AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

Visual assessment of [^{18}F]flutemetamol PET images can detect early amyloid pathology and grade its extent

L.E. Collij, G. Salvadó, M. Shekari, I. Lopes Alves, J. Reimand, A.M. Wink, M. Zwan, Aida Niñerola-Baizán, Andrés Perissinotti, P. Scheltens, G. Farrar, J.L. Molinuevo2, F. Barkhof, C. Buckley, B.N.M. van Berckel & J.D. Gispert

AAIC 2020

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Disclosure(s)

- C Buckley and G Farrar are GE Healthcare employees.
- All other authors have nothing to disclose.

Featured Research Session
The value of amyloid PET beyond dichotomization

Speaker Chatroom Q&A - Scheduled Time
Date: 28 July 2020
Time: 7:30 AM - 7:55 AM *(U.S. Central Time)*
A separate video-chat room will also be made available

1. A multi-study analysis of the spatial-temporal progression of amyloid deposition and its utility for longitudinal studies (I. Lopes Alves)

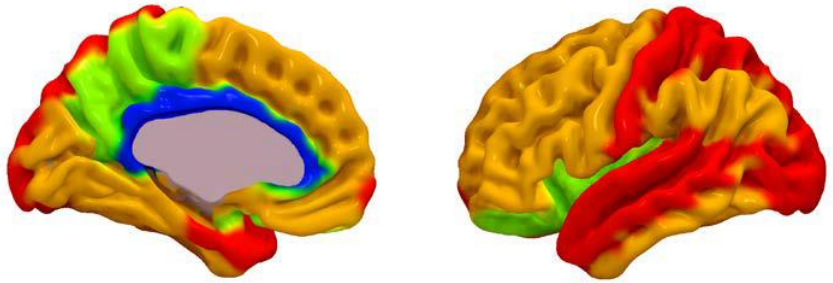
2. Examining Centiloid quantification against visual assessment using [^{18}F]flutemetamol PET (L.E. Collij)

3. Converging evidence for a “gray-zone” of amyloid burden and its relevance (S. Bullich)

4. Emerging beta-amyloid pathology is associated with tau, synaptic, neurodegeneration and gray matter volume differences (JL Molinuevo)

Visualizing the spatial-temporal ordering of amyloid

- Amyloid staging models to capture regional amyloid deposition[1]:
  - 4 stages were defined from N=400 CN scans across 4 tracers to **ensure between-tracer applicability**
  - Successfully applied to 99% of *N*=4783 scans



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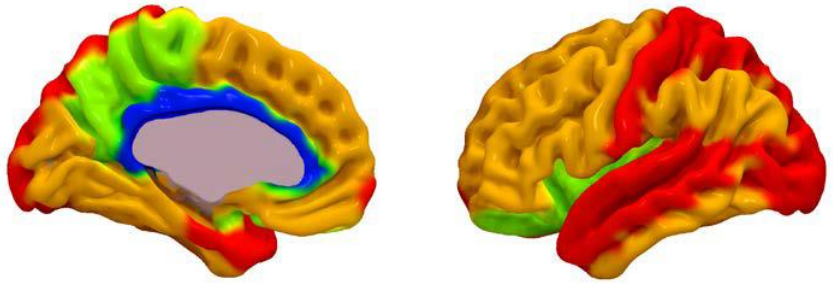
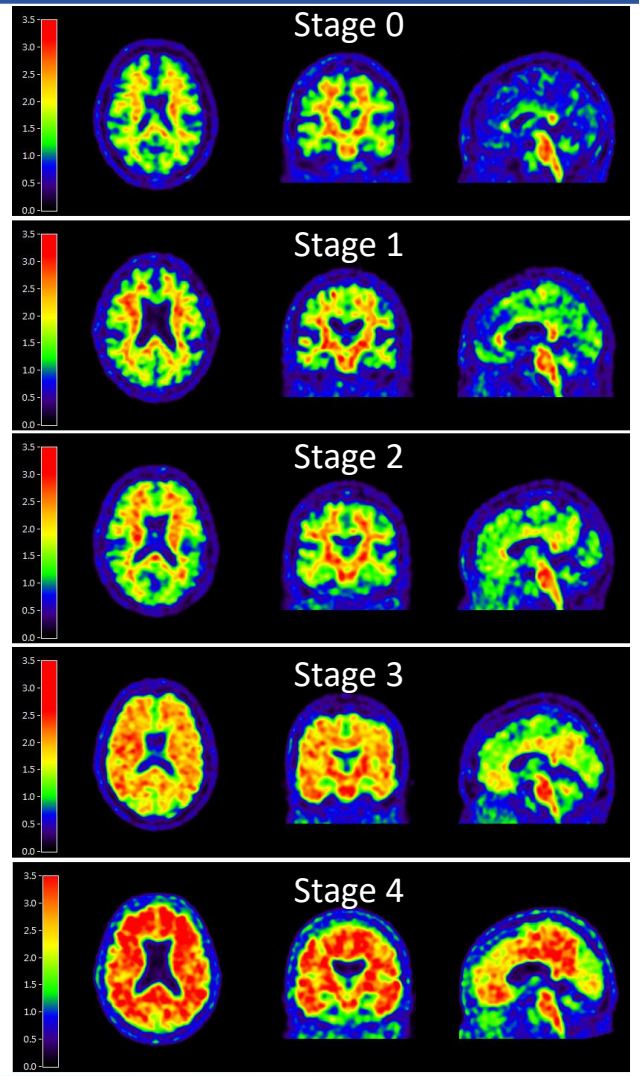


- Can we visually identify 'stages'?

- Visual read (VR) in clinical routine:
  - Generally, only the final classification (negative/positive) is documented
  - Guidelines were developed to capture established pathology in clinical populations → considered *conservative*

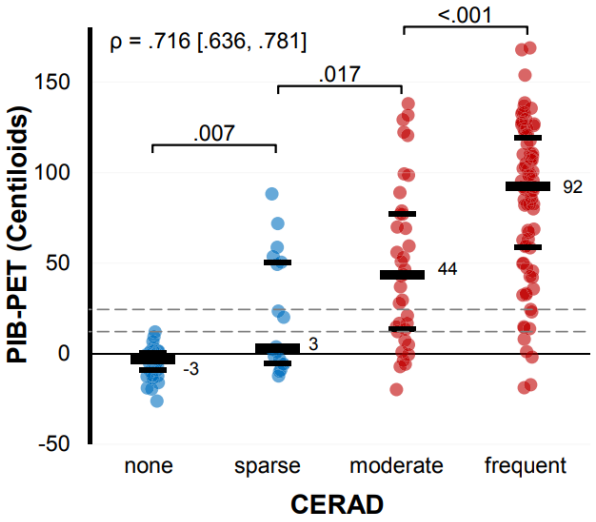


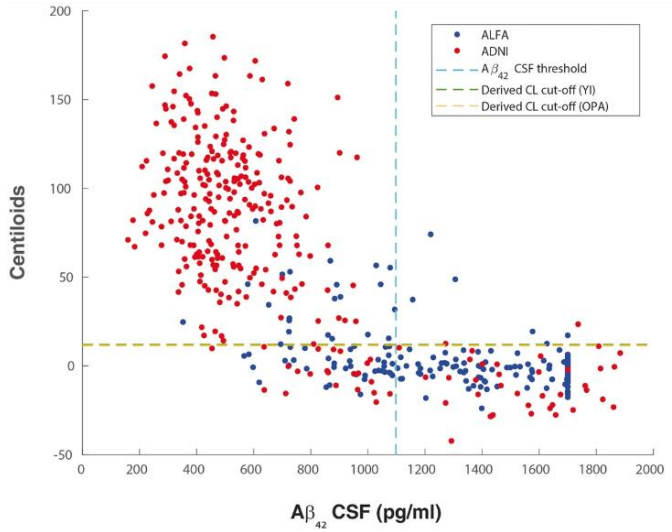
1) Collij et al., 2020, *In press*

Quantification has focused on early amyloid pathology

- Centiloid (CL) method: harmonization of amyloid PET data[1]
  - 0 CL = young controls & 100 CL = early AD dementia

- CL vs. *post-mortem* and CSF:
  - 12 CL = early amyloid pathology[2,3,4]
  - 24-30 CL = established amyloid pathology[2,3,4]

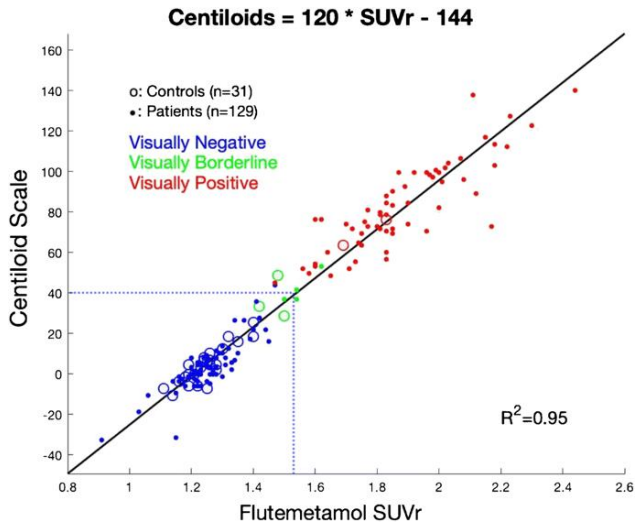


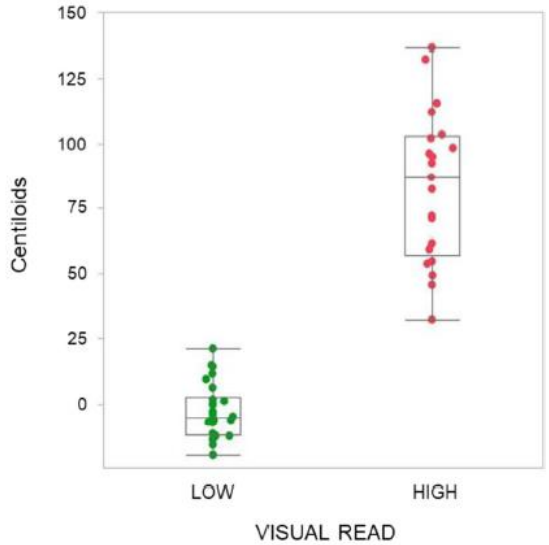


1) Klunk et al., 2015
2) La Joie et al., 2019
3) Amadoru et al., 2020
4) Salvadó et al., 2019

Centiloid against Visual Read

- CL vs. VR:
  - Cut-offs higher compared to *post-mortem* and CSF (i.e. CL=24-42)[1,2,3]





- Limitations in current literature:
  - Limited number of subjects in the gray-zone band (CL = 12-30)
  - Mainly clinical and end-of-life populations

1) Amadoru et al., 2020
2) Battle et al., 2019
3) Hanseeuw et al., 2020

Aims

Pooled [^{18}F]flutemetamol scans of two complementary cohorts that allowed us to cover both early and established pathology

1. Investigate the agreement between VR and CL-based classification of amyloid PET scans using previously proposed cut-offs for early (CL=12) and established (CL=30) amyloid pathology.

2. Characterize and assess the utility of regional VR positivity to stage amyloid burden across the AD *continuum*.

- 497 [^{18}F]flutemetamol scans:
  - 352 cognitively unimpaired (for ALzheimer's and Families (ALFA+) cohort)
  - 145 cognitively impaired (Dutch Flut Study Amsterdam Dementia Cohort [ADC])

- Visual assessment:
  - According to GE guidelines
  - Final classification (negative/positive)
  - Regional read for 5 ROIs
    - Frontal
    - PC/PCC
    - Lateral temporal
    - Temporo-parietal
    - Striatum

- Quantification:
  - Standard Centiloid (CL) pipeline

	Pooled (N = 497)	ALFA+ CU population (N = 352)	ADC Clinical Population (N = 145)	p-value
Age (years)	61.7 ± 4.9	61.5 ± 4.6	62.2 ± 5.6	n.s.
Sex F (%)	281 (56.5%)	215 (61.1%)	66 (45.5%)	<0.01
MMSE	27.2 ± 3.5	29.2 ± 1.0	23.4 ± 3.4	<0.01
APOE ε4 carriership	280 (56.3%)	193 (54.8%)	87 (60.0%)	n.s.
Centiloid	18.7 ± 38.8	2.9 ± 17.2	56.8 ± 48.9	<0.01
VR+	144 (29.0%)	49 (13.9%)	95 (65.5%)	<0.01

Statistical analyses

Only the assessment of Reader 1 was available for the majority of cases (*N*=447)

Majority visual read was available for a sub-set (*N*=50).

VR vs CL classification

- Kappa statistics: VR against CL cut-offs of early (CL=12) and established (CL=30) amyloid pathology
- ROC analysis: identify CL cut-off using VR as the reference (Youden's J Index)

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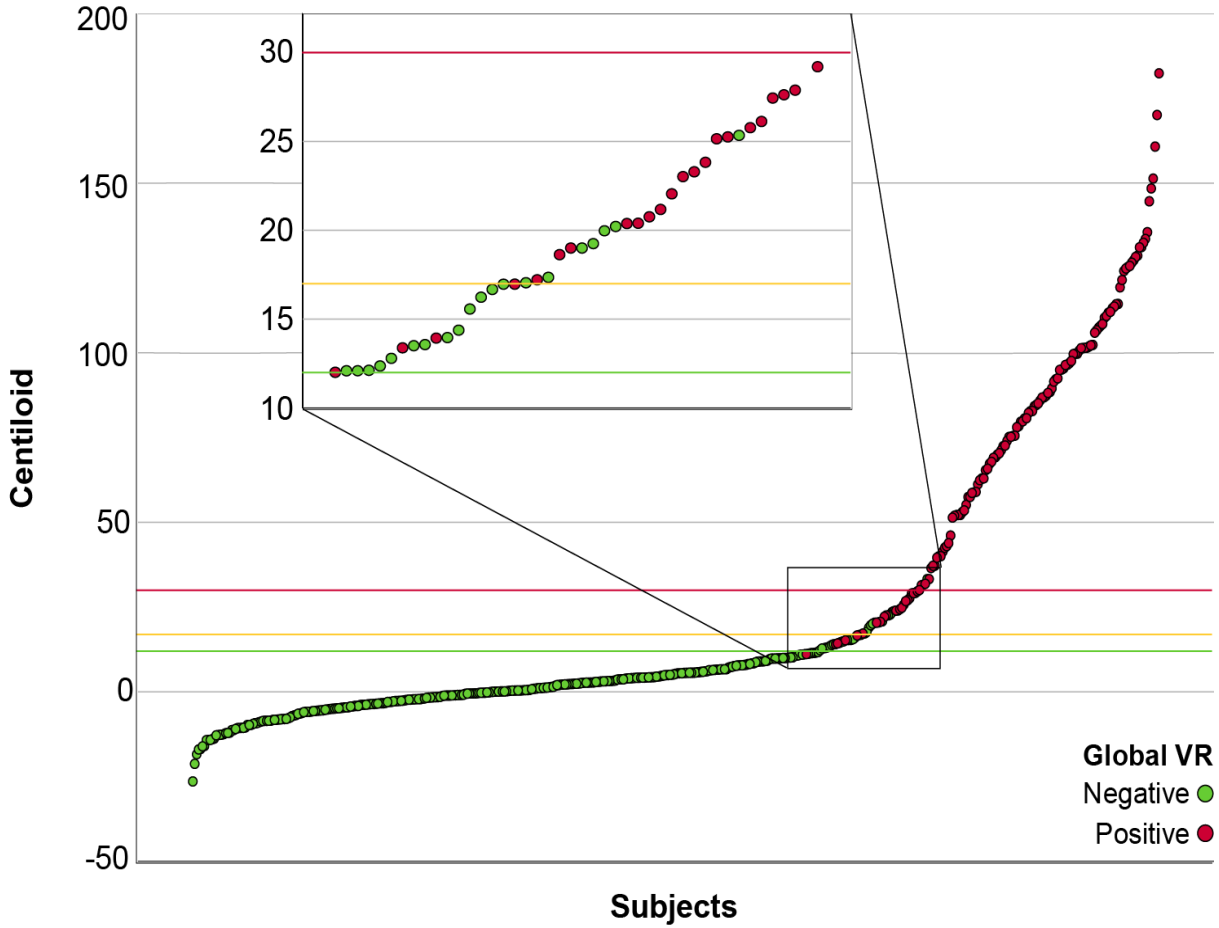
Regional VR vs CL burden

- One-way ANOVA: differences in CL burden depending on number of visually positive regions and VR stages.
- Chi-squared tests: distribution of VR stages across clinical diagnosis.

RESULTS

VR shows excellent agreement with CL-based classification



CL=30 cut-off (established pathology)[1]:
κ=.87
100%/93.1% sens/spec

CL=12 cut-off (early pathology)[2]:
κ=.88
86.5%/99.1% sens/spec

1) Salvadó et al., 2019
2) La Joie et al., 2019
3) Su et al., 2018

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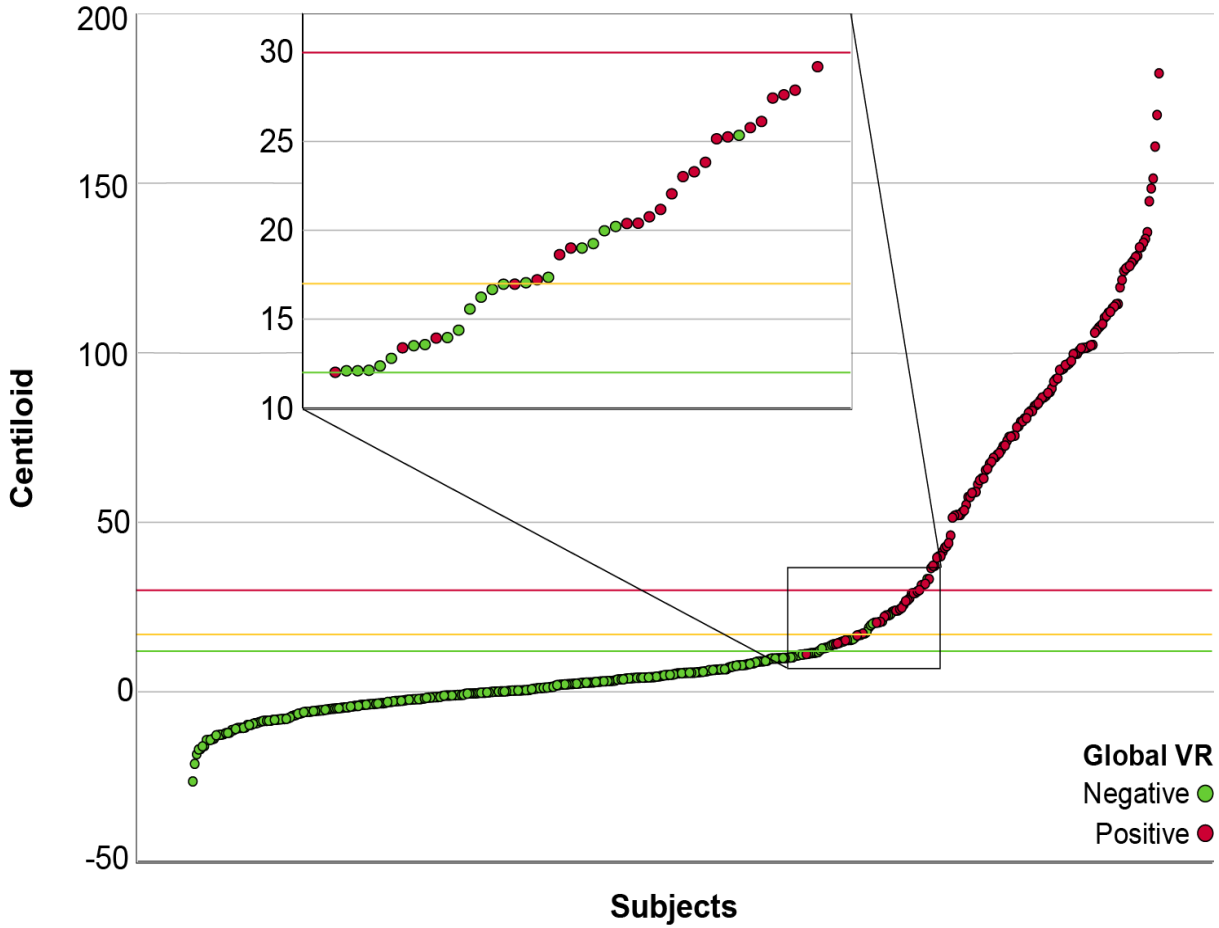


CL=30 cut-off (established pathology)[1]:
κ=.87
100%/93.1% sens/spec

CL=12 cut-off (early pathology)[2]:
κ=.88
86.5%/99.1% sens/spec

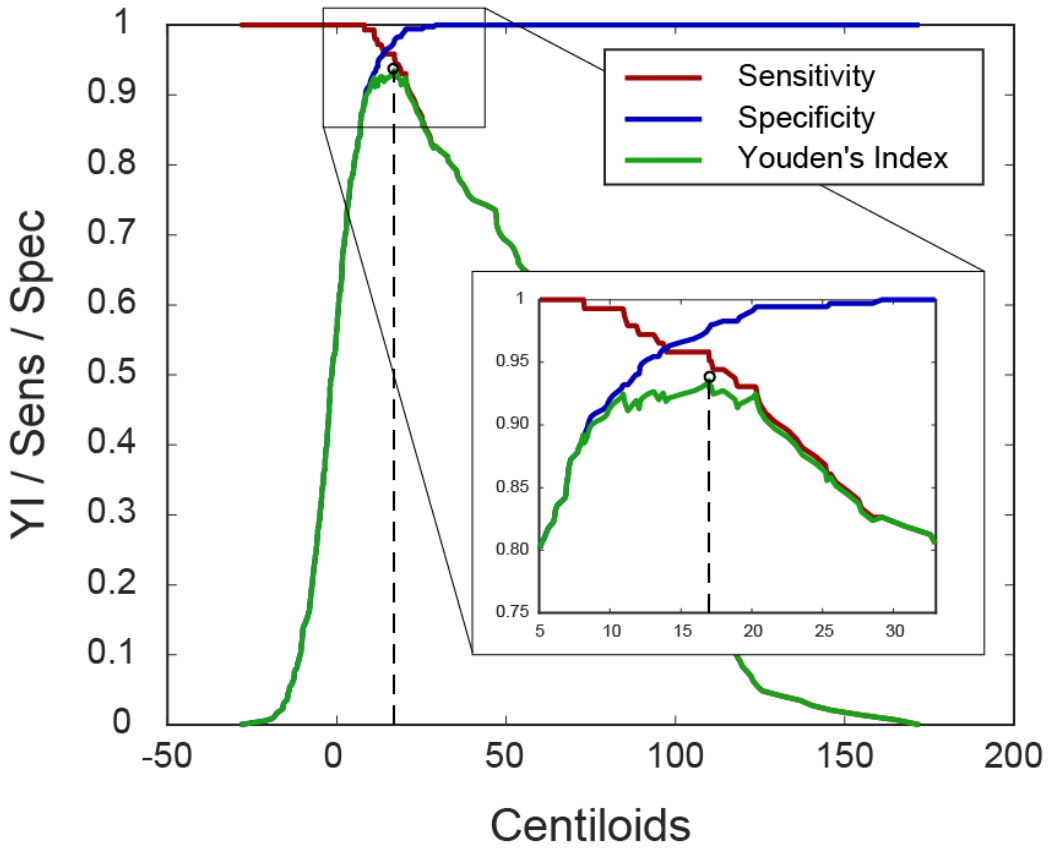
CL=17 cut-off:
ROC analyses with VR as reference
93.9%/98.2% sens/spec
AUC of .996 (95% CI: .993-.999)
Youden index: 0.936

Note, CL quantification is dependent on local processing[3] → range of cut-off between 14-20.

1) Salvadó et al., 2019
2) La Joie et al., 2019
3) Su et al., 2018

Gray-zone zoom in

ROC results



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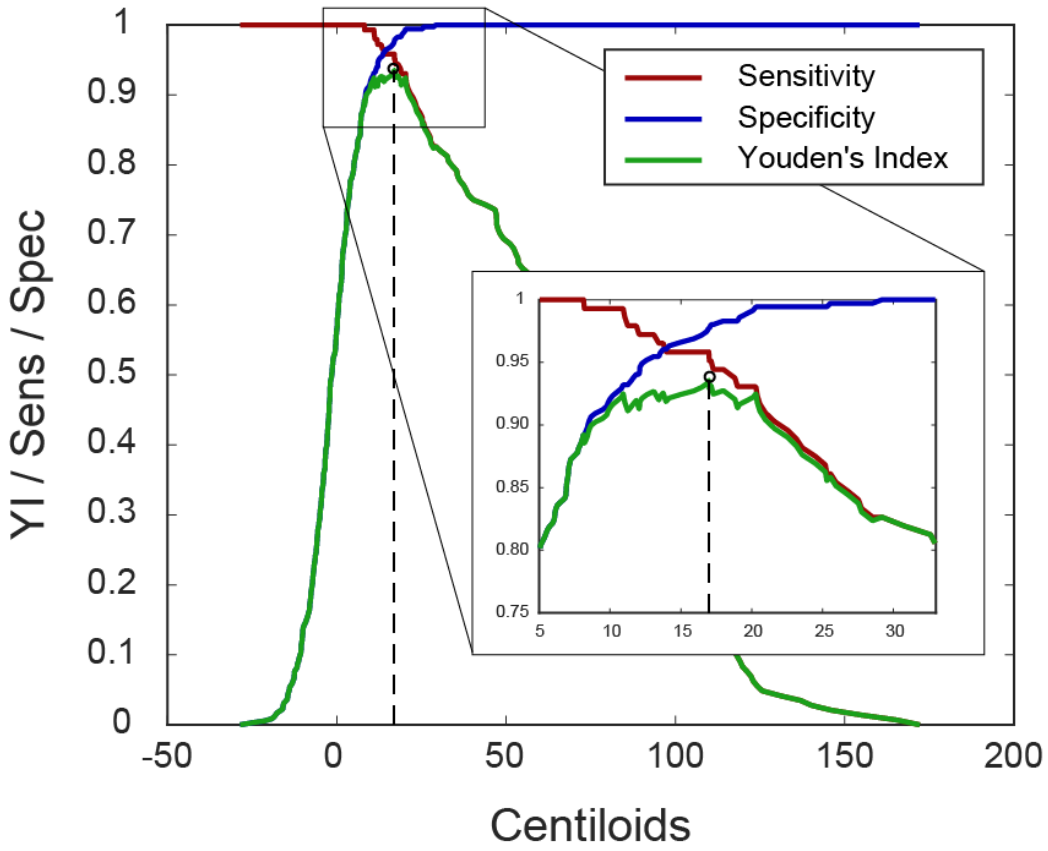
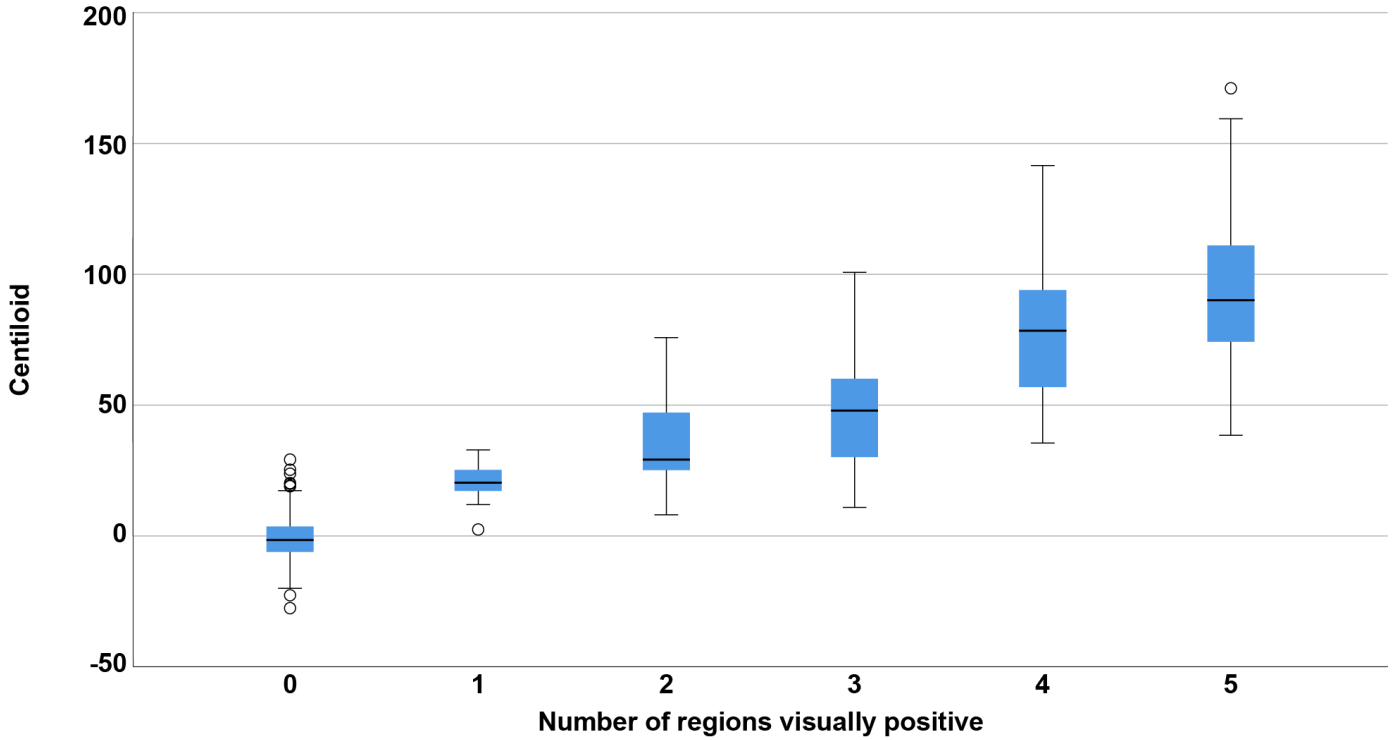


Intra- and inter-reader agreement

- Selected 50 scans: emphasis on gray-zone subjects
- Intra- and inter-reader agreement was good (k=.68)[1]
- Scans with a CL~25 are generally classified as VR+ across all readers.[2]
- 7/11 of scans with a CL 17-25 were also classified as VR+ by at least 2 out of 3 readers.

1) Collij et al., 2019
2) Amadoru et al., 2020

Number of visually+ regions relates to CL values



N	353	13	21	15	21	74
Centiloid	-1.0±8.1	20.5±8.1	35.6±18.1	48.8±26.6	76.2±28.9	92.9±25.9

It can be clinically relevant to visually capture the *extent* of amyloid burden in addition to negative/positive classifications.

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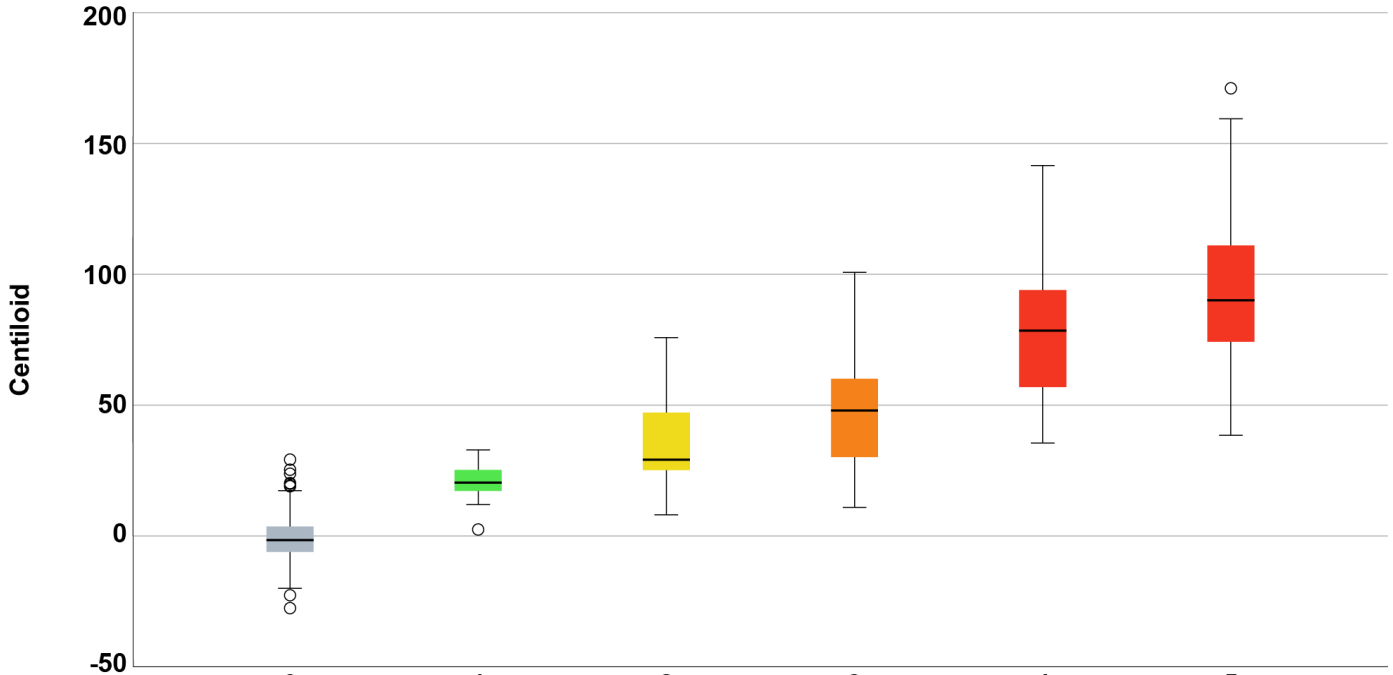

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1 region VR+: emerging amyloid pathology[1,2,3]

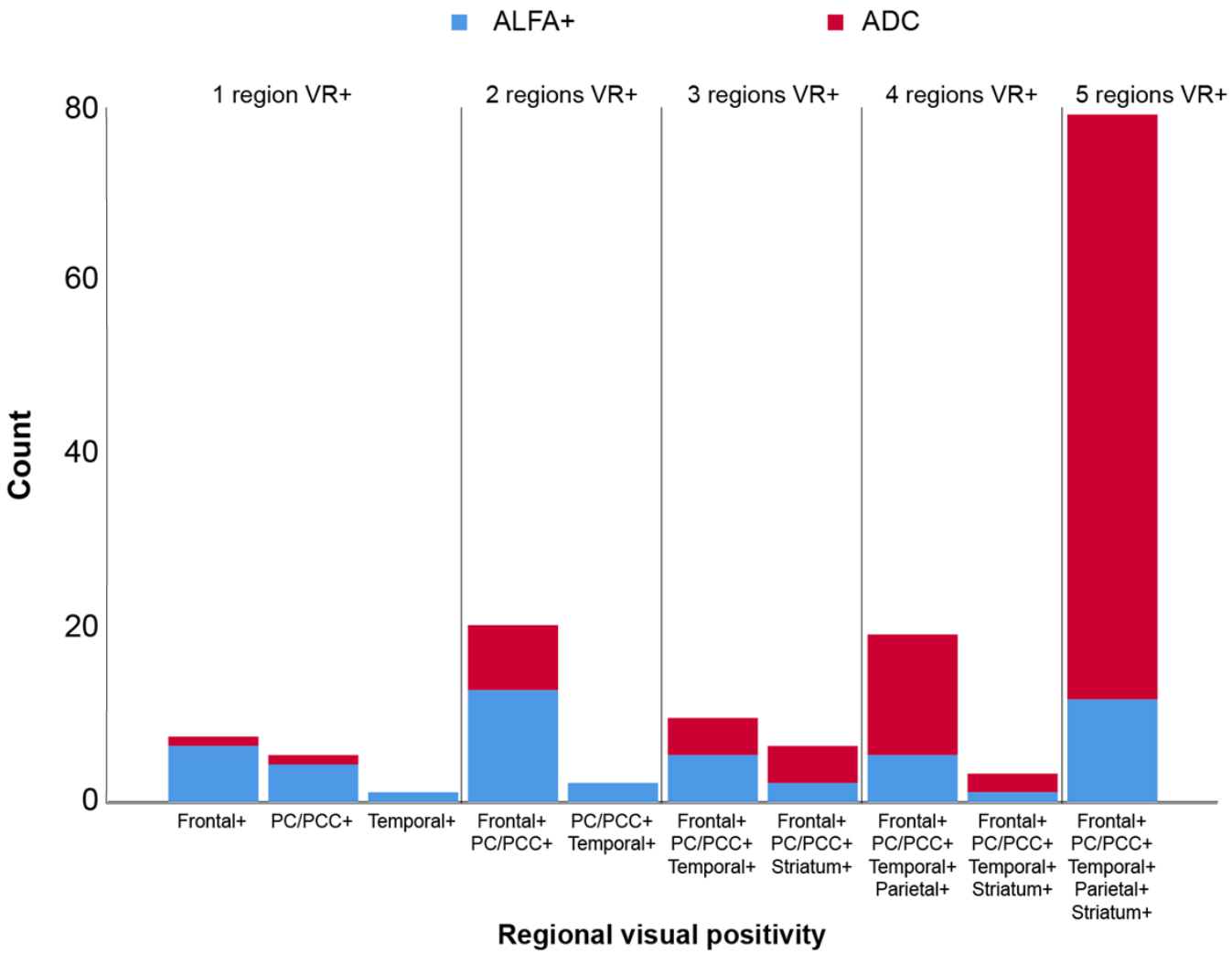
2 regions VR+: established amyloid pathology[1,3]

3 regions VR+: predictive for clinical progression[4]

4&5 regions VR+: representative of clinical dementia population[5,6]

1) La Joie et al., 2019
2) Amadoru et al., 2020
3) Salvadó et al., 2019
4) Hanseeuw et al., 2020
5) Leuzy et al., 2019
6) Rowe et al., 2020

Regional visual read patterns



Frontal and PC/PCC regions were read positive most often (27.4% and 27.2%)
followed by lateral temporal (21.7%), temporo-parietal (18.5%), and striatal region (16.7%)

Suggests general ordering:

- VR stage 1: Frontal *or* PC/PCC
- VR stage 2: Frontal *and* PC/PCC
- VR stage 3: Positivity beyond these regions

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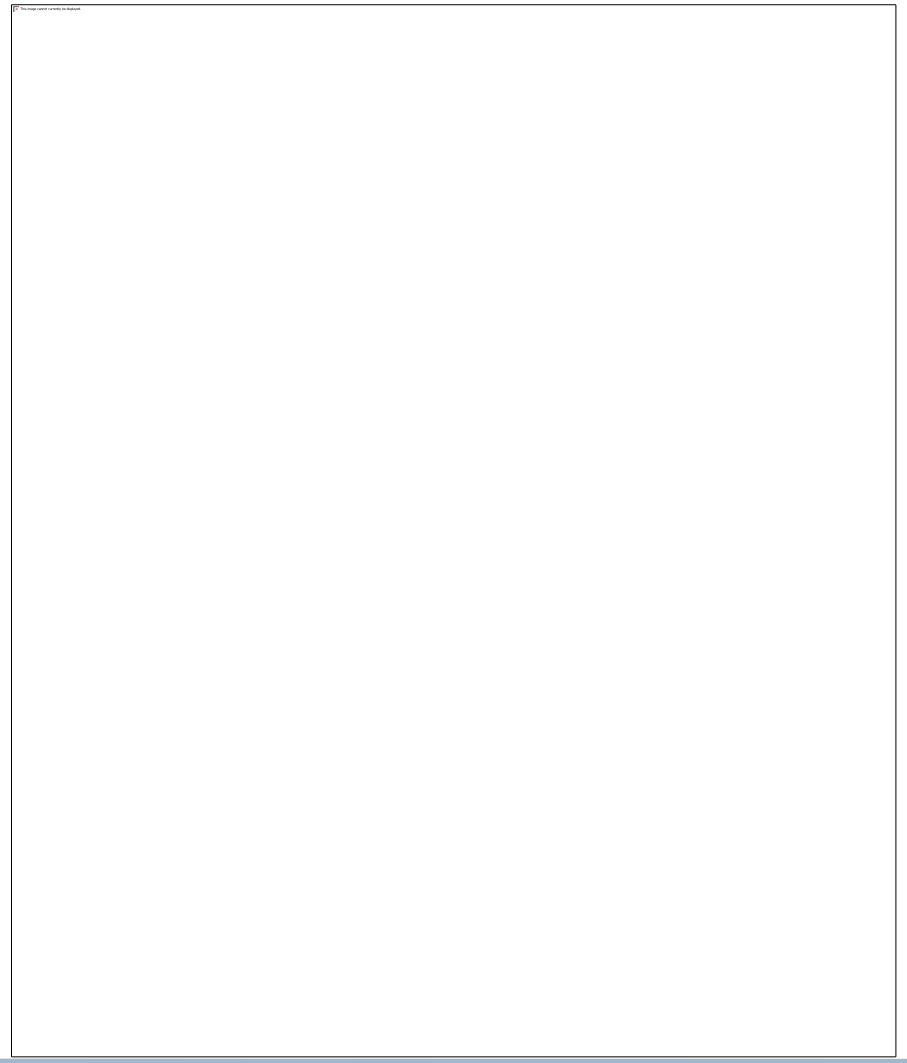

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VR stages strongly related to Dx

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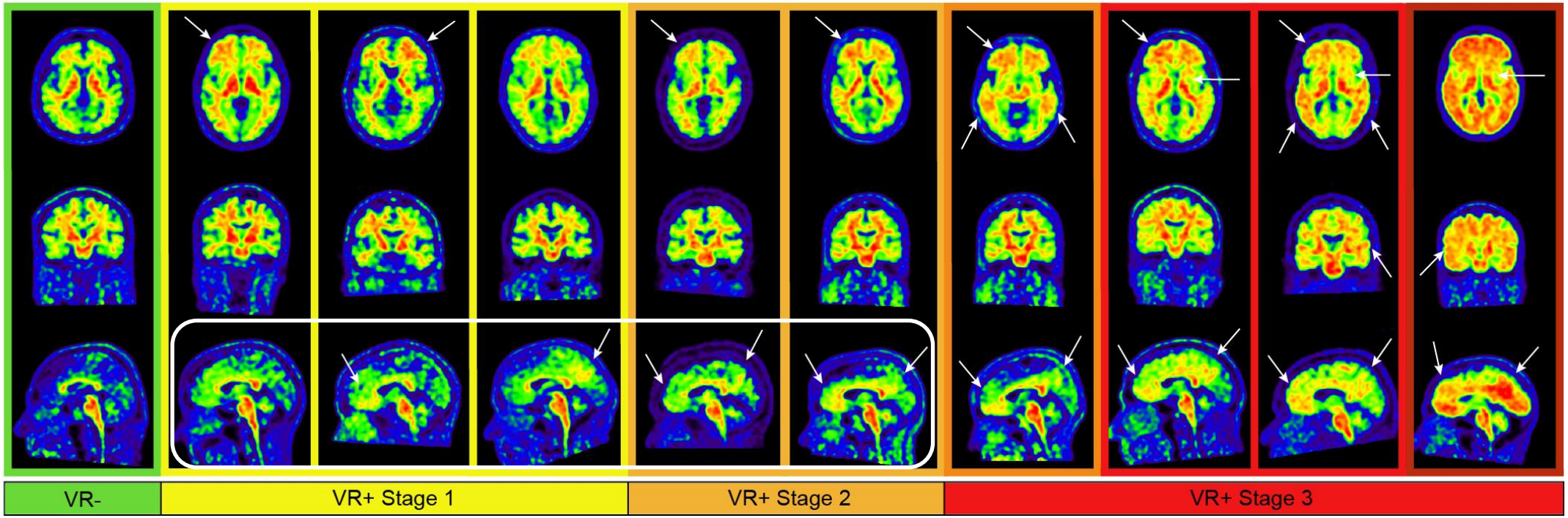
Integrating our results

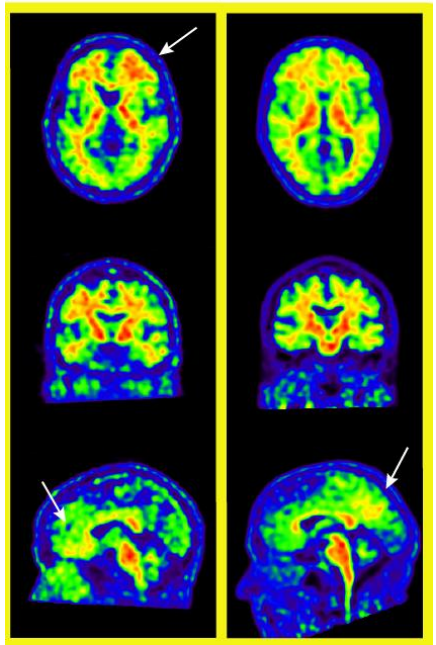
Frontal	-	+	+	-	+	+	+	+	+	+
PC/PCC	-	-	-	+	+	+	+	+	+	+
Lat.Temporal	-	-	-	-	-	-	+	+	+	+
Parietal	-	-	-	-	-	-	-	-	+	+
Striatum	-	-	-	-	-	-	-	+	+	+
Centiloid	2	17	19	27	32	35	38	47	57	81



Medial regions and VR sensitivity

- Sagittal plane seems optimal for assessing early amyloid pathology
  - Medial orbitofrontal cortex and precuneus/posterior cingulate cortex

+	-
-	+
-	-
-	-
-	-
19	27



1) Collij et al., 2020 *In press*
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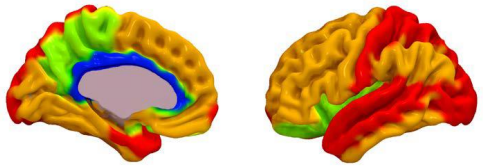
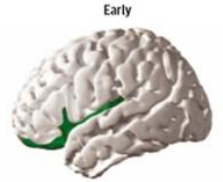
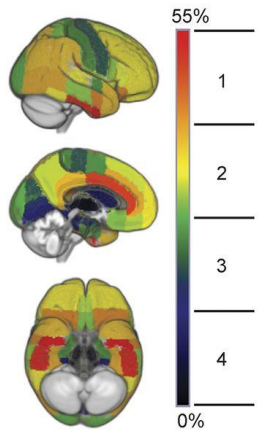
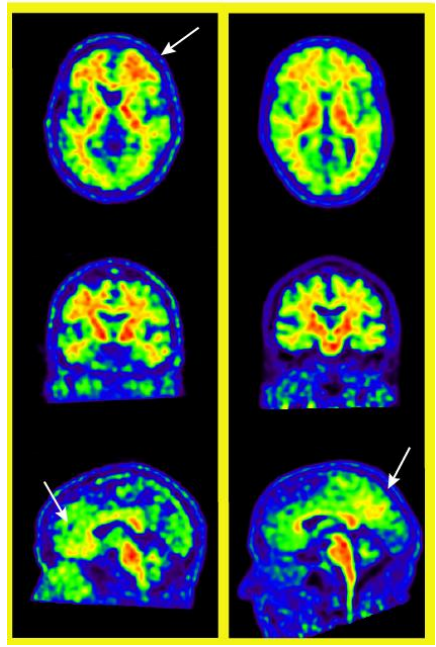


- Sagittal plane seems optimal for assessing early amyloid pathology
  - Medial orbitofrontal cortex and precuneus/posterior cingulate cortex
- Importance of these regions supported by amyloid staging work[1,2,3] and recent review on spatial-temporal ordering of amyloid pathology[4]
- Sensitivity of medial regions is partly influenced by signal distortion[5]:
  - Proximity to white matter and signal from the contralateral hemisphere
  - Medial regions are visually more frequently classified as abnormal compared to lateral counterparts, while levels of pathology are comparable.



+	-
-	+
-	-
-	-
-	-
19	27





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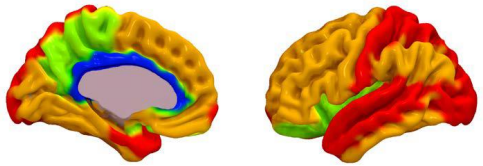

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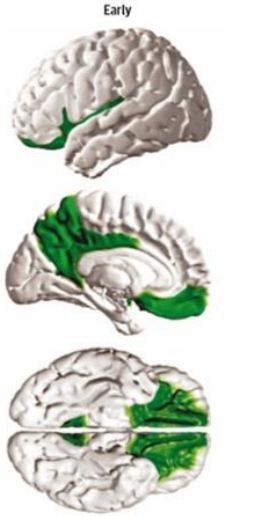
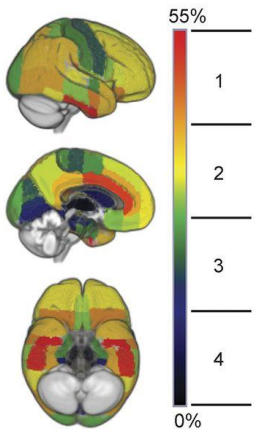
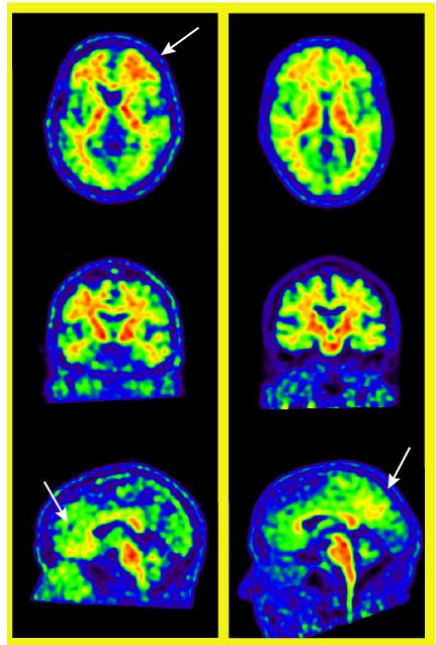
  - Medial regions are visually more frequently classified as abnormal compared to lateral counterparts, while levels of pathology are comparable.
- Regional VR is robust across readers:
  - Frontal 74% (37/50), PC/PCC 78% (39/50), temporo-parietal 78% (39/50), lateral temporal 82% (41/50), and striatum 74% (37/50).



+	-
-	+
-	-
-	-
-	-
19	27





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Conclusions

General conclusion

Similar to Centiloid quantification, VR can capture early amyloid pathology and the extent of amyloid burden.

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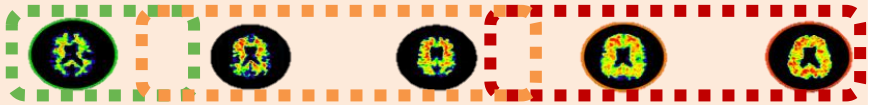
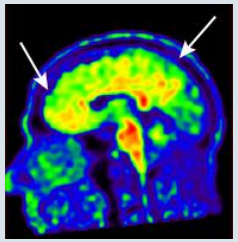
Documenting the *extent* of amyloid burden could be a valuable asset in addition to the final read classification of amyloid negative/positive.



Research and trials

Readers could benefit from focusing on the *medial regions*, using the sagittal view as the primary orientation for visual assessment of early amyloid pathology.



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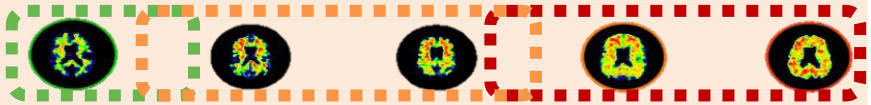

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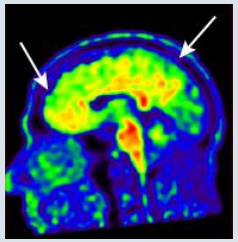

Future work: generalizability

Differences between radiotracers include reader 'signs', use of different color scales, and possibly distinct influence of WM uptake in the distortion of the PET signal in medial regions.

Acknowledgements

AMYPAD consortium

Gemma Salvadó Blasco
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Fiona Heeman
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Alle Meije Wink
Adriaan Lammertsma
Ronald Boellaard

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Featured Research Session
The value of amyloid PET beyond dichotomization

Speaker Chatroom Q&A - Scheduled Time
Date: 28 July 2020
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