AMYPAD
Amyloid imaging to prevent
Alzheimer´s Disease

A multi-study analysis of the spatial-temporal progression of amyloid deposition and its utility for longitudinal studies

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AAIC 2020

www.amypad.eu

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Video and audio recording are prohibited.

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)

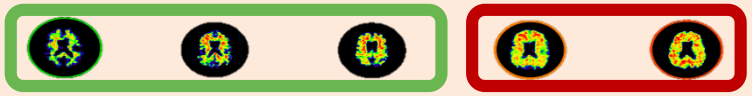
4. Emerging beta-amyloid pathology is associated with tau, synaptic, neurodegeneration and gray matter volume differences (JL Molinuevo)

Capitalizing on the value of imaging: topography

Clinical routine

Diagnostic **support**, in addition to other clinical assessments

Detection of **abnormal levels**, validated against *post-mortem* data

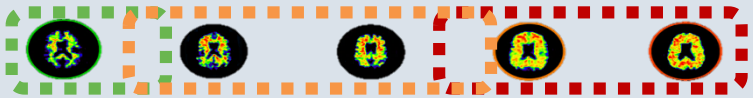


Dichotomized status may be sufficient

Research and trials

Value in **quantitative** assessment, including **multiple measurements**

Understanding the **disease progress** in space and time



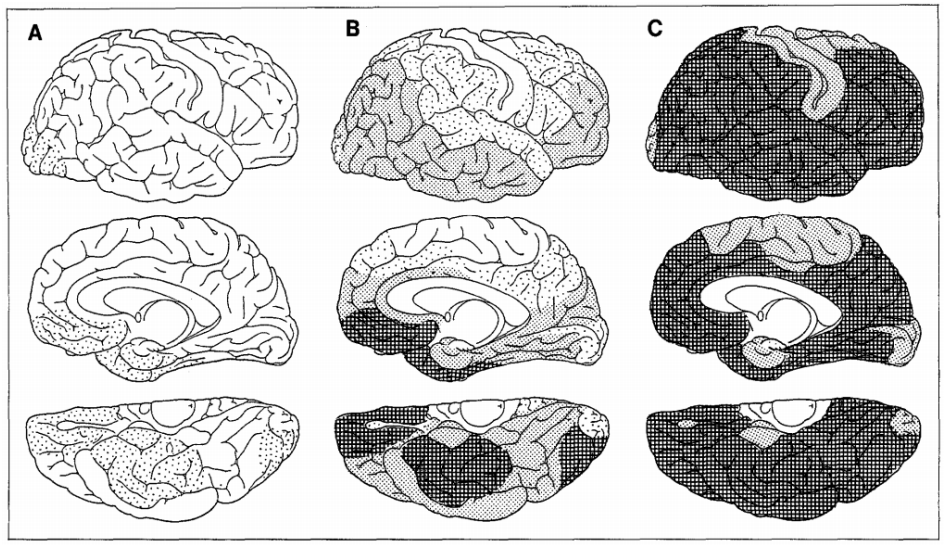
More fine-grained information is needed!

Aim(s)

What do we know about the spatial-temporal development of β-amyloid pathology in the brain? Are findings consistent across studies?

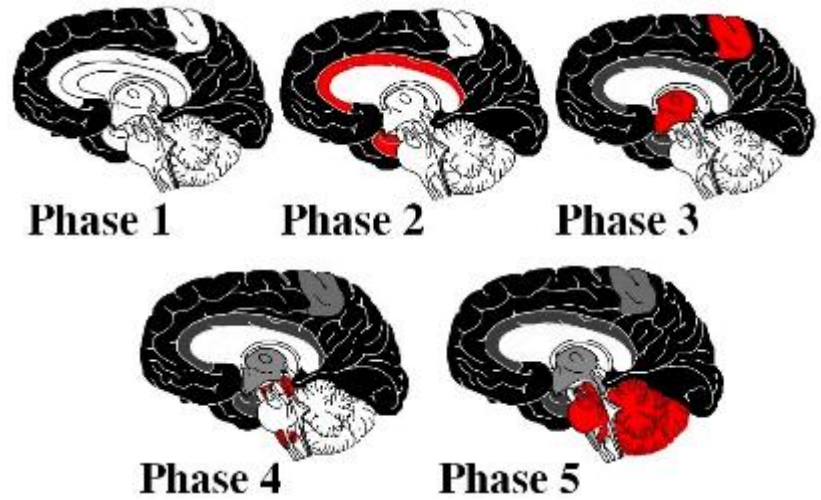
Is this information of value? In which setting(s)?

Neuropathology findings



Braak 1991

- Post-mortem data from *N*=83 demented and non-demented elderly patients (age range 47-96y)
- Ordering based on frequency and density of plaques in certain regions (*N*=24)
- Three stages starting at **basal temporal, frontal and occipital lobes**

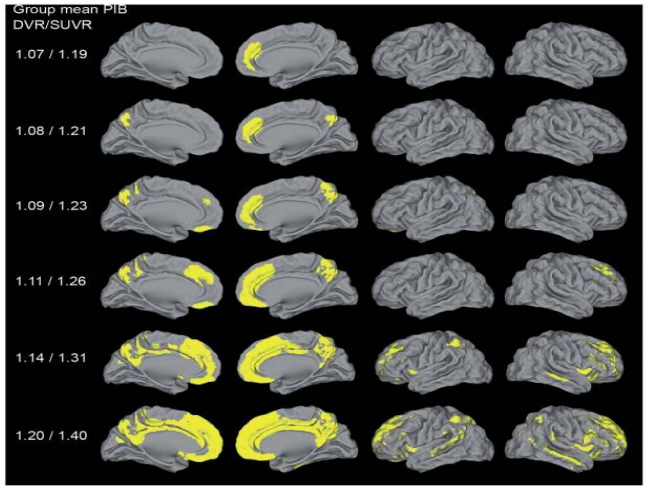


Thal 2002

- Post-mortem data from *N*=47 demented and non-demented elderly patients (age range 42-93y)
- Ordering based on frequency, ***but not density*** of plaques in certain regions (*N*=7)
- Five phases starting **throughout the neocortex (without regional details)**

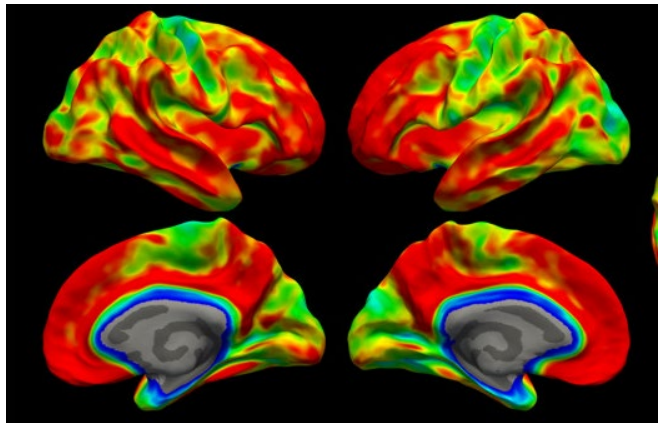
More detailed description of early phases in Braak 1991, and of later in Thal 2002.
Both agree that **neocortex precedes subcortical pathology**.

Earliest *in vivo* signal in amyloid PET images across the AD spectrum



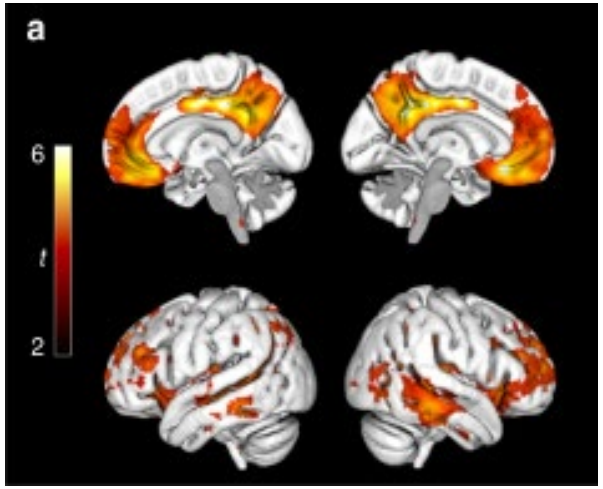
Villeneuve 2015

- DVR from *N*=222 subjects across the AD spectrum
- Iteratively aligning statistically significant elevated [^{11}C]PiB DVRs, the authors found an initial deposition of amyloid in **medial cortical regions, followed by more lateral regions, finally involving the lateral temporal lobes**



Cho 2016

- Z-transformed SUVr from *N*=195 subjects across the AD spectrum based on signal in CNs
- The difference in frequency of regional involvement was determined, where the reported ordering **started at precuneus, while the cingulate, inferior temporal and the insular cortex came somewhat later**

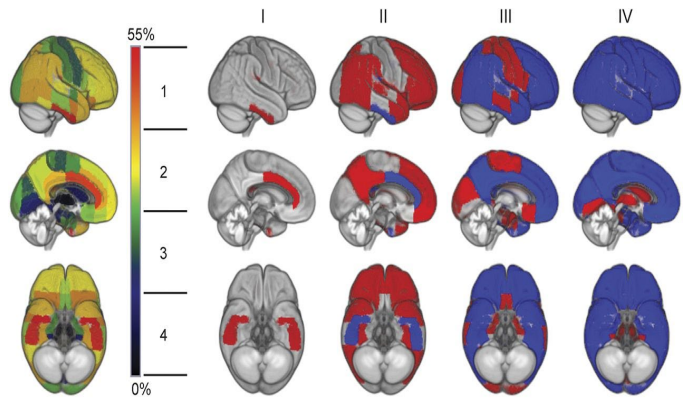


Palmqvist 2017

- Assessed the longitudinal patterns in amyloid deposition across *N*=406 PET/CSF $A\beta_{42}$ groups (CSF-/Amy- vs CSF+/Amy- vs CSF+/Amy+)
- **Cingulate, orbitofrontal, precuneus and insula** identified as early regions, while central, occipital, temporal and some frontal regions were identified as late(r) regions.

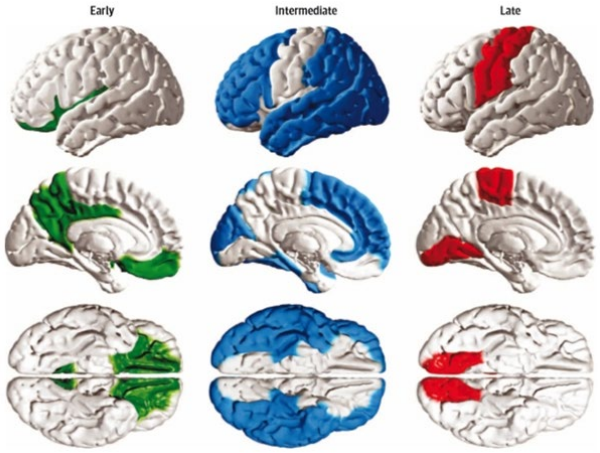
Across different methodologies, **medial regions** (especially precuneus, cingulate and frontal cortices) display high PET signal earlier than remaining regions in the neocortex

Topography used to stage amyloid burden *in vivo*



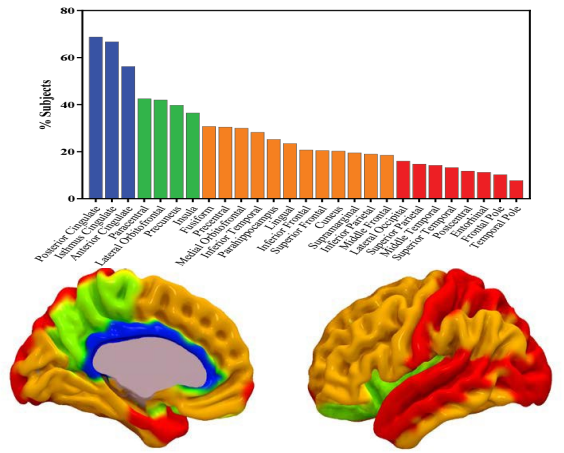
Grothe 2017

- Ranked the frequency of regional involvement in amyloid deposition across *N*=179 ADNI CN cases, **analogous to traditional methodology from post-mortem studies**
- **4 stages of amyloid deposition** were described, where early involvement of temporal regions was more pronounced than in previous amyloid PET work



Mattsson 2019

- Sequence to Palmqvist's work, where a third set of regions was defined as those accumulating but not in early or late groups
- **Defined 3 stages starting by the precuneus, posterior and isthmus cingulate, insula, and medial and lateral orbitofrontal cortices**
- Applicable to separate cohort and tracer



Collij 2020, *in press*

- Similar to Grothe, 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
- **Cingulate as the earliest detectable stage, followed by common medial regions such as precuneus and orbitofrontal cortices**

Multiple staging systems **generally agree in ordering of detectable regional amyloid pathology**, although slight tracer-differences may apply

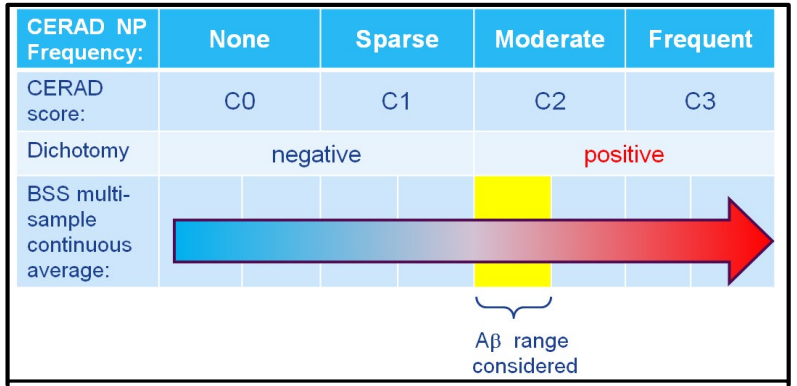
Post-mortem vs in-vivo

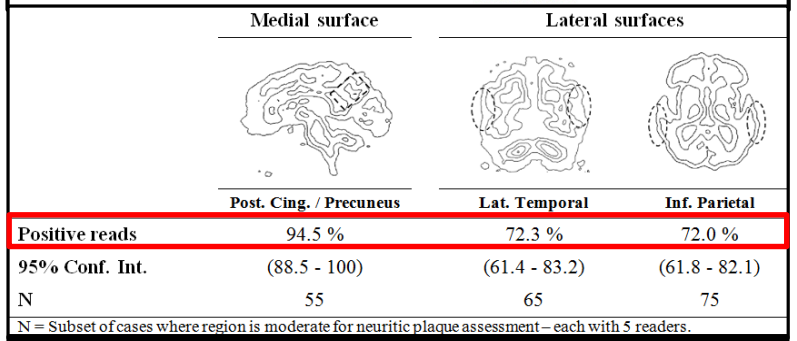
Neuropathology studies

1. Limited detail due to low number of samples and tissue available for analysis
2. **<u>No clear distinction between medial and lateral brain regions</u>**
3. Neocortex before sub-cortical structures, generally starting with basal regions

Amyloid PET studies

1. Heterogeneous methodology, tracer used and population analyzed, but with high level of regional detail available
2. **<u>Medial regions</u>** displaying high signal generally **<u>earlier than lateral counterparts</u>**
3. Cingulate, precuneus and frontal regions consistently identified as early regions; *discrepancies in placement of temporal regions*





	Medial surface	Lateral surfaces	
	Post. Cing. / Precuneus	Lat. Temporal	Inf. Parietal
Positive reads	94.5 %	72.3 %	72.0 %
95% Conf. Int.	(88.5 - 100)	(61.4 - 83.2)	(61.8 - 82.1)
N	55	65	75

N = Subset of cases where region is moderate for neuritic plaque assessment – each with 5 readers.

PET signal distortion in medial regions (spill in from white matter and contralateral hemisphere) can produce discrepancies to neuropathological findings

Earlier detection in PET is possible, but might not directly reflect the first pathological signs of the disease – instead, it reflects the **<u>earliest detectable signs of amyloid pathology</u>**

The utility in amyloid PET topographical quantification

Early pathological detection - *studying the earliest phases of AD*

Determining risk of subsequent cognitive decline - *resolving the temporal disconnect between amyloid and cognition*

Optimal subject selection for anti-amyloid interventional trials – *specific disease stage and balancing amyloid levels across trial arms*

Reducing required sample sizes in anti-amyloid interventional trial

Early pathological detection and tracking progression

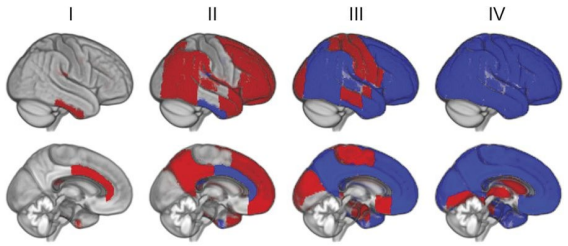


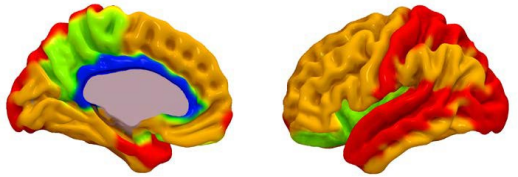
Table 2 Amyloid stages in comparison to dichotomous classifications and CSF amyloid

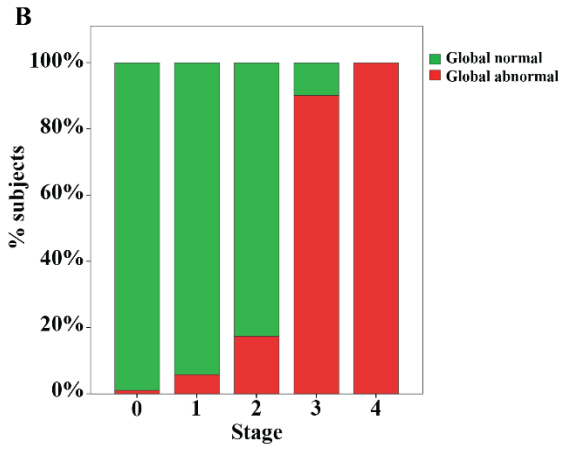
	0	I	II	III	IV
n	249	68	63	127	152
$SUVR_{Cer}$ > 1.17	1 (<1%)	3 (4%)	33 (52%)	118 (93%)	152 (100%)
$SUVR_{Cer}$ > 1.10	6 (2%)	13 (19%)	47 (75%)	123 (97%)	152 (100%)
CSF Aβ42[a] (mean ± SD)	224 ± 36	209 ± 39[b]	160 ± 39[c]	138 ± 24[c]	127 ± 20[c]

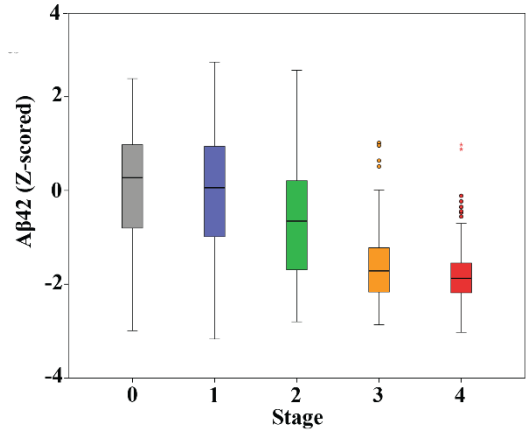
Abbreviations: CSF Aβ42 = CSF levels of Aβ42 (pg/mL); $SUVR_{Cer}$ = standard uptake value ratio with whole cerebellar reference region.
[a] CSF biomarker values were only available for a subset of participants (n = 597).
[b] Significantly different from stage 0 at $p < 0.05$.
[c] Significantly different from stage 0 at $p < 0.001$.

Grothe 2017

- Agreement between stages and global classification only becomes high (>90%) at stage III
- Earlier stages show **increased focal signal**, but not sufficient for global positivity





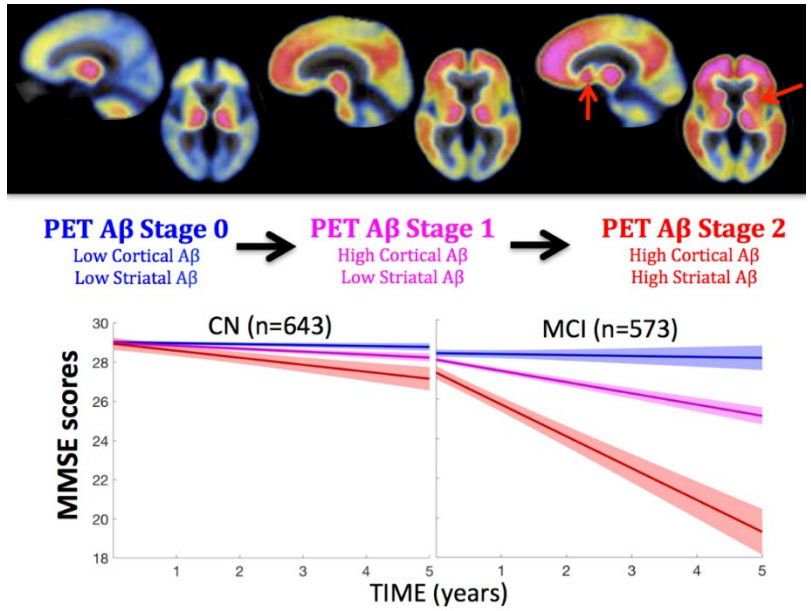


Collij 2020, *in press*

- More than 80% of subjects in stages 1 and 2 are classified as negative with a global cut-off, despite increased focal signal
- CSF $A\beta_{42}$ levels are similar between stages 3 and 4, despite differences in topography and risk of cognitive decline (next slide)

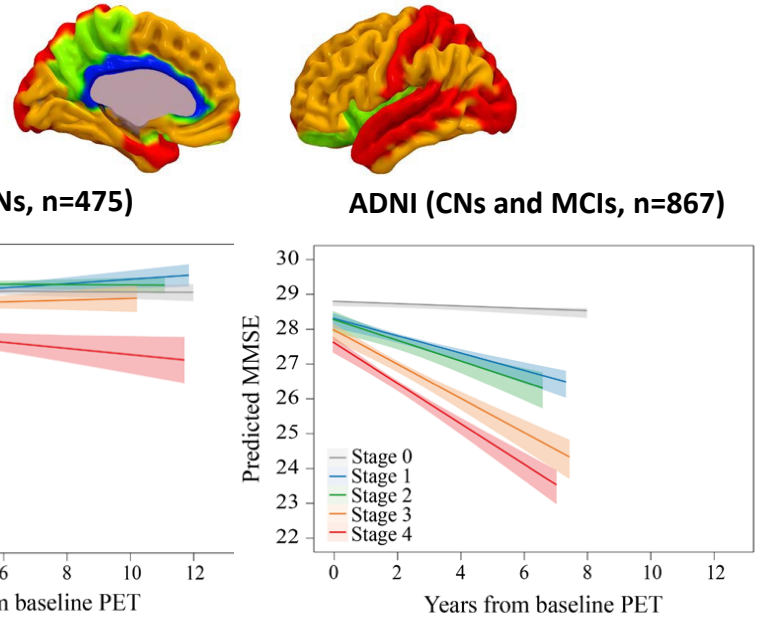
Topographical information can help **identify increased signal earlier than traditional global cut-offs** and continues to **track disease progression beyond plateau phase of CSF**

Risk of subsequent cognitive decline



Hanseeuw 2018

PET-Aβ stage 2 individuals (high cortical + high striatal signal) have the fastest cognitive decline than any other group in both CNs and MCIs

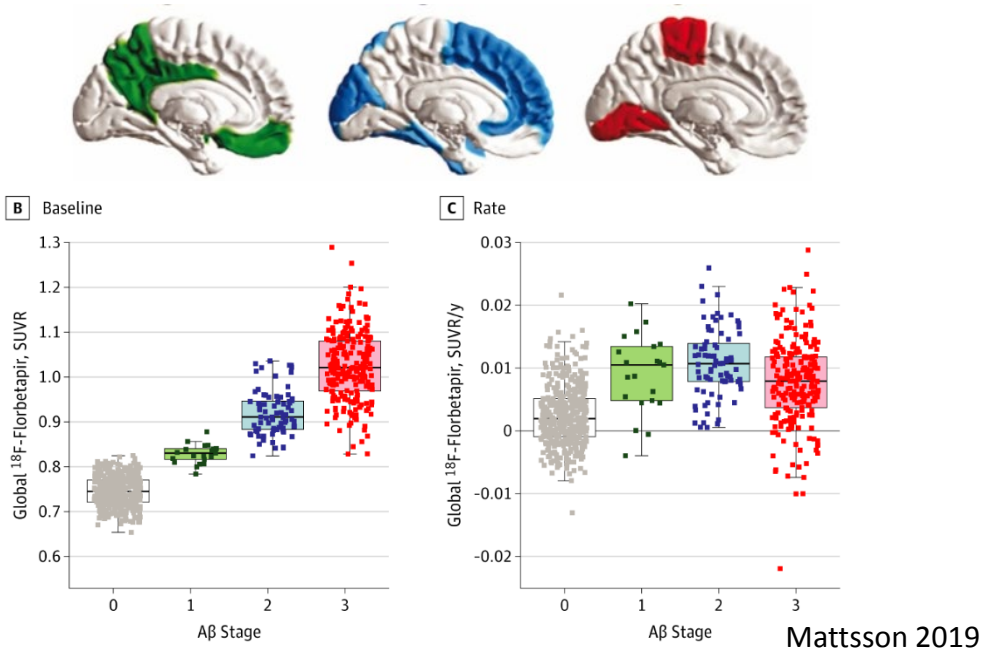


Collij 2020, *in press*

A step-wise effect of stage on cognitive decline is apparent in a cohort including a large proportion of impaired subjects (ADNI), while only the stage 4 related to faster decline in OASIS, a cohort consisting mainly of CNs.

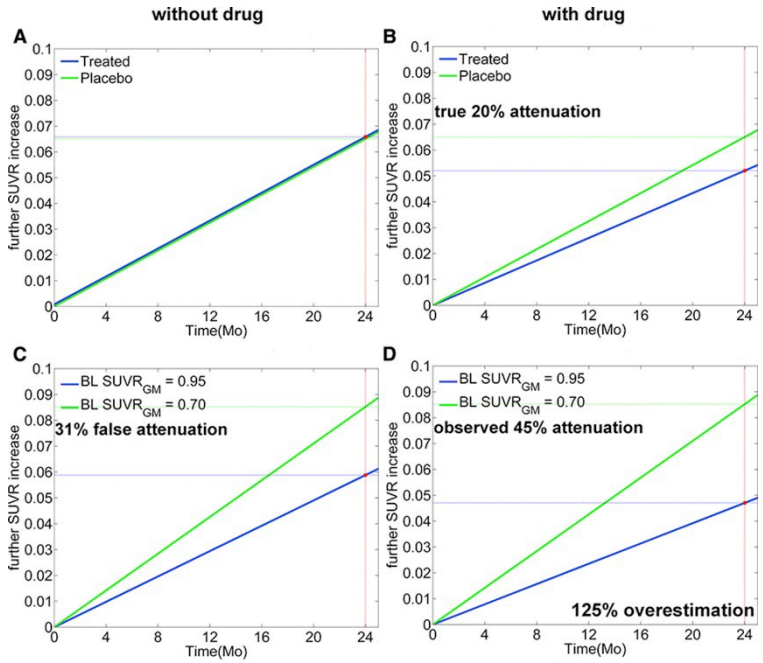
Information on the extent of amyloid burden provides prognostic information on cognitive performance, and can support a more fine-grained risk profiling of individuals throughout the *AD continuum*

Optimal subject selection for interventional trials



Mattsson 2019

Different levels of amyloid burden at baseline correspond to distinct accumulation rates, with those at intermediate levels (blue) displaying the highest rates of change in amyloid PET signal

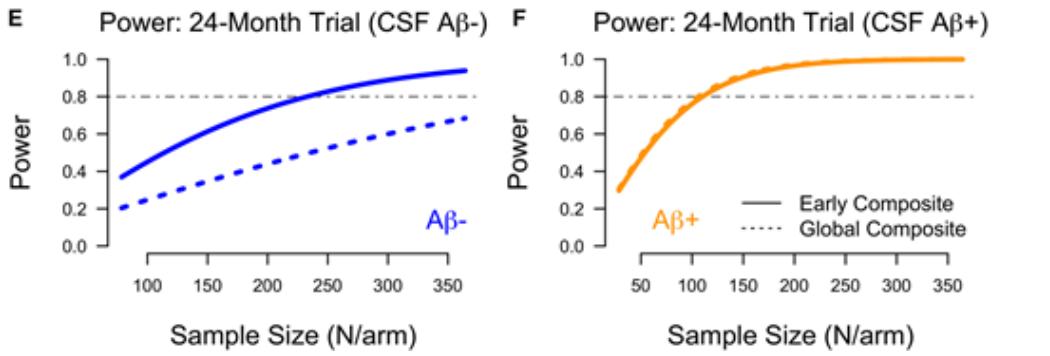


Guo 2018

When trial arms are unbalanced for entry level amyloid burden, false treatment effects can be detected due to differences in accumulation rates between placebo and treatment groups

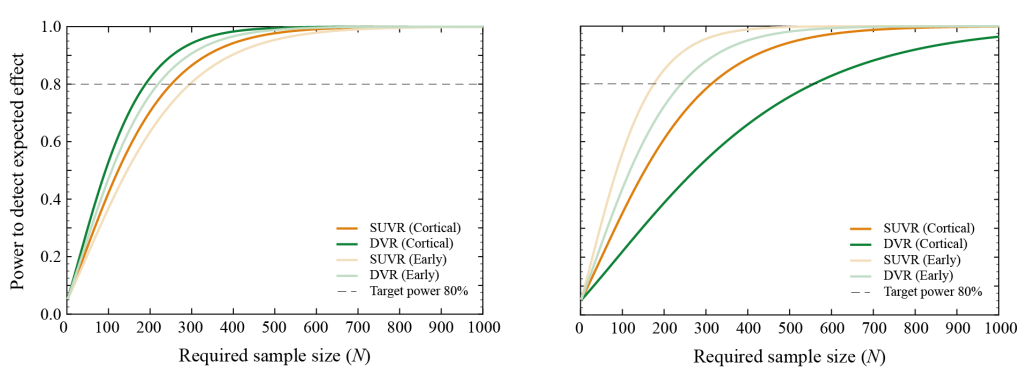
Determining the specific phase of amyloid accumulation not only **enables selection of subjects earlier in the disease**, but is also crucial to balance trial arms and **ensure the correct detection of treatment effects**

Reducing sample size requirements in trials



Insel 2020

- Amyloid β PET uptake levels in the posterior cingulate and precuneus start high and immediately increase with small increases of disease time -> early composite ROI
- Utilizing the early composite improves power compared to global composite in primary prevention trials, but not in secondary prevention ones

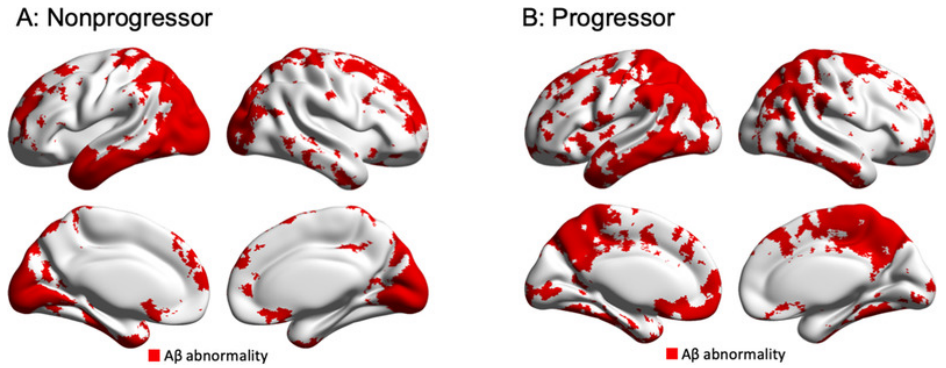


Lopes Alves 2020, *in prep*

- Precuneus, isthmus cingulate and lateral orbitofrontal identified as earliest accumulating regions -> early composite ROI
- Utilizing the early composite improves power compared to global composite in primary prevention trials, but not in secondary prevention ones

Targeting regions involved in specific phases of the disease provides **great reductions in sample size requirements**, or alternatively, can significantly **increase the achieved statistical power** in pre-determined studies

Potential utility within clinical setting?



Pascoal 2020

- Subjects who converted to dementia had similar global amyloid burden to those who did not convert
- The **topographical pattern of converters is "traditionally AD-like",** while those of non-converters includes more temporal and occipital regions instead

Frontal	Temporal	Temporo/parietal insula	Posterior Cingulate & Precuneus	Striatum	N	%
					84/97	87%
					3/97	3%
					1/97	1%
					1/97	1%
					2/97	2%
					1/97	1%
					2/97	2%
					1/97	1%
					2/97	2%
93%	93%	91%	97%	98%		

Molinuevo 2019

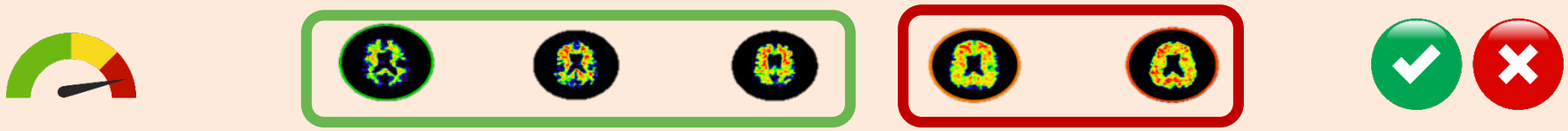
- Although generally not reported, regional visual assessment shows that some subjects have focal uptake that can be detected visually
- Regions most often focally positive are in line with amyloid PET studies of early accumulation and staging of amyloid burden

Can the topography of amyloid burden, beyond overall levels, be of use for prognosis in the clinical setting (especially in the presence of disease-modifying therapies)?

From “if” to “when” and “where”

IF

clinical routine and ‘simple’ questions



Yes/No may be sufficient to determine abnormality and (in the future) propose treatment

WHEN and WHERE

research (and maybe clinical routine) and comprehensive view

Capitalizing on the topography and spatial-temporal knowledge of amyloid pathology can bring several advantages:

Early detection

Risk prediction

Subject selection

Efficient trials

Prognosis and selected treatment

Thank you

"The project leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115952. This Joint Undertaking receives the support from the European Union's Horizon 2020 research and innovation programme and EFPIA".