In Vivo assessment of brain white matter inflammation in multiple sclerosis with (18)F-PBR111 PET

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Abstract

PET radioligand binding to the 18-kD Translocator Protein (TSPO) in brains of patients with multiple sclerosis (MS) primarily reflects activated microglia and macrophages. We previously developed genetic stratification for accurate quantitative estimation of TSPO using second generation PET radioligands. In this study, we used ^{18}F-PBR111 PET and MRI to measure relative binding in lesional, peri-lesional, and surrounding normal appearing white matter of MS patients, as an index of the innate immune response.

Methods: ^{18}F-PBR111 binding was quantified in 11 MS patients and 11 age-matched healthy volunteers, stratified according to the rs6971 *TSPO* gene polymorphism. Fluid attenuated inversion recovery (FLAIR) and magnetization transfer ratio (MTR) MRI were used to segment the white matter in MS patients as lesions, perilesional volumes, non-lesional white matter with reduced MTR and non-lesional white matter with normal MTR.

Results: ^{18}F-PBR111 binding was higher in the white matter lesions and perilesional volumes of MS patients than in white matter of healthy controls ($p<0.05$). Although there was substantial heterogeneity in binding between different lesions, a within-subject analysis showed higher ^{18}F-PBR111 binding in MS lesions ($p<0.05$) and in perilesional ($p<0.05$) and non-lesional white matter with reduced MTR ($p<0.005$) than in non-lesional white matter with a normal MTR. A positive correlation was observed between the mean ^{18}F-PBR111 V_T increase in lesions relative to non-lesional white matter with a normal MTR and the multiple sclerosis severity score (MSSS) (Spearman's $\rho=0.62$, $p<0.05$).

Conclusions: This study demonstrates that quantitative TSPO PET with a second generation radioligand can be used to characterize innate immune responses in MS *in vivo*, and provides further evidence supporting an association between the white matter TSPO PET signal in lesions

and disease severity. Our approach is practical for extension to studies of the role of the innate immune response in MS for differentiation of anti-inflammatory effects of new medicines and their longer term impact on clinical outcome.

Keywords

Multiple sclerosis, TSPO, microglia, lesion, PET, MTR

INTRODUCTION

A prominent neuropathological feature of Multiple Sclerosis (MS) is the activation of microglia, resident brain innate immune response cells, in the white matter (WM) particularly within demyelinating lesions, but also extending into adjacent WM tissue (*1-4*).

MRI markers specifically associated with microglial and macrophage activation are limited. Correlational post-mortem neuropathology and MRI in MS have confirmed that T1-weighted gadolinium (Gd) contrast enhancement and associated T2-weighted hyperintensity changes in WM reflect the adaptive immune response, but do not specifically inform on relative macrophage or microglial involvement (*5*). T2-weighted white matter hyperintensities also are non-specifically associated with other pathological features including demyelination, axonal loss and astrogliosis (*6*). A recent study found that subtle reductions in the MRI magnetization transfer ratio (MTR) in peri-lesional WM volumes are associated with increased microglia density (*7*). However, decreases in MTR reflect other changes in tissue microstructure, such as demyelination, as well and do not provide specific biomarker for innate immune activation.

PET radioligand binding to the 18-kD Translocator Protein (TSPO) in brains of patients with MS primarily reflects activated microglia and macrophages (*8, 9*). However, the interpretation of the findings of early studies, using the first generation PET tracer ^{11}C-(R)-PK11195, is limited by the rather poor signal-to-noise ratio for this tracer and non-specific binding, which challenge accurate quantitation of the signal (*8, 10-12*).

A number of second generation TSPO PET radioligands with improved signal-to-noise ratio relative to ^{11}C-(R)-PK11195, have been developed (*13*). Unexpectedly, the first two studies using newer TSPO radioligands did not report increases in WM binding of MS patients relative to healthy controls (*14, 15*). However, the analyses did not take into consideration the

population variation in binding of radioligands associated with the rs6971 *TSPO* gene single nucleotide polymorphism (SNP) (*16*). Heterogeneity of binding across carriers of different alleles may have contributed to the failure to differentiate brain TSPO radioligand binding between MS patients and healthy controls successfully.

^{18}F-PBR111 is a second generation TSPO ligand with promising imaging characteristics (*17*). A recent study showed increased ^{18}F-PBR111 uptake corresponding specifically to activated microglia in experimental autoimmune encephalomyelitis (EAE) (*18*). We have developed a robust approach for quantitative *in vivo* assessment of specific ^{18}F-PBR111 binding to TSPO (*19*).

Here, we have used ^{18}F-PBR111 PET co-registered with MRI to evaluate regional binding to WM in healthy volunteers and in MS patients who were stratified genetically according to the rs6971 SNP. Based on post-mortem descriptions of activated microglia and macrophage distributions (*1, 7, 20*), we predicted increased ^{18}F-PBR111 binding in regions of T2-hyperintense lesions, in the immediate peri-lesional volumes, and in non-lesional volumes with reduced MTR, compared to that in WM of healthy volunteers and WM with a normal MTR ("normal appearing") in MS patients. The reproducibility of ^{18}F-PBR111 signal also was assessed in five subjects (four healthy volunteers and one MS patient).

MATERIALS AND METHODS

Study Design

This was an open-label study in patients with relapsing-remitting MS and age-matched healthy volunteers (n=11 per group, see Supplemental Data for details). All subjects were genotyped for the rs6971 SNP, that determines variations in affinity between subjects (who express either a

high affinity (HAB) or low affinity (LAB) or co-expression of both binding states (MAB)) for second-generation TSPO radioligands (*16*). Patients with MS and healthy volunteers were matched for the rs6971 SNP (Supplemental Table 1).

Each participant underwent an MRI scan and a ^{18}F-PBR111 PET scan on the same day. Four healthy volunteers and one MS patient (all HABs) underwent a second ^{18}F-PBR111 PET scan on the following day in order to evaluate the reproducibility of the PET signal.

Disability was assessed by an experienced consultant neurologist using the Expanded Disability Status Scale (EDSS). The Multiple Sclerosis Severity Score (MSSS) was calculated based on EDSS scores and disease duration according to Roxburgh *et al.* (*21*).

Imaging Methods

Details on radioligand synthesis, PET protocol and MRI protocol are described in the Supplemental Data.

^{18}F-PBR111 was injected as an intravenous bolus over approximately 20 seconds and PET emission data collected in 3D-mode for 120 min post injection. The injected activity was similar in healthy volunteers and MS patients (164.6 MBq ± 9 and 169.7 MBq ± 12.4 [mean ± SD], respectively).

Definition of Volumes of Interest. The definition of the whole WM and T2- Fluid attenuated inversion recovery (FLAIR) hyperintense WM volumes is described in details in the Supplemental Methods.

The remaining WM in the MS patients (remaining after exclusion of the T2-FLAIR hyperintense lesions) was further segmented to three Volumes of Interest (VOIs) as follows: perilesional volumes, including voxels within a 6 mm-thick volume disposed around T2-

hyperintense lesions (Fig. 1A and B); non-lesional low MTR (NLLM) voxels, with MTR ranging between 90-98% of the non-lesional mean WM MTR (*7*) (Fig. 1C); non-lesional high MTR (NLHM) voxels, showing MTR ≥ 98% of the non-lesional mean WM MTR (*7*). The NLHM VOI was assumed to be representative of the normal WM tissue.

PET Quantification. Dynamic PET data were corrected for motion via frame-to-frame image registration and aligned with the individual's structural T1 MRI image using SPM5 (Wellcome Trust Center for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) with a mutual information cost function.

A two-tissue compartment kinetic model with a metabolite-corrected plasma input function was applied to the dynamic PET data using a fixed blood volume correction of 5% (*19*). For each VOI examined, the total Volume of Distribution (V_T) was estimated from the rate constants as described previously (*22*). The Logan graphical method (*23*) employing a plasma input, using a fixed blood volume correction of 5% and a linear start time at 35 minutes was also used to estimate the V_T of each VOI and further applied at the voxel level to produce parametric V_T maps. Model fitting and parameter estimation was performed using software implemented in Matlab R2008b (The MathWorks Inc., Natick, MA, USA).

Summary of statistics

We expressed ^{18}F-PBR111 V_T for the whole WM as V_T^{WM}. For each subject the mean ^{18}F-PBR111 V_T uptake of all lesions larger than 100 voxels (V_T^{L}) and perilesional volumes (V_T^{PL}), respectively, was computed. Uptake of ^{18}F-PBR111 in NLLM and NLHM were expressed as V_T^{NLLM} and V_T^{NLHM}, respectively. We used non-parametric statistic analysis with contrasts of V_T^{WM} in healthy controls to each of MS patients' ROIs (V_T^{WM}, V_T^{L}, V_T^{PL}, V_T^{NLLM}, V_T^{NLHM}). Similarly we used non-parametric tests for the contrasts within MS patients

(V_T^L, V_T^{PL}, and V_T^{NLLM} were separately compared to V_T^{NLHM}). Details of the statistical analyses are presented in the Supplemental Methods. The relative increase (Δ) in ^{18}F-PBR111 uptake in lesions, perilesional, and NLLM volumes vs NLHM, was computed as follows:

$$\Delta_L = (V_T^L - V_T^{NLHM})/V_T^{NLHM}$$

$$\Delta_{PL} = (V_T^{PL} - V_T^{NLHM})/V_T^{NLHM}$$

$$\Delta_{NLLM} = (V_T^{NLLM} - V_T^{NLHM})/V_T^{NLHM}$$

The variability across individual lesions, within each MS patient, was expressed using the coefficient of variation (C_V) in V_T^L across individual lesions, as follows:

$$C_V = \text{Standard Deviation}(V_T^L)/\text{Mean}(V_T^L)$$

Test-retest variability of V_T^{WM} was studied in four healthy volunteers and one MS patient, and was expressed as the absolute difference between the two consecutive days scans divided by the mean of the two scans. For the MS patient who was studied twice in consecutive days, we assessed test-retest variability of individual V_T^L and V_T^{PL}. Additionally, we calculated test-retest variability of individual *normalized* lesional and perilesional Distribution Volume Ratio (DVR) by normalising the corresponding V_T values by V_T^{NLHM}. The DVR was computed as follows:

$$DVR_L = V_T^L/V_T^{NLHM}$$

$$DVR_{PL} = V_T^{PL}/V_T^{NLHM}$$

Details on correlational analyses are presented in the Supplemental Methods.

RESULTS

The demographic and clinical characteristics of study participants are presented in Supplemental Table 1. MS patients (10 F, 1 M) and healthy controls (5 F, 6 M) were matched for genotype (7 HABs, 2 MABs, and 2 LABs in each group) and had similar age distributions (healthy controls 51 years (28 – 65) [median (range)] and MS patients 42 years (28 – 59), Wilcoxon Rank p=0.80).

Between Subjects Contrasts

We observed a significant effect of *TSPO* genotype on WM binding of ^{18}F-PBR111 over the whole population (V_T^{WM}, HABs 3.53 (2.12 – 5.40) [median (range)]; MAB 3.00 (2.50 – 4.43); and LAB 1.47 (1.18-1.70); Kruskal-Wallis p<0.01).

Whole white matter

We saw a trend towards lower whole WM binding in healthy controls compared to MS patients (V_T^{WM}, healthy controls 2.50 (1.18 – 5.23); MS patients 3.53 (1.62 – 4.55); Wilcoxon Rank p=0.06)(Fig. 2A and Supplemental Fig. 1). In MS patients, the V_T^{WM} correlated with disease duration in HABs (Fig. 2B) (Spearman's ρ=0.86; p=0.03, corrected for age). The relationship between V_T^{WM} and disease duration was not assessed in the MAB and LAB groups separately, as each of these groups had only 2 subjects per group.

MRI Segmentation-Based VOIs. One hundred sixty-three T2 FLAIR lesions were identified in the patients [median total lesion volume per patient, 12708 mm^3 (range, 392-32672 mm^3)]. 96/163 individual lesions were larger than 100 voxels in volume (median number of lesions larger than 100 voxels per patient, 8; range, 1-17).

Both V_T^{L} (median, 3.88; range, 1.44 – 5.50) and V_T^{PL} (median, 3.61; range: 1.59 – 4.66) were greater than the V_T^{WM} from healthy controls (median, 2.50; range, 1.18 – 5.23; Wilcoxon Rank p=0.02 and p=0.03, respectively for V_T^{L} and V_T^{PL}; Fig. 3). Direct contrasts between healthy

controls V_T^{WM} and MS patients V_T^{NLHM} and V_T^{NLLM} demonstrated trends to greater binding in the patients' VOIs (Wilcoxon Rank p=0.09 and p=0.06, respectively; Fig. 3 and Supplemental Fig. 1).

Within Subjects Contrasts

Relative ^{18}F-PBR111 V_T values for individual lesions and perilesional volumes, and in the NLHM and NLLM voxels, are presented separately for each MS patient (see Fig. 4). The median C_V in V_T^L across individual lesions within the patients was 15.2% (range, 9 - 25%).

We found V_T in lesional (Δ_L, 10.7% (-9.5 – 35.6) [median (range)]; Wilcoxon Rank p=0.03), perilesional (Δ_{PL} 5.2% (-3.5 – 14.6); Wilcoxon Rank p=0.01) and NLLM volumes (Δ_{NLLM} 1.2% (0 – 2.4); Wilcoxon Rank p=0.004) was increased relative to the V_T in NLHM volumes within the MS patients. The maximum ^{18}F-PBR111 uptake increase relative to NLHM volumes was higher in lesions (89%) than in the perilesional volumes (54%). 60% of lesions and 67% of perilesional volumes had higher ^{18}F-PBR111 V_T relative to NLHM.

Fig. 5 (A-C) overlays locally thresholded ^{18}F-PBR111 V_T increases on T2 FLAIR hyperintense volumes in two patients with different clinical characteristics. In a patient who had experienced high disease activity (5 relapses in the last 2 years; Supplemental Table 1, case 9), T2 FLAIR hyperintense lesion areas correspond to areas of increased ^{18}F-PBR111 signal. Conversely, in a patient with a more benign disease course and with no history of new neurological symptoms reported over the past 2 years (Supplemental Table 1, case 4), focal areas of increased radiotracer binding correspond poorly with T2 hyperintense regions of WM (Fig. 5, D-F).

Disease severity, as assessed from MSSS scores, correlated with the mean ^{18}F-PBR111 V_T increase in lesions for each patient (expressed relative to that in individual NLHM WM) (Spearman's ρ=0.62; p=0.05; Fig. 6).

Test-Retest Reproducibility

The test-retest variability in ^{18}F-PBR111 V_T^{WM} across subjects (four healthy volunteers, one MS patient) was 23% (12% - 55%) [median (range)]. The test-retest variabilities in ^{18}F-PBR111 V_T^{L} and V_T^{PL} across the 18 T2- hyperintense lesion volumes identified in the MS patient who was studied twice on consecutive days were 25% (12% - 57%) and 27% (17% - 36%), respectively, while the median test-retest variabilities for the normalized DVR^{L} and DVR^{PL} were 8% (range 1%-31%) and 4% (range 0%-9%), respectively.

DISCUSSION

TSPO PET can be used to assess the innate immune response in patients with MS *in vivo*, although methodological and technical challenges have limited its wide application. We have illustrated how corrected, quantitative measures with a second generation TSPO radioligand, ^{18}F-PBR111, promise new insights concerning clinical-pathological correlations relevant to disease progression. We found increased ^{18}F-PBR111 V_T in the WM lesional and perilesional volumes of MS patients compared to healthy volunteers. ^{18}F-PBR111 V_T was higher in lesions, perilesional and non-lesional volumes with decreased MTR (NLLM) in MS patients relative to the normal-appearing WM of the same subjects. Moreover, relative ^{18}F-PBR111 V_T increase in the MS lesions was positively correlated with disease severity, adding to recent *in vivo* data consistent with a role for the innate immune response in the progression of neurodegeneration in MS (*24*).

Post-mortem autoradiographic studies in brains of patients with MS have consistently demonstrated that increased uptake of TSPO-targeted radioligands co-localizes with markers of activated microglia (*8, 11, 25, 26*). An immunohistochemical analysis of post-mortem MS brain

tissue was largely consistent with these findings, suggesting that most cells expressing TSPO in acute MS lesions were macrophages or microglia (*9*), although it should be cautioned that antibody-based localization of the TSPO peptide and expression of the binding domain for the TSPO radioligands need not be the same. In a relapsing-remitting EAE model (*18*), increased ^{18}F-PBR111 uptake co-localizes with activated microglia and macrophages and parallels the temporal dynamics of their up regulation during experimentally induced relapses.

We observed an increased ^{18}F-PBR111 uptake in approximately two-thirds of MRI-defined lesions and perilesional volumes in MS patients relative to their normal appearing WM (NLHM). *Ex vivo* pathology studies show that acute, active lesions are characterized by a hypercellular inflammatory core, marked by prominent lymphocyte infiltration with high density of activated microglia and macrophages distributed evenly throughout the lesion (*27*). Case 9 (Fig. 5, top row) illustrates the strong co-localisation of increased ^{18}F-PBR111 V_T with T2-hyperintense lesions in active disease. In chronic active lesions, microglia are increased relative to distant normal WM tissue and are more concentrated at the lesion edge than within the lesion. The hypercellular margin, characterized by a high density of activated microglia surrounding demyelinating plaques, is a consistent finding across neuropathological studies (*2, 28, 29*).

By contrast, approximately one third of the MRI-defined lesions and perilesional volumes were associated with ^{18}F-PBR111 uptake similar to, or lower than, that of the normal appearing NLHM WM. Case 4 (Fig. 5, bottom row) is an illustrative example of poor correspondence between areas of increased ^{18}F-PBR111 V_T and T2 FLAIR hyperintensities. We speculate that these volumes represent chronic inactive lesions that are hypocellular or have enlarged extracellular spaces leading to a relatively low density of all cells, including microglia. Our findings of regional variation thus are consistent with post-mortem pathology observations in MS patients.

The median within-subject C_V in lesional ^{18}F-PBR111 uptake was above 15%. This indicates a moderately high variability of the observed ^{18}F-PBR111 signal between the T2 hyperintense lesions even within a single MS patient, and further highlights that T2-hyperintense MRI contrast change reflects a wide range of neuropathology in MS lesions non-specifically (*30*).

An elegant study by Moll *et al.* (*7*), using combined post-mortem pathology and MR imaging, reported that regions appearing normal on T2-weighted MR, but displaying reduced MTR, were associated with microglial activation and axonal degeneration. By applying the same image segmentation approach as Moll *et al.*, we observed a consistently increased ^{18}F-PBR111 uptake in regions with reduced MTR (NLLM) across our study group.

Focal areas of activated microglia identified neuropathologically in WM areas without apparent loss of myelin (*1, 2*) may represent areas at risk for the development of acute inflammatory lesions. They have been described previously as "pre-active lesions" (*5*) or regions of chronic microglial activation that may contribute independently to progressive neurodegeneration (*31*). Alternatively, WM microglial activation in the absence of inflammatory demyelination may represent secondary reactive changes, perhaps associated with Wallerian degeneration (*32*). Direct tests of these alternative hypotheses now seem possible using serial MRI observations to follow the course of these WM changes identified by TSPO PET.

Although this work has gone further than previous studies in using a second generation TSPO radioligand for MRI image-correlated quantitative analyses, our findings are in general agreement with those of some TSPO-targeted PET studies in MS. Previous work using ^{11}C-(R)-PK11195 demonstrated increased uptake to correspond to WM Gd-enhancing lesions (*8, 10, 11*). One early study suggested the presence of focal areas of increased uptake in normal appearing white (and grey) matter (*8*). However, patterns of ligand uptake in T2-weighted hyperintensities, and correlations between ^{11}C-(R)-PK11195 uptake and disease duration and

disability have been inconsistent in previous studies (*8, 10, 33*). This could reflect differences in patient populations, differences in the proportion of specific (displaceable) signal between ^{18}F-PBR111 and ^{11}C-(R)-PK11195 or accurate modeling, which is particularly challenging for the lower affinity ^{11}C-(R)-PK11195 (*24, 34*).

This is the first study using a second generation TSPO ligand to successfully detect significant differences in radioligand uptake between MS patients and healthy controls. The lack of differences seen in previous studies may be explained by failure to control for the variance introduced by the rs6971 TSPO SNP (*14, 15*).

There are a number of limitations of our study.

We studied only a small number of patients. Further characterization of the heterogeneity of the disease is needed. The use of disease-modifying treatments in the majority of MS patients studied may have influenced the ^{18}F-PBR111 signal. A study by Ratchford and colleagues showed a 3.2% reduction in ^{11}C-(R)-PK11195 in relapsing-remitting MS patients after 1-year treatment with glatiramer acetate, for example (*35*). This estimate of treatment effect is much lower than the differences in binding we found between healthy volunteers and patients overall, however (approximately 40% in the whole white matter). However, in future work, it will be important to investigate the effects of various MS treatments on TSPO specific binding.

MS patients and healthy controls were not matched for gender, although to our knowledge there have been no reports of a gender effect on TSPO binding in humans. Studies in rodents suggested a higher number of microglia and astrocytes in adult females (*36, 37*), so we cannot exclude the possibility that a higher prevalence of women in the MS group may have contributed to the higher ^{18}F-PBR111 V_T in patients.

Finally, increased TSPO is seen not just in activated microglia, but also in rare, activated astrocytes (*9*) and in lymphocytes (*38*), as well as in brain vascular endothelia (*39*). The interpretation of increased ^{18}F-PBR111 V_T reported here as arising largely from activated macrophages or microglia is based on prior neuropathological studies demonstrating large numbers of these cells post-mortem in the regions studied and on the relatively high binding to them relative to other inflammatory cells (*2, 27-29*). A contribution from other inflammatory cell types cannot be excluded, but binding (B_{max}) to lymphocytes is relatively much lower (*40*). Further technical aspects are considered in the Supplemental Data.

CONCLUSION

This study demonstrates that quantitative TSPO PET with a second generation radioligand is sensitive to an element of the inflammatory response in MS not apparent on MRI and so otherwise occult *in vivo.* It highlights opportunities for the integration of MRI and molecular imaging for understanding the evolution of the dynamic neuropathology of MS.

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Figure Legends

Figure 1. **A)** T2 FLAIR image of a representative MS patient (case 1, Supplemental Table 1). Hyperintense areas correspond to demyelinating lesions. **B)** Lesion (dark blue) and perilesional areas (light blue) corresponding to the intersection of 6 mm diameter sphere traced around lesions within the image plane **C)** Non-lesional voxels with MTR values ranging between 90-98% of the mean MTR of non lesional WM tissue (NLLM) (copper).

Figure 2. A) ^{18}F-PBR111 V_T in the whole WM of MS patients and genotype- and age- matched healthy control subjects. The line in the middle of the boxes are median values, while the hinges represent the 25th and the 75th percentile respectively. Whiskers represent the maximum and minimum values. The contrast between MS patients and healthy controls showed a trend for higher ^{18}F-PBR111 V_T^{WM} in MS patients (Wilcoxon Rank p=0.062). **B)** Relationship between whole WM ^{18}F-PBR111 V_T and disease duration in MS patients for patients with different rs6971 genotypes (Pearson's partial correlation in HABs: r=0.83; p<0.05, corrected for age).

Figure 3. ^{18}F-PBR111 uptake in healthy volunteers and across MS patients ROIs. The line in the middle of the boxes are median values, while the hinges represent the 25th and the 75th percentile respectively. Whiskers represent the maximum and minimum values. Between-groups contrasts showed: MS patients' ^{18}F-PBR111 V_T^L and V_T^{PL} > healthy volunteers' V_T^{WM} (Wilcoxon Rank p<0.05). Within MS patients contrasts showed: $V_T^L > V_T^{NLHM}$ and $V_T^{PL} > V_T^{NLHM}$ (Wilcoxon Rank p<0.05), and $V_T^{NLLM} > V_T^{NLHM}$ (Wilcoxon Rank p<0.005).

Figure 4. Relative ^{18}F-PBR111 uptake (relative to the NLHM WM) in NLLM WM, in individual T2 FLAIR lesions and in perilesional volumes for the MS patients studied. The ordinant represents the relative difference in ^{18}F-PBR111 V_T in lesions (◇), perilesional volumes ●, and in NLLM WM (∗) relative to normal-appearing WM (NLHM WM). On the abscissa, MS patients (see Supplemental Table 1) are separately indicated.

Figure 5. A, D) T2 FLAIR images **B, E**) ^{18}F-PBR111 V_T parametric maps, overlaid (in warm colors) on T2 FLAIR images, and **C, F**) overlap between T2 FLAIR lesions (marked in blue) and ^{18}F-PBR111 V_T (in warm colors) from two illustrative patients. The lower threshold for V_T parametric maps corresponds to the value of ^{18}F-PBR111 V_T in the NLHM volume for each of the two patients. The upper threshold is twice the V_T in the NLHM.

The upper row illustrates a patient with recent active disease (Supplemental Table 1, case 9). Here, T2 FLAIR hyperintense lesional areas correspond to areas of increased ^{18}F-PBR111 signal. The lower row illustrates a patient (Supplemental Table 1, case 4) with a relatively benign disease course showing focal regions of increased ^{18}F-PBR111 V_T that correspond poorly to T2 FLAIR hyperintense areas.

Figure 6. Positive relationship between MSSS scores and ^{18}F-PBR111 uptake in lesions (expressed relative to that in normal-appearing WM) (Pearson's $r=0.66$, $p<0.05$).

DISCLOSURE

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