**SUPPLEMENTARY MATERIAL**

**Table e-1. Associations of DTI and TSPO-PET measures in the segmented NAWM with disability and disease severity among MS patients (n = 55)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **EDSS** | | **MSSS** | |
|  | Spearman correlation, ρ | *p* value | Spearman correlation, ρ | *p* value |
| **Segmented NAWM** |  |  |  |  |
| ***Frontal*** |  |  |  |  |
| FA | -0.36 | 0.015\* | -0.32 | 0.094 |
| MD (mm2/sec) | 0.43 | 0.005\* | 0.45 | 0.004\* |
| AD (mm2/sec) | 0.38 | 0.033\* | 0.42 | 0.010\* |
| RD (mm2/sec) | 0.46 | 0.002\* | 0.44 | 0.006\* |
| DVR | 0.35 | 0.049\* | 0.21 | 0.367 |
| ***Parietal*** |  |  |  |  |
| FA | -0.42 | 0.005\* | -0.25 | 0.148 |
| MD (mm2/sec) | 0.35 | 0.011\* | 0.38 | 0.016\* |
| AD (mm2/sec) | 0.22 | 0.290 | 0.38 | 0.018\* |
| RD (mm2/sec) | 0.41 | 0.005\* | 0.36 | 0.036\* |
| DVR | -0.08 | 0.567 | -0.32 | 0.069 |
| ***Temporal*** |  |  |  |  |
| FA | -0.50 | <0.001\* | -0.29 | 0.146 |
| MD (mm2/sec) | 0.38 | 0.010\* | 0.41 | 0.013\* |
| AD (mm2/sec) | 0.14 | 0.323 | 0.40 | 0.015\* |
| RD (mm2/sec) | 0.45 | 0.002\* | 0.38 | 0.028\* |
| DVR | 0.31 | 0.060 | 0.21 | 0.367 |
| ***Occipital*** |  |  |  |  |
| FA | -0.55 | <0.001\* | -0.27 | 0.148 |
| MD (mm2/sec) | 0.49 | <0.001\* | 0.40 | 0.013\* |
| AD (mm2/sec) | 0.23 | 0.290 | 0.45 | 0.005\* |
| RD (mm2/sec) | 0.56 | <0.001\* | 0.36 | 0.036\* |
| DVR | -0.16 | 0.472 | -0.21 | 0.367 |
| ***Cingulate*** |  |  |  |  |
| FA | -0.51 | <0.001\* | -0.34 | 0.078 |
| MD (mm2/sec) | 0.50 | <0.001\* | 0.27 | 0.095 |
| AD (mm2/sec) | 0.31 | 0.116 | 0.11 | 0.431 |
| RD (mm2/sec) | 0.52 | <0.001\* | 0.30 | 0.059 |
| DVR | 0.33 | 0.057 | 0.45 | 0.003\* |
| ***Deep WM*** |  |  |  |  |
| FA | -0.36 | 0.015\* | -0.22 | 0.148 |
| MD (mm2/sec) | 0.39 | 0.009\* | 0.19 | 0.178 |
| AD (mm2/sec) | 0.27 | 0.214 | 0.19 | 0.335 |
| RD (mm2/sec) | 0.41 | 0.005\* | 0.20 | 0.147 |
| DVR, | 0.34 | 0.057 | 0.48 | 0.001\* |
| **Whole NAWM** |  |  |  |  |
| FA | -0.51 | <0.001\*\* | -0.32 | 0.018\*\* |
| MD (mm2/sec) | 0.47 | <0.001\*\* | 0.39 | 0.004\*\* |
| AD (mm2/sec) | 0.30 | 0.031\*\* | 0.34 | 0.013\*\* |
| RD (mm2/sec) | 0.51 | <0.001\*\* | 0.38 | 0.005\*\* |
| DVR | 0.37 | 0.005\*\* | 0.22 | 0.107 |
| \* Significant at the level of p<0.05, adjusted with the Holm correction for the number of brain regions (6). \*\* Significant at the level of p<0.05, Spearman’s nonparametric correlation test. AD = axial diffusivity; DVR = distribution volume ratio; EDSS = expanded disability status scale; FA = fractional anisotropy; MD = mean diffusivity; MS = multiple sclerosis; MSSS = multiple sclerosis severity scale; NAWM = normal appearing white matter; RD = radial diffusivity. | | | | |

**Table e-2. Associations between DTI measurements and NAWM DVR in the segmented NAWM for all MS patients and separately for RRMS and SPMS patients.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **All MS** | | **RRMS** | | **SPMS** | |
| Parameter | Spearman correlation, ρ | *p* value | Spearman correlation, ρ | *p* value | Spearman correlation, ρ | *p* value |
|
| **Segmented NAWM** |  |  |  |  |  |  |
| ***Frontal*** |  |  |  |  |  |  |
| FA | -0.14 | 1 | -0.09 | 1 | -0.10 | 1 |
| MD (mm2/sec) | 0.14 | 1 | 0.15 | 1 | 0.00 | 1 |
| AD (mm2/sec) | 0.08 | 1 | 0.12 | 1 | -0.11 | 1 |
| RD (mm2/sec) | 0.13 | 1 | 0.09 | 1 | 0.06 | 1 |
| ***Parietal*** |  |  |  |  |  |  |
| FA | -0.16 | 1 | -0.07 | 1 | -0.39 | 0.891 |
| MD (mm2/sec) | 0.09 | 1 | 0.02 | 1 | 0.30 | 1 |
| AD (mm2/sec) | 0.07 | 1 | 0.03 | 1 | 0.27 | 1 |
| RD (mm2/sec) | 0.11 | 1 | 0.04 | 1 | 0.30 | 1 |
| ***Temporal*** |  |  |  |  |  |  |
| FA | -0.39 | 0.020\* | -0.47 | 0.014\* | -0.07 | 1 |
| MD (mm2/sec) | 0.41 | 0.014\* | 0.43 | 0.034\* | 0.20 | 1 |
| AD (mm2/sec) | 0.37 | 0.036\* | 0.45 | 0.030\* | 0.26 | 1 |
| RD (mm2/sec) | 0.43 | 0.007\* | 0.48 | 0.012\* | 0.20 | 1 |
| ***Occipital*** |  |  |  |  |  |  |
| FA | -0.11 | 1 | -0.35 | 0.147 | 0.27 | 1 |
| MD (mm2/sec) | 0.09 | 1 | 0.24 | 0.744 | -0.05 | 1 |
| AD (mm2/sec) | 0.09 | 1 | 0.10 | 1 | 0.03 | 1 |
| RD (mm2/sec) | 0.13 | 1 | 0.33 | 0.201 | -0.21 | 1 |
| ***Cingulate*** |  |  |  |  |  |  |
| FA | -0.14 | 1 | -0.01 | 1 | -0.16 | 1 |
| MD (mm2/sec) | 0.10 | 1 | -0.08 | 1 | 0.40 | 0.822 |
| AD (mm2/sec) | 0.10 | 1 | -0.03 | 1 | 0.49 | 0.386 |
| RD (mm2/sec) | 0.11 | 1 | -0.06 | 1 | 0.40 | 0.868 |
| ***Deep WM*** |  |  |  |  |  |  |
| FA | -0.32 | 0.088 | -0.34 | 0.148 | -0.21 | 1 |
| MD (mm2/sec) | 0.10 | 1 | 0.04 | 1 | 0.17 | 1 |
| AD (mm2/sec) | 0.01 | 1 | -0.03 | 1 | 0.00 | 1 |
| RD (mm2/sec) | 0.13 | 1 | 0.08 | 1 | 0.19 | 1 |
| **Whole NAWM** |  |  |  |  |  |  |
| FA | -0.30 | 0.029\*\* | -0.23 | 0.157 | -0.25 | 0.375 |
| MD (mm2/sec) | 0.33 | 0.016\*\* | 0.33 | 0.042\*\* | 0.31 | 0.265 |
| AD (mm2/sec) | 0.28 | 0.039\*\* | 0.32 | 0.051 | 0.30 | 0.277 |
| RD (mm2/sec) | 0.34 | 0.013\*\* | 0.31 | 0.057 | 0.26 | 0.347 |
|  | | | | | | |

\* Significant at the level of p<0.05, adjusted with the Holm correction for the number of brain regions (6). \*\* Significant at the level of p<0.05, Spearman’s nonparametric correlation test. AD = axial diffusivity; DVR = distribution volume ratio; EDSS = expanded disability status scale; FA = fractional anisotropy; MD = mean diffusivity; MS = multiple sclerosis; NAWM = normal appearing white matter; RD = radial diffusivity RRMS=relapsing remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis.

**Figure e-1. Associations between [11C](R)-PK11195 binding in the NAWM and absolute T2 lesion load (A) and the regional T2 lesion burden in segmented brain areas (B) among MS patients (n = 55).**

The correlations are visualized with linear regression lines and Spearman correlation coefficient, significant at the level of *p*<0.05; Lesion burden was evaluated as ratio of lesion volume to volume of respective NAWM region. CIN = cingulate white matter; dWM = deep white matter; DVR=distribution volume; FRO = frontal white matter; MS= multiple sclerosis; NAWM=normal appearing white matter; OCC = occipital white matter; PAR=parietal white matter; RD=radial diffusivity; RRMS=relapsing remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis TMP = temporal white matter;

r = 0.42, p = 0.001

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**Description of the MRI protocol for cMRI sequences**

3D T1-weighted turbo field echo imaging parameters were equal with TR = 8.1ms, TE = 3.7 ms, TA= 4.23 min:sec, FOV=256x256 mm, spatial resolution 1x1x1 mm, acquisition matrix 256x256 mm, flip angle = 7°, 176 slices acquired with acceleration factor 2; FLAIR-VISTA 1mm thick images applied with spectral attenuated inversion recovery (SPAIR) fat suppression method acquired with TR/TI = 8000/2400 ms, TE = 337 ms, TA= 11.12 min:sec, FOV=256x256 mm, acquisition matrix 256x256 mm, 180 slices acquired with acceleration factor 2; T2-weighted turbo spin echo imaging performed with TR/TE = 3756/80 ms, FOV=230x186 mm, acquisition matrix 400x250 mm, 40 slices were acquired with 3mm thickness, flip angle = 90°, TA= 02.15 min:sec.