Overview of region merging in PMOD (AAL-merged)

Frontal region: Precentral_l, Precentral_r, Rolandic_Oper_l, Rolandic_Oper_r, Supp_Motor_Area_l, Supp_Motor_Area_r, Olfactory_l, Olfactory_r, Frontal_Sup_l, Frontal_Sup_r, Frontal_Mid_l, Frontal_Mid_r, Frontal_Inf_l, Frontal_Inf_r, Rectus_l, Rectus_r, Paracentral_Lobule_l, Paracentral_Lobule_r

Insular region: Insula_l, Insula_r

Anterior cingulate region: Cingulum_Ant_l, Cingulum_Ant_r

Posterior cingulate region: Cingulum_Post_l, Cingulum_Post_r

Temporal region: Hippo_Parahippo_l, Hippo_Parahippo_r, Amygdala_l, Amygdala_r, Fusiform_l, Fusiform_r, Heschl_l, Heschl_r, Temporal_l, Temporal_r

Parietal region: Postcentral_l, Postcentral_r, SupraMarginal_l, SupraMarginal_r, Angular_l, Angular_r, Parietal_l, Parietal_r

Precuneal region: Precuneus_l, Precuneus_r

Occipital region: Calcarine_l, Calcarine_r, Cuneus_l, Cuneus_r, Lingual_l, Lingual_r, Occipital_l, Occipital_r

Pons: Pons

Cerebellar cortex: Vermis, Cerebellum_Crus_l, Cerebellum_Crus_r, Cerebellum_l, Cerebellum_r

Composite region: all of the above in addition to Cingulum_Mid_l and Cingulum_Mid_r

Regions not included: CaudateNucl_l, CaudateNucl_r, Putamen_l, Putamen_r, Pallidum_l, Pallidum_r, Thalamus_l, Thalamus_r, Medulla, Midbrain.

Overview of region merging in CortexID

1. Prefrontal left + prefrontal right/2 = frontal region
2. Anterior cingulate left + anterior cingulate right /2 = anterior cingulate region
3. Precuneus/Posterior cingulate left + Precuneus/Posterior cingulate right/2 = Prec.PCC region
4. Parietal left + parietal right / 2 = parietal region
5. Temporal lateral left + temporal lateral right + temporal mesial left + temporal mesial right /4 = temporal region

The occipital and sensorimotor regions from CortexID was included in the composite score but not included in regional analyses.

Overview of region merging in SyngoVia

1. Posterior cingulate + precuneus / 2 = Precuneus / Posterior cingulate cortex region.
    All other SyngoVia regions were used as they are displayed in the software.

PMOD, PNEURO v. 4.0 processing steps for AAL-merged pipeline

Subheadings follow the user manual for PNEURO version 4.0 from PMOD (page 64–83) (17).

PET image loading and time averaging

Crop PET. No motion correction or image denoising was applied.

MR image loading and segmentation:

Crop MR. Varied between autocrop and manual crop, depending on the results from segmentation. Default settings were applied: Denoising: low, Segmentation: 3 probability maps, sampling: 3 pix, bias regularization: light 60, cleanup: light, Affine regularization: European brains.

PET to MR matching

Segmentation was manually inspected. "PET-MR Matching required" was chosen. Matching sampling 3 mm was applied.

MR-based normalization

Matching was manually verified. Probability Maps transformation was applied. Split brain was chosen.

Brain segments calculation

Normalization was verified manually. AAL-merged atlas was chosen if not already selected. Inspection of «validate split» was performed, although not relevant for this study. White matter parcellation was not performed.

Outlining of brain structures

In Result space – "Input": "MR" was chosen and «Mask by» «Probability». "Individual" was used with the following thresholds: GM → 0.3 and CSF → 0.5. "Mask non-cortical regions" was not applied.

Brain VOI editing and statistics calculation

If VOIs included non-brain structures (most often meninges) the eraser function was used to correct the VOIs. Otherwise, no changes were applied. PVC was applied using the "Region based voxel-wise, using a resolution of 2 mm×2 mm×2 mm (based on measurements from the scanner used).

All edited VOIs were saved after editing. All protocols were saved.

PMOD, PNEURO v.4.0 processing steps for Centiloid pipeline

All processing steps were applied according to the PMOD Application note version 3.9 for Centiloid Analysis (19).
PET: CROP 20×30×20 as autocrop size.
MR: CROP 20×30×20 as autocrop size.
Denoising: medium, Segmentation: 3 prob maps, Sampling: 3 mm, Bias regularization: Medium, 60 kernel, Cleanup: light, Affine registration: European brains
→Segment MR
PET-MR matching required, PET: 4.0 x 4.0 x 4.0, Matching sample: 2 mm
→ Match PET to MR
Inspect, No split brain, Inspect
→Segment brain
Result space: Atlas, Mask by: Probability – Individual, Mask by GM: 0.0, No CSF mask, Mask non-cortical regions
→Outline
No partial volume correction was applied, QC (quality control) (yes)
→Statistics
Relative to WC (whole cerebellum). Save protocol. Inspect images from quality control

Table S1 Overview of differences in software

	SyngoVia	CortexID	PMOD AAL-merged	PMOD Centiloid
Reference region/s	Pons, cerebellum whole, cerebellar cortex	Pons, cerebellum whole, cerebellar cortex	Optional	Cerebellum whole
Number of regions	6 cortical	16 cortical	71 cortical and white matter	1 cortical composite
Uni/bilateral regions	Bilateral	Unilateral	Unilateral	Bilateral
3D MRI obligatory	No	No	Yes	Yes
PVC applied	No	No	Yes	No
SUV for each region	Yes	No	Yes	Optional
Volume for each region	No	No	Yes	Optional
SUVR displayed	Yes	Yes	No	Optional

3D MRI, volumetric magnetic resonance imaging; PVC, partial volume correction; SUV, standardized uptake value; SUVR, standardized uptake value ratio.

Table S2 Results from ROC curves of regional uptake against regional visual classification

Region	Area under the curve		
	PMOD, n=86	CortexID, n=191	SyngoVia, n=191
Frontal SUVRpons	0.990	0.997	0.996
Frontal SUVRcer	0.986	0.988	0.990
Temporal SUVRpons	0.988	0.995	0.989
Temporal SUVRcer	0.978	0.972	0.966
Parietal SUVRpons	0.980	0.982	0.976
Parietal SUVRcer	0.979	0.974	0.984
Posterior cingulate/Precuneus SUVRpons	0.994	0.996	0.993
Posterior cingulate/Precuneus SUVRcer	0.988	0.984	0.970

ROC, receiver operating characteristic; SUVR, Standardized uptake value ratio; SUVRpons, SUVR normalized to pons; SUVRcer, SUVR normalized to cerebellar cortex.

Table S3 Related samples sign test of regional SUVRpons (n=86)

Regional SUVR	Software tested	Negative diff.	Positive diff.	Ties	P value
Frontal SUVRpons	SyngoVia – PMOD	86	0	0	<0.001
	CortexID – PMOD	84	2	0	<0.001
	SyngoVia – CortexID	75	11	0	<0.001
Ant.cing SUVRpons	SyngoVia – PMOD	86	0	0	<0.001
	CortexID – PMOD	85	1	0	<0.001
	SyngoVia – CortexID	58	26	2	0.001
Temporal SUVRpons	SyngoVia – PMOD	76	10	0	<0.001
	CortexID – PMOD	79	7	0	<0.001
	SyngoVia – CortexID	22	64	0	<0.001
Parietal SUVRpons	SyngoVia – PMOD	86	0	0	<0.001
	CortexID – PMOD	77	9	0	<0.001
	SyngoVia – CortexID	85	1	0	<0.001
Post.cing/precuneus SUVRpons	SyngoVia – PMOD	79	7	0	<0.001
	CortexID – PMOD	86	0	0	<0.001
	SyngoVia – CortexID	16	70	0	<0.001

SUVR, standardized uptake value ratio; SUVRpons, SUVR normalized to pons; diff, difference; Ant.cing, anterior cingulate cortex; Post.cing, posterior cingulate cortex.

Table S4 Related samples sign test of regional SUVRcer (n=86)

Regional SUVR	Software tested	Negative diff.	Positive diff.	Ties	P value
Frontal SUVRcer	SyngoVia - PMOD	38	48	0	0.332
	CortexID - PMOD	64	22	0	<0.001
	SyngoVia - CortexID	13	73	0	<0.001
Ant.cing SUVRcer	SyngoVia - PMOD	48	38	0	0.332
	CortexID - PMOD	78	8	0	<0.001
	SyngoVia - CortexID	5	81	0	<0.001
Temporal SUVRcer	SyngoVia - PMOD	86	0	0	<0.001
	CortexID - PMOD	42	44	0	0.914
	SyngoVia - CortexID	2	84	0	<0.001
Parietal SUVRcer	SyngoVia - PMOD	58	28	0	0.002
	CortexID - PMOD	48	38	0	0.332
	SyngoVia - CortexID	67	19	0	<0.001
Post.cing/precuneus SUVRcer	SyngoVia - PMOD	12	74	0	<0.001
	CortexID - PMOD	63	23	0	<0.001
	SyngoVia - CortexID	1	85	0	<0.001

SUVR, standardized uptake value ratio; SUVRcer, SUVR normalized to cerebellar grey matter; diff, difference; Ant.cing, anterior cingulate cortex; Post.cing, posterior cingulate cortex.

Table S5 Semi-quantitative measures per diagnosis group

	n	SyngoVia		CortexID		n	PMOD		
		SUVRpons	SUVRcer	SUVRpons	SUVRcer		SUVRpons	SUVRcer	CL
AD	76	0.75 (0.15)	2.46 (0.48)	0.75 (0.14)	2.17 (0.41)	32	0.83 (0.18)	2.08 (0.47)	79 (40.0)
AD mixed	29	0.63 (0.17)	2.19 (0.65)	0.64 (0.16)	1.86 (0.49)	11	0.79 (0.21)	1.96 (0.64)	65 (53.0)
VaD	13	0.45 (0.09)	1.55 (0.24)	0.47 (0.10)	1.38 (0.27)	3	0.66 (0.24)	1.68 (0.56)	40 (43.0)
FTD	4	0.42 (0.06)	1.36 (0.18)	0.43 (0.04)	1.22 (0.12)	2	0.55 (0.03)	1.38 (0.00)	14 (5.0)
PPA[†]	9	0.63 (0.19)	2.09 (0.65)	0.63 (0.19)	1.79 (0.51)	5	0.73 (0.25)	1.84 (0.69)	52 (57.0)
DLB	7	0.58 (0.12)	1.96 (0.46)	0.58 (0.94)	1.72 (0.32)	4	0.63 (0.11)	1.52 (0.26)	35 (25.0)
PDD	1	0.41 (0.00)	1.35 (0.00)	0.42 (0.00)	1.22 (0.00)	0	–	–	–
Park plus	3	0.50 (0.15)	1.84 (0.17)	0.51 (0.16)	1.60 (0.22)	1	0.64 (0.00)	1.61 (0.00)	42 (0.0)
Other	49	0.45 (0.09)	1.47 (0.31)	0.46 (0.09)	1.22 (0.26)	28	0.52 (0.09)	1.29 (0.18)	12 (17.0)

†, including patients with logopenic variant of primary progressive aphasia. Values are displayed as mean (standard deviation). n, number of patients; SUVRpons, standardized uptake value ratio with normalization to pons; SUVRcer, standardized uptake value ratio with normalization to cerebellar cortex; CL, centiloids; AD, Alzheimer´s disease; VaD, Vascular dementia; FTD, Frontotemporal lobar degeneration; PPA, Primary progressive aphasia; DLB, Dementia with Lewy Bodies; PDD, Parkinson disease dementia; Park plus, Parkinson plus disorders.