Optimizing Regions-of-Interest composites for capturing treatment effects on brain amyloid in Alzheimer`s Disease clinical trials

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FDA-Industry Statistics Workshop
24th September, 2014
Washington DC

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ADNI Alzheimer's Disease Neuroimaging Initiative

Alzheimer`s Disease Neuroimaging Initiative

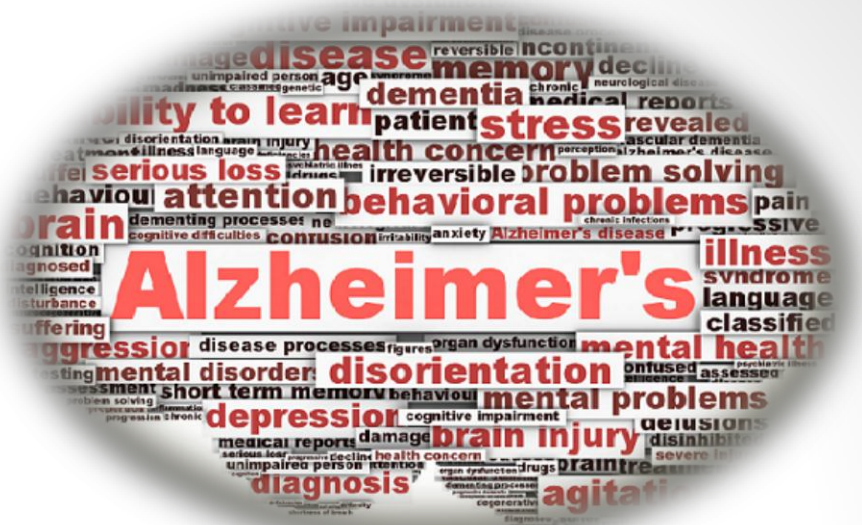
Outline

1. Background
2. PiB PET SUVR for capturing disease progression
3. Regions-of-Interest composite optimization

Part 1

BACKGROUND

Alzheimer`s Disease



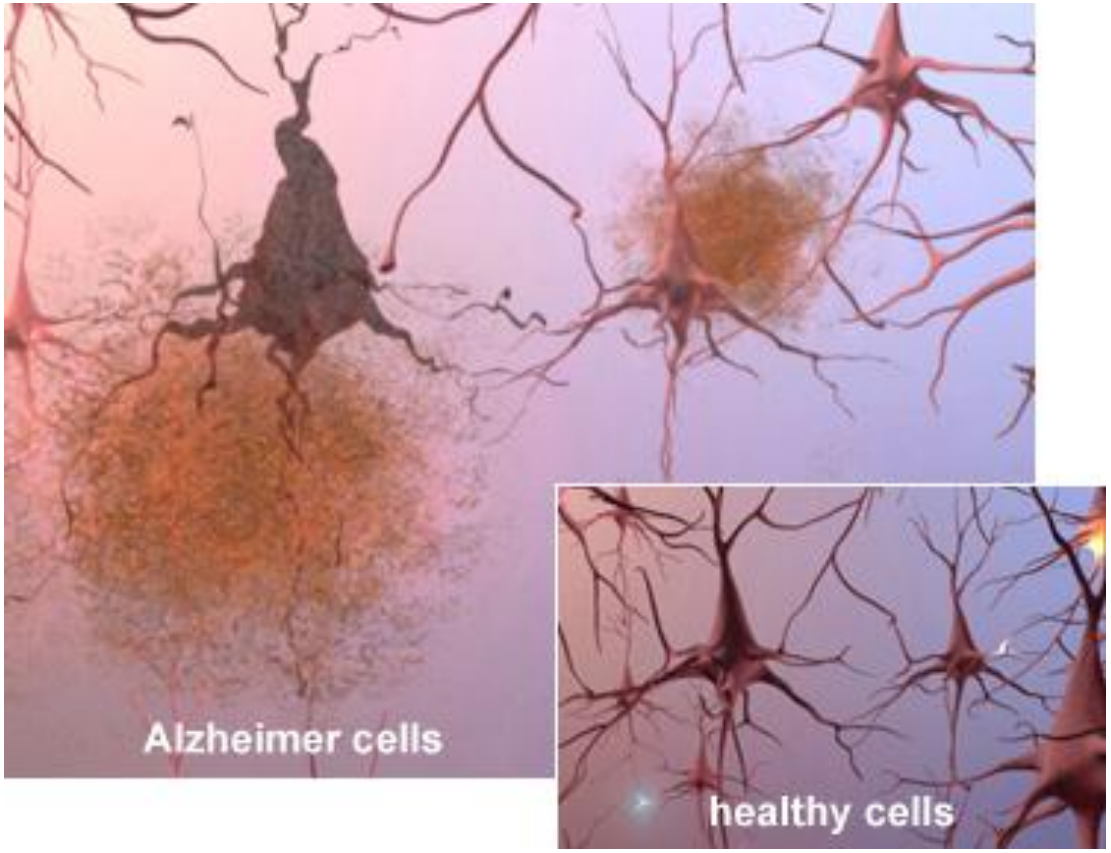
- Definition: Alzheimer's disease is a **progressive** disease that destroys memory and other important mental functions, intellectual and social skills.

- Current state: Drug after drug has failed to effectively treat AD so far. Currently **there is no cure for AD**. Drugs that are offered to AD patients focus on symptoms, but they do not stop or reverse the disease.

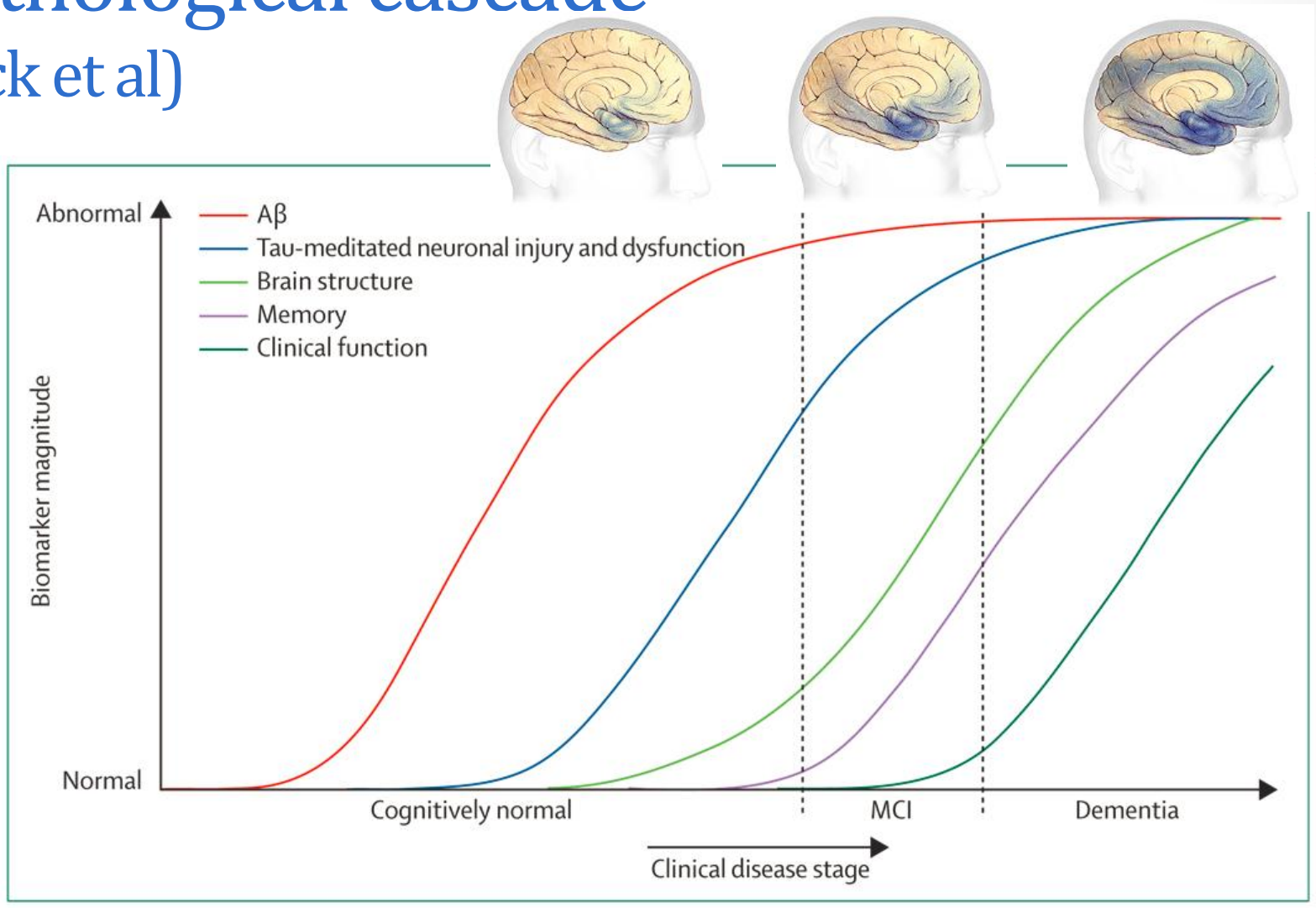
Alzheimer`s Disease Hypothesis

Amyloid hypothesis

beta-amyloid (A_β) deposits are the fundamental cause of the disease



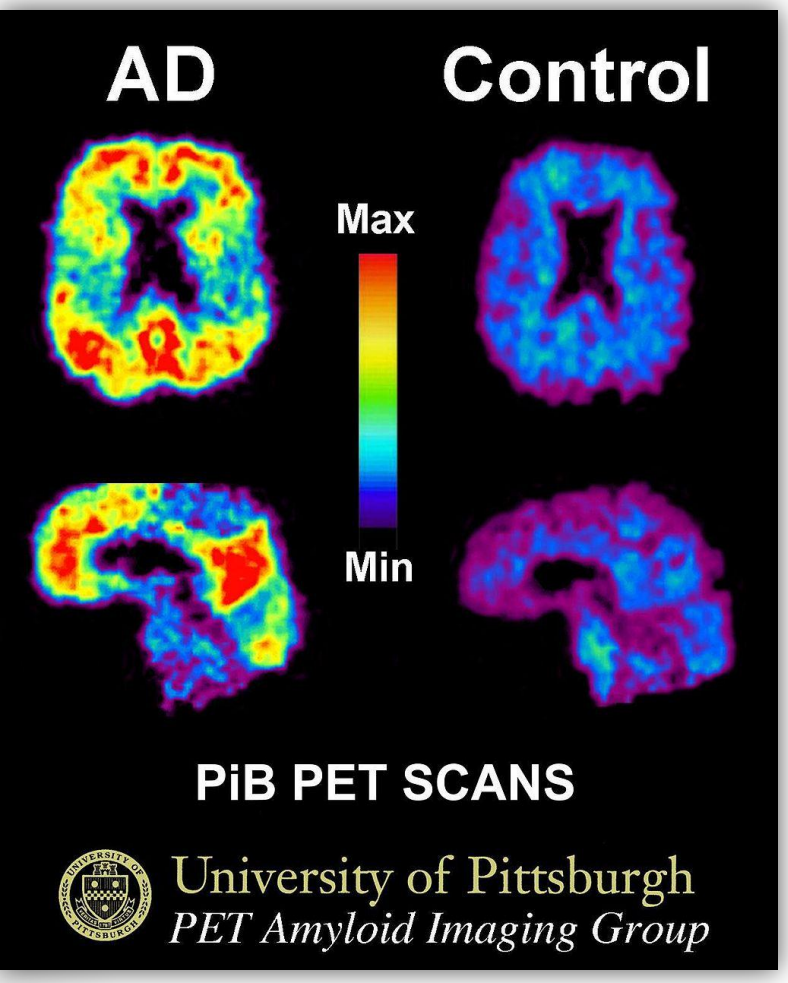
Dynamic biomarkers of the Alzheimer`s pathological cascade (Jack et al)



Part 2

PIB PET SUVR FOR CAPTURING DISEASE PROGRESSION

PiB PET Imaging

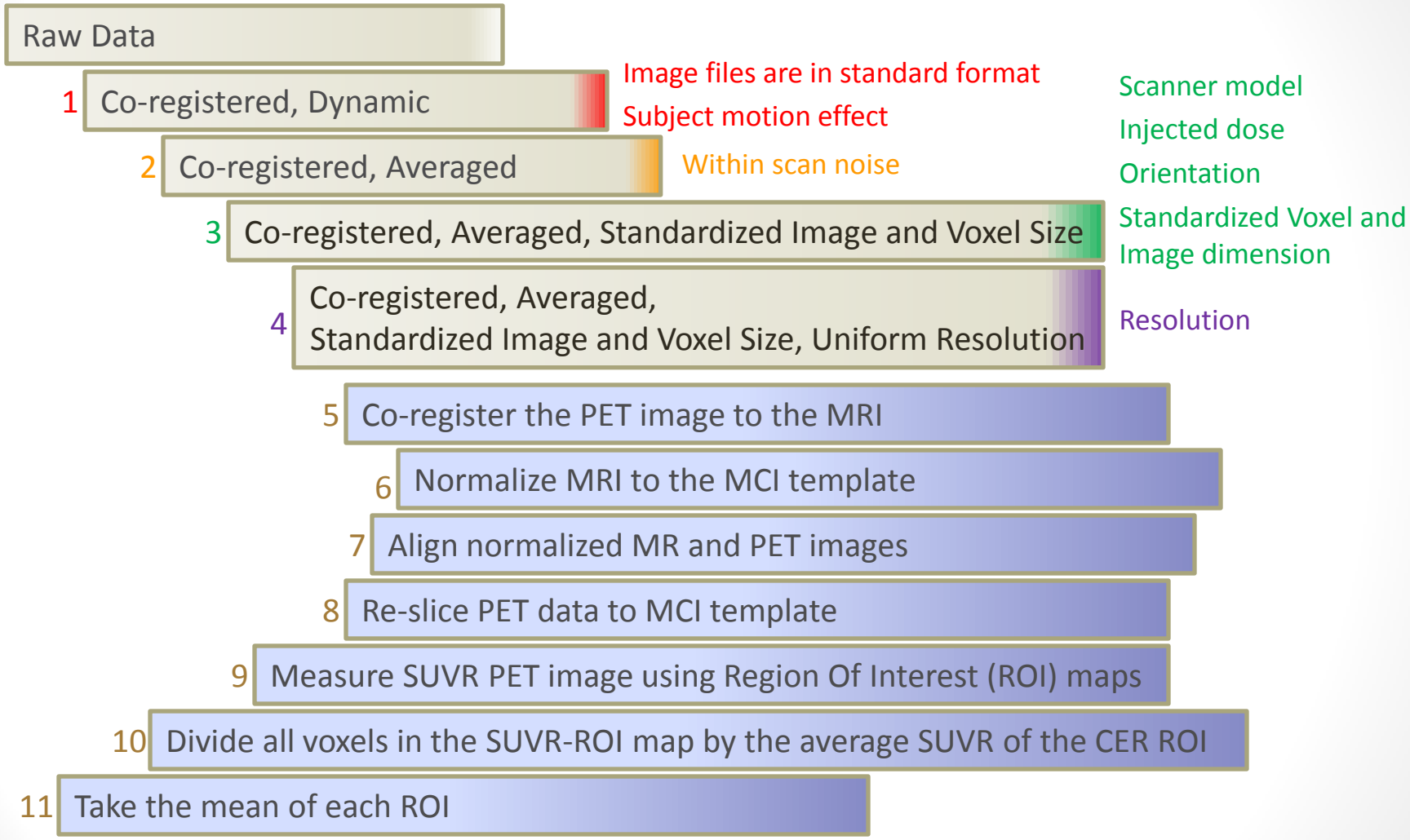


Amyloid-β in the brain can be visualized in vivo using molecular imaging technology, such as PET scan

Pittsburgh compound B (PiB) was the first radiotracer capable of highlighting deposits of β amyloid in the brain

The PET scans measure the uptake of the PiB radiotracer that targets beta-amyloid

ADNI PiB PET data preprocessing



Standardized Uptake Value Ratio

Good numerator

- Maximum separation and low variability across categories of interest (e.g. diagnostic categories)
- Large shift from zero and low variability within category of interest

$$SUVR = \frac{SUVR_{Region\ Of\ Interest}}{SUVR_{Reference\ Region}}$$

Good denominator

- Minimum/no amyloid binding for all subjects regardless of the disease status
- Low variability, compared to other regions
- Low within subject variability (no change over time for each individual)

Standardized Uptake Value Ratio for capturing disease progression

- Composite measure consisting of a several Regions of Interest with the ability to capture amyloid accumulation, therefore disease progression
- Optimal Reference Region with minimal amyloid accumulation and low variability
- High Mean/SD of change in amyloid accumulation over time ratio

Part 3

REGIONS-OF-INTEREST COMPOSITE OPTIMIZATION

PiB PET data available for analysis

Table 1: Regional data

ROI	Abbreviation
Anterior cingulate	ACG
Anterior ventral striatum	AVS
Cerebellum	CER
Frontal cortex	FRC
Lateral temporal cortex	LTC
Mesial temporal cortex	MTC
Occipital cortex	OCC
Occipital pole	OCP
Parietal cortex	PAR
Precuneus cortex	PRC
Pons	PON
Sensory motor cortex	SMC
Sub-cortical white matter	SWM
Thalamus	THL

Table 2a: Number of subjects in each cohort observed at each time point

Visit, years	Alzheimer`s Disease	Mild Cognitively Impaired	Cognitively Normal	Total
base line	**19**	**65**	**19**	**103**
Year 1	13	50	17	80
Year 2	2	26	11	39

Table 2b: Number of subjects in each cohort observed at each time point (with modified baseline)

Visit, years	Alzheimer`s Disease	Mild Cognitively Impaired	Cognitively Normal	Total
base line	**25**	**56**	**22**	**103**
Year 1	16	44	20	80
Year 2	2	25	12	39

PiB PET data considerations

Population:

- Only PiB-positive subjects (1.5 SUVR cut-off), mostly comprised of MCI (70%)
- Only 2-year completers (N=20)

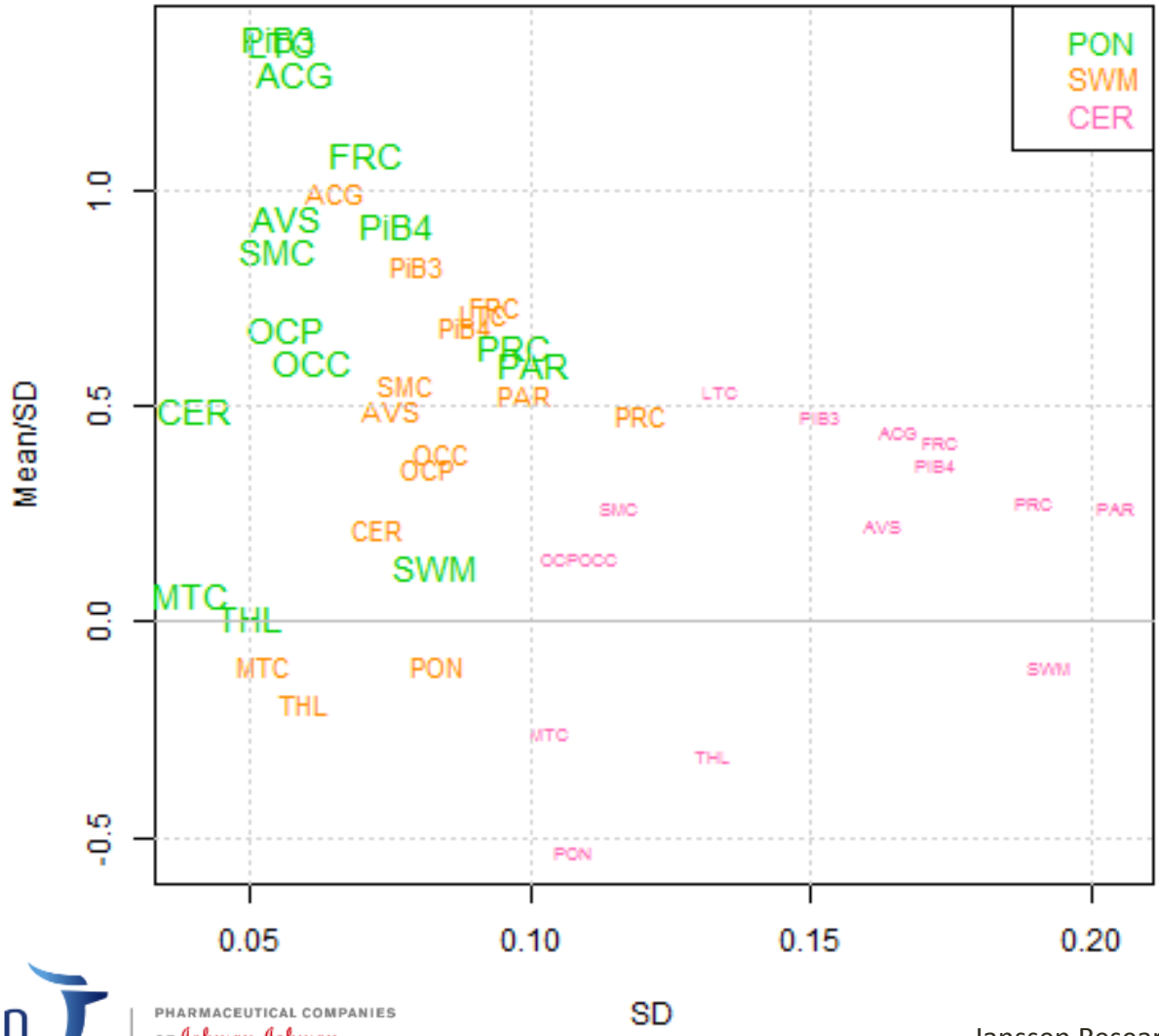
Reference region:

- Has been used – CER
- We evaluated two alternative regions, proposed in the literature – PON and SWM

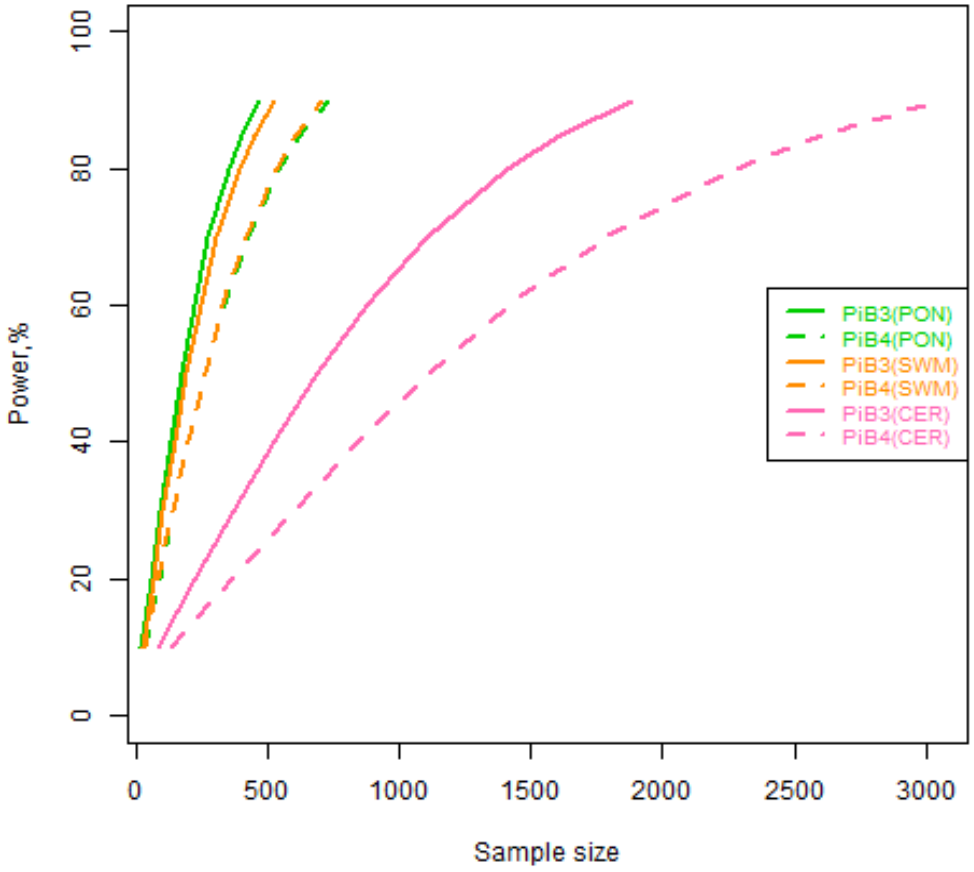
Composite SUVR:

- Has been used – PiB4 (ACG, FRC, PAR, PRC)
- A novel composite was developed – PiB3(ACG, FRC, LTC)

Standardized mean 2-year change from baseline versus SD of 2-year change from baseline in PiB-positive completers



Sample size reduction for improved reference region and composite - PiB3(PON)



	PiB4(PON)	PiB4(SWM)	PiB3(PON)	PiB3(SWM)
PiB4(CER)	76%	77%	85%	83%
[illegible]	N/A	N/A	75%	72%

Summary

Reference region:

- The data suggest that CER may degrade the signal because it accumulates amyloid
- **PON** and **SWM** – alternative RRs - produce significant sample size reduction (>70%), compared to CER

SUVR composite:

- Novel SUVR composite **PiB3** appeared to be more sensitive to change in amyloid than PiB4, exhibiting further sample size reduction with additional 10% savings

Future consideration:

- Define optimal weights for regions in the composite

References:

Manuscript “Optimizing Regions-of-Interest Composites for Capturing Treatment Effects on Brain Amyloid in Clinical Trials” by Tryputsen et al. has been accepted for publication in Journal of Alzheimer`s Disease (2014)

Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-131979
IOS Press

Optimizing Regions-of-Interest Composites for Capturing Treatment Effects on Brain Amyloid in Clinical Trials

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Handling Associate Editor: Tim Schultz

Accepted 28 June 2014

Abstract.
Background: Pittsburgh Compound B (PiB) positron emission tomography (PET) neuroimaging is a powerful research tool to characterize amyloid evolution in the brain. Quantification of amyloid load critically depends on (i) the choice of a reference region (RR) and (ii) on the selection of regions of interest (ROIs) to derive the standard uptake value ratios (SUVRs).
Objective: To evaluate the stability, i.e., negligible amyloid accumulation over time, of different RRs, and the performance of different PiB summary measures defined by selected ROIs and RRs for their sensitivity to detecting longitudinal change in amyloid burden.
Methods: To evaluate RRs, cross-sectional and longitudinal analyses of focal regional and composite measures of amyloid accumulation were carried out on the standardized PiB-PET regional data for cerebellar grey matter (CER), subcortical white matter (SWM), and pons (PON). RRs and candidate composite SUVR measures were further evaluated to select regions and develop novel composites, using standardized 2-year change from baseline.
Results: Longitudinal trajectories of PiB4—average of anterior cingulate (ACG), frontal cortex (FRC), parietal cortex, and precuneus—demonstrated marked variability and small change from baseline when normalized to CER, larger changes and less variability when normalized to SWM, which was further enhanced for the composite in PON-normalized settings. Novel composite PiB3, comprised of the average SUVRs of lateral temporal cortex, ACG, and FRC was created.
Conclusion: PON and SWM appeared to be more stable RRs than the CER. PiB3 showed compelling sample size reduction and gains in power calculations for clinical trials over conventional PiB4 composite.

Keywords: Alzheimer's disease, amyloid imaging, brain, pons, ^{11}C-PiB

For Review Author Proof

Thank you!

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