Can target-to-pons ratio be used as a reliable method for the analysis of $[^{11}C]$PIB brain scans?

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Rationale: $[^{11}C]$PIB is the most widely used PET imaging marker for amyloid in dementia studies. In the majority of studies the cerebellum has been used as a reference region. However, cerebellar amyloid may be present in genetic Alzheimer’s (AD), cerebral amyloid angiopathy and prion diseases. Therefore, we investigated whether the pons could be used as an alternative reference region for the analysis of $[^{11}C]$PIB binding in AD. The aims of the study were to: 1) Evaluate the pons as a reference region using arterial plasma input function and Logan graphical analysis of binding. 2) Assess the power of target-to-pons ratios to discriminate controls from AD subjects. 3) Determine the test-retest reliability in AD subjects. 4) Demonstrate the application of target-to-pons ratio in subjects with elevated cerebellar $[^{11}C]$PIB binding.

Methods: 12 sporadic AD subjects aged 65±4.5 yrs with a mean MMSE 21.4±4 and 10 age-matched control subjects had $[^{11}C]$PIB PET with arterial blood sampling. Three additional subjects (two subjects with pre-symptomatic presenilin-1 mutation carriers and one probable familial AD) were also studied. Object maps were created by segmenting individual MRIs and spatially transforming the gray matter images into standard stereotaxic MNI space and then superimposing a probabilistic atlas. Cortical $[^{11}C]$PIB binding was assessed with an ROI (region of interest) analysis. Parametric maps of the volume of distribution ($V_T$) were generated with Logan analysis. Additionally, parametric maps of the 60–90 min target-to-cerebellar ratio (RATIO_CER) and the 60–90 min target-to-pons ratio (RATIO_PON) were computed.

Results: All three approaches were able to differentiate AD from controls ($p<0.0001$, nonparametric Wilcoxon rank sum test) in the target regions with RATIO_CER and RATIO_PON differences higher than $V_T$ with use of an arterial input function. All methods had a good reproducibility (intraclass correlation coefficient >0.83); RATIO_CER performed best closely followed by RATIO_PON. The two subjects with presenilin-1 mutations and the probable familial AD case showed no significant differences in cortical binding using RATIO_CER, but the RATIO_PON approach revealed higher $[^{11}C]$PIB binding in cortex and cerebellum.

Conclusion: This study established 60–90 min target-to-pons RATIOs as a reliable method of analysis in $[^{11}C]$PIB PET studies where cerebellum is not an appropriate reference region.

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Introduction

Alzheimer’s disease (AD) is characterized by amyloid plaques and neurofibrillary tangles in the brain. The clinical diagnosis is based on the NINCDS-ADRDA (McKhann et al., 1984) and DSM 1 V criteria (American Psychiatric Association, 1994). $[^{11}C]$PIB or Pittsburgh compound B, binds to fibrillar amyloid with high affinity and has been widely used for in vivo PET imaging of amyloid load (Kluck et al., 2001). Several studies have shown a significant increase in cortical binding in AD subjects compared to controls (Edison et al., 2007; Forsberg et al., 2007; Kemppainen et al., 2007; Klunk et al., 2004). $[^{11}C]$PIB binding is also significantly increased in 50–70% of subjects with mild cognitive impairment, 70–80% of subjects with dementia with Lewy body disease, and a minority of subjects with Parkinson’s disease with later dementia (Edison et al., 2008; Forsberg et al., 2007; Comperts et al., 2008; Kemppainen et al., 2007). Although a tauopathy, frontotemporal dementia cases can also on occasion show a significant amyloid load (Rabinovici et al., 2007).

In vitro studies suggest that thioflavins bind to fibrillar amyloid plaques and not to diffuse plaques (Kluck et al., 2001; Klunk et al., 2003; Mathis et al., 2002; Mathis et al., 2003), however, the specificity...
of PIB binding has been disputed in another study (Lockhart et al., 2007). [11C]PIB studies using arterial input function analysis have demonstrated that there is no significant difference between sporadic AD and control subjects in cerebellar uptake (Edison et al., 2009; Price et al., 2005). Price et al. (2005) suggested that the preferred method of quantification is to use ratio of the volume of distribution in the target region over the volume of distribution in the cerebellar gray matter where volumes of distributions are estimated through the Logan graphical analysis with arterial input. Since then simplified methods of analysis such as the Logan distribution volume ratio and the 60–90 minute target–to–cerebellum ratio RATIOCER methods have been applied to clinical [11C]PIB studies and shown to be valid (Drzegza et al., 2007; Edison et al., 2007; Engler et al., 2006; Forsberg et al., 2007; Kemppainen et al., 2007; Iopresti et al., 2005).

In large clinical studies it is now usual to use 60–90 minute or 40–70 minute target–to–cerebellum ratios for quantitation.

Pathological studies in Prion disease have shown significant amyloid deposits in the cerebellum (Mead et al., 2008; Watanabe and Duchen, 1993). Additionally, a recent [11C]PIB PET study reported significant amyloid deposition in the cerebellum of familial AD subjects (Kaufe et al., 2008; Klunk et al., 2007). Hereditary cerebral hemorrhage with amyloidosis, Icelandic type (HCHWA-I) is an autosomal dominant disorder characterized by massive amyloid deposition within small arteries and arterioles of leptomeninges, cerebral cortex, basal ganglia, brainstem and cerebellum (Ghiso and Frangione, 2001). Cerebellum may not be a suitable reference tissue in advanced or severe AD cases where there might be not only diffuse but also dense amyloid plaques in the cerebellar cortex. Given this, the cerebellum is not always a suitable reference for the quantification of [11C]PIB PET. Therefore, an alternative reference region, the pons, is to be proposed. Here, we set out to (1) Evaluate the pons as a reference region using arterial plasma input function and Logan graphical analysis of binding, (2) assess the power of target–to–pons ratios to discriminate controls from AD subjects, (3) determine the test–retest reliability in a cohort of sporadic AD subjects, 4) demonstrate the application of target–to–pons ratio in subjects with elevated cerebellar [11C]PIB binding.

Subjects and methods

Study population

Subjects were recruited from the Imperial College Healthcare NHS trust, and the National Hospital for Neurology and Neurosurgery, London, UK. 12 sporadic AD subjects, two additional presymptomatic presenilin-1 mutation carriers (PS1 M146I and PS1 Y115C), one probable familial AD (no genetic confirmation), and 10 control subjects were scanned. Majority of these scans were acquired as a part of previously published studies (Edison et al., 2007, 2009). All AD patients met the DSM-IV and NINDS-ADRDA (McKhann et al., 1984) criteria for a diagnosis of clinically probable AD. All subjects were assessed neurologically which included taking a history from a carer and/or relative and routine blood analysis and electroencephalography. All subjects had detailed neuropsychometry including the Mini Mental State Examination (MMSE) and tests of recognition, verbal and visual memory, attention, executive / working memory, visuoconstruction, language, letter fluency and category fluency. The inclusion and exclusion criteria for AD subjects were as previously described (Edison et al., 2007). Age matched healthy controls were recruited from friends of the patients. The age of the AD subjects were 64.8 ± 4.9 years (mean ± standard deviation), the MMSE scores of the subject were 20.7 ± 3.9, and the duration of diagnosis was 14.5 ± 6.5 months. Eight subjects out of the thirteen AD subjects were males. The age of the control subjects was 65.3 ± 5.7 years, their MMSE scores were 29.9 ± 0.27. Six of the control subjects were males. Another AD subject was a 55 year old lady who presented to the memory clinic with difficulties in spelling, and failure to remember daily activities. Her husband noticed she was taking a long time to do the daily chores and occasional spatial disorientation. She had an MMSE score of 17/30, was able to recognize 3/4 famous faces, needed prompting for picture description and was non-fluent. Her cognitive estimates were poor, she scored 2/3 in 3 stage commands and her reading showed some paraphasic errors. She had ideomotor apraxia of the right hand. Her nervous system examination was unremarkable. An EEG showed low voltage EEG dominated by theta activity with runs of theta and slow waves bilaterally, with anterior predominance. There was very scanty alpha rhythm at 8 Hz. Unfortunately the patient declined genetic studies. As the patient was not in touch with the family for several years, the family history was unreliable.

[11C]PIB PET

[11C]PIB was manufactured by Hammersmith Imanet (Cyclotron building, Hammersmith Hospital). All subjects and the controls had an intravenous bolus injection of 370 (± 18) MBq of [11C]PIB and scans were acquired on a Siemens ECAT EXACT HR+ scanner as described previously (Edison et al., 2009). All subjects except the two subjects with presenilin-1 mutation had radial artery cannulation. Continuous online blood sampling was performed for the first 15 min, and discrete samples were taken according to the sampling protocol summarized below.

MRI

MRIs were obtained with a 1.5 Tesla GE scanner. A T1-weighted volumetric MRI (3D T1 volume, pulse sequence RF-Fast, acquisition times TR 30 ms, TE 3 ms, flip angle 30°, FOV 25 cm, matrix 156 × 256, voxel dimensions 0.98 × 0.98 × 1.6 mm) was acquired for co-registration with the PET images while T2-weighted images were acquired to rule out any structural abnormality in AD and control subjects.

Generation of the plasma input function and parametric maps

For the generation of the plasma input functions, the time course of the plasma-to-blood ratio, obtained from the first six discrete arterial samples at 5, 10, 15, 20, 30 and 40 min scan times was fitted to a sigmoidal function with four free parameters. Then arterial whole blood activities recorded by the continuous detector system (Ranicar et al., 1991) were corrected to obtain a plasma activity curve for the first 15 min of the scan. This curve was then combined with the discrete plasma activity measurements at 20, 30, 40, 50, 60, 75 and 90 min to generate an input function describing the plasma activity throughout the entire scan. An input function of the activity concentration due to unmetabolised [11C]PIB in plasma was then created by multiplying the total plasma activity input function with the function obtained from the fit of a sigmoidal model for the parent fraction in plasma to the eight measurements of the parent compound during the scan. Finally, the time delay of the arrival of the radioactivity bolus at the peripheral sampling site relative to the brain was determined (Hinz and Turkheimer, 2006). All calculations were performed using Matlab® (The MathWorks, Inc., Natick, MA, USA) on Sun UltraTM 10 workstations (Sun Microsystems, Inc., Santa Clara, CA, USA).

The linear model developed by Logan et al. (Logan, 2000) has been suggested as the preferred method of analysis for [11C]PIB. Parametric images were generated with Receptor Parametric Mapping software (Gunn et al., 1997). The parameter settings used were: 0.0005663 s−1 as the decay constant for 11C and 35 min linear time as the threshold for the Logan analysis (Lopresti et al., 2005; Price et al., 2005).
60–90 minute target-to-cerebellar ratio (RATIOCER)

The $[^{11}C]$PIB target region-to-cerebellar ratio image was created by dividing the integrated 60–90 minute image by the integrated 60–90 minute value of cerebellar gray matter. Initially a 60–90 minute $[^{11}C]$PIB sum image was created by integrating the activity collected from 60 to 90 min in Matlab 6. This image was co-registered to the individual’s MRI using SPM 99. This coregistered image was then spatially transformed into MNI space. Cerebellar activity concentration was then calculated by sampling the 60–90 minute sum image using the cerebellar gray matter object map (see below) in Analyze. The 60–90 minute $[^{11}C]$PIB add image was then divided by the cerebellar activity concentration value to create a 60–90 minute ratio (RATIOCER) image using image calculator in Analyze. RATIOCER is also referred as SUVR CER. (Standard uptake value ratio using cerebellum).

60–90 minute target-to-pons ratio (RATIOPONS)

Anatomically pons is ventral to the cerebellum, rostral to the mid-brain, and inferiorly the pons is continuous with the medulla oblongata. The pons contains both gray and white matter. In creating RATIOPONS, initially a 60–90 minute $[^{11}C]$PIB image was generated by integrating the activity collected from 60 to 90 min in Matlab 7.5. This image was co-registered to the individual’s MRI using SPM99. This co-registered image was then spatially transformed into MNI space. The pons was traced manually as a polygonal three-dimensional contour on individual MRI images in MNI space, where the tracing reached the edges of the pons. The regional activity concentration in the pons was then calculated by sampling the 60–90 minute sum image using the ‘pons object map’ in Analyze. The 60–90 minute add image was then divided by the activity concentration value in pons to create a 60–90 minute ratio (RATIOPONS) image using image calculator in Analyze. RATIOPONS is also referred as SUVRpons (Standard uptake value ratio using pons).

Region of interest (ROI) analysis and definition of ROIs

Creation of object map

We used statistical parametric mapping software (SPM99, Wellcome Department of Imaging Neuroscience, UCL, London, UK; http: www.fil.ion.ucl.ac.uk/spm) to perform the following image pre-processing steps. MRIs were segmented into gray matter, white matter and CSF, and the gray matter images were thresholded at 50% probability. These gray matter images were then spatially transformed into MNI space. We convolved this binarised grey matter map with the latest version of a probabilistic brain atlas (Hammers et al., 2003) to create individualized object maps including that of cerebellum for each subject.

Pons was manually traced as described above. We then sampled $[^{11}C]$PIB Logan $V_T$, RATIOPONS, and RATIOCER images in the following regions: frontal, temporal and parietal association cortices, anterior and posterior cingulate, striatum, thalamus, pons and cerebellar gray matter.

Statistical analysis

Statistical interrogations of ROI data were performed using SPSS for Windows version 14 (SPSS, Chicago, Illinois, USA). We used the nonparametric Wilcoxon rank sum test to interrogate a statistically significant difference between AD and controls’ outcome measures Logan $V_T$, RATIOCER, and RATIOPONS ($\alpha = 0.05$, two sided).

Percentage difference between the AD and control subjects were then calculated as

$$\delta(\%) = \frac{(AD - HC)}{HC} \times 100,$$

where, $\delta$ denotes percentage difference, AD denotes the cohort mean parameter in the Alzheimer’s disease subjects, and HC denotes the cohort mean parameter in the control subjects.

The percentage variability

$$ABS(AD_2 - AD_1)/( (AD_2 + AD_1)/2) \times 100\%$$

where $\lambda$ denotes percentage variability, $AD_2$ denotes the parameter estimate in the second scan, $AD_1$ denotes the parameter estimate in the first scan and ABS() refers to the absolute value.

SPSS for Windows version 14 was used to calculate the intraclass correlation coefficient (ICC) using one way random single measures (Shrout and Fleiss convention) in 5 AD subjects. ICC was calculated as

$$ICC = \frac{BSMSS - WSMSS}{BSMSS + (n-1)WSMSS}$$

where, BSMSS is the mean sum of squares between subjects, WSMSS is the mean sum of squares within subjects, and $n$ is the number of repeated observations ($n = 2$ in this test–retest paradigm). This coefficient estimates the reliability of the measurement and ranges between -1 (no reliability, that is, $BSMSS = 0$) and 1 (maximum reliability, achieved in the case of identity between test and retest, that is, $BSMSS = 0$).

Results

Fig. 1 shows the $[^{11}C]$PIB scan outcome parameters in a patient group of 12 AD subjects and a cohort of 10 control subjects in six different target regions (anterior and posterior cingulate, striatum, frontal, temporal and parietal cortices) and the two reference regions considered (cerebellar gray matter and pons) using the arterial input Logan $V_T$ (Fig. 1A), the target tissue-to-cerebellum ratio RATIOCER (Fig. 1B) and the target tissue-to-pons ratio RATIOPONS (Fig. 1C) as the outcome parameters.

For the two reference regions, Fig. 1A confirms that there is no significant difference in the cohort mean $V_T$ for pons or cerebellum. In both study groups, the pons $V_T$ exceeds that of cerebellum. As a general observation, the cortical RATIOPONS values in Fig. 1C are lower than the RATIOCER values in Fig. 1B. However, further visual inspection then also reveals that all these methods can provide a clear group differentiation between AD and control subjects in the target regions.

A quantitative assessment of the discriminatory power between these two study groups is provided in Table 1. The minimum percentage group difference in the six target regions for the three outcome measures considered was an increase of 57% in patients relative to controls (in temporal cortex using the Logan $V_T$ target-to-cerebellum ratio). The statistical significance of the group difference in all six target regions was confirmed by the Wilcoxon rank sum test ($p = 0.0001$). On the other hand, for the two reference regions considered cerebellum and pons, there were no statistically significant differences between the two groups for any of the three outcome measures. Taken together these results confirm the suitability of either cerebellum or pons as a reference region for the group discrimination between controls and AD subjects.

Table 2 shows the results on the reproducibility of the three outcome measures as assessed by the group mean variability and the intraclass correlation coefficient (ICC) in a test–retest study of five AD patients. The mean variability for any of the five cortical target regions was at most 8.9% ($Logan V_T$ in the anterior
cingulate and RATIOPONS in the frontal cortex, respectively). On the whole, the mean variability was lowest for RATIOCER followed by RATIOPONS in anterior cingulate, posterior cingulate, frontal and parietal cortex. Only in striatum, temporal cortex and cerebellum the mean variability of Logan VT was smaller than that of RATIOPONS.

Fig. 1. Comparison of three different $[^{11}C]$PIB outcome measures for the discrimination between a cohort of 12 AD patients (filled triangles pointing up) and a group of 10 control subjects (open triangles pointing down). Individual data points are shown for six different target regions (anterior and posterior cingulate, striatum, frontal, temporal and parietal cortices) and the two reference regions considered (cerebellum and pons). The outcome parameters are arterial input analysis Logan total volume of distribution $V_T$ (A), target tissue-to-cerebellum ratio RATIOCER (B) and target tissue-to-pons ratio RATIOPONS (C). In Fig. 1A demonstrates the Logan VT in the young onset (possibly familial) AD. A statistically significant group difference between patients and controls was found in all six target regions for all three outcome measures ($p < 0.0001$, two-sided Wilcoxon rank sum test with $\alpha = 0.05$).
In terms of the ICC, RATIO\textsubscript{CER} also scored highest of the three outcome measures in one AD subject with noticeable elevated cerebellar \textsuperscript{11}C\textsubscript{PIB} binding is shown in Table 4. As shown in Table 4, \textsuperscript{11}C\textsubscript{PIB} binding in the cerebellum of presenilin 1 mutation carriers relative to the control cohort. Note that these two subjects were not scanned with an arterial input function, therefore no Logan \( V_t \) are available.

A visual impression of parametric images generated with the target-to-pons ratio approach is provided by Fig. 2. Fig. 2A shows a sporadic AD subject, while Fig. 2B shows the presenilin-1 mutation carrier FAD2 from Table 4. There appears a qualitative difference between the three cases shown. For the control subject, only a few focal areas of increased binding in white matter are visible whereas the \textsuperscript{11}C\textsubscript{PIB} binding in this AD patient is characterized by higher RATIO\textsubscript{PONS} values mostly in cortical gray matter with no apparent differences in the gray matter of the cerebellum. An impression dominated by rather scattered spots of high \textsuperscript{11}C\textsubscript{PIB} signal not clearly associated with either gray or white matter is given by the RATIO\textsubscript{PONS} parametric map of FAD2.

Discussion

In this study we evaluated the use of the target-to-pons ratio RATIO\textsubscript{PONS} for the analysis of \textsuperscript{11}C\textsubscript{PIB} brain PET scans. As comparator
study outcome parameters, the total volume of distribution \( V_1 \) obtained with Logan graphical analysis of reversible binding using the metabolite corrected arterial plasma input function (Price et al., 2005) and the target-to-cerebellum ratio \( \text{RATIO}_{\text{CER}} \) were used. First, \( \text{RATIO}_{\text{PONS}} \) was able to discriminate a group of 12 sporadic AD patients from a cohort of 10 control subjects in five cortical target regions and the striatum with high statistical significance \( (p < 0.0001, \text{nonparametric Wilcoxon rank sum test}) \). Second, a test–retest reproducibility study performed in five AD patients demonstrated the high reliability of the \( \text{RATIO}_{\text{PONS}} \) as an outcome measure with intraclass correlation coefficients \( (\text{ICC}) \) of 0.87 or higher in the same set of six target regions. Overall, \( \text{RATIO}_{\text{PONS}} \) gave higher ICCs than the arterial input function Logan \( V_1 \) for the target regions though the ICCs were still lower than those of \( \text{RATIO}_{\text{CER}} \). Third, from the study of a single AD subject with elevated cerebellar \( \text{[11C]PIB} \) binding there is evidence that \( \text{RATIO}_{\text{PONS}} \) can be used for the analysis of \( \text{[11C]PIB} \) studies where \( \text{RATIO}_{\text{CER}} \) failed to differentiate from the control mean values.

In one AD case, Logan analysis with metabolite corrected arterial plasma input function showed elevated binding of \( \text{[11C]PIB} \) in both cortex and cerebellum. The \( \text{RATIO}_{\text{CER}} \) analysis detected only a smaller difference compared to the \( \text{RATIO}_{\text{PONS}} \), which detected around two-fold higher values in the cortical regions of this single AD subject. This subject in Fig. 3A relative to the peak height of the cerebellar TAC in both cases (Fig. 3A and Fig. 3B). Note the visible washout from the pons appears to be clearly slower than in the cerebellum and in the cortex of the control subject but still faster than in the white matter as represented by the TACs from the centrum semiovale are only about half the height of the peaks of the cerebellar TACs in both cases (Fig. 3A and Fig. 3B). This subject declined genetic analysis but may have a mutation accounting for the high \( \text{[11C]PIB} \) binding differences (Table 4).

### Table 3

| Region | Logan \( V_1 \) in ml/cm³ | \( \text{RATIO}_{\text{CER}} \) | \( \text{RATIO}_{\text{PONS}} \) | Per cent difference | Per cent difference |
|--------|----------------|----------------|----------------|----------------|----------------|
| A-Cing | 5.64 | 2.52±0.36 | 124 | 1.52 | 1.12±0.11 | 36 | 1.47 | 0.69±0.06 | 113 |
| P-Cing | 5.80 | 2.51±0.36 | 131 | 1.50 | 1.09±0.05 | 37 | 1.46 | 0.68±0.09 | 114 |
| Striation | 4.99 | 2.68±0.36 | 86 | 1.25 | 1.10±0.04 | 13 | 1.21 | 0.68±0.06 | 77 |
| Frontal | 5.42 | 2.47±0.38 | 119 | 1.44 | 1.09±0.07 | 32 | 1.40 | 0.67±0.06 | 108 |
| Temporal | 5.08 | 2.46±0.36 | 107 | 1.35 | 1.07±0.04 | 27 | 1.32 | 0.66±0.06 | 100 |
| Parietal | 5.59 | 2.46±0.38 | 127 | 1.51 | 1.09±0.05 | 39 | 1.46 | 0.67±0.06 | 117 |
| C’bellum | 3.64 | 2.42±0.35 | 50 | 1 | 1±0 | 0 | 0.97 | 0.64±0.07 | 52 |
| Pons | 4.14 | 3.45±0.41 | 20 | 1.05 | 1.59±0.17 | −34 | 1 | 1±0 | 0 |

Table 3 shows the percentage difference between a single case AD subject with increased cerebellar \( \text{[11C]PIB} \) uptake and a group of 10 control subjects using three different outcome parameters (arterial input analysis Logan \( V_1 \), target tissue-to-cerebellum ratio \( \text{RATIO}_{\text{CER}} \) and target tissue-to-pons ratio \( \text{RATIO}_{\text{PONS}} \)) in six different target regions and the two reference regions considered. The percentage difference was calculated as \( \delta(\%) = \frac{\text{AD} - \text{HC}}{\text{HC}} \times 100 \) where \( \delta \) denotes percentage difference, AD denotes the parameter estimated in each of the familial Alzheimer’s disease subject, and HC denotes the cohort mean parameter in the control subjects. SD stands for standard deviation.

### Table 4

| Controls | First case FAD 1 | Second case FAD 2 | Controls | First case FAD 1 | Second case FAD 2 |
|---------|----------------|----------------|---------|----------------|----------------|
| \( \text{RATIO}_{\text{CER}} \) | Mean±SD | Per cent difference | Mean±SD | Per cent difference | Mean±SD | Per cent difference |
| A-Cing | 1.12±0.11 | 1.14 | 2.2 | 1.05 | −5.9 | 0.69±0.06 | 1.15 | 66.8 | 1.01 | 46.5 |
| P-Cing | 1.09±0.05 | 1.43 | 30.7 | 1.13 | 3.3 | 0.68±0.09 | 1.44 | 111.1 | 1.09 | 59.8 |
| Striation | 1.10±0.04 | 1.25 | 13.4 | 0.97 | −12.0 | 0.68±0.06 | 1.26 | 84.5 | 0.93 | 36.2 |
| Frontal | 1.09±0.07 | 1.20 | 10.1 | 1.06 | −2.7 | 0.67±0.06 | 1.21 | 79.4 | 1.02 | 51.2 |
| Temporal | 1.07±0.04 | 1.08 | 1.3 | 1.05 | −1.6 | 0.66±0.06 | 1.09 | 64.7 | 1.01 | 52.7 |
| Parietal | 1.09±0.05 | 1.20 | 10.5 | 1.15 | 5.9 | 0.67±0.06 | 1.21 | 79.6 | 1.10 | 63.3 |
| C’bellum | 1±0 | 1 | 0 | 1 | 0 | 0.64±0.07 | 1.01 | 58.7 | 0.96 | 50.9 |
| Pons | 1.59±0.17 | 0.99 | −37.8 | 1.04 | −34.6 | 1±0 | 0 | 1 | 0 |

Table 4 shows the percentage difference between two pre-symptomatic PS1 mutation carriers and a group of 10 control subjects using two simplified outcome parameters (target tissue-to-cerebellum ratio \( \text{RATIO}_{\text{CER}} \) and target tissue-to-pons ratio \( \text{RATIO}_{\text{PONS}} \)) in six different target regions and the two reference regions considered. The percentage difference was calculated as \( \delta(\%) = \frac{\text{AD} - \text{HC}}{\text{HC}} \times 100 \) where \( \delta \) denotes percentage difference, AD denotes the parameter estimated in each of the familial Alzheimer’s disease subjects, and HC denotes the cohort mean parameter in the control subjects. SD stands for standard deviation.
...fects. In the top row (panel A) the sagittal sections from a control participant are shown. Superimposed on both the PET and the MR images are the two reference regions, in yellow the cerebellar gray matter and in magenta the pons, respectively. Notice the low \([11C]\text{PIB}\) binding throughout the brain with only few focal areas of increased binding in white matter. In the middle panel B, the pattern of \([11C]\text{PIB}\) binding in this AD patient is characterised by a \(\text{RATIOPONS}\) of one or higher in most of the cortical gray matter. The inserted color bar applies to all three \(\text{RATIOPONS}\) images shown on the left hand side. The familial AD subject FAD2 (Table 4) in the bottom section (panel C) exhibits rather scattered spots of high \([11C]\text{PIB}\) signal not clearly associated with either gray or white matter. Note that this also includes the cerebellar gray matter.

**Fig. 2.** Parametric images of the target-to-pons ratio \(\text{RATIOPONS}\) (left) and structural images (right). In the top row (panel A) the sagittal sections from a control participant are shown. Superimposed on both the PET and the MR images are the two reference regions, in yellow the cerebellar gray matter and in magenta the pons, respectively. Notice the low \([11C]\text{PIB}\) binding throughout the brain with only few focal areas of increased binding in white matter. In the middle panel B, the pattern of \([11C]\text{PIB}\) binding in this AD patient is characterised by a \(\text{RATIOPONS}\) of one or higher in most of the cortical gray matter. The inserted color bar applies to all three \(\text{RATIOPONS}\) images shown on the left hand side. The familial AD subject FAD2 (Table 4) in the bottom section (panel C) exhibits rather scattered spots of high \([11C]\text{PIB}\) signal not clearly associated with either gray or white matter. Note that this also includes the cerebellar gray matter.

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**Fig. 3.** Tissue time-activity curves (TACs) in an AD subject (A) and a control (B). In each case, the TACs for the gray matter cerebellum, the gray matter temporal cortex as an example for the cortical regions, the pons and the central semiovalie representing white matter are shown.

In conclusion, this is the first study to evaluate the use of target-to-pons ratios for the analysis of \([11C]\text{PIB}\) brain scans and to assess the test–retest variability in comparison to the arterial input analysis. We have demonstrated that the target-to-pons ratio has low test–retest variability and high reproducibility and can be used as a simplified method of quantification when the use of the cerebellum as a reference is not confirmed.

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