Cerebellar Amyloid-β Plaques: How Frequent Are They, and Do They Influence ^{18}F-Florbetaben SUV Ratios?

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SUV ratios (SUVRs) are used for relative quantification of ^{18}F-florbetaben scans. The cerebellar cortex can be used as a reference region for quantification. However, cerebellar amyloid-β (Aβ) plaques may be present in Alzheimer disease (AD). The aim of this study was to assess the influence of Aβ pathology, including neuritic plaques, diffuse plaques, and vascular deposits, in ^{18}F-florbetaben SUVR when cerebellum is used as the reference. **Methods:** Using immunohistochemistry to demonstrate Aβ plaques and vascular deposits, and using the Bielschowsky method to demonstrate neuritic plaques, we performed a neuropathologic assessment of the frontal, occipital, anterior cingulate, and posterior cingulate cerebral cortices and the cerebellar cortex of 87 end-of-life patients (64 with AD, 14 with other types of dementia, and 9 nondemented aged volunteers; mean age ± SD, 80.4 ± 10.2 y) who had undergone ^{18}F-florbetaben PET before death. The lesions were rated as absent (none or sparse) or present (moderate or frequent). Mean cortical SUVRs were compared among cases with different cerebellar Aβ loads. **Results:** None of the 83 evaluable cerebellar samples showed frequent diffuse Aβ or neuritic plaques; 8 samples showed frequent vascular Aβ deposits. Diffuse Aβ plaques were rated as absent in 78 samples (94%) and present in 5 samples (6%). Vascular Aβ was rated as absent in 62 samples (74.7%) and present in 21 samples (25.3%). No significant differences in cerebellar SUVs were found among cases with different amounts or types of Aβ deposits in the cerebral cortex. Both diffuse and neuritic plaques were found in the cerebral cortex of 26–44 cases. No significant SUVR differences were found between these brains with different cerebellar Aβ loads. **Conclusion:** The effect of cerebellar plaques on cortical ^{18}F-florbetaben SUVRs appears to be negligible even in advanced stages of AD with a higher cerebellar Aβ load.

Key Words: Alzheimer disease; florbetaben; positron emission tomography

J Nucl Med 2016; 57:1740–1745
DOI: 10.2967/jnumed.115.171652

Histopathologic confirmation of the in vivo detection of amyloid-β (Aβ) plaques by means of ^{18}F-florbetaben PET imaging supports the use of this tracer as a biomarker for identifying brain Aβ burden in clinical practice (*1*). Visual assessment, using a systematic methodology developed for this amyloid PET tracer, has shown high accuracy in the identification of positive and negative scans (*2,3*). However, potential subtle changes in Aβ burden over time may not be apparent by visual inspection of the images. Thus, quantitative analysis has been found necessary for longitudinal observational studies and interventional trials when a change in amyloid burden measured by PET serves as a treatment endpoint (*4,5*).

The main quantification method used in brain Aβ PET imaging is the SUV ratio (SUVR), a relative measurement defined as the ratio of SUV (percentage injected dose per body weight) in the target region to SUV in the reference region. There are theoretic requirements for a reference region, such as to have cellular and blood flow characteristics similar to those of the target region and to be devoid of specific binding sites (i.e., amyloid-free)—thus having the same nondisplaceable activity (free + nonspecific binding) as the target region (*4*). The cerebellar cortex is commonly used as a reference region for ^{18}F-florbetaben quantification (*4,6*). This region fulfills all the requirements except that it may contain Aβ plaques in the most advanced stage of Alzheimer disease (AD) (*7*) and in some types of familial AD (*8*). In these cases, the increase of specific Aβ binding in the cerebellum might lead to an underestimation of cortical SUVR measurements of Aβ plaque load. This possibility has raised some concern about relying on this area as a reference region (*4,8*). Correlations of in vivo ^{18}F-florbetaben PET SUVRs with postmortem neuropathologic assessments of cerebral cortical and cerebellar Aβ plaques would allow this concern to be investigated. Therefore, using the cerebellar cortex as the reference region, we assessed the influence of cerebellar amyloid pathology—including neuritic plaques, diffuse Aβ plaques, and vascular Aβ deposits—on ^{18}F-florbetaben PET SUVRs by performing a post hoc analysis of the correlation between PET results and pathologic results from a phase 3 clinical trial.

MATERIALS AND METHODS

Subjects

We analyzed ^{18}F-florbetaben PET scans and brain tissue samples from 87 end-of-life patients who had participated in a phase 3 study

Received Feb. 5, 2016; revision accepted Apr. 14, 2016.
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Published online Jun. 30, 2016.

that had included a PET scan during life and subsequent neuropathologic assessment at autopsy. These patients comprised 64 with AD (mean age ± SD, 79.6 ± 9.9 y), 14 with other forms of dementia (88.2 ± 9.3 y), and 9 who were nondemented aged volunteers (77.1 ± 11.4 y). The study was conducted in accordance with the Declaration of Helsinki. Approvals by regulatory authorities and ethics committees were obtained (*1*).

^{18}F-Florbetaben PET

^{18}F-florbetaben PET images were acquired 90–110 min after intravenous injection of 300 MBq (±20%) ^{18}F-florbetaben according to a standardized acquisition and image-processing protocol (*1*). Three-dimensional volumetric T1-weighted brain MRI data were also collected.

Quantification was performed using the method described by Barthel et al. (*6*). A standardized volume-of-interest template was applied to the spatially normalized gray matter PET image based on a gray/white/cerebrospinal fluid segmentation of the participant's T1-weighted volumetric MRI.

SUVs were obtained from both cerebellar cortex and cerebral cortical regions using the corresponding segmented gray portion of the template volume of interest. The cerebral cortical regions included 2 regions likely to contain high numbers of Aβ plaques (frontal cortex and posterior cingulate gyrus) and 2 regions likely to contain lower numbers of Aβ plaques (occipital cortex and anterior cingulate gyrus/precuneus). Cerebral cortical SUVRs were then calculated using the cerebellar cortex as the reference region.

Neuropathology

Sections for histologic analysis were cut from formalin-fixed paraffin-embedded tissue blocks from the 4 cerebral cortical regions and the single cerebellar cortical region as detailed previously (*1*). Analysis for the presence or absence of neuritic plaques, diffuse Aβ plaques, and vascular Aβ deposits was performed by 3 experienced neuropathologists as previously described (*1*).

In sections from each tissue block, diffuse Aβ plaques and vascular Aβ deposits were assessed by Aβ immunohistochemistry (monoclonal 6E10 Aβ antibody; Zytomed Systems), and neuritic plaques were assessed by Bielschowsky silver staining.

Both types of plaques and vascular Aβ deposits were quantified according to a semiquantitative scoring system that was originally developed for neuritic plaques (*9*) and uses the categories none, sparse, moderate, and frequent. In the absence of any other semiquantitative scoring system for diffuse Aβ plaques and vascular Aβ deposits, the same scoring system was applied to these, thus additionally allowing for semiquantitative comparison across pathologic subtypes. Pathology was rated as absent when the score for each category (neuritic plaques, diffuse Aβ plaques, and vascular Aβ deposits) was none or sparse and present when the score was moderate or frequent.

Statistical Analysis

The mean cerebellar SUVs and cerebral SUVRs for ^{18}F-florbetaben were compared among different cerebellar Aβ scores by 2-way ANOVA using cerebellar diffuse Aβ plaques and vascular Aβ deposits as factors potentially influencing SUV and SUVR. Because of the negligible amount of neuritic cerebellar plaques found, these were not considered in the ANOVA analysis.

RESULTS

Cerebellar Cortex Pathology

The results for Aβ pathology in the cerebellar cortex are summarized in Table 1. In total, 83 cases with a sample of cerebellar cortex were evaluable. Neuritic plaques were scored as none in all but a single cerebellar sample, which was scored as sparse. Therefore, neuritic plaques were rated as absent in all samples. According to the semiquantitative scoring system, diffuse Aβ plaques were rated as absent in 78 samples (94%) and present in 5 samples (6%), all of which had a moderate amount of pathology. No samples contained frequent diffuse Aβ plaques in the cerebellum. Vascular Aβ was the most frequently detected type of Aβ deposit. It was rated as absent in 62 samples (74.7%) and present in 21 samples (25.3%) (Table 1).

Of the 21 samples showing vascular Aβ deposits, 18 (86%) contained only vascular Aβ pathology whereas 3 (14%) also contained moderate diffuse Aβ plaques in the cerebellar cortex (molecular layer). On the other hand, 3 (60%) of the 5 samples with moderate diffuse Aβ plaques also contained vascular Aβ deposits (Fig. 1; Table 1). The only sample with sparse neuritic plaques also contained both sparse diffuse Aβ plaques and moderate vascular Aβ deposits.

^{18}F-Florbetaben Quantification and Pathology

Cerebellar SUV ranged from 0.26 to 1.79 (mean ± SD, 0.90 ± 0.32; 95% confidence interval, 0.83,0.97). No significant SUV differences were found in the cerebellar cortex among brains with none, sparse, or moderate cerebellar Aβ pathology ($P_{diffuse}$ = 0.49, $P_{vascular}$ = 0.43) (Fig. 1). In subjects rated for presence of

TABLE 1
Cerebellar Cortex Pathology Results

		Vascular Aβ deposits				
		Absent (n = 62)		Present (n = 21)		
Diffuse Aβ plaques		None	Sparse	Moderate	Frequent	Total
Absent (n = 78)	None	25	14	3	2	44
	Sparse	8	13	8*	5	34
Present (n = 5)	Moderate	1	1	2	1	5
	Frequent	0	0	0	0	0
Total		34	28	13	8	83

*One subject in this group also showed sparse neuritic plaques.
Data are number of samples with corresponding pathology finding.

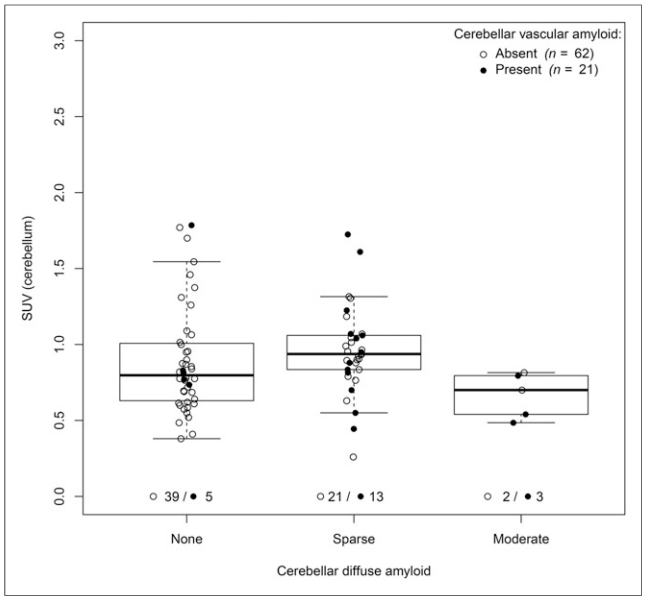

FIGURE 1. ^{18}F-florbetaben cerebellar SUV distribution according to different cerebellar diffuse Aβ plaque loads. "None" and "sparse" scores were rated as absence of Aβ plaques.

cerebral cortical plaques (i.e., moderate or frequent Aβ diffuse and neuritic plaques, in 26–44 cases, depending on the region under consideration; see subsample Table 2), who are the most likely to have Aβ deposits in the cerebellum, SUVR was 0.91–2.37 in the frontal cortex, 1.10–2.13 in the occipital cortex, 0.83–2.49 in the anterior cingulate cortex, and 0.95–2.84 in the posterior cingulate cortex. No significant SUVR differences among brains with different amounts of cerebellar Aβ pathology (i.e., scores of none, sparse, or moderate) were found (Table 2; Figs. 2 and 3). Neither the nature nor the amount of Aβ deposits in the cerebellum had any effect on cortical SUVRs. In the full cohort of patients, including those with either the absence or the presence of cortical Aβ plaques, SUVR was 0.66–2.37 in the frontal cortex, 1.07–2.13 in the occipital cortex, 0.47–2.49 in the anterior cingulate cortex, and 0.95–2.84 in the posterior cingulate cortex. In the full cohort, the amount of cerebellar Aβ pathology positively correlated with the amount of amyloid plaques in the cerebral cortex as measured using SUVRs (Table 2; Fig. 4).

DISCUSSION

To the best of our knowledge, this was the first study comparing postmortem pathologically confirmed cerebellar Aβ pathology with antemortem ^{18}F-florbetaben PET scan quantification within the same subjects to investigate the appropriateness of the use of the cerebellum as a reference region. Neuropathologic studies have shown that Aβ is present in the cerebellum only in the most advanced stage of AD, when other cerebral regions including the cortex are already severely affected (*7*). We therefore investigated the potential influence of cerebellar Aβ on cortical SUVR quantification in patients with cerebral cortical Aβ plaques, and we found that potential binding of ^{18}F-florbetaben to cerebellar amyloid does not influence the SUVR in cerebral cortical regions. Most of the cerebellar amyloid deposits were in the form of either diffuse Aβ plaques or vascular Aβ, which have been reported to influence cerebral cortical SUVR measurements using ^{18}F-florbetaben (*10*). However, in our study the cerebellar SUV was not influenced by either the amount or the type of Aβ deposition, probably because of the relatively low levels of Aβ deposits detected in the cerebellum. One explanation for our finding is that the signal from any potential ^{18}F-florbetaben binding in the cerebellum will be small, is likely to fall within the margins of error in PET signal measurement, and will therefore not be detectable. Another possible explanation may be the morphologic and immunocytochemical differences between the neuropathologic lesions of AD in the cerebral cortex and cerebellum (*11*). As expected, the amount of cerebellar Aβ deposition assessed pathologically correlated positively with cortical SUVRs in the full sample of patients; subjects without Aβ deposition in the cerebral cortex did not show Aβ deposition in the cerebellum, and the higher the amount of cerebellar Aβ deposition was, the higher was the cerebral cortical SUVR.

Cerebellar Pathology in AD

It is well established in the literature that Aβ deposits can be found in the cerebellum of patients with AD and Down syndrome. Cerebellar amyloid plaques were detected in "familial organic psychosis (Alzheimer type)" as early as 1934 (*12*), and the existence of diffuse Aβ plaques in the cerebellum has been noted with the introduction and increasingly widespread use of Aβ immunohistochemistry (*13–15*). The presence of cerebellar Aβ deposits has been reported especially—but not exclusively—in familial forms of AD, such as in patients with *APP* and *PSEN1* mutations (*16,17*), in severe early-onset cases of AD (*15*), and in the late stages of sporadic AD. In Braak and Braak's neuropathologic staging of AD, the presence of cerebellar pathology is mentioned only in stage C (*18*), and in the more recent analysis of the sequence of Aβ deposition in the AD brain by Thal et al., the presence of cerebellar Aβ deposits is described in the final stage of the disease (phase 5) (*7*).

The amount of diffuse Aβ plaques and neuritic plaques detected in the cerebellum in our study is fully in keeping with earlier descriptions (*13,15,19*): although sparse neuritic plaques as determined by Bielschowsky silver staining were identified only in a single case, diffuse Aβ plaques in varying amounts were identified in 39 cases (47%). Since the number of Aβ deposits in most of these cases did not meet the criteria to be scored as moderate, Aβ pathology was overall rated as absent, and only 6% ($n = 5$) of cases had moderate quantities of Aβ pathology, which was rated as present according to the agreed criteria for this study. A larger sample of cases with cerebellar Aβ pathology would have been desirable to investigate whether a subtle ^{18}F-florbetaben uptake in the cerebellum may have any effects on cortical SUVR.

Vascular Aβ deposition was present in 25.3% of the 83 evaluable cerebellar samples in this study. In the cerebellar samples from AD patients ($n = 60$), vascular Aβ deposition was found in 17 cases (28.3%). Thus, the overall frequency of cerebellar vascular Aβ deposits in this sample is somewhat less than reported for some earlier series of AD patients (*13,14,20*), but the vascular deposits still occurred in a significant portion of samples. This finding is not surprising, since the phase 3 clinical trial that provided the patients for this study included end-of-life patients only, often in advanced clinical stages of AD (*1*). Therefore, this series of patients is considered representative of the late neuropathologic stages of AD in most cases. However, in the target clinical population for diagnostic amyloid PET imaging, the cerebellum is likely to be devoid of Aβ pathology, as this population is likely to be in the early stages of AD and may include difficult-to-diagnose atypical cases of cognitive impairment (*21*) in which the AD pathology may not be advanced.

TABLE 2
^{18}F-Florbetaben SUVRs by Cerebral Cortical Region, Type of Cerebellar Aβ Deposit, and Cerebellar Aβ score

Scope	Region	Deposit	Score				$P_{diffuse}$	$P_{vascular}$
			Absent	Sparse	Moderate	Frequent		
Full sample	Frontal (n = 83)	Diffuse plaques	1.36 ± 0.35 (1.29,1.43)	1.70 ± 0.33 (1.62,1.77)	1.82 ± 0.29 (1.76,1.89)	—	$<10^{-4}$	0.003
		Vascular	1.31 ± 0.35 (1.23,1.38)	1.66 ± 0.34 (1.56,1.74)	1.66 ± 0.33 (1.59,1.73)	1.77 ± 0.24 (1.72,1.82)		
	Occipital (n = 82)	Diffuse plaques	1.44 ± 0.21 (1.40,1.49)	1.66 ± 0.24 (1.61,1.71)	1.69 ± 0.26 (1.64,1.75)	—	$<10^{-4}$	0.001
		Vascular	1.41 ± 0.21 (1.36,1.46)	1.63 ± 0.21 (1.59,1.68)	1.65 ± 0.30 (1.58,1.71)	1.66 ± 0.19 (1.62,1.70)		
	AC (n = 82)	Diffuse plaques	1.37 ± 0.40 (1.29,1.46)	1.74 ± 0.38 (1.66,1.82)	1.86 ± 0.31 (1.80,1.93)	—	$<10^{-4}$	0.03
		Vascular	1.35 ± 0.37 (1.27,1.43)	1.65 ± 0.45 (1.56,1.75)	1.67 ± 0.43 (1.58,1.77)	1.91 ± 0.18 (1.87,1.95)		
	PC (n = 82)	Diffuse plaques	1.59 ± 0.39 (1.51,1.67)	1.87 ± 0.37 (1.79,1.95)	1.86 ± 0.24 (1.81,1.92)	—	0.004	0.13
		Vascular	1.56 ± 0.37 (1.48,1.64)	1.80 ± 0.39 (1.72,1.89)	1.81 ± 0.43 (1.72,1.90)	1.96 ± 0.22 (1.91,2.01)		
Subsample	Frontal (n = 44)	Diffuse plaques	1.64 ± 0.34 (1.54,1.74)	1.77 ± 0.29 (1.69,1.85)	1.73 ± 0.24 (1.66,1.80)	—	0.47	0.83
		Vascular	1.64 ± 0.33 (1.54,1.74)	1.74 ± 0.32 (1.65,1.84)	1.75 ± 0.26 (1.67,1.83)	1.79 ± 0.28 (1.71,1.87)		
	Occipital (n = 41)	Diffuse plaques	1.67 ± 0.21 (1.60,1.73)	1.68 ± 0.23 (1.61,1.75)	1.60 ± 0.16 (1.55,1.65)	—	0.77	0.08
		Vascular	1.50 ± 0.22 (1.43,1.56)	1.68 ± 0.19 (1.62,1.74)	1.74 ± 0.23 (1.67,1.81)	1.74 ± 0.17 (1.68,1.79)		
	AC (n = 26)	Diffuse plaques	1.73 ± 0.39 (1.58,1.88)	1.77 ± 0.36 (1.63,1.90)	1.74 ± 0.18 (1.67,1.81)	—	0.97	0.57
		Vascular	1.77 ± 0.16 (1.70,1.83)	1.72 ± 0.48 (1.54,1.91)	1.63 ± 0.18 (1.56,1.70)	1.92 ± 0.21 (1.84,2.00)		
	PC (n = 32)	Diffuse plaques	1.91 ± 0.44 (1.77,2.06)	1.94 ± 0.34 (1.82,2.06)	1.79 ± 0.20 (1.72,1.86)	—	2	0.96
		Vascular	1.90 ± 0.42 (1.76,2.05)	1.90 ± 0.43 (1.75,2.05)	1.89 ± 0.29 (1.79,1.99)	1.98 ± 0.26 (1.89,2.07)		

AC = anterior cingulate; PC = posterior cingulate.
Data are mean ± SD followed by 95% confidence interval in parentheses, with cerebellar cortex as reference region.

The nature and distribution of the Aβ plaques deposited in the cerebellar samples in this study are fully in keeping with earlier descriptions (*11,13*). Most of the diffuse Aβ plaques in the cerebellum were present in the molecular layer, although in some AD cases diffuse Aβ plaques have been observed in the Purkinje cell and granular cell layers (*13–17*). It has been suggested that the pathology of cerebellar Aβ plaques is similar but not identical to the respective Aβ deposits in the cerebral cortex, as some of the accompanying elements of AD pathology, including neurofibrillary tangles and microglial activation, appear to be either absent in the cerebellum or much less common there (*11,22*). Thus, compared with cerebral Aβ plaques in AD, cerebellar Aβ plaques have been considered to possibly represent an earlier form of plaque evolution or even an attenuated stage in the process of plaque maturation. These suggestions may reflect the observation that cerebellar pathology in AD is not as readily demonstrable by either classic neuropathologic staining techniques or classic neuroimaging methods.

Cerebellum as Reference Region in ^{18}F-Florbetaben Amyloid PET

Selection of the reference region in the brain has been emphasized as one of the most critical factors affecting Aβ PET measurements (*4*). One reason that the cerebellar cortex was selected for the first Aβ PET studies with ^{11}C-Pittsburgh compound B (PIB) was the finding that clearance of this tracer from the cerebellar gray matter is more similar to its clearance from the cerebral gray matter target regions than from cerebral white matter (*23*). Moreover, in most patients for whom diagnostic use of brain Aβ imaging is intended, the cerebellum is likely to be devoid of Aβ. Cerebellar retention of ^{11}C-PIB in familial AD patients has been reported (*8*), leading to the suggestion that the cerebellum may not be an appropriate reference region for ^{11}C-PIB in subjects with a likelihood of cerebellar Aβ plaques (*24*). However, to the best of our knowledge, these previous studies did not perform correlations between the in vivo ^{11}C-PIB PET findings and the postmortem cerebellar pathologic findings in the same individuals. No familial AD cases were included in our study; thus, the potential effect of ^{18}F-florbetaben binding to cerebellar Aβ in the SUVR in these cases remains unknown. However, Aβ PET imaging has been considered inappropriate when the diagnosis is based solely "on a positive family history of dementia or presence of *Apolipoprotein E (APOE)ε4*" (*21*). The results from our study show that ^{18}F-florbetaben retention in the cerebellum (SUV) is not affected by the presence of cerebellar Aβ pathology in end-of-life patients (including those with advanced AD) and that when ^{18}F-florbetaben is used as an Aβ PET tracer with cerebellar cortical gray matter as the reference region, the potential influence of cerebellar Aβ deposits on cortical SUVRs is negligible. From a biologic perspective, the cerebellar cortex is the most appropriate reference region for Aβ PET quantification, and this study supports its use in ^{18}F-florbetaben Aβ PET scans.

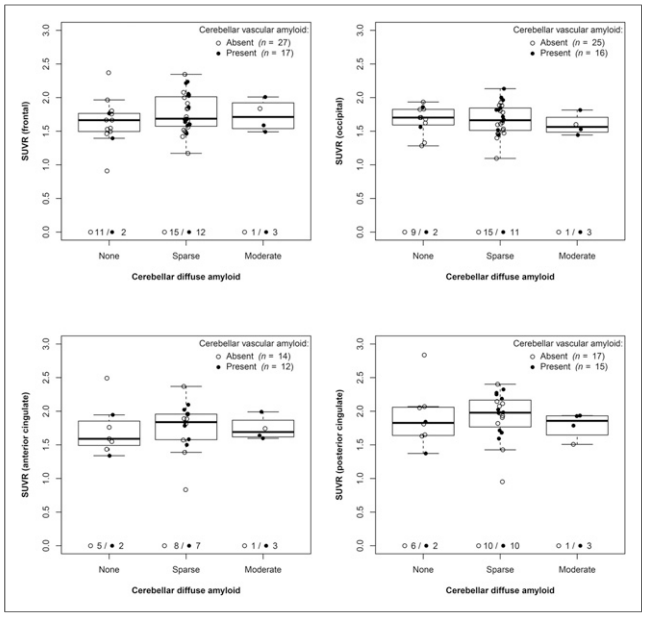

FIGURE 2. ^{18}F-florbetaben SUVR distribution in 4 cortical regions studied according to different cerebellar diffuse Aβ plaque loads in subjects with presence of cerebral cortical Aβ plaques. "None" and "sparse" scores were rated as absence of Aβ plaques.

In the absence of direct PET-and-pathology correlation studies to address the influence of cerebellar Aβ pathology on cortical SUVRs when other Aβ PET tracers are used, the search for alternative reference regions to the cerebellum for each amyloid PET tracer has been the subject of recent active research. The pons and the subcortical white matter are the two main regions studied as an alternative reference region to the cerebellum (*7,25,26*). Whereas the pons has similar blood flow characteristics to the cerebral cortex (*27*), supporting its use as a reference region in brain ^{18}F-FDG and ^{18}F-flutemetamol PET scans, this is not the case for the subcortical white matter (*23,28*). The pharmacokinetics of ^{11}C-PIB in the pons (and subcortical white matter) differ from those in cerebral cortical areas in subjects without brain Aβ deposition

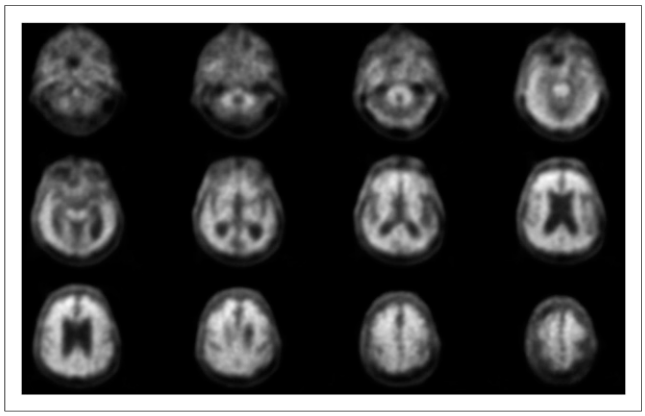

FIGURE 3. Representative ^{18}F-florbetaben PET images of subject with sparse diffuse Aβ plaques in cerebellum and frequent diffuse Aβ plaques in all cortical regions, with moderate neuritic plaques in frontal cortex and moderate vascular Aβ in occipital cortex. SUVR is 2.08 in frontal cortex, 1.50 in occipital cortex, 2.26 in anterior cingulate cortex, and 2.22 in posterior cingulate cortex.

(*23*). Therefore, ^{11}C-PIB pharmacokinetics in the pons may not adequately represent the cerebral cortical tissue kinetics of nonspecifically bound and free ^{11}C-PIB. Nevertheless, SUVRs using the pons as the reference region have been applied for ^{11}C-PIB when there is retention in the cerebellum (*24*). The presence of subcortical white matter abnormalities with different flow and cellular characteristics across aged subjects, such as white matter vascular pathology, is frequent in the elderly population (*29–31*), and therefore the SUV in this region is not stable, thus weakening the rationale for exploring the subcortical white matter as a reference region for Aβ PET quantification.

Potential issues arising from the use of the cerebellar cortex as the reference region include technical factors. In PET centers with little experience in brain PET scans and head positioning, the proximity of the cerebellum to the edge of the scanner field of view may lead to signal noise and truncation (*4*). The small volumes of interest, which contain low counts, may lead to statistical noise and high variability of measurements. This may explain in part the rationale for attempting to use the subcortical white matter as the reference region in patients followed longitudinally with ^{18}F-florbetapir (*32*). However, the use of the whole cerebellum (including gray and white matter) in the volume of interest would increase the statistical counts in the reference region. A recent study on patients with different cerebral Aβ statuses compared, across time, different reference regions across different amyloid tracers (^{18}F-flutemetamol, $n = 258$; ^{18}F-florbetapir, $n = 184$; and ^{18}F-florbetaben, $n = 211$) under different clinical conditions. For ^{18}F-florbetaben, cerebellar gray matter was found to be the most stable reference region across the examined conditions, but for ^{18}F-flutemetamol and ^{18}F-florbetapir, a composite of the subcortical white matter + pons and the subcortical white matter, respectively, were reported as the most stable reference regions (*33*). Although a longitudinal comparison of different reference regions using ^{18}F-florbetaben was not an objective of our current study, our results with ^{18}F-florbetaben are consistent with the findings of

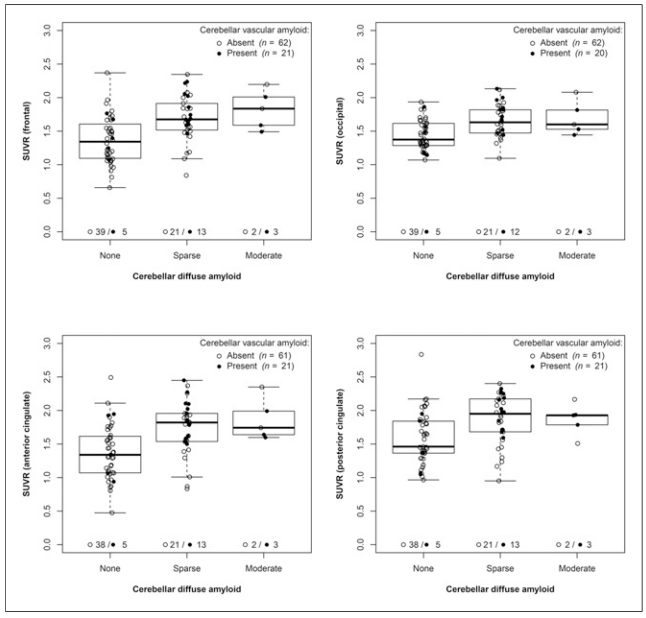

FIGURE 4. ^{18}F-florbetaben SUVR distribution in 4 cortical regions studied according to different cerebellar diffuse Aβ plaque loads in full sample of subjects rated with either absence or presence of cerebral cortical Aβ plaques. "None" and "sparse" scores were rated as absence of Aβ plaques.

that previous study (*33*), reinforcing the appropriateness of the cerebellar cortex as a reference region for this tracer. A cross-sectional study comparing ^{18}F-florbetaben SUVR results across the cerebellar cortex, whole cerebellum, pons, and white matter as reference regions showed no significant differences in effect sizes, correlation coefficients, test–retest variability, or intraclass correlation coefficients across the different reference regions (*34*). Altogether, these results show that ^{18}F-florbetaben quantification is very robust and that the cerebellar cortex is the most appropriate reference region for ^{18}F-florbetaben from both theoretic and biologic perspectives and can be used in any clinical setting in which this amyloid tracer is used.

CONCLUSION

This study, a within-subject PET-and-pathology correlation, addressed the potential influence of cerebellar Aβ pathology on ^{18}F-florbetaben quantification in an end-of-life population that included cases of advanced-stage AD. The effect of cerebellar Aβ pathology on ^{18}F-florbetaben SUVR quantification was found to be negligible, even in subjects with a high Aβ load in the cerebral cortex. Thus, our findings support the use of cerebellar cortical gray matter as the reference region for ^{18}F-florbetaben SUVR quantification.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. The trial was funded by Bayer Pharma AG, Berlin (Germany), and Piramal Imaging S.A., Matran (Switzerland). No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank Aleksandar Jovalekic for his editorial and coordination contributions. We also thank the whole florbetaben study group.

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