitals in and around London, and the scans were performed at the Imperial College Clinical Imaging Facility, Hammersmith Hospital. After obtaining the written informed consent, all subjects had detailed clinical and neurological examination. All subjects had a full blood count, renal, bone and liver function profile, and clotting screen. Each subject had a detailed neuropsychometric battery of tests lasting up to 2hours to evaluate any evidence of cognitive impairment. This included pen and paper and computer based tests assessing visuospatial memory, learning, naming, verbal learning, executive functions, language and recall tests. From the human blood-based work we carried out, the HAB affinity was 2.4 nM and the LAB affinity was 38 nM (ratio of 15.9). This ratio was maintained in human MS tissue, although the absolute affinities were lower (15 nM:174 nM). For the clinical study, we have selected high affinity and mixed affinity binders, as low affinity binders may not show any signal. In our previous paper, we have already demonstrated that the studies in high affinity and mixed affinity binders could be translated to the entire population in controls, AD and MCI subjects.

The HAB healthy controls were matched to the MAB subjects in terms of age range, mean age, sex, education, and MMSE. There were no significant differences in body weight and injected dose between HAB and MAB. There was no evidence of vascular changes in the brain as assessed and confirmed by MRI observation.

	Age Mean (SD)	Age range	Sex (Male/Total)	MMSE Mean (SD)	NART Mean (SD)	Injection dose (MBq)
HAB	62 (6.0)	52 – 68	3/6	29.3 (1.3)	112.8 (8.6)	183.5 (4.7)
MAB	58 (7.9)	51 – 69	3/4	29.5 (1.0)	105.3 (18.6)	180.5 (2.3)
Total	60 (6.8)	51 – 69	6/10	29.3 (1.1)	110.0 (12.5)	182.3 (4.2)

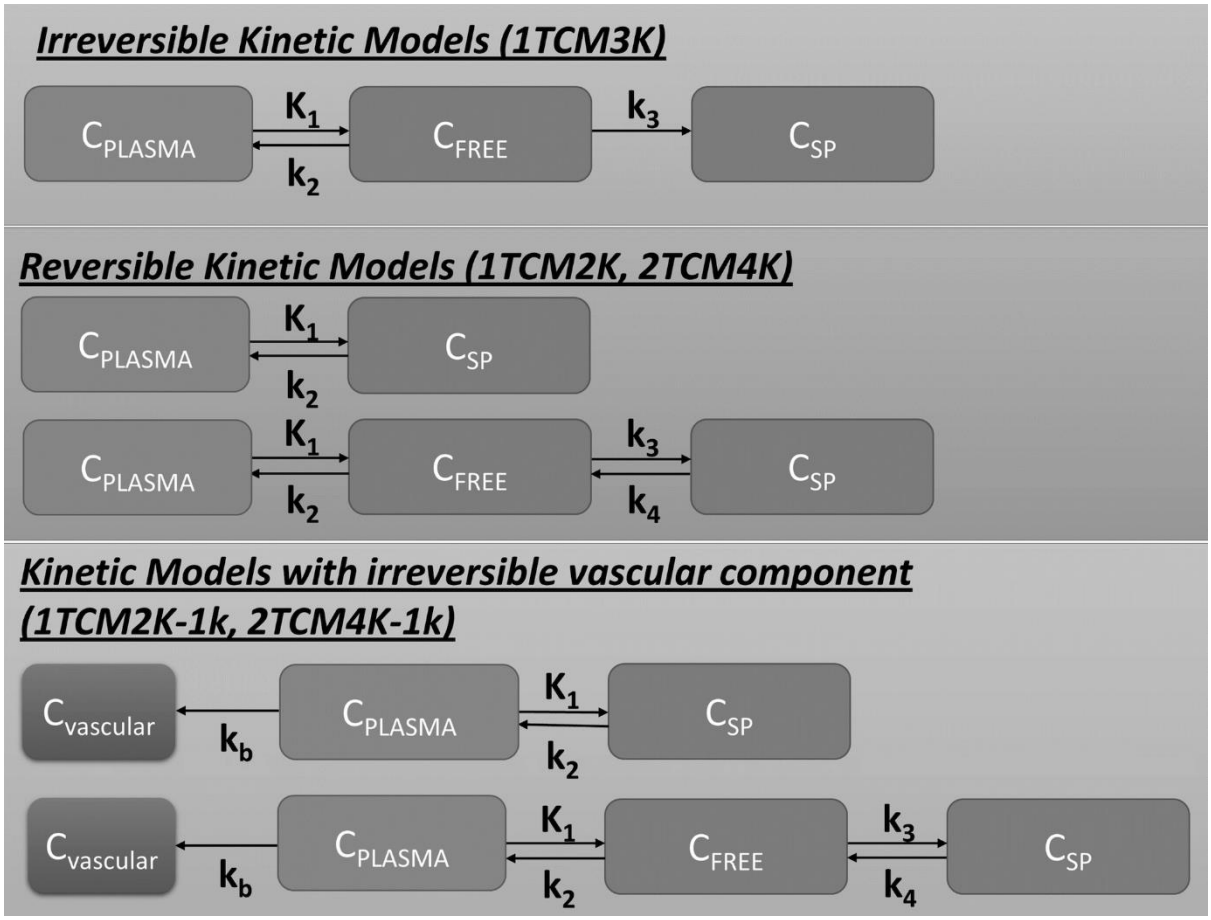
SD = Standard deviation; NART = National Adult Reading Test IQ; HAB = High affinity binders; and MAB = Mixed affinity binders.

MRI

All subjects have undertaken MRI scans with a 3 Tesla Siemens 32-channel Verio scanner. T1-weighted MRI image were acquired to provide high resolution brain structure in assisting the coregistration with PET image and assessing volumetric analysis. While T2-weighted MRI images were used to evaluate any vascular and structural abnormalities.

Different compartment models.

Upper panel displayed one irreversible kinetic model (1TCM3k); and two reversible compartment models (one-tissue: 1TCM2k and two-tissue: 2TCM4k); and bottom panel showed two models with one irreversible vascular compartment (one-tissue: 1TCM2k-1k and two-tissue: 2TCM4k-1k). C_{PLASMA} denotes the parent tracer concentration in plasma; $C_{FREE+NS}$ denotes tracer concentration of free and nonspecific binding, C_{SP} denotes tracer concentration of specific binding and $C_{vascular}$ denotes tracer concentration which trapped in irreversible vascular component. K implies the rate constants for tracer to transport between different kinetic compartments.



Two tissue compartment model for ^{18}F-GE180

Two-tissue reversible models (2TCM4k) model computed V_b value of 0.06±0.027 and showed good precision of parameter estimation, due to the low coefficient of variation (CV) of V_T with CV of 19.6%, in all cortical regions. In the 2TCM4k model, both HAB and MAB subgroups showed good dispersion of the data with relatively low standard deviations in k1, k2, k3 and k4. The ratio of k3/k4 with the 2TCM4k model was 0.495 (CV = 0.25).

HAB	K1 (Mean ± SD)	K2 (Mean ± SD)	K3 (Mean ± SD)	K4 (Mean ± SD)	V_b (Mean ± SD)	V_T (Mean ± SD)
Frontal	*0.0067±0.0023*	*0.0616±0.0072*	*0.0202±0.008*	*0.0392±0.014*	*0.0462±0.0036*	*0.1687±0.0631*
Temporal	*0.007±0.0021*	*0.0567±0.0073*	*0.0219±0.0082*	*0.0667±0.049*	*0.0555±0.0048*	*0.1822±0.0734*
Parietal	*0.0067±0.0022*	*0.0635±0.009*	*0.019±0.01*	*0.0328±0.0115*	*0.0496±0.0056*	*0.1686±0.0527*
Occipital	*0.0082±0.0023*	*0.065±0.0107*	*0.0153±0.0053*	*0.0342±0.0207*	*0.0629±0.0048*	*0.199±0.0582*
Whole brain	*0.0071±0.0023*	*0.0635±0.0054*	*0.0226±0.0089*	*0.0433±0.0166*	*0.0518±0.0044*	*0.1748±0.0672*
MAB						
Frontal	*0.0076±0.0032*	*0.0854±0.0154*	*0.015±0.012*	*0.0427±0.0094*	*0.0729±0.0389*	*0.1211±0.0492*
Temporal	*0.0073±0.0029*	*0.0749±0.0088*	*0.0137±0.0061*	*0.0459±0.0089*	*0.0861±0.0442*	*0.1255±0.0503*
Parietal	*0.0076±0.0035*	*0.0836±0.0171*	*0.0175±0.0175*	*0.0437±0.0165*	*0.0806±0.0437*	*0.124±0.0517*
Occipital	*0.0083±0.0037*	*0.0796±0.0245*	*0.0097±0.0062*	*0.0312±0.0031*	*0.0998±0.0574*	*0.1351±0.0527*
Whole brain	*0.0076±0.0032*	*0.0811±0.0146*	*0.0144±0.0116*	*0.0426±0.0091*	*0.0823±0.0442*	*0.1242±0.0495*

SD = Standard deviation; V_b = Blood volume; V_T = Volume of distribution; Frontal = Frontal Lobe; Temporal = Temporal Lobe; Parietal = Parietal Lobe; Occipital = Occipital Lobe; HAB = High affinity binders; and MAB = Mixed affinity binders.

Logan parametric mapping for ^{18}F-GE180

For 10 healthy controls, ROI analysis of ^{18}F-GE180 Logan parametric maps yielded a V_T of 0.17±0.07 in frontal lobe, 0.19±0.07 in temporal lobe, 0.17±0.07 in parietal lobe and 0.20±0.07 in occipital lobe. Among subcortical regions, thalamus showed the highest Logan V_T values of 0.21±0.07. Whole brain V_T was 0.19±0.06 in HAB and 0.17±0.06 in MAB subgroups. Across ROI regions, the thalamus revealed the highest V_T values, 0.22±0.06 in HAB and 0.19±0.06 in MAB. Regional Logan V_T for 18F-GE180 in all healthy controls, and separated as two TSPO subgroup HABs and MABs.

18F-GE180 LOGAN		**FL**	**TL**	**PL**	**OL**	**WB**	**P-Cing**	**Thalamus**	**Brainstem**	**Striatum**	**MTL**	**Hippo**	**CB**
All Subjects	**Mean**	0.17	0.19	0.17	0.20	0.18	0.19	0.21	0.20	0.16	0.20	0.21	0.19
	SD	*0.07*	*0.07*	*0.07*	*0.07*	*0.07*	*0.07*	*0.07*	*0.09*	*0.06*	*0.07*	*0.08*	*0.08*
TSPO Subgroup													
HAB	**Mean**	0.18	0.20	0.18	0.21	0.19	0.20	0.22	0.21	0.16	0.21	0.22	0.20
	SD	*0.06*	*0.06*	*0.05*	*0.06*	*0.06*	*0.06*	*0.06*	*0.08*	*0.05*	*0.06*	*0.07*	*0.07*
MAB	**Mean**	0.16	0.18	0.17	0.19	0.17	0.18	0.19	0.19	0.15	0.19	0.19	0.18
	SD	*0.06*	*0.06*	*0.05*	*0.06*	*0.06*	*0.06*	*0.06*	*0.08*	*0.05*	*0.06*	*0.07*	*0.07*
HAB vs. MAB	**t test**	*0.41*	*0.37*	*0.45*	*0.41*	*0.41*	*0.37*	*0.33*	0.38	*0.44*	*0.36*	*0.34*	*0.33*
	Increase	8%	10%	4%	7%	7%	10%	14%	11%	5%	11%	13%	14%

*$p<0.05$; FL = Frontal Lobe; TL = Temporal Lobe; PL = Parietal Lobe; OL = Occipital Lobe; WB = Whole Brain; P-Cing = Posterior Cingulate; MTL = Medial Temporal Lobe; Hippo = Hippocampus; CB = Cerebellum; HAB = High affinity binders; and MAB = Mixed affinity binders.