

Results: The VSAB value used, previously derived from an independent dataset, for a z-score threshold of 7 was 1.46%. Out of 352 total subjects tested using a z-score threshold of 7, 139 of 150 visually positive subjects were classified correctly as positive (92.7%) and 196 of 202 visually negative subjects were classified correctly as negative (97.0%), for an overall accuracy of 95.2% and kappa=0.90. This compares favorably to the results of the training set from the previous study with an accuracy of 97% and the agreement was 0.94.

Conclusion: VSAB provided excellent agreement with expert visual assessment on a large dataset using a cutoff determined from an independent training set, suggesting this metric may provide a robust and accurate method for the quantitative assessment of amyloid images.

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Peak Location of Amyloid PET Tracer Uptake within Cortical Gray Matter: Topographic Patterns and Diagnostic Application in Alzheimer's Disease. S. Minoshima*,¹ D. J. Cross,¹ A. Y. Wang,² N. L. Foster,² A. E. Drzezga,³ ¹Radiology, University of Utah, Salt Lake City, Utah, ²Neurology, University of Utah, Salt Lake City, Utah, ³University Hospital of Cologne, Cologne, Germany. (1357)

Objectives: This study is to investigate topographical analysis of peak location of cortical laminar deposition of amyloid tracer uptake within gray matter and its potential diagnostic application in Alzheimer's disease.

Methods: Hypothesizing that progressive amyloid deposition would encompass a greater extent of cerebral cortical laminae, the distance between the peak gray matter uptake of amyloid tracer and the gray-white matter interface (determined by non-specific white matter uptake, normal atlas based) was estimated along the line perpendicular to the brain surface at each cortical pixel using the three-dimensional surface projections (3D-SSP) algorithm following spatial normalization of each amyloid PET scan. The estimated values were assigned to stereotactically pre-defined cortical surface pixels covering the entire cerebral cortex, constituting an absolute millimetric map of peak location of cortical laminar deposition (PCLD) of the amyloid tracer (3D-SSP-PCLD). Using [F-18]florbetapir PET data from the ADNI (165 normal controls, age 75±6.9 years old, 78 female and 148 AD patients, age 75±8.2 years old, 62 female), an image-based database of 3D-SSP-PCLD was constructed from the normal controls, and topographical distribution of PCLD was examined individually and for the entire AD group using 3D-SSP-PCLD Z-score maps in comparison to the database. We assessed the discrimination between normal controls vs AD patients by comparing 3D-SSP-PCLD and Standard Uptake Value Ratio (SUVR) analysis (3D-SSP-SUVR, pons reference).

Results: In AD patients, the peak location of cortical laminar deposition of the amyloid tracer from the gray-white matter interface was estimated at 1.74±1.37mm (mean±sd) over the entire cerebral cortex, with regional values ranging from 1.58±2.29mm; 1.93±1.77mm; 2.18±2.31mm; and 4.20±2.81mm in the occipital, frontal, parietal, and temporal association cortices, respectively. Corresponding regional SUVR %increases in AD were 28%; 31%; 37%; and 36%, with the average increase of 30% in the entire cortex. Individual and group Z-score maps of 3D-SSP-PCLD and 3D-SSP-SUVR showed grossly concordant patterns of regional changes in AD patients, most conspicuously involving temporo-parieto-frontal association cortices and the posterior cingulate cortex, but also some regional discordance such as seen in the medial frontal cortex. The discrimination efficacy of normal controls vs AD patients was Z=12.2 (U=2462) using 3D-SSP-PCLD and Z=12.0 (U=2584) using 3D-SSP-SUVR (Mann-Whitney test using individual ranking). Receiver Operating Characteristics (ROC) showed the Area-under-the-ROC-Curve of 0.90±0.018 (mean±se) using 3D-SSP-PCLD and 0.91±0.018 3D-SSP-SUVR, indicating a nearly identical discriminatory power for normal controls vs AD patients.

Conclusion: The regional pattern of topographical peak location of amyloid tracer uptake within the gray matter in AD was similar to the pattern shown with intensity-based SUVR assessment. Positive amyloid deposition places the peak location of gray matter uptake into cortical laminae distant from the underlying white matter. This analysis allows the construction of image-based normal database and the Z-score analysis of individual patients as well as groups similar to SUVR. 3D-SSP-PCLD, the absolute quantitative map of geometric location of peak cortical laminar deposition of the tracer, is an objective measure of amyloid deposition with potential diagnostic utility that does not require a reference region thus avoids a source of possible measurement variability inherent with SUVR.

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Is there an interest to perform regional Amyloid quantification in comparison to overall cortical index in MCI patients? T. Gerard,¹

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Objectives: Although visual analysis of amyloid PET has been considered sufficient to discriminate Alzheimer patients from healthy elderly subjects, early stages of Alzheimer degenerative process, ongoing years before the clinical stage, may exhibit fewer amyloid deposits. The level of amyloid load in MCI patients due to AD should therefore be more challenging to detect reason why cortical sub-region analysis could theoretically be considered to detect focal amyloid deposits, not yet spread to the whole cerebral cortex.

Methods: In this study, the result of global neocortical index SUVR computed with PNEURO 3.5 was compared to 10 different cortical sub-regions, known to visually show high discriminant F18-Flutemetamol uptake in AD patients compared to healthy elderly controls. 30 healthy controls and 62 MCI were reviewed for the analysis. The ten regions, regrouping left and right structures (to limit the analysis), were designed as such:

- 1_NC: whole neocortex
- 2_NC+SP: neocortex + specific regions (described hereunder)
- 3_SP: sum of specific regions: orbitofrontal cortex, striatum (caudate nucleus & putamen), superior parietal cortex and posterior cingulate cortex.
- 4_PSCP: superior parietal cortex and posterior cingulate cortex.
- 5_PC: parietal cortex.
- 6_FC: frontal cortex.
- 7_OFC: orbitofrontal cortex.
- 8_OC: occipital cortex.
- 9_TC: temporal cortex.
- 10_ST: striatum (caudate nucleus & putamen).

The gold-standard method to characterize positive or negative amyloid scan stayed the visual reading as recommended. Global and regional cut-off values were arbitrary defined at the PC-90 value of the control group to consider a positive amyloid load.

Results: The regional statistics and comparison between the control and MCI groups for each sub-region are given below:

Conclusion: Even if each sub-region showed a significant difference between control and MCI groups, the last results demonstrated no particular interest to perform additional sub-regional amyloid quantification beside the global neocortex quantification, due to the high consistency of positive or negative pattern in nearly all regions of interest.

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Simultaneous [18F]Florbetaben amyloid PET/arterial spin labeling MRI for dual biomarker assessment of Alzheimer's disease.

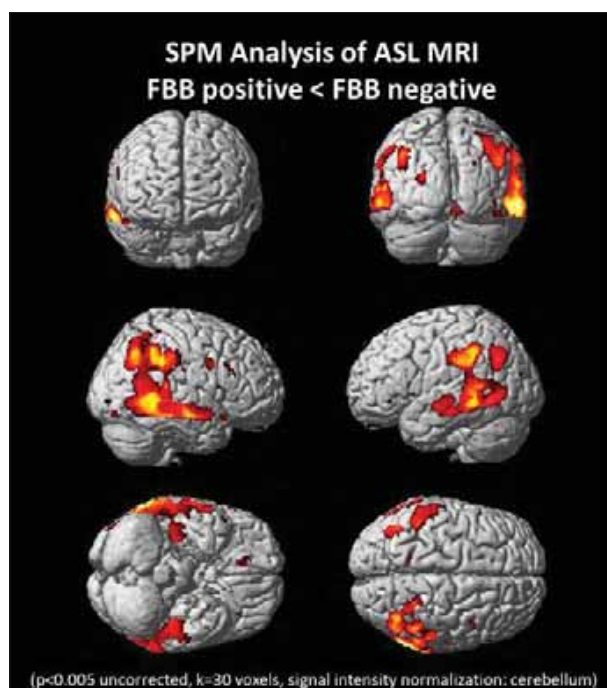
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Objectives: Biomarkers are increasingly employed to supplement clinical diagnosis of Alzheimer's disease (AD). For that purpose, depending on the concept, pathology/neurodegeneration or diagnosis/progression biomarkers are used¹. However, so far it was not possible to derive both biomarker categories within one brain imaging session². This project investigated the respective potential of PET/MRI to simultaneously image cerebral amyloid load and relative cerebral blood flow (rCBF) by arterial spin labeling (ASL).

Methods: 65 subjects (68±10yrs, 31 female) with cognitive deficits (CDR≥1, MMSE=23±6, MCI: n=38, probable AD dementia (ADD): n=12, possible ADD: n=15) underwent simultaneous [18F]Florbetaben PET/MRI (Siemens 3T mMR). The [18F]Florbetaben PET data were acquired 90-110min p.i. of 300MBq. They were analyzed visually (binary evaluation) and relative quantitatively (PMOD, composite SUVRs). Simultaneously, the ASL MRI data were acquired (PICORE Q2TIPS, 18 slices a 4mm in 64x64 matrix, TE/TI/TR = 16/2400/3400ms). They were analyzed visually (image quality, binary judgment: normal/abnormal, pattern recognition) and using a voxel-based approach (SPM).

Results: 32% of the ASL images were visually judged as of inappropriate quality for individual analysis. Of the remaining cases with pathological amyloid PET images, 79% had AD patterns in ASL MRI, while 53/17/30% of the remaining cases with normal amyloid PET images had normal/FTLD/AD patterns in ASL MRI. In the possible/probable ADD patients, 53% were pathologic in amyloid PET only, and 25% both in amyloid PET and ASL MRI. In the MCI subjects, all pathologic amyloid PET cases had an AD pattern in ASL MRI. SPM analysis confirmed the ASL MRI differences between amyloid PET-positives vs. -negatives (see supplementary figure).

Conclusion: While ASL MRI provides promising results with typical pathology patterns on a group level, the current data quality is not sufficient for individual AD neurodegeneration/progression biomarker information. The individualization of acquisition parameters may improve the quality of ASL MRI, which then may enable combined amyloid PET/ASL MRI in a one-stop shop fashion.



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In vivo Amyloid Plaques Quantification using F18-Flutemetamol in

30 Healthy Elderly Controls and 62 MCI patients: SUVR comparison between PMOD 3.2 and PNEURO 3.5 analysis. R. Lhommel*,¹ T. Gerard,² B. J. Hanseeuw,³ A. Ivanoiu⁴; ¹Nuclear Medicine dpt, Cliniques Universitaires Saint Luc, Brussels, Brabant, Belgium, ²Cliniques Universitaires Saint-Luc, Bruxelles, Belgium, ³Massachusetts General Hospital, Boston, Massachusetts, ⁴Neurology, Cliniques Universitaires Saint Luc, Brussels, Belgium. (538)

Objectives: Although visual analysis of Amyloid PET has been considered sufficient to discriminate Alzheimer's patients from healthy elderly subjects, early stage of the degenerative process (MCI stage), exhibiting fewer amyloid deposits, may be more challenging to interpret. In this situation, a robust quantitative analysis may not only be helpful to reinforce the visual analysis but also to allow longitudinal evaluation of the amyloid load in this population.

Methods: As part of a academic study evaluating the impact of biomarkers to stratify MCI patients, 30 healthy controls (70±5.5 y) and 62 (70.8±8.0 y) patients presenting Mild Cognitive Impairment (MCI) were imaged 90 min PI with F18-Flutemetamol scan (GE Healthcare; target ID 185 MBq). SUVR (neocortex/cerebellum) values computed with step-by-step analysis based on several PMOD 3.2 tools (see previously published data) were compared to those obtained with a more recent evolution of the PMOD software (PNEURO 3.5) implementing several useful improvements for clinical translation (semi-automatic workflow, more accurate MRI segmentation for VOI delineation...). However, those methodological changes could also potentially influence the results, reason why a front-to-front comparison was performed.

Results: PMOD 3.2 and PNEURO 3.5 SUVR (Mean±SD/Median/PC90) of the control group were respectively 1.40±0.23/1.33/1.69 and 1.29±0.16/1.26/1.49, both significantly different from the MCI group analysis (1.67±0.39/1.57(P=0.002) and 1.55±0.35/1.42 (p<0.0001)). Despite a good correlation (r2: 0.95), pooled SUVR PNEURO 3.5 values were significantly lower than the previously computed PMOD 3.2 values

($P < 0.0001$; bias(d): -0.12, SD of bias: 0.09; 95% limits of agreement: from -0.29 to 0.06). The SUVmean of the cerebellar region of reference (Mean $\pm$ SD/Median) was not statistically different between controls and MCI: $0.59 \pm 0.15 / 0.59$ vs $0.63 \pm 0.15 / 0.61$ ($P = 0.28$) for PMOD 3.2 and $0.63 \pm 0.14 / 0.64$ vs $0.67 \pm 0.14 / 0.65$ ($P = 0.42$) for PNEURO 3.5 . However, a significant difference was observed ($P < 0.0001$) between the two methods of analysis, with slightly higher cerebellar SUVmean values using PNEURO 3.5 (bias: 0.04; SD of bias: 0.04; 95% limits of agreement: from -0.03 to 0.12). PC90 SUVR of the control group used as discriminating cutoff to separate positive from negative amyloid scans, perfectly correlates with the binary visual analysis scans in all cases, whatever the method used. Finally, SUVR workflow reproducibility using PNEURO 3.5 was also tested between two independent observers for $n = 24$ scans selected at random, with excellent results (bias: 0.002; SD of bias: 0.012; 95% limits of Agreement, from -0.021 to 0.026 (-1.22 to 1.53%)).

Conclusion: SUVR computation based of PNEURO 3.5 seems a easy way to quantify the neocortical amyloid load in MCI patients, providing similar results than the visual scan reading but with the advantage to be independent of the physician's degree of expertise.

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Classification of positive and negative 18F-Florbetaben scans: Comparison of SUVR cutoff quantification and visual assessment performance. S. Bullich,¹ A. M. Catafau,¹ J. Seibyl,² S. De Santi^{*3},¹Piramal Imaging GmbH, Berlin, Germany, ²Molecular Neuroimaging, New Haven, Connecticut, ³Piramal Pharma Inc, Boston, Massachusetts. (1276)

Objectives: Classification of 18F-florbetaben (FBB) PET scans as positive or negative for brain beta-amyloid can be made by either visual inspection of the images or quantification using standardized uptake value ratios (SUVRs) cutoff values. However, comparative data of these two methods using different reference regions (RR) to calculate SUVR is limited. The aim of this study was to compare the performance of the FBB scan visual assessment (VA) and the SUVR cutoff with different RRs, for classifying positive and negative FBB scans.

Methods: FBB scans from end-of-life subjects ($n = 78$, 80.1 ± 10.4 yrs; diagnosis: $n = 56$ Alzheimer's Disease (AD), $n = 9$ non-demented volunteer, $n = 13$ other dementia) who underwent autopsy after death were included. Histopathology confirmation of the presence or absence of neuritic beta-amyloid plaques was performed using Bielschowsky silver stain and immunohistochemistry. FBB scans were visually assessed using the FBB training methodology by 8 independent readers blinded to clinical diagnosis and pathology results. Visual classification into positive or negative was based on the majority read results. A composite SUVR (mean of frontal, occipital, parietal, lateral temporal and posterior and anterior cingulate regions) was calculated for different RRs: cerebellar gray matter (GCER), whole cerebellum including cerebellar white and grey matter (WCER), pons (PONS), and subcortical white matter (SWM). A SUVR cutoff value for each RR was generated using a different sample of FBB scans: 143 subjects with lower average age (69.5 ± 7.5 yrs; $n = 75$ AD, $n = 68$ healthy volunteers) who were previously assessed by 3 blinded readers as positive and negative. Receiver Operating Characteristic (ROC) analysis was performed and the visual assessment used as standard of truth. Highest accuracy was used as criteria for SUVR cutoff selection for each RR. Composite SUVR cutoff generated values for each RR were 1.43 (GCER); 0.96 (WCER); 0.78 (PONS); 0.71 (SWM). The number of correctly or incorrectly classified scans according to pathology results using VA and SUVR cutoffs for each RR was compared.

Results: The number of scans correctly classified was higher using VA than using SUVR cutoff across RRs, although only significantly different when the SWM was used as RR (p-values: 0.09 (VA vs. GCER), 0.73 (VA vs WCER), 0.73 (VA vs. PONS) and 0.02 (VA vs SWM). A range of 63-71 cases were correctly classified by both SUVR cutoff (across RRs) and VA, while 1-3 cases (across RRs) were incorrectly classified by both SUVR cutoff and VA. SUVR cutoff method misclassified more cases (range: 3-10 cases) than VA (range: 1-3 cases) for any RR.

Conclusion: VA and SUVR cutoff quantification perform similarly in classifying FBB scans as positive or negative for brain beta-amyloid. However, the use of SUVR cutoff did not improve VA classification of FBB scans independently of the RR used. These results indicate that VA is a robust method for the correct classification of FBB scans, and suggest limited additional contribution of SUVR cutoff for the detection of presence or absence of neuritic beta-amyloid plaques.

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68Ga-PSMA-HBED-CC ligand uptake in cervical, coeliac and sacral ganglia as an important pitfall in prostate cancer PET imaging. C. Rischpler*,¹ S. OKAMOTO,¹ P. T. Meyer,² M. Schwaiger,¹ T. Maurer,³ M. Eiber¹,¹Dept. of Nuclear Medicine, Technical University Munich, Munich, Germany, ²Dept. of Nuclear Medicine, University Hospital Freiburg, Freiburg, Germany, ³Dept. of Urology, Technical University Munich, Munich, Germany. (1804)

Objectives: The prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancer (PC) cells and can be imaged using 68Ga-PSMA-HBED-CC PET. However, there are reports describing non-specific uptake both in non-prostatic benign (such as in the sympathetic nervous system) and malignant non-PC lesions. The aim of this retrospective study was to investigate the PSMA-ligand uptake in PET in cervical, coeliac and sacral ganglia as a pitfall for lymph node metastases (LN-mets) in prostate cancer imaging.

Methods: 308 patients who underwent a 68Ga-PSMA-HBED-CC PET (combined with a diagnostic CT) between October 2012 and March 2014 were randomly selected and retrospectively analyzed. The mean injected activity was 158 ± 22 [120;240] MBq and acquisition was started approximately 60 min after tracer injection. The number of PSMA-PET-positive cervical, coeliac and sacral ganglia was determined and the SUVmax for each ganglion was measured. Furthermore, the SUVmax of adjacent LN-mets in the respective region (cervical, coeliac or sacral) was determined.

Results: PSMA-ligand uptake above background was found in 285 (94%) patients in cervical ganglia, in 269 (88%) patients in coeliac ganglia, and in 122 (40%) patients in sacral ganglia. The PSMA-ligand uptake was highest in coeliac ganglia (mean SUVmax 2.9 ± 0.8 vs. cervical (mean SUVmax 2.6 ± 0.6) and sacral (mean SUVmax 1.9 ± 0.4) ganglia, both $p < 0.0001$). There was a significant correlation between the PSMA-ligand uptake in cervical and coeliac ganglia ($R = 0.3$, $p < 0.0001$) and a strong trend towards a correlation between cervical and sacral ganglia ($R = 0.16$, $p = 0.08$). Furthermore, the PSMA-ligand uptake was more intense on the left compared to the right side for cervical (left: 2.6 ± 0.7 , right: 2.5 ± 0.6 , $p < 0.0001$) and coeliac ganglia (left: 3.1 ± 0.9 , right: 2.9 ± 1.0 , $p < 0.01$), while no side predominance was found for sacral ganglia (left: 1.9 ± 0.3 , right: 2.0 ± 0.6 , $p = \text{NS}$). The PSMA-ligand uptake was significantly more intense in adjacent LN-mets compared to the respective ganglia (cervical: 16.2 ± 15.7 vs. 2.6 ± 0.7 , $p < 0.0001$; coeliac: 13.2 ± 11.8 vs. 3.0 ± 1.0 , $p < 0.0001$; sacral: 15.3 ± 11.3 vs. 1.9 ± 0.4 , $p < 0.0001$).

Conclusion: PSMA-ligand uptake along the sympathetic chain as assessed by 68Ga-PSMA-HBED-CC PET is an important pitfall in PC PET imaging. The PSMA-ligand uptake is higher in coeliac ganglia compared to cervical or sacral ganglia and the level of PSMA-ligand uptake seems to be patient-related. For differentiation between LN-mets and ganglia both intensity of PSMA-ligand-uptake as well as exact localization and configuration of the respective lesion should be taken into account.

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