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ADVANCES IN NEURODEGENERATIVE AND PSYCHIATRIC IMAGING SPECIAL FEATURE: FULL PAPER

Quantitative evaluation of beta-amyloid brain PET imaging in dementia: a comparison between two commercial software packages and the clinical report

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Objective: To compare commercially available image analysis tools Hermes BRASS and Siemens *Syngo.VIA* with clinical assessment in ^{18}F-Florbetapir PET scans

Methods: 225 scans were reported by clinicians and quantified using two software packages. Scans were classified into Type A (typical features) or non-Type A (atypical features) for both positive and negative scans. For BRASS, scans with z-score ≥ 2 in 2 ≥ region of interest were classed positive. For *Syngo.VIA* a positive scan was indicated when mean cortical standardized uptake value ratio (mcSUVR) ≥ 1.17.

Results: 81% scans were Type A, and 19% scans were non-Type A. The sensitivity of BRASS and *Syngo.VIA* for Type A scans was 98.8 and 96.3%, specificity was 73 and 92%, respectively. Sensitivity for non-Type A scans was 95.8 and 79.2%, specificity was 36.8 and 57.9%, respectively.

A third threshold of identifiable levels of plaque (1.08 ≤ mcSUVR ≤ 1.17) was recommended for *Syngo.VIA* to increase detection of false negative scans.

The false positive rate of BRASS significantly decreased when an alternative positive threshold value of mcSUVR ≥ 1.18.

Introduction of alternative criteria did not improve prediction outcome for non-Type A scans. More complex solutions are recommended.

Conclusion: Hermes criteria for a positive scan leads to a high sensitivity but a low specificity. Siemens *Syngo.VIA* criteria gives a high sensitivity and specificity and agrees better with the clinical report. Alternative thresholds and classifications may help to improve agreement with the clinical report.

Advances in knowledge: Software packages may assist with clinical reporting of more difficult to interpret cases that require a more experienced read.

INTRODUCTION

This work looks at ^{18}F-florbetapir data in patients evaluated for Alzheimers Disease (AD). Evidence of beta-amyloid neuritic plaques (Aβ) in the brain is required to make a neuropathological diagnosis of Alzheimer's disease. Positron emission tomography (PET/CT) is a diagnostic tool used to confirm the presence of Aβ in the brain which can then be used to support a clinical diagnosis of AD. However, a positive amyloid PET/CT scan by itself, showing the presence of Aβ is not diagnostic for AD or indicative of severity, without supporting clinical symptoms of progressive cognitive impairment.[1]

^{18}F-florbetapir non-specifically binds to white matter (WM) in all individuals. In patients with mild cognitive impairment (MCI) and AD, Aβ deposits in the grey matter (GM) resulting in the ligand accumulating in both the GM and the WM, leading to poor grey-white matter (GWM) differentiation. When reporting, a binary method is used where a negative scan indicates absence or sparse levels of amyloid plaque deposition and a positive scan indicates moderate or high levels of amyloid plaque deposition, which would be compatible with a neuropathological diagnosis of AD. Poor GWM differentiation in two or more of the region of the cerebral cortex is considered a positive scan.[2] Alternatively, if intense uptake is seen in GM which is clearly much higher than that of adjacent WM, in only one area, the scan

is also considered positive. The change in anatomy that occurs as a result of brain atrophy, another symptom of AD, can make brain structures more difficult to differentiate, resulting in some scans being more difficult to accurately interpret accurately and consistently. Also, in cases with subtle loss of GWM differentiation, it becomes more difficult to identify the GWM interface and differentiate between the two.

The reporting of ^{18}F-florbetapir amyloid PET/CT scans by visual assessment is considered the gold standard in this modality, this is since the use of cerebral spinal fluid (CSF) would be invasive and results have not been consistent across different bioanalysis labs. For the patients imaged here there is no autopsy/histopathology available but our group intends to perform a 3–5 year follow-up. Although the reading of ^{18}F-florbetapir amyloid PET/CT is binary, the imaging characteristics are not homogeneous. In order to characterize the features of ^{18}F-florbetapir amyloid PET/CT further, we classified our cohort of scans into those with typical features (Type A) and atypical features (Non-Type A). Non-Type A was further subtyped into Types B, C and D according to imaging characteristics (Figure 1).

The table below (Table 1) summarizes how scans were classified, and interpreted from the amyloid imaging data. Type A was classified as positive or negative based on reader training criteria.[2] The non-Type A was characterized using criteria set by our centre, outlined in Table 1.

The majority of scans seen in the clinical domain have typical features and can be classified as Type A scans. They are binary reads and can be interpreted by a trained reader. We found that Type A scans with typical features are very common and usually straightforward to interpret, whereas non-Type A scans are much less common and less consistently read between different readers.[3]

It is assumed that quantification packages may aid the visual reporting of amyloid scans which are difficult to interpret. Various software packages have been created to provide quantitative analysis to support clinical interpretation[4] but the reliability of the software must be assessed carefully. Hermes BRASS (Hermes Medical Solutions AB, Stockholm, Sweden) and Siemens *Syngo.VIA* Amyloid Plaque (Siemens Medical Solutions Inc., Malvern, PA, USA) software packages allow for quantitative analysis of brain amyloid PET/CT scans.

Hermes Medical Solutions[5] provides the Hermes BRASS software (hereinafter referred to as Software 1) that can be used to view and perform automatic fitting and quantification of brain amyloid PET/CT images. It compares patient images to a three-dimensional reference template from a normal database of 80 healthy controls (HC). Software 1 produces two different parameters, standardized uptake value ratio (SUVR) and z-score. The SUVR is the ratio of the SUV of six regions of interest (frontal medial orbital cortex, anterior cingulate, lateral temporal lobes, precuneus, posterior cingulate and parietal lobe) to the SUV of the entire cerebellum (reference region). It also outputs the mean cortical SUVR (mcSUVR). The cerebellum is used as a reference region since the uptake of ^{18}F-florbetapir in this region is low in HC, patients with MCI and AD are taken to be the normal reference point for the remainder of the cerebrum. Average cortical SUVR are higher in patients with AD than in HC. The z-score is also reported, it is the number of standard deviations (SD) the SUVR is from the mean SUVR of that ROI in the normal database. The amyloid scan is interpreted as a positive scan in Software 1 if z-score ≥2 in ROI ≥2. Software 1 automatically highlights any z-score values that are greater than or equal to 2, which previous work as shown to correlate to a SUVR of 1.17.

Siemens *Syngo.VIA*[6] software (hereinafter referred to as Software 2) is based on the method by Fleisher et al.[7] In this study differences in PET ^{18}F-Florbetapir images for patients with probable AD, MCI and older HC's in trials was assessed. mcSUVR cut-off threshold criteria were introduced after PET images were compared with post-mortem samples to correlate actual plaque levels with Aβ identifiable on the image. The mcSUVR thresholds hypothesized were 1.17 for pathological levels of Aβ and increased likelihood of AD (a positive scan interpretation); and 1.08 for identifiable levels of Aβ. When using Software 2, the scans are first fused with a registration PET template and spatially normalized before being compared to an amyloid PET normalized data set. The SUVR of the six ROI relative to the cerebellum, and the number of SD away from the normal data set are computed for all regions.

The aim of this study was to compare the two commercially available amyloid PET analysis tools with the final dual read clinical reports from experienced readers in ^{18}F-Florbetapir PET/CT in patients under investigation for possible dementia. Scans were subcharacterized as typical or atypical and quantified by the two software packages based on positive criteria, interpreting them as positive or negative amyloid scans. The final result was compared against the final clinical report. The usefulness of quantification in these typical and atypical scans was also investigated. Previous work carried out at the centre identified good/excellent inter-reader concordance between three qualified readers for typical scans but less consistent agreement for atypical scans. The clinical impact of this study was that the diagnosis from the ^{18}F Florbetapir PET/CT agreed with other methodologies in 66% of cases, caused a change in diagnosis in 31% and induced a change in management in 47%.[8] From this it was concluded that the vast majority of Type A scans can be read with excellent interobserver concordance and with high confidence. Non-Type A scans can be more difficult to interpret, with lower interobserver agreement and confidence highlighting that there may be a demand for quantification software for these more difficult scans.

METHODS

225 patients (median age = 68, range = 41–88) at Imperial College Healthcare NHS Trust (ICHNT, London UK) who were referred for amyloid scans were injected with 333–370 MBq ^{18}F-Florbetapir and imaged 40 min post-injection on the Biograph TruePoint PET/CT system (Siemens Medical Solutions Inc., Malvern, PA, USA).The patients were placed supine on the scanning bed with their head supported to minimise movement. One PET bed position was acquired in list mode for 20 min centred over the

Figure 1. Local subtype A–D positive and negative ^{18}F-florbetapir (Amyvid) scans

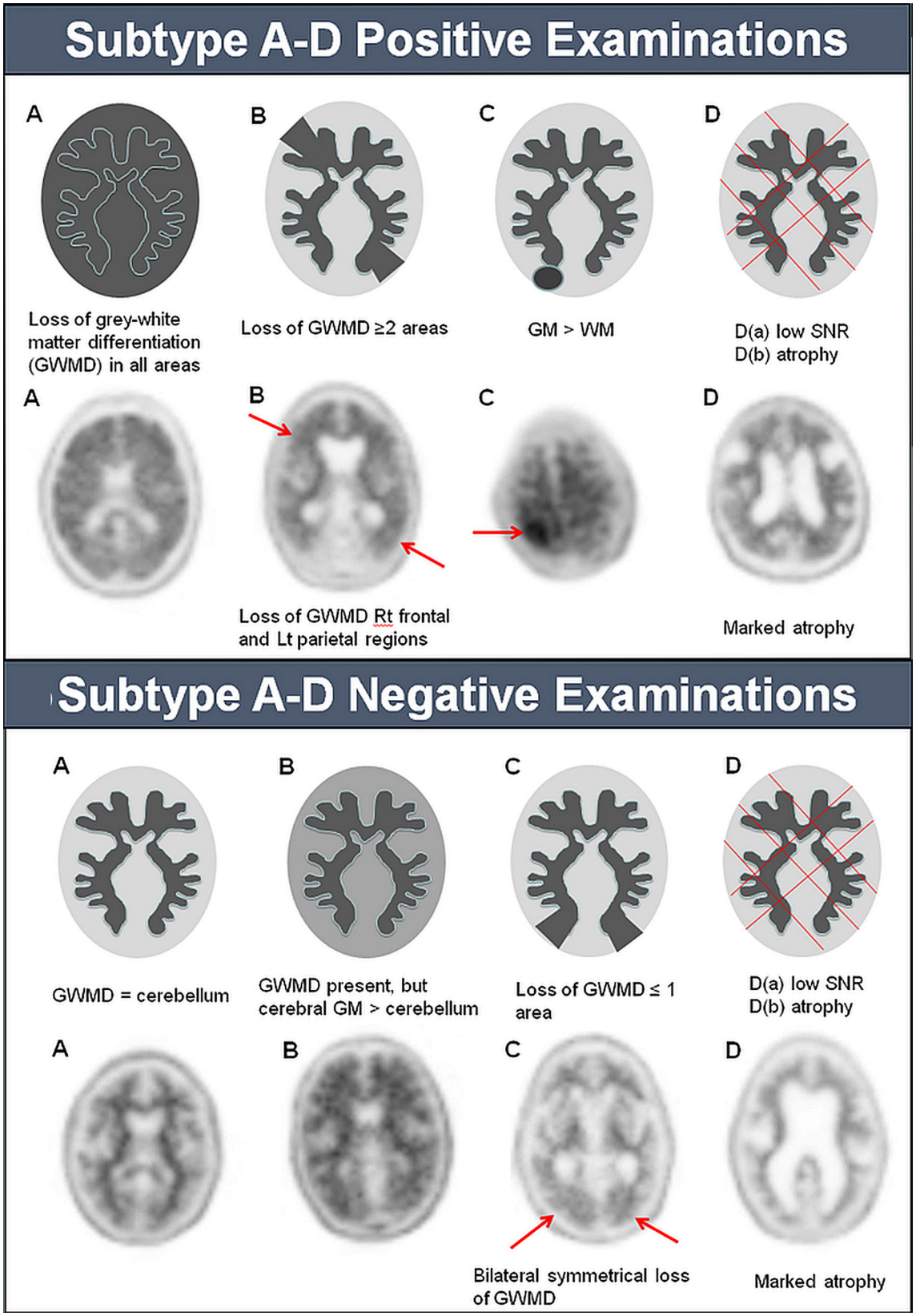


Table 1. Classification and interpretation of typical (Type A) and atypical (non-Type A) scans as positive or negative in the final clinical report

Type	Positive	Negative
A	Complete loss or indistinct GWM differentiation in all regions of the cerebrum.	Clear GWM differentiation where the grey matter intensity is similar to that of the cerebellum which is used as the normal reference region for the remainder of the cerebrum.
B	Loss of GWM differentiation in two regions of the cerebrum (which cannot be symmetrical).	GWM differentiation is maintained but cerebral GM uptake is slightly higher compared to the cerebellum GM but lower than that of cerebral WM.
C	One region where uptake is much higher compared to that of the adjacent WM.	There is loss of GWM differentiation in one region of the cerebrum only (symmetrical loss of GWMD bilaterally in the same cortex represents one region).
D	Loss of GWM differentiation in two or more regions associated with mild atrophy or low SNR.	GWM differentiation is maintained throughout the cerebrum but there is marked atrophy or low SNR (noisy image).

GWM, grey-white matter; SNR, signal-to-noise ratio; WM, white matter.

entire brain, including the cerebellum. A low dose CT image was also acquired and used for attenuation correction and anatomical localization of the PET images.

The acquired list mode data were first reconstructed into 20 × 1 minute dynamic frames and assessed for motion. The frames that included excess motion were removed with a minimum of 10 motion free consecutive frames used for reconstruction (OSEM3D, 4 iterations, 14 subsets, a matrix size of 168 × 168 (2mm/pixel), and a 3 mm FWHM Gaussian filter).

The reconstructed attenuation corrected images were first characterised as typical (Type A) or atypical (Type B/C/D using Table 1) and then reported according to Amyvid read criteria[2] and using the positive and negative characteristics by at least two clinicians (independently reviewed and co-reported) who had completed certified Amyvid reader training (Eli Lilly), and a final consensus clinical report generated. All of the reconstructed images were uploaded and analyzed using both Software 1 and Software 2.

In total, 225 ^{18}F-Florbetapir amyloid scans were analyzed using both the Software 1 and Software 2 amyloid quantification packages. The scans were classified as being Type A (typical features) or non-Type A (atypical features), Figure 1. They were then further classified as positive or negative based on referenced criteria. The classification of these scans as positive or negative by the software packages was compared against the final consensus read report.

The Software 1 positive scan criterion of z-score ≥2 in ROI ≥2 as well as a second criteria based on previous work at ICHNT were investigated to establish where the best agreement with the clinical report is observed. Software 2 states that a mcSUVR value of 1.17 is indicative of pathological levels of Aβ but that a mcSUVR value of 1.08 can be used for identifiable levels of Aβ so both threshold values were assessed.

RESULTS

Of the 225 ^{18}F-Florbetapir amyloid scans, 182 (81%) scans were classified as Type A, and 43 (19%) scans were non-Type A. The majority of the amyloid PET/CT scans were classified as Type A scans. These scans can be read based on typical features by experienced clinicians and are most likely the type of scans that the software packages were designed for.

AGREEMENT BETWEEN CLINICAL REPORT AND SOFTWARE

The κ score (κ) was used to assess agreement between the clinical report and Software 1, the clinical report and Software 2 and between Software 1 and Software 2. The κ score classification is based on Altman.[9]

Good to very good agreement was found between the methods when all scans were included ($0.64 < \kappa < 0.78$, $n = 225$) and for Type A scans ($0.70 < \kappa < 0.79$, $n = 182$). Fair to moderate agreement was found for non-Type A scans ($0.34 < \kappa < 0.56$, $n = 43$) (Figure 2).

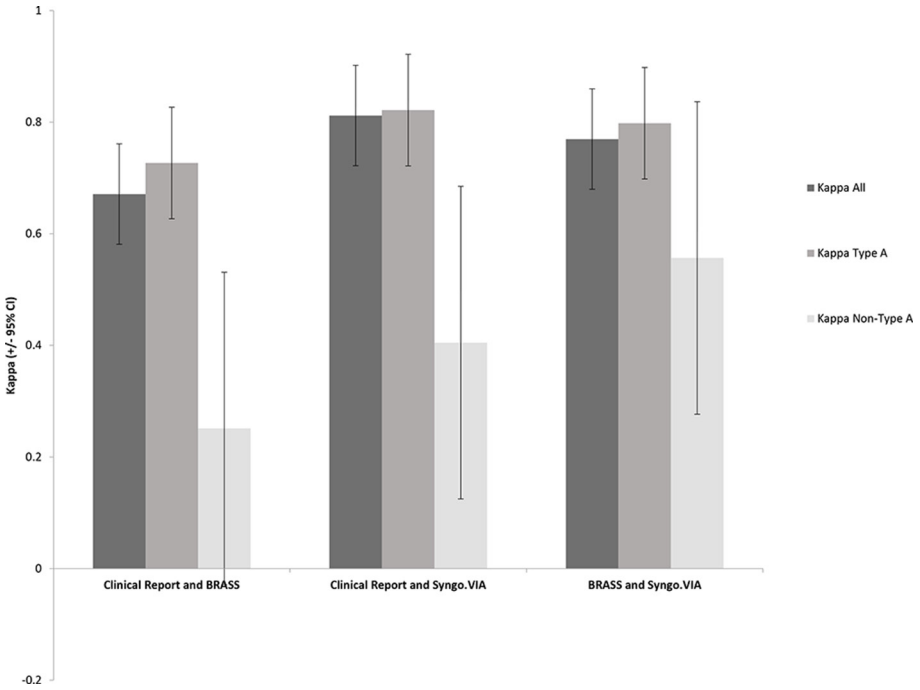
Agreement between Software 1 and Software 2

Typical scans

The true-positive rate (sensitivity), and true-negative rate (specificity) for each of the software packages for Type A (typical) scans was assessed (Table 2).The sensitivity of Software 1 and Software 2 was 98.8 and 96.3% respectively and the specificity was 73 and 92% respectively. Software 2 has good agreement with the clinical report when using this package to interpret positive Type A scans. Whilst the sensitivity of both packages was high, the specificity of Software 1 requires improvement (specificity = 73%, false-positive rate, FPR = 27%). An alternative method of classification was evaluated where instead of a Type A scan being classified as positive if z-score ≥2 in ROI ≥2, the mcSUVR value of 1.18 as a positive cut-off (derived from previous receiver operating characteristic (ROC) analysis performed by our group on 80 amyloid type A scans[3]), to see if this lead to an increased specificity. The sensitivity and specificity for Type A scans using Software 2 are adequate for the intended application.

Disagreement in positive Type A scans was seen in 27 cases between Software 1 and the clinical report; and eight cases between Software 2 and the clinical report. Software 1 disagreed in all eight cases where Software 2 disagreed with the clinical report.

Figure 2. κ score classifications for agreement



In scans where both software packages gave false positive results (n = 8), the mcSUVR for each patient was quite high, and all well above the Fleisher[7] threshold of 1.17. In scans where only Software 1 gave a false positive the mcSUVR values were lower than the mcSUVR threshold of 1.17. The high FPR of Software 1 (73% specificity for Type A scans) was suggestive that the initial positive criteria of $z \geq 2$ in ROI ≥2 may not be appropriate and the use of mcSUVR cut off may increase the specificity (decrease the FPR) of software 1 in line with software 2 and give a result in agreement with the clinical report.

When looking at the scans that are classified incorrectly positive by only Software 1 due to the criteria chosen, *i.e.* positive on Software 1 but negative on the clinical report; we find that if the mcSUVR for these scans had been considered using an mcSUVR threshold value of 1.18 (optimized from ROC analysis done previously by our group), the majority of the scans would have in fact been classified as negative to match the clinical report. The default classification ($z \geq 2$ in ROI ≥2) used to classify a positive scan has shown to lead to a decrease in specificity for Type A scans. Using mcSUVR >1.18 as a positive cut-off would raise the specificity of Software 1 for Type A scans to 91% from the previous value of 73% based on the default criteria ($z \geq 2$ in ROI ≥2). A change in the positive threshold value from the default criteria ($z \geq 2$ in ROI ≥2) to average SUVR ≥1.18 did not change any positive Type A results (sensitivity).

It is seen from these results that the identifiable levels of Aβ (mcSUVR ≥1.08) recognised by Software 2 better agrees with the diagnosis agreed in the clinical report. Two out of the three false-negative Software 2 scans showed indication of plaque (1.08 ≤ mcSUVR ≤ 1.17).

Both software perform equally very well for Type A scans which are the vast majority of scans seen in clinical practice.

Atypical scans

Of the 225 scans analyzed there are 43 (19%) that were classified as Non-Type A. The sensitivity of Software 1 and Software 2 was 95.8% was 79.2%, respectively. This shows excellent true-positive rate (TPR) agreement between Software 1 and the clinical report and a reduced TPR for Software 2. The specificity of both software packages was quite low (Table 3).

Table 2.Sensitivity and specificity of both software packages for Type A scans

	Software 1	Software 2
Sensitivity (%):	98.8	96.3
Specificity (%) using default criteria ($z \geq 2$ in ROI ≥ 2) for software one and mcSUVR for indicative/identifiable levels of plaques for software 2:	73	92
Specificity (% using mcSUVR > 1.18 as a positive cut off for software 1 (improvement) and mcSUVR for indicative/identifiable levels of plaques for software 2::	91	92

Table 3. Sensitivity and specificity of both software packages for non-Type A scans

	Software 1	Software 2
Sensitivity:	95.8	79.2
Specificity:	36.8	57.9

Disagreement in clinically positive non-Type A scans was seen in five cases between Software 2 and the clinical report; and in one case between Software 1 and the clinical report. Software 2 also disagreed in the one case where Software 1 disagreed with the clinical report.

Three of the scans correctly classified as positive when using the default Software 1 threshold would have been incorrectly classified as negative if the alternative positive cut-off of mcSUVR ≥1.18 had been used, reducing the sensitivity from 95.8 to 83%.

There is considerably more disagreement with non-Type A negative scans for both software packages than for Type A scans.. It was decided that more sophisticated algorithms would be needed for non-Type A scans.

As seen from Table 1 in atypical scans we normally find two or more abnormal regions. For this reason mcSUVR may not be the best parameter to use to interpret these scans. A more regional-based methodology should be adapted, and therefore a larger sample of atypical scans is required to perform ROC analysis. The high sensitivity of both software for atypical scans shows that they will detect an abnormality but the low specificity means that it is not assured if the interpretation is correct. This may have something to do with the fact that the positive criteria used for Type A scans is not what should be used for non-Type A scans. The reader should recognize a non-Type A scan before quantification is performed. In these scans quantification (using mcSUVR) should be used cautiously or not at all.

Regional-based analysis was performed on the non-Type A scans. There are two ROIs where both the z-score ≥2 and mcSUVR ≥1.18 criteria were fulfilled in nearly every case; the precuneus and the posterior cingulate. The regional analyses of Software 1 results show that in this case it was primarily the precuneus and the posterior cingulate that resulted in the false positive result. Although the sample size is small the precuneus shows large amyloid plaque deposits.

Regional methods need to be performed with caution as movement can lead to a misinterpretation of results, so a form of motion correction is advised if proceeding with such methodology.

DISCUSSION

This is the first study that looks at comparing two commercially available automated amyloid quantification software packages. Previous studies have looked at comparing automated software delineation to manual delineation. These include automatic image quantification protocols built on FreeSurfer[10] and commercially available packages that cover all processing steps such as PMOD PNEURO, MIMneuro and Amyloid^{IQ}.[11–13] These studies have found that the use of automated software delineation for analysis gives superior results than manual delineation, while also being less time-consuming and reducing inconsistent delineation.[14] These software packages have shown to be a beneficial contribution to the diagnosis of AD but have also been shown to have limitations when reviewing certain scans. The use of criteria to separate scan types based on imaging characteristics partitions the scans that would most benefit from automation from those that need additional manual reads, leading to a more accurate interpretation and saving on time and resources.

This study evaluated the agreement of interpretation given by both Software 1 and Software 2 against the consensus clinical report read. The software packages suggest the use of certain criteria that allow the reporter to classify the scan as either positive or negative. The suggested criteria for Software 1 is that a positive scan is one where two or more regions have a z-score (the number of SD the SUVR is from the mean SUVR of that ROI in the normal database) greater than or equal to two. Software 2 is based on the Fleisher method where a scan is classed as positive if the average of the uptake ratio relative to the cerebellum of six regions is ≥1.17.

If Software 1 is to be used then both criterion of $z \geq 2$ in ROI ≥2 (TPR = 99%) or mcSUVR > 1.18 (TPR = 99%) are suitable cut-offs to use in support of reporting Type A scans by trained readers but when using a threshold mcSUVR >1.18, we see a higher specificity (91% compared to 73% for $z \geq 2$ in ROI ≥2 criterion) and more importantly evidence of lower false positives of typical amyloid scans.

The Software 2 criteria which is based on mcSUVR gives a high sensitivity (96.3%) and specificity (92%) for Type A scans. If a medial probability value of 1.08 ≤ mcSUVR ≤ 1.17 was introduced, false-negative scans may be highlighted as needing further investigation with Software 2 and possibly reclassified in line with the clinical report. If a third threshold for a Software 2 diagnosis of medial probability was introduced, with medial probability classified as 1.08 ≤ mcSUVR ≤ 1.17 and a positive scan classified as mcSUVR ≥ 1.17, these scans would have been identified and further investigated.

The quantification packages did not perform well for atypical (non-Type A) scans. When the alternative Software 1 threshold of a mcSUVR >1.18 as a positive cut-off was applied to atypical scans it lead to a decrease in the sensitivity from 95.8 to 83%. This suggests that the mcSUVR threshold for Type A scans cannot be used for non-Type A scans, and an optimized threshold for scans with atypical imaging features needs to be evaluated separately. Regional-based analysis could be a powerful tool in assessing atypical scans and is currently possible, as the individual ROI information is given by the software, but would only be necessary for more difficult to interpret scans. Therefore, classification into Type A (typical features) or non-Type A (subtypes B–D, atypical features) according to imaging characteristics is the first step towards the efficient use of automatic quantification software packages. The use of regional-based analysis is beyond the scope of this work as it will require a larger cohort of patients

with atypical features. Future work would include increasing the database of atypical scans and using region based SUVR cut-offs with ROC analysis to derive (once a sufficient sample is available, *i.e.* ~84 non-Type A patients) criteria to reduce FPR, increase TPR, increase reader confidence and improve agreement of atypical scan reporting.

Overall, amyloid imaging quantification analysis in combination with visual reporting may increase reader confidence, and reduce FPRs.

The interpretation from the quantification software packages may be in the future considered a gold standard for typical scans, as we have shown that there is very good agreement (high sensitivity and specificity) between the interpretation of the software packages (based on mean cortical SUVR) and the final clinical read for scans with typical features (Type A scans). A good agreement between the packages and the visual read provide confidence to the interpretation of typical scans, which are the majority of scans read in amyloid imaging. In the future, a follow up will be conducted and compared over 3–5 years.

CONCLUSION

Beta-amyloid imaging has been shown to impact evaluation of AD. This study looks at Amyloid Imaging Quantification using two software packages: Hermes BRASS (Software 1) and Siemens *Syngo.VIA* (Software 2), and how the interpretations of these different software packages compares with the final consensus clinical reports from clinicians experienced in reading these scans.

ICHNT has performed 350+ scans to date, of which 225 scans have been analysed in this study. The clinicians at ICHNT are well experienced in reading ^{18}F-Florbetapir Aβ PET scans and have had extensive training by the radiopharmaceutical manufacturers. Both these software applications give parameters that can support the interpretation of the amyloid scans.

The quantification analysis produced by the different software packages has proven to be useful in assisting clinical reporting of amyloid PET/CT scans in the case of typical scans which represent the majority of patients. They may also help experienced readers with the more difficult to interpret cases where quantification will help with the final interpretation. These atypical scans have lower interobserver agreement and confidence, and lower sensitivity and specificity when quantification software is applied. For these atypical scans, quantification algorithms may support interpretation. These non-Type A scans should be double or even triple read (if possible) to reach a consensus opinion. The findings and difficulty of read should be relayed and discussed in a multidisciplinary setting with the clinician, and collaborated with other clinical and investigative findings and biomarkers.

SUVR-based quantification could play a major supportive role for visual evaluation of beta-amyloid PET studies where visual evaluation of GWM differentiation may be difficult. These packages are particularly useful in scans with typical imaging characteristics, which represent the vast majority of scans in clinical practice, and would be most useful in single-handed clinical practice. Quantification has been shown to work well and aid the visual interpretation of these typical scans.

From this work it can be concluded that the two software packages show comparable sensitivity and specificity for typical scans and neither one outperformed the other. It can also be concluded that neither should be used for more difficult to interpret scans (non-Type A) without more robust solutions, such as the regional based analysis. More scans characterized as non-Type A are required to conduct an ROC analysis and interpret the optimal SUV threshold. This work shows that the threshold for Type A scans does not apply to non-Type A scans and these require a more regional based analysis. When interpreting amyloid scans, the reader should recognize a non-Type A scan before quantification is performed. In these scans quantification should be used cautiously or not at all (and a second/third specialist opinion should be sort or the uncertainty should be communicated with the referrer or at the Dementia Multi Disciplinary meetings). The quantification software packages described here provide a useful aid (high sensitivity and specificity) to the visual read for typical Type A scans that are the vast majority of scans seen in the clinical setting.

If the distribution of biomarkers such as Aβ and τau tangles in patients with AD could be mapped and machine learning algorithms applied for regional analysis of the distribution it may become a powerful tool to help focus the research on the prevention of the disease, help optimize the current and future treatments or help refine screening and management of patients with probable AD.

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REFERENCES

1. Revett TJ, Baker GB, Jhamandas J, Kar S. Glutamate system, amyloid ß peptides and tau protein: functional interrelationships and relevance to Alzheimer disease pathology. *J Psychiatry Neurosci* 2013; **38**(no. 1): 6–23. doi: https://doi.org/10.1503/jpn.110190
2. Amyvid. "Amyvid Florbetapir F18 Injection," 11 2017. *Online]. Available* 2018; **11**Accessed.
3. Patel NH, Fakhey-Darian D, Nijran KS, Khan S, Win Z. Assessment and Optimisation of Hermes Amyloid BRASS as a Quantitative Diagnostic Tool in Reporting 18F-Florbetapir (Amyvid) Investigations," *Joural of Nuclear Medicine*. 2018; **1**(no. 1011): 59vol. p..
4. Tuszynski T, Rullmann M, Luthardt J, Butzke D, Tiepolt S, Gertz H-J, et al. Evaluation of software tools for automated identification of

neuroanatomical structures in quantitative β-amyloid PET imaging to diagnose Alzheimer's disease. *Eur J Nucl Med Mol Imaging* 2016; **43**(no. 6): 1077–87. doi: https://doi.org/10.1007/s00259-015-3300-6

5. Solutions HM. Hermes Medical Solutions," [Online]. Available..
6. Siemens. "Quantitative Software Evaluation of Beta-Amyloid Brain PET Imaging in Dementia: White Paper," Siemens Medical Solutions Inc.. *USA* 2015;.
7. Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, et al. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol* 2011; **68**(no. 11): 1404–11. doi: https://doi.org/10.1001/archneurol.2011.150
8. Carswell CJ, Win Z, Muckle K, Kennedy A, Waldman A, Dawe G, et al. Clinical utility of amyloid PET imaging with (18)F-florbetapir: a retrospective study of 100 patients. *J Neurol Neurosurg Psychiatry* 2018; **89**(no. 3): 294–9. doi: https://doi.org/10.1136/jnnp-2017-316194
9. Altman D. *Practical Statistics For Medical Research 1st Edn*. London: Chapman & Hall; 1991.
10. Su Y, D'Angelo GM, Vlassenko AG, Zhou G, Snyder AZ, Marcus DS, et al. Quantitative analysis of PIB-PET with FreeSurfer ROIs. *PLoS One* 2013; **8**(no. 11): e73377): e73377: vol. p.. doi: https://doi.org/10.1371/journal.pone.0073377
11. Brendal M, Hogenauer M, Delker A, et. al. Imporved Longitudinal [F-18]-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction," *NeuroIamge*. 2015; **108**: 450–9.
12. Choi WH, Um YH, Jung WS, Kim SH. Automated quantification of amyloid positron emission tomography: a comparison of PMOD and MIMneuro. *Ann Nucl Med* 2016; **30**(no. 10): 682–9. doi: https://doi.org/10.1007/s12149-016-1115-6
13. Whittington A, Gunn RN. "Amyloid load - a more sensitive biomarker for amyloid imaging," *Journal of Nuclear Medicine. P* 2018;.
14. Tuszynski T, Rullmann M, Luthardt J, Butzke D, Tiepolt S, Gertz H-J, et al. Evaluation of software tools for automated identification of neuroanatomical structures in quantitative β-amyloid PET imaging to diagnose Alzheimer's disease. *Eur J Nucl Med Mol Imaging* 2016; **43**(no. 6): 1077–87. doi: https://doi.org/10.1007/s00259-015-3300-6