Amyloid Staging Models: Semi-Quantitative versus Quantitative Measures

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Introduction

Assessment of amyloid pathology using **P**ositron **E**mission **T**omography (**PET**) is generally performed by a visual read resulting in a binary negative/positive classification.

In a preclinical population, however, amyloid accumulation is more strongly ongoing and subtle regional amyloid burden can be missed on a visual read. Recently, Grothe et al., (2017) proposed an amyloid staging model (ASM) using regional standard uptake value ratio (SUVR) PET values to enable identifying cognitively healthy elderly subjects with early amyloid pathology.

However, it has been shown that SUVR is influenced by both flow and wash-out effects, resulting in a biased measure compared to a non-displaceable binding potential (BP_{ND}), derived from dynamic PET acquisition.

Aim

To assess the generalizability of the previously proposed ASM and to investigate the effect of using fully quantitative measures compared to semi-quantitative measures.

Methods

Subjects

190 cognitively healthy subjects ≥ 60 years (Table 1).

PET scanning

- Dynamic [^{18}F]-Flutemetamol (FFM) scanning using the *coffee-break protocol* (0-30 min. scanning, 60 min. break, 90-110 min. scanning).
- RPM1 used for generation of parametric BP_{ND} images.
- SUVR images were generated based on the 90- to 110-min interval.
- Reference region: cerebellar grey matter.

Visual assessment of PET images

Images were read as positive (binding in one cortical brain region or striatum unilaterally) or negative (predominantly white matter binding).

Constructing the amyloid staging models

Parametric SUVR and BP_{ND} PET images were brought to MNI standard space using SPM12. Regional values were extracted using the Harvard-Oxford atlas. Regional positivity was determined using a global cut-off (SUVR = 1.52, BP_{ND} = 0.26). Frequencies of positivity in the control population were plotted. Ranked anatomical regions were merged into 4 larger anatomical divisions based on equally sized proportions of the observed range of involvement frequencies.

Classification

Our control population was classified according to the 1) Grothe's previously proposed model and the models based on our cohort using the 2) SUVR and 3) BP_{ND} values. To be classified into a stage, 50% of the regions belonging to that stage had to be positive. To be classified into a higher stage, the previous stage had to be positive.

Statistical Analysis

Cohen's κ was used to assess agreement between the three classifications. Classifications were related to clinical measures (i.e. CSF $A\beta_{42}$, age, and MRI scales).

Table 1. Demographics and (Semi-)Quantitative PET Values

Demographics		
Gender	113 women (59.5%)	
Age	70.44 (± 7.56 y)	
MMSE	29 (± 1.13)	
Quantitative Measures		
SUVr	1.33 (± .21, range = .79 – 2.13)	
BP_{ND}	.16 (± .12, range = .20 - .66)	
MRI scales		
GCA score	.78 ± .71	
MTA score	.63 ± .71	
Fazekas score (WMH)	1.18 ± .82	
CSF	$A\beta_{42}$	893.02 ± 314.88
	$A\beta_{40}/A\beta_{42}$	.10 ± .03

Results – Generalizability

The main difference between the previously proposed ASM and the newly constructed models was the absence of basal temporal regions in phase I in both VUmc models. The Anterior Cingulate Cortex (ACC) was consistently early in all models (**Figure 1A & 2A**). The later stages showed higher agreement between the models. The Normalized Kandall's tau distance was 42% (difference) between the ADNI and VUmc SUVR models.

Results – [^{18}F]-Flutemetamol models

Classification of our data based on the two SUVR models showed an agreement of K = .17. This low agreement was mainly due to the disagreement in classification of stage I subjects (**Figure 1b&c**).

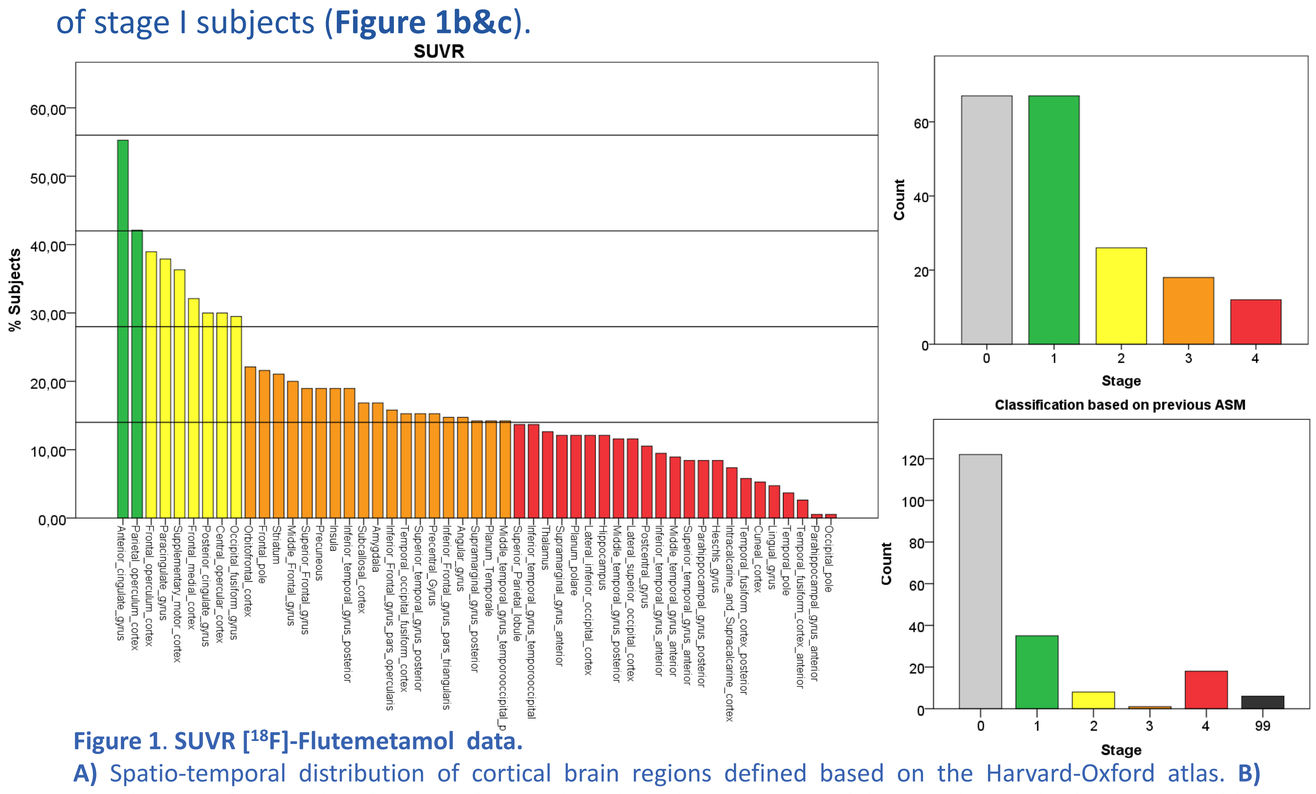

Figure 1. SUVR [^{18}F]-Flutemetamol data.
A) Spatio-temporal distribution of cortical brain regions defined based on the Harvard-Oxford atlas. **B)** Distribution of stage classification of our cohort based on VUmc model using the method as proposed by Grothe et al., (2017). **C)** Distribution of stage classification of our cohort ADNI ASM.

Using the BP_{ND} data resulted in a more gradual decline in frequency of regional positivity and subsequently the inclusion of more regions in stage I **(Figure 2A).** Classification of our data based on the two SUVR models compared to the BP_{ND} models showed an agreement of K = .12 with the previous ASM and of K = .38 with the VUmc SUVR ASM. Again, this low agreement was mainly due to the disagreement in classification of stage I subjects.

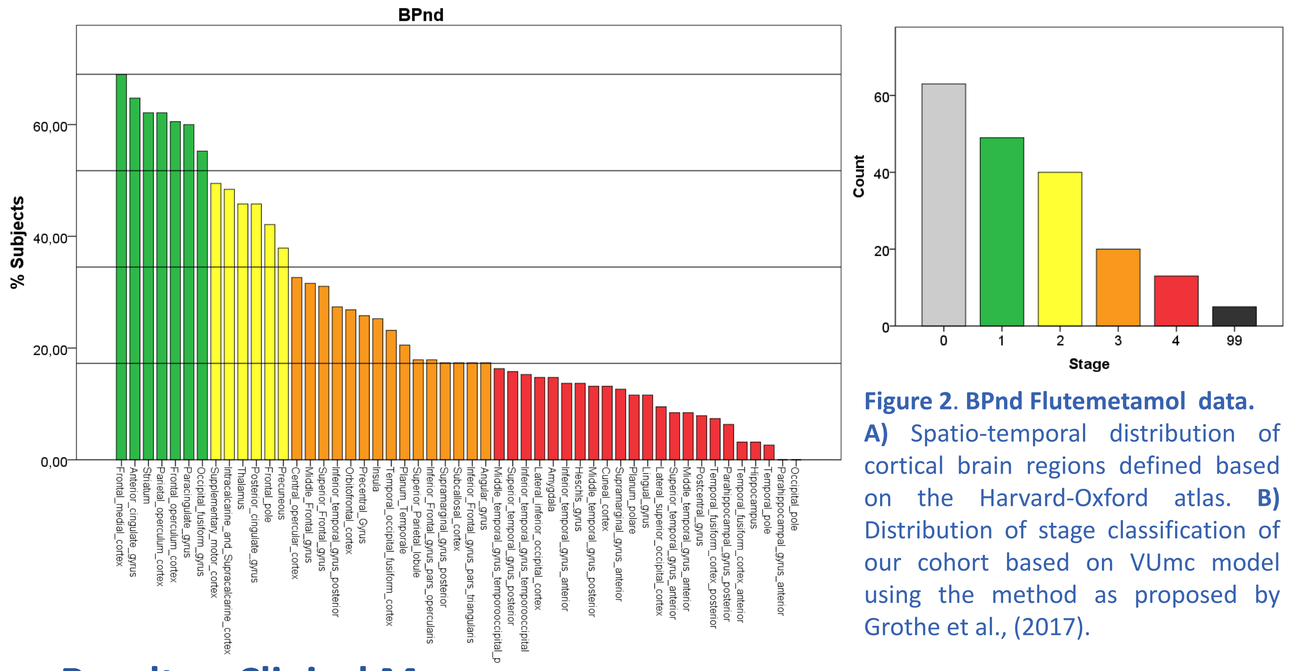

Figure 2. BPnd Flutemetamol data.
A) Spatio-temporal distribution of cortical brain regions defined based on the Harvard-Oxford atlas. **B)** Distribution of stage classification of our cohort based on VUmc model using the method as proposed by Grothe et al., (2017).

Results – Clinical Measures

Comparison between the ASM-classification and the visual read showed that for VUmc-SUVR, 100% of stage-0, 90% of stage-I and 79% of stage-II were read as negative, while all stage-III/IV participants were read as positive. For VUmc-BP_{ND}, all stage-0/I/II participants were read as negative and 65% of stage-III, 92% of stage-IV were read as positive.

Both the VUmc SUVR- and BP_{ND}-ASM-classifications showed a positive effect of age ($p < .05$), but no relationship with APOE ε4 carriership and visual scores GCA and WMH. Both SUVR and BP_{ND}-based stage-III participants had a higher hippocampal atrophy visual score than stage-0/I/II participants. For both models, there was no relationship with CSF $A\beta_{42}$ levels, but BP_{ND}-based stage-III participants had a significantly lower $A\beta_{40}/A\beta_{42}$ ratio compared to stage-0/I/II.

Conclusion

Generalizability of the model to a different population and tracer is not straightforward. In future work we aim to investigate whether this is mainly a population or tracer driven difference by applying this method to an independent [^{18}F]-Florbetapir PET dataset.

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