Resting-state functional MRI signal fluctuation amplitudes are correlated with brain amyloid-β deposition in patients with mild cognitive impairment

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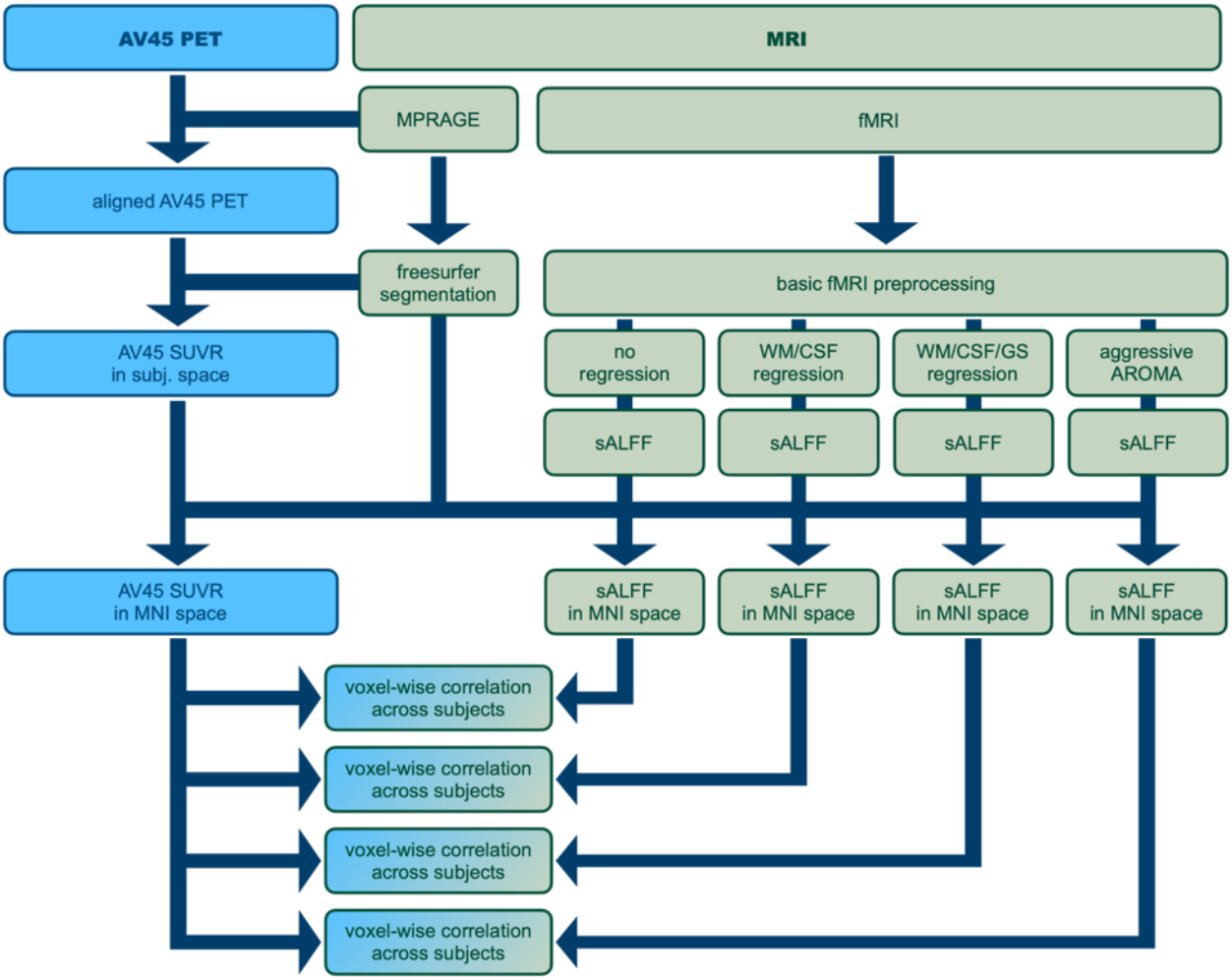
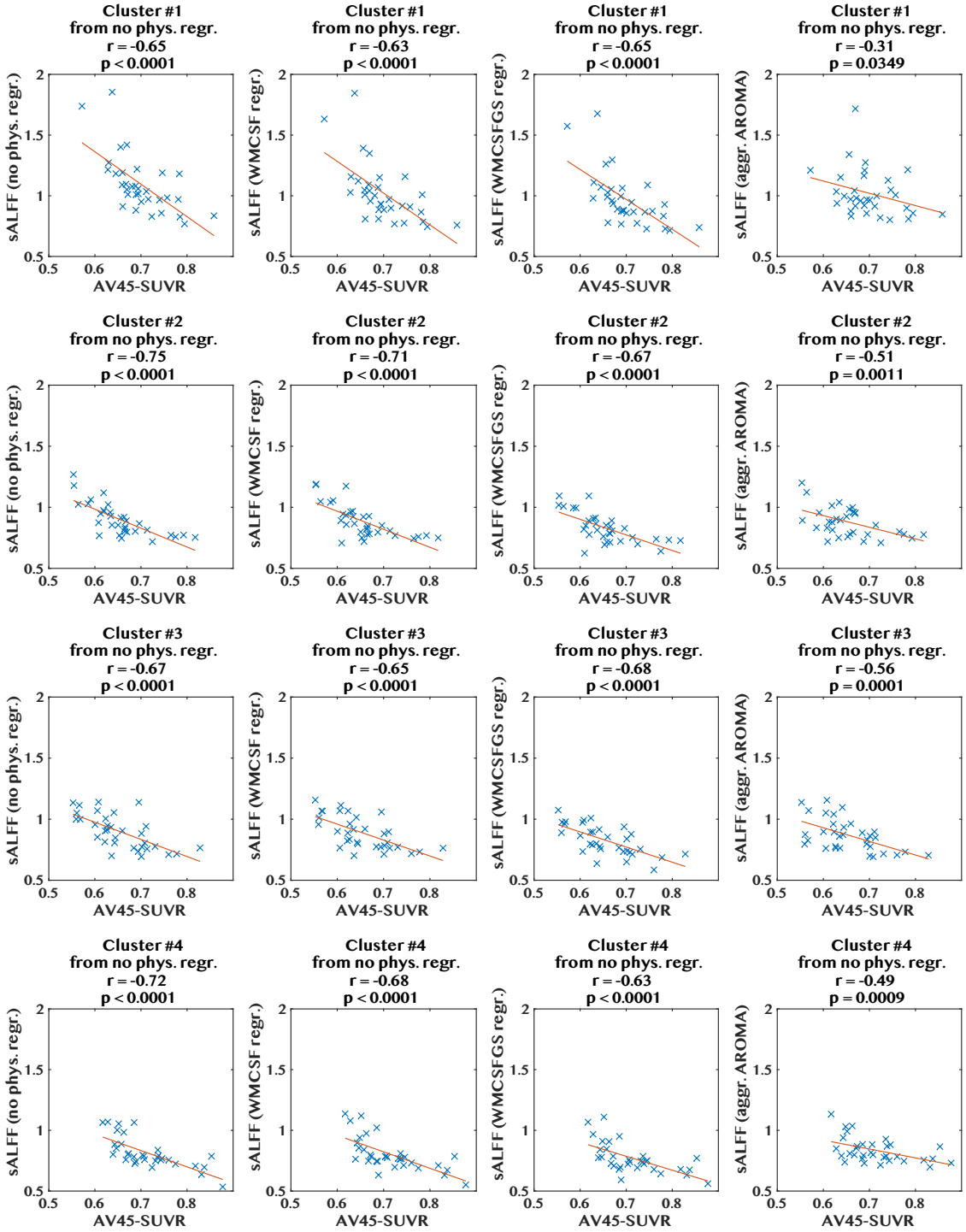
Supplementary material



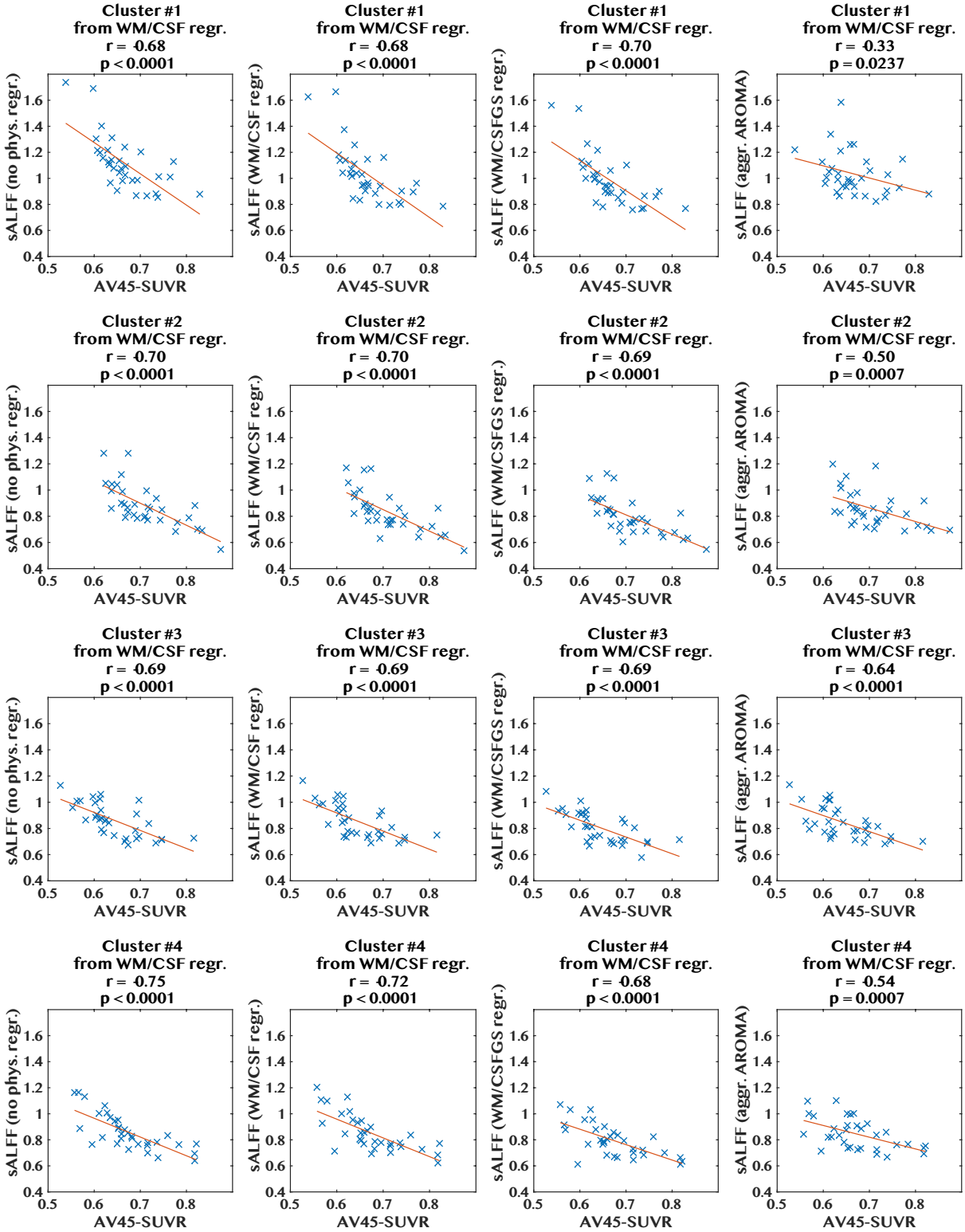
Sup. Figure 1. MRI and AV45 PET processing flowchart.

Methodological considerations for AV45-SUVR calculation

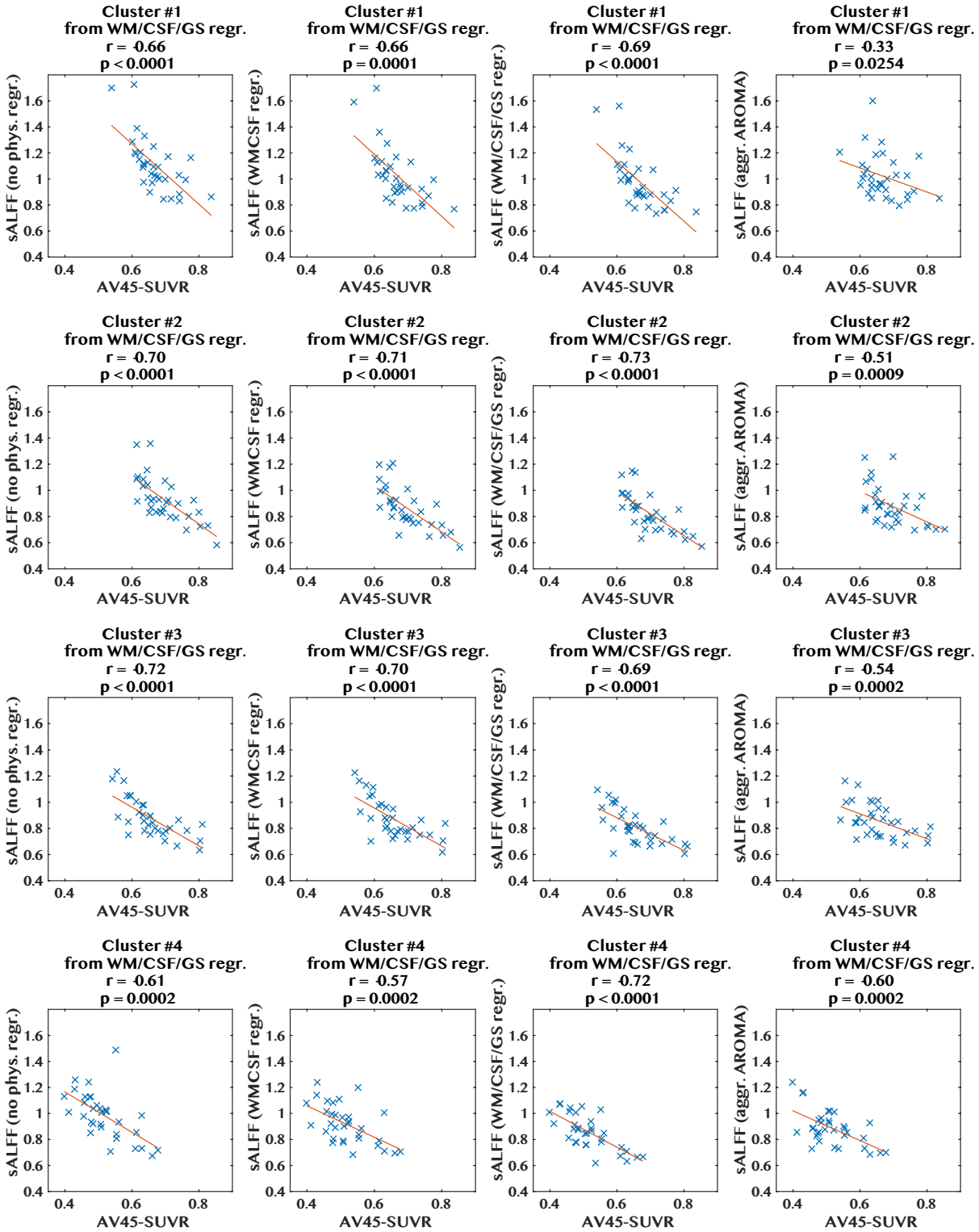
For calculating the PET AV45-SUVR, we chose white matter (WM) instead of the more traditional cerebellum as the reference for normalization. The comparison between reference regions has been comprehensively discussed by Brendel et al..[1] In their study, they performed a discrimination analysis of healthy controls (HC) vs. mild cognitive impairment vs. Alzheimer's disease of roughly 1000 subjects from the ADNI dataset. They compared the PET AV45-SUVR discriminative power using different reference regions, including the cerebellum, brainstem, and cortical white matter. Their receiver operating characteristics (ROC) analyses found that using white matter as the reference had the best performance in discriminating the diagnosis groups. Specifically, when compared to the more typical cerebellar reference scaling, a higher discriminatory power between healthy controls and participants with Alzheimer's disease was found when the white matter was used as a reference. Inter-subject variability was lowest when the white matter was used as a reference as well. Assessment of the longitudinal amyloid deposition was also more reliable and consistent when using white matter as the reference. Using white matter as the reference for the PET AV45-SUVR calculation, Brendel et al. showed that additional partial volume effect correction could lead to 0-2% higher scores in sensitivity and specificity, thus reaching the highest discriminative power of all comparisons. Since the effect of partial volume correction appeared small and its benefits have not been consistent,[2] we analyzed the AV45 data without partial volume correction. We repeated our analyses with the cerebellum as the reference for AV45-SUVR calculation, finding the same trend of negative correlation between local sALFF and AV45-SUVR (data not shown).



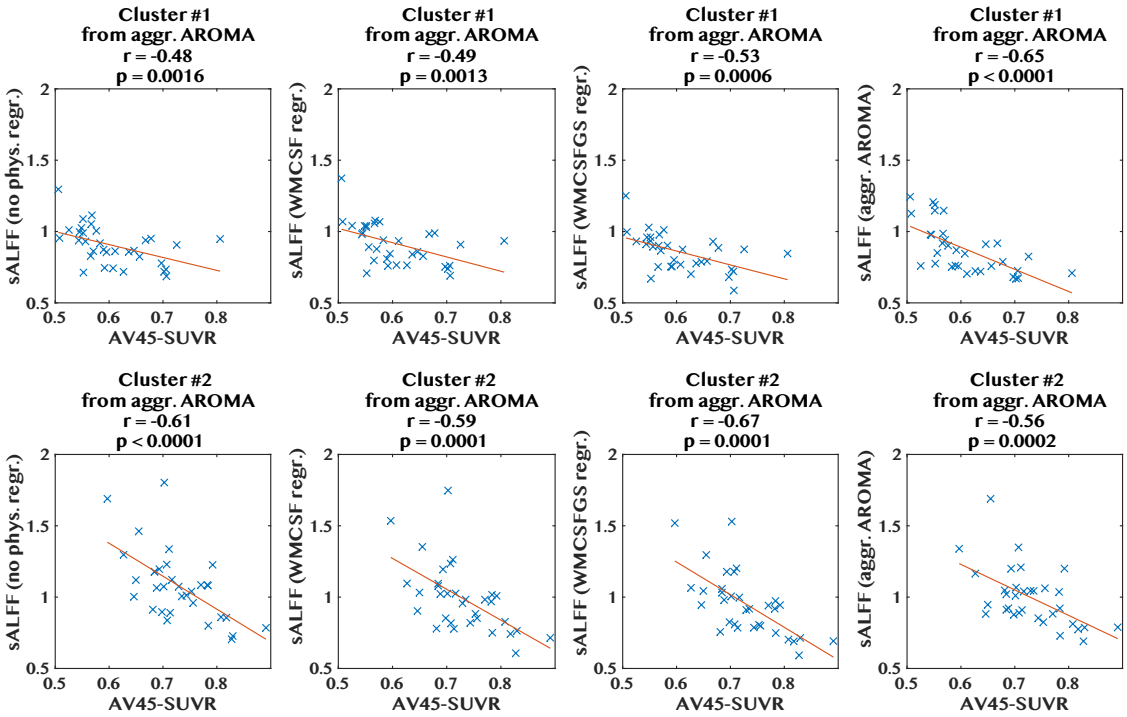
Sup. Figure 2. Correlation of brain amyloid-β deposition and the amplitude of low-frequency BOLD signal fluctuations (sALFF) - Table 2 "No physiological regression" Clusters #1-#4 (rows): columns depict the scatter-plots for each physiological/vascular regression procedure, left to right: "no physiological regression", "WM/CSF regression", "WM/CSF/GS regression", and "aggressive AROMA". Blue crosses represent the 33 subjects, using mean sALFF and mean AV45-SUVR within each cluster. Statistical *p* values are derived from 10,000 random permutations. The plots show reduced correlation strength going from column 1 to column 4 for each cluster.



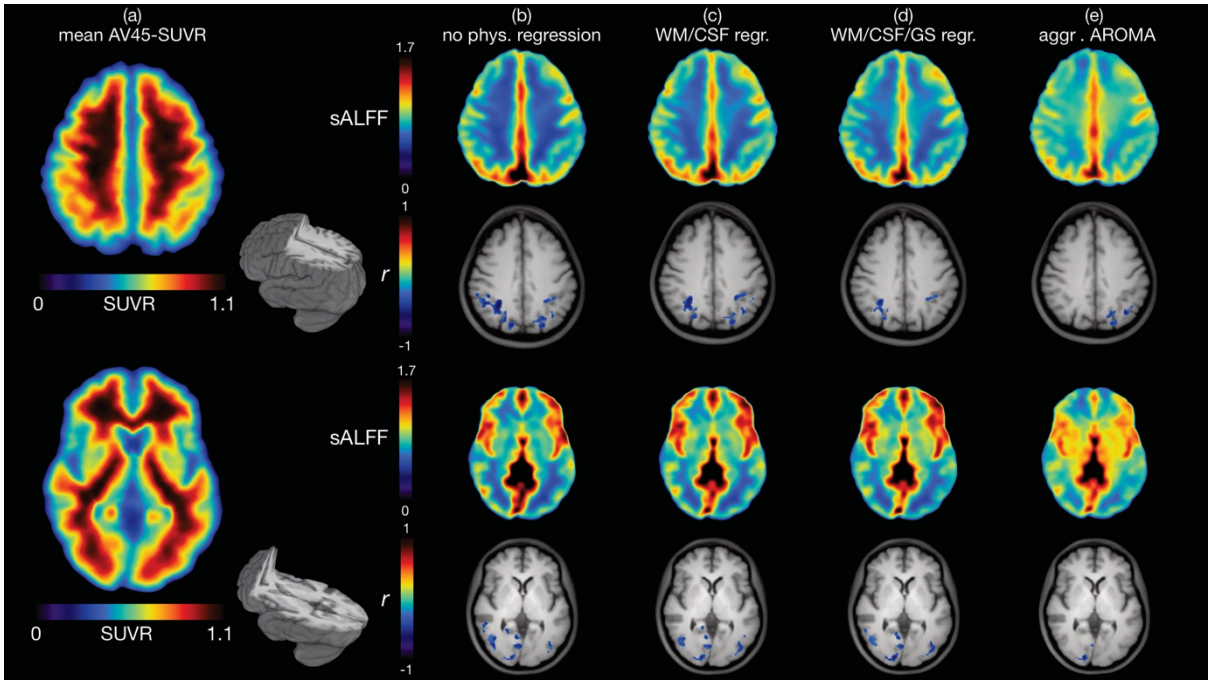
Sup. Figure 3. Correlation of brain amyloid-β deposition and the amplitude of low-frequency BOLD signal fluctuations (sALFF) - Table 2 "WM/CSF regression" Clusters #1-#4 (rows): columns depict the scatter-plots for each physiological/vascular regression procedure, left to right: "no physiological regression", "WM/CSF regression", "WM/CSF/GS regression", and "aggressive AROMA". Blue crosses represent the 33 subjects, using mean sALFF and mean AV45-SUVR within each cluster. Statistical *p* values are derived from 10,000 random permutations. The plots show reduced correlation strength going from column 1 to column 4 for each cluster.



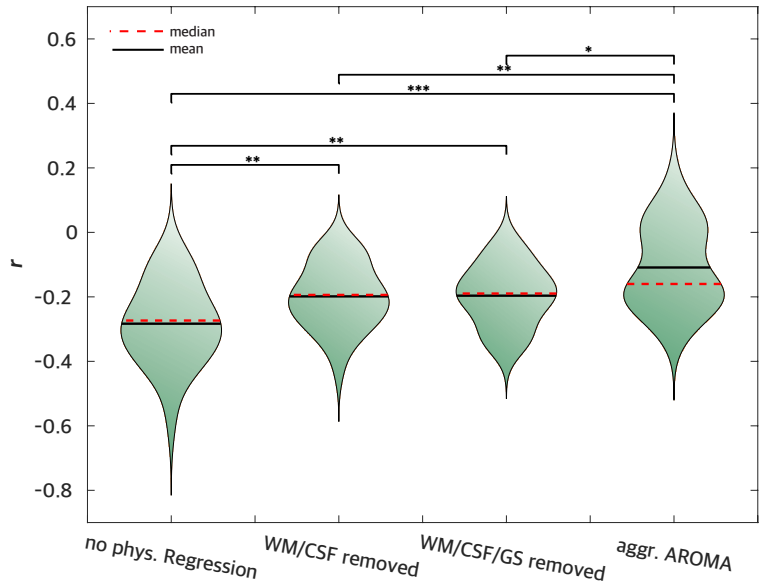
Sup. Figure 4. Correlation of brain amyloid-β deposition and the amplitude of low-frequency BOLD signal fluctuations (sALFF) - Table 2 "WM/CSF/GS regression" Clusters #1-#4 (rows): columns depict the scatter-plots for each physiological/vascular regression procedure, left to right: "no physiological regression", "WM/CSF regression", "WM/CSF/GS regression", and "aggressive AROMA". Blue crosses represent the 33 subjects, using mean sALFF and mean AV45-SUVR within each cluster. Statistical *p* values are derived from 10,000 random permutations. The plots show reduced correlation strength going from column 1 to column 4 for each cluster.



Sup. Figure 5. Correlation of brain amyloid-β deposition and the amplitude of low-frequency BOLD signal fluctuations (sALFF) - Table 2 "aggressive AROMA" Clusters #1 and #2 (rows): columns depict the scatter-plots for each physiological/vascular regression procedure, left to right: "no physiological regression", "WM/CSF regression", "WM/CSF/GS regression", and "aggressive AROMA". Blue crosses represent the 33 subjects, using mean sALFF and mean AV45-SUVR within each cluster. Statistical *p* values are derived from 10,000 random permutations. The plot shows increased correlation strength going from column 1 to column 4 for cluster #1.



Sup. Figure 6. Voxel-wise correlation analysis between brain amyloid-β deposition and the standardized amplitude of low-frequency BOLD signal fluctuations (sALFF) - axial. Images represent an axial slice (top half) above the corpus callosum (42mm in inferior-superior plane MNI) and an axial slice (bottom half) across the thalamus (0.75mm in inferior-superior plane MNI). (**a**) mean AV45-SUVR (standardized uptake value ratio with white matter scaling) color maps of 33 amnestic mild cognitive impairment participants are shown, along with the corresponding mean sALFF (standardized amplitude of low-frequency fluctuations) color maps after the physiological signal cleaning procedures of (**b**) "no physiological regression", (**c**) "WM/CSF regression", (**d**) "WM/CSF/GS regression", and (**e**) "aggressive AROMA". Significant correlation clusters between AV45-SUVR and sALFF for each regression procedure (b)-(e) are shown in the row below the mean sALFF images. Clusters are depicted in blue, as *r* values are negative (see Table 2 for detailed statistical analysis data). AV45-SUVR maps are nearly identical if the cerebellum, instead of white matter, is used as a reference, except the color scale range becomes 0 to 2. As more global variance is removed with each regression step, the normalization of sALFF reveals local signal oscillations.



Sup. Figure 7. Impact of stepwise regression of upper-stream vascular effects on the correlations between brain amyloid-β deposition and the amplitude of low-frequency BOLD signal fluctuations (sALFF) within the brain of each subject, across 116 AAL brain regions. Stars on brackets denote significance levels of paired Mann-Whitney U-tests with $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$. Fisher *z* transformed *r*-value distributions shown in violin plots. Across the different procedures the Kruskal-Wallis test yielded a significant χ^2 of 25.94 ($p < 0.001$). This comparison shows a stepwise *decrease* of negative correlation magnitude as more aggressive physiological signal removal procedures were applied. For each regression procedure, the Wilcoxon signed rank test showed a significant difference from the null distribution with $p < 0.001$.

Subgroup analysis on APOE4 genotype

Seven of the 33 subjects in this study carried the APOE4 gene. Our exploratory investigation showed that on average, within the significant clusters from the previous analysis (Figure 2 and Table 2), the AV45-SUVR was 5.3% higher for the seven APOE4 gene carriers with an average of 0.69, vs. 0.66 for the 26 APOE4 negative subjects. In these clusters, sALFF was 2.8% lower in the APOE4 gene carriers with an average of 0.88 vs. 0.91 for the APOE4 negative subjects. Also, correlation strength between AV45-SUVR and sALFF was 26.1% stronger for the APOE4 gene carriers with an average *r* of -0.87 vs. -0.64 for the APOE4 negative subjects. See Sup. Tables 1-3 for details. This exploratory analysis replicated findings of higher Aβ burden among APOE4 gene carriers.[3] The trends of lower sALFF among APOE4 gene carriers in the default-mode and visual related regions suggests a stronger impairment, leading to an even more pronounced anti-correlation between Aβ burden and BOLD signal fluctuation amplitudes.

AV45 SUVR	APOE4- (n=26)		APOE4+ (n=7)		*z*	*p*	difference of the mean	% difference
	mean	std	mean	std				
Cluster #1 from no phys. regr.	0.69	0.05	0.74	0.07	-1.56	0.12	0.05	6.97
Cluster #2 from no phys. regr.	0.65	0.05	0.69	0.09	-1.56	0.12	0.04	6.42
Cluster #3 from no phys. regr.	0.65	0.06	0.69	0.09	-1.21	0.23	0.04	5.92
Cluster #4 from no phys. regr.	0.71	0.06	0.74	0.09	-0.55	0.58	0.03	3.92
Cluster #1 from WM/CSF regr.	0.66	0.05	0.71	0.08	-1.48	0.14	0.05	7.03
Cluster #2 from WM/CSF regr.	0.70	0.06	0.73	0.09	-0.46	0.64	0.03	3.69
Cluster #3 from WM/CSF regr.	0.64	0.06	0.67	0.09	-0.77	0.44	0.03	4.26
Cluster #4 from WM/CSF regr.	0.67	0.07	0.71	0.09	-1.30	0.19	0.04	5.65
Cluster #1 from WM/CSF/GS regr.	0.66	0.05	0.71	0.08	-1.39	0.17	0.05	6.90
Cluster #2 from WM/CSF/GS regr.	0.69	0.06	0.72	0.10	-0.46	0.64	0.03	3.96
Cluster #3 from WM/CSF/GS regr.	0.65	0.07	0.69	0.09	-1.21	0.23	0.04	6.10
Cluster #4 from WM/CSF/GS regr.	0.51	0.06	0.54	0.09	-0.64	0.52	0.03	5.43
Cluster #1 from aggr. AROMA	0.60	0.06	0.62	0.11	0.20	0.84	0.02	3.41
Cluster #2 from aggr. AROMA	0.72	0.06	0.76	0.07	-1.17	0.24	0.04	5.01

Sup. Table 1. Amyloid-β beta burden, measured by AV45-SUVR and normalized by the white-matter signal in the resulting clusters suggest an APOE4 genotype dependency. Seven of all 33 subjects presented with an APOE4 positive genotype. Mann-Whitney U-tests did not produce significant results, but corresponding *z* values trend negatively. On average, within the significant clusters, AV45-SUVR is 5.3% higher for APOE4 gene carriers.

sALFF	APOE4- (n=26)		APOE4+ (n=7)		*z*	*p*	difference of the mean	% difference
	mean	std	mean	std				
Cluster #1 from no phys. regr. - sALFF(no phys. regr.)	1.11	0.25	1.03	0.21	0.95	0.34	-0.08	-7.66
Cluster #2 from no phys. regr. - sALFF(no phys. regr.)	0.90	0.12	0.88	0.18	0.73	0.47	-0.02	-2.11
Cluster #3 from no phys. regr. - sALFF(no phys. regr.)	0.91	0.15	0.85	0.10	0.99	0.32	-0.06	-7.19
Cluster #4 from no phys. regr. - sALFF(no phys. regr.)	0.81	0.12	0.84	0.17	0.20	0.84	0.03	3.54
Cluster #1 from WMCSF regr. - sALFF(WM/CSF regr.)	1.04	0.22	1.00	0.21	0.68	0.49	-0.04	-4.34
Cluster #2 from WMCSF regr. - sALFF(WM/CSF regr.)	0.83	0.15	0.85	0.20	-0.07	0.95	0.02	2.41
Cluster #3 from WMCSF regr. - sALFF(WM/CSF regr.)	0.86	0.13	0.84	0.11	0.20	0.84	-0.02	-2.91
Cluster #4 from WMCSF regr. - sALFF(WM/CSF regr.)	0.86	0.14	0.81	0.16	0.73	0.47	-0.05	-6.08
Cluster #1 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	0.99	0.21	0.93	0.19	0.68	0.49	-0.05	-5.60
Cluster #2 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	0.82	0.14	0.83	0.19	0.15	0.88	0.01	0.78
Cluster #3 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	0.82	0.13	0.77	0.12	0.73	0.47	-0.05	-6.31
Cluster #4 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	0.87	0.13	0.81	0.14	1.17	0.24	-0.06	-7.37
Cluster #1 from aggr. AROMA - sALFF(aggr. AROMA)	0.87	0.16	0.91	0.21	-0.24	0.81	0.04	4.15
Cluster #2 from aggr. AROMA - sALFF(aggr. AROMA)	1.00	0.21	0.99	0.22	0.00	1.00	0.00	-0.48

Sup. Table 2. The standardized Amplitude of Low Frequency Fluctuations (sALFF) in the resulting clusters might suggest an APOE4 genotype dependency. Seven of all 33 subjects presented with an APOE4 positive genotype. Mann-Whitney U-tests did not produce significant results, but corresponding *z* values trended positively. On average, sALFF was 2.8% lower in APOE4 gene carriers.

correlation AV45-SUVR/sALFF	all subjects		APOE4- (n=26)		APOE4+ (n=7)		difference correlation	% difference
	r	*p*	*r*	*p*	*r*	*p*		
Cluster #1 from no phys. regr. - sALFF(no phys. regr.)	-0.65	≤0.001	-0.63	0.0005	-0.81	0.0072	0.18	22.31
Cluster #2 from no phys. regr. - sALFF(no phys. regr.)	-0.75	≤0.001	-0.73	≤0.001	-0.82	0.0003	0.09	10.92
Cluster #3 from no phys. regr. - sALFF(no phys. regr.)	-0.67	≤0.001	-0.64	0.0003	-0.91	0.0028	0.27	29.62
Cluster #4 from no phys. regr. - sALFF(no phys. regr.)	-0.72	≤0.001	-0.62	0.0001	-0.98	0.0009	0.36	36.52
Cluster #1 from WMCSF regr. - sALFF(WM/CSF regr.)	-0.68	≤0.001	-0.68	≤0.001	-0.82	0.0038	0.15	17.90
Cluster #2 from WMCSF regr. - sALFF(WM/CSF regr.)	-0.70	≤0.001	-0.60	0.0004	-0.96	0.0006	0.35	36.96
Cluster #3 from WMCSF regr. - sALFF(WM/CSF regr.)	-0.69	≤0.001	-0.68	0.0001	-0.83	0.0012	0.14	17.24
Cluster #4 from WMCSF regr. - sALFF(WM/CSF regr.)	-0.72	≤0.001	-0.63	0.0003	-0.96	0.0004	0.33	34.08
Cluster #1 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	-0.69	≤0.001	-0.67	≤0.001	-0.86	0.0026	0.19	22.08
Cluster #2 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	-0.73	≤0.001	-0.62	0.0001	-0.97	0.001	0.35	36.50
Cluster #3 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	-0.69	≤0.001	-0.62	0.0004	-0.95	0.0011	0.33	34.98
Cluster #4 from WMCSFGS regr. - sALFF(WM/CSF/GS regr.)	-0.72	≤0.001	-0.68	≤0.001	-0.83	0.0077	0.15	17.62
Cluster #1 from aggr. AROMA - sALFF(aggr. AROMA)	-0.65	≤0.001	-0.56	0.0004	-0.87	0.0086	0.30	35.06
Cluster #2 from aggr. AROMA - sALFF(aggr. AROMA)	-0.56	0.0001	-0.56	0.0016	-0.65	0.0335	0.09	13.35

Sup. Table 3. The correlation of AV45-SUVR amyloid-β burden and the standardized Amplitude of Low Frequency Fluctuations (sALFF) in the resulting clusters highly suggests an APOE4 genotype dependency. Seven of all 33 subjects presented with an APOE4 positive genotype. Statistical *p* values were derived from 10,000 random permutations. While all clusters showed a significant difference, on average, correlation was 26.1% higher for APOE4 gene carriers.

References

1. Brendel M, Högenauer M, Delker A, et al. Improved longitudinal [18F]-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction. *Neuroimage*. 2015;108:450-459. doi:10.1016/j.neuroimage.2014.11.055

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