Supplementary Material

FMRI Complexity Correlates with Tau-PET and Cognitive Decline in Late-Onset and Autosomal Dominant Alzheimer's Disease

Motion as Potential Bias on MSE Calculation

Framewise displacement

In trying to understand whether motion could present a potential bias in computing multi-scale entropy (MSE) and comparing across the groups we calculated and compared the framewise displacement (FD) between all groups using 3-way ANOVAs.

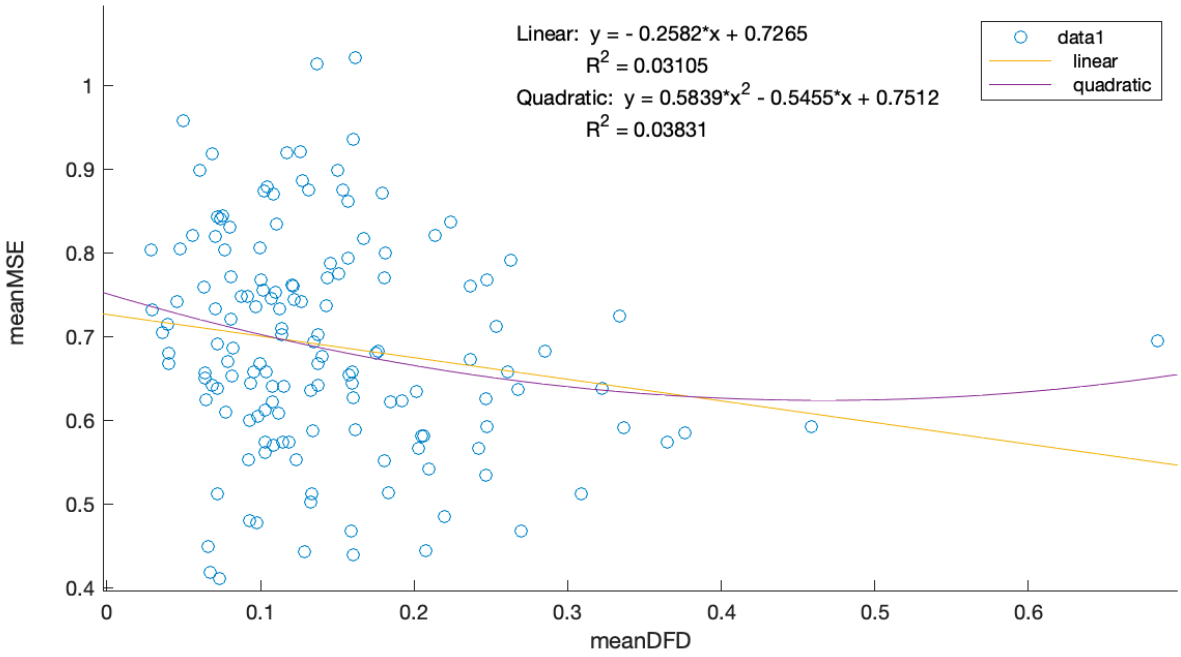
The analysis of FD values showed that there was no statistical difference between the amount of motion across groups. Supplementary Table 1 lists the mean and standard deviation (std) values of FD for each group in each cohort as well as the F and p values resulting from the ANOVAs.

Supplementary Table 1. Analysis of head motion by means of framewise displacement for both cohorts across all diagnostic groups.

ADNI	**meanFD**	**std**	**ANOVA**	
CN	0.14	0.07	F=0.96	p=0.387
MCI	0.15	0.12		
AD	0.18	0.07		
EEAJ-AP	**meanFD**	**std**	**ANOVA**	
CN	0.11	0.10	F=0.31	p=0.732
MCI	0.15	0.22		
AD	0.14	0.16		
EEAJ-PA	**meanFD**	**std**	**ANOVA**	
CN	0.08	0.03	F=1.4	p=0.26
MCI	0.12	0.12		
AD	0.08	0.05		

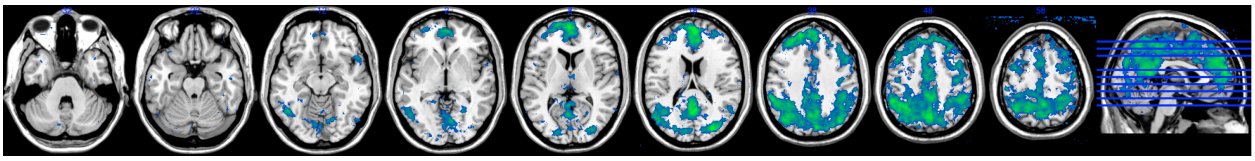
CN, cognitive normal; MCI, mild cognitive impairment; AD, Alzheimer's disease

Despite the non-significant differences in FD, we calculated the correlation between meanFD and global GM-MSE as well as for voxel-wise MSE. We observed a significant but weak association between meanFD and global GM-MSE (r=-0.1762 p=0.0328) suggesting that the more a subject moved the lower the complexity. However, whether this is an effect of head motion on entropy calculation or an indirect effect caused by the fact that more impaired subject tend to move more and a real physiological cause of reduced entropy remains unknown.



Supplementary Figure 1. Association between mean framewise displacement and global grey matter mean multi-scale entropy (MSE) in the ADNI3 cohort.

And finally, there was a significant ($p<0.05$, uncorrected - to show the full extent of potential bias) negative association [colorscale -0.1 to -0.3] between FD and complexity on a voxel-wise level that could be observed mainly in areas of the default mode network. This specific spatial pattern could be interpreted in consideration that there is a relation of motion indexes and arousal: when participants become increasingly drowsy during fMRI scans they display higher head motions. Similarly with increasing drowsiness the complexity in the default mode network might decrease. However, these associations are so far unknown and should be subject to further examinations.

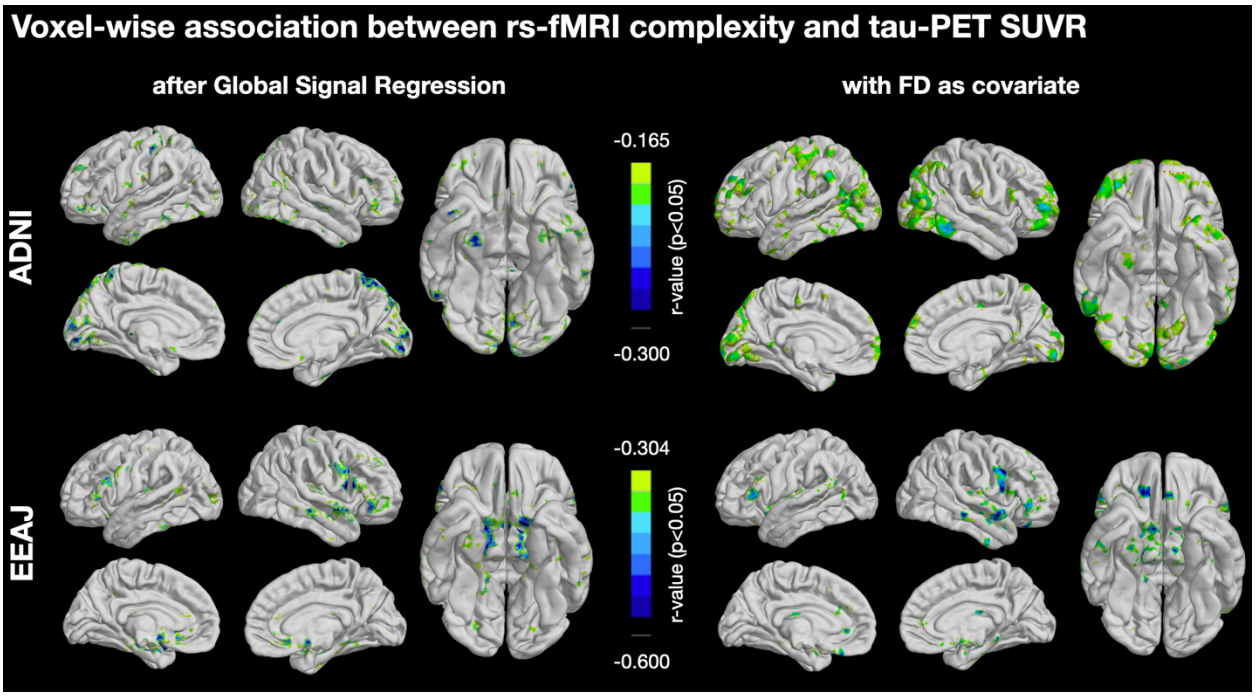


Supplementary Figure 2. Voxel-wise correlation between mean FD and MSE in the ADNI3 cohort.

Global signal regression and inclusion of FD as covariate in analyses

Global signal regression has been discussed as a means to reduce motion related artifacts and the with-it associated signal variability. We therefore performed an additional preprocessing step that removes the global signal from all timeseries and recalculated the MSE maps and corresponding correlation map with tau-PET. Similarly, we also recalculated the correlation between MSE and tau-PET including FD as an additional covariate. The results of these additional analyses are shown in the Supplementary Figure 3 below.

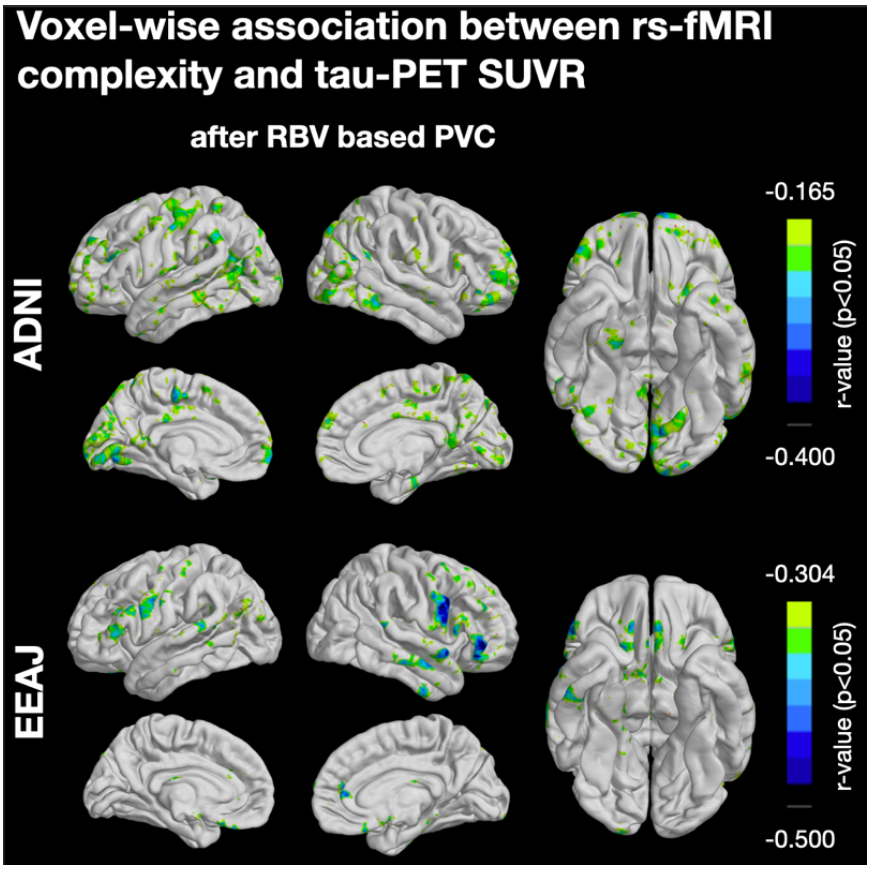
The results of these analyses consistently show negative association between MSE and tau-PET in overlapping areas with the original results. However, GSR and FD-covariate appear to increase the effect, which is notably apparent in the ADNI cohort using FD as a covariate. Understanding the effect of motion on MSE should be systematically explored in future research while here we present supplementary results accounting for different preprocessing steps and inclusion of FD in the statistical model. The main finding of our study however did not change as all analyses revealed negative associations between MSE and tau-PET in inferior temporal areas.



Supplementary Figure 3. Voxel-wise associations between tau-PET SUVR and rs-fMRI complexity after Global Signal Regression (GSR) or including mean Framewise Displacement (FD) as a covariate in the regression model. Top row represents the ADNI cohort the bottom row the EEAJ cohort. ($p<0.05$, uncorrected)

Partial Volume Correction of PET Data

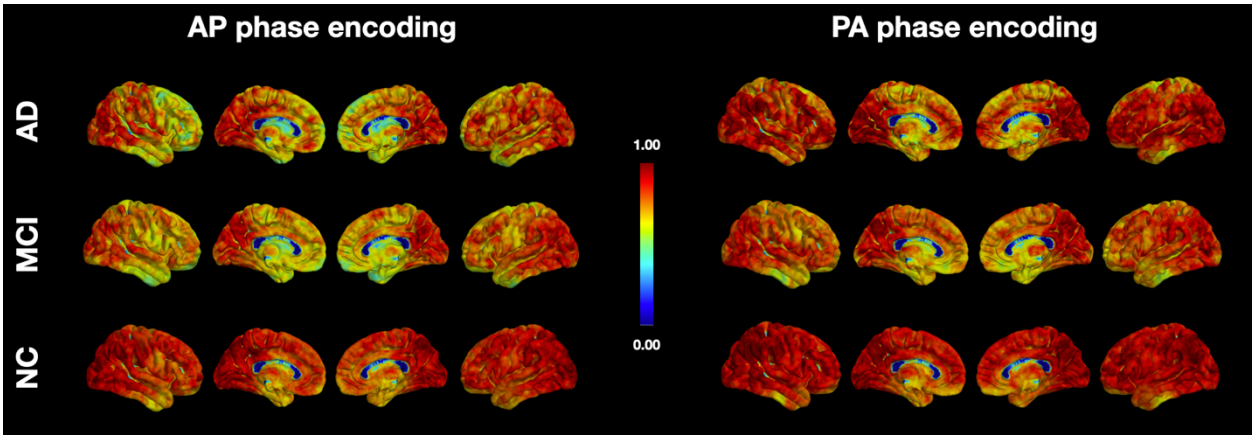
While our main analysis included a voxel-wise covariate for GM probability, partial volume correction (PVC) of PET data has been proposed to account for interindividual differences in atrophy and thus biased PET SUVR values. We repeated the tau-PET preprocessing including PVC based on the region-based voxel-wise (RBV) method implemented in the PetSurfer extension of FreeSurfer. Using these PVC-RBV tau-PET we recalculated correlation with MSE for EEAJ and ADNI cohorts, respectively. Supplementary Figure 4 shows the results for this additional analysis and corroborate the original findings showing negative associations between the two metrics in inferior temporal cortex as well as in parietal and dorsolateral prefrontal cortex.



Supplementary Figure 4. Voxel-wise associations between rs-fMRI complexity and Partial Volume Corrected (PVC) tau-PET SUVR. The region-based voxel-wise (RBV) method was used for PVC. ($p<0.05$, uncorrected)

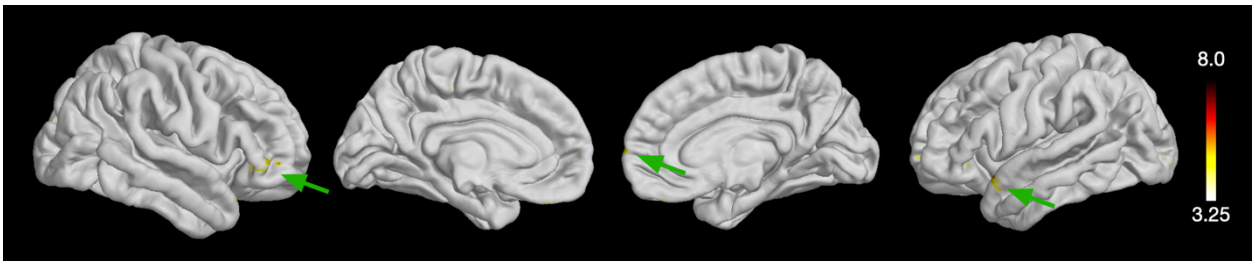
MSE Maps for fMRI Runs with Different Phase-Encoding Direction

The MSE maps for the two fMRI runs with different phase-encoding direction in the EEAJ cohort look qualitatively similar showing the decline of MSE with more severe diagnosis. However, there are some differences in local values as is expected from a measure that is based on resting state fMRI which reflects physiological variability.



Supplementary Figure 5. Mean MSE maps for all diagnostic groups for the two fMRI series in the EEAH cohort with different phase encoding directions. AP, anterior-posterior; PA, posterior-anterior

We statistically tested if there is a significant interaction effect between phase encoding direction) and diagnostic group on MSE values using an ANOVA with factors AP/PA and NC/MCI/AD. There were some areas showing statistically significant interaction effects between encoding direction and group, but these findings did not survive multiple comparison correction. Therefore, a bias of phase encoding direction on the averaged AP/PA maps used in the main manuscript is unlikely.

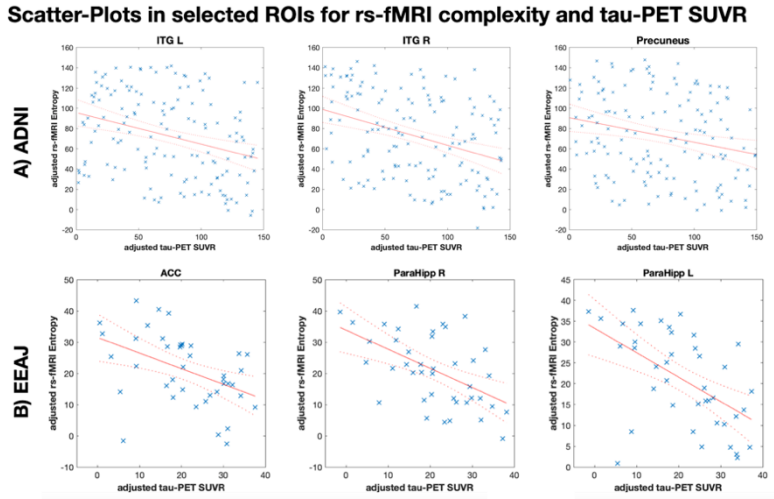


Supplementary Figure 6. ANOVA F-map visualizing the interaction effects between phase-encoding direction and diagnostic group on MSE values. ($p<0.05$, uncorrected)

Added-Variable Plots Displaying the ROI Partial Correlation Analyses

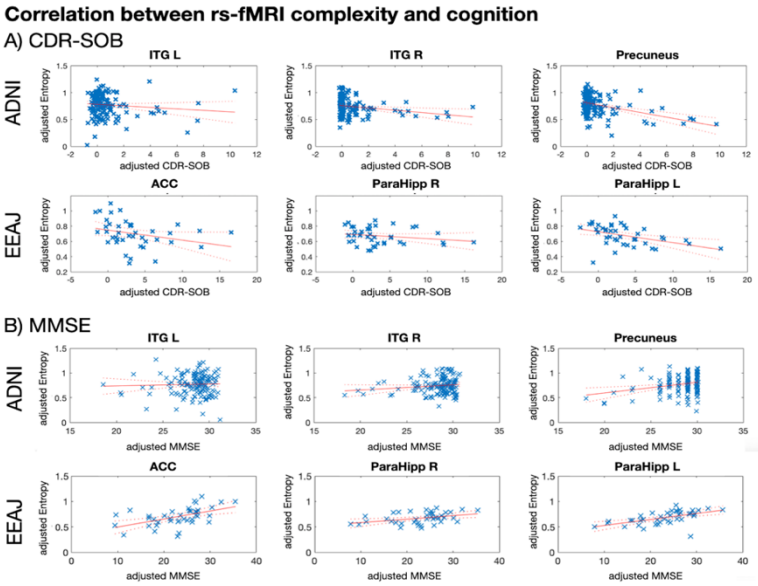
Partial-regression plots, are the multivariate analogue of a simple scatter plot. The values on the x and y axes are representing the residuals of the dependent and independent variables after removing the effects of the covariates.

Partial Spearman-Rank correlation between MSE and tau-PET



Supplementary Figure 7. Partial correlation plots between rs-fMRI complexity and tau-PET SUVR. Partial-regression plots, are the multivariate analogue of a simple scatter plot. The values on the x and y axes are representing the residuals of the dependent and independent variables after removing the effects of the covariates.

Partial Spearman-Rank correlation between MSE and cognitive scores.



Supplementary Figure 8. Partial correlation plots between rs-fMRI complexity and cognition. Partial-regression plots, are the multivariate analogue of a simple scatter plot. The values on the x and y axes are representing the residuals of the dependent and independent variables after removing the effects of the covariates.

MMSE, Mini-Mental State Exam; CDR, Cognitive Dementia Rating; ACC, anterior cingulate cortex; ITG R/L, inferior temporal gyrus left/right; ParaHipp L/R, parahippocampal gyrus left/right