

Supplementary Material

Noninvasive Gamma Sensory Stimulation May Reduce White Matter and Myelin Loss in Alzheimer's Disease

Supplementary Table 1. White matter volume (cm³) for 52 structures at baseline. No statistically significant difference between the Sham group and the Active Treatment group was observed for white matter volumes for all 52 white matter structures at baseline.

Region	Sham (n=13) Mean ± SE	Active Treatment (n=25) Mean Change ± SE	p
Bankssts	5.21±0.20	5.27±0.21	0.817
Caudal Anterior Cingulate	4.67±0.22	4.76±0.15	0.740
Caudal Middle Frontal	12.64±0.53	11.97±0.40	0.328
Cingulate Lobe	24.03±0.94	23.78±0.61	0.825
Cuneus	6.40±0.29	5.75±0.23	0.091
Entorhinal	1.73±0.12	1.70±0.09	0.883
Frontal Lobe	149.04±5.26	145.67±4.45	0.629
Frontal Pole	0.75±0.04	0.69±0.02	0.218
Fusiform	12.68±0.38	12.48±0.42	0.729
Inferior Parietal	20.72±0.88	20.62±0.79	0.930
Inferior Temporal	11.87±0.38	12.14±0.53	0.677
Insula	18.71±0.73	18.29±0.61	0.669
Insula Lobe	18.47±0.75	18.18±0.60	0.771
Isthmus Cingulate	7.40±0.27	7.02±0.22	0.279
Lateral Occipital	22.24±0.65	20.64±0.72	0.108
Lateral Orbitofrontal	14.08±0.53	13.37±0.38	0.293
Left Cingulate Lobe	12.65±0.57	12.48±0.33	0.798
Left Frontal Lobe	74.08±2.83	72.59±2.27	0.684
Left Insula Lobe	9.37±0.37	9.19±0.31	0.702
Left Occipital Lobe	23.23±0.61	22.00±0.80	0.231
Left Parietal Lobe	48.20±1.91	46.96±1.73	0.636
Left Temporal Lobe	31.81±1.16	31.40±1.18	0.805
Lingual	12.17±0.51	11.61±0.36	0.381
Medial Orbitofrontal	8.39±0.27	7.91±0.25	0.199
Middle Temporal	11.22±0.40	10.90±0.45	0.596
Occipital Lobe	47.90±1.42	44.67±1.53	0.130
Paracentral	9.10±0.39	8.80±0.28	0.536
Parahippocampal	2.91±0.12	3.01±0.09	0.514
Parietal Lobe	97.84±3.60	96.07±3.31	0.720
Pars Opercularis	6.63±0.28	6.36±0.24	0.462
Pars Orbitalis	2.43±0.11	2.33±0.07	0.425
Pars Triangularis	6.49±0.26	6.09±0.21	0.242
Pericalcarine	7.81±0.30	7.12±0.32	0.120
Postcentral	16.50±0.82	15.77±0.52	0.460
Posterior Cingulate	7.88±0.31	7.97±0.19	0.797

Precentral	31.14±1.35	29.47±0.99	0.328
Precuneus	18.79±0.81	18.92±0.75	0.908
Right Cingulate Lobe	11.37±0.41	11.30±0.30	0.878
Right Frontal Lobe	74.96±2.50	73.09±2.20	0.578
Right Insula Lobe	9.10±0.41	9.00±0.32	0.852
Right Occipital Lobe	24.67±0.88	22.66±0.81	0.103
Right Parietal Lobe	49.65±1.75	49.11±1.63	0.823
Right Temporal Lobe	30.46±0.95	29.90±1.06	0.695
Rostral Anterior Cingulate	4.24±0.19	4.20±0.14	0.866
Rostral Middle Frontal	24.33±0.94	24.50±1.32	0.915
Superior Frontal	34.27±1.10	35.52±1.32	0.470
Superior Parietal	24.99±1.03	24.20±0.77	0.542
Superior Temporal	15.78±0.61	15.06±0.58	0.395
Supramarginal	18.46±0.76	17.99±0.70	0.651
Temporal Lobe	62.27±1.98	61.30±2.23	0.745
Temporal Pole	1.59±0.09	1.41±0.04	0.086
Transverse Temporal	1.60±0.08	1.56±0.07	0.644

Supplementary Table 2. T1w/T2w ratio for 52 structures at baseline. No statistically significant difference between the Sham group and the Active Treatment group was observed for T1w/T2w ratio in all 52 white matter structures at baseline.

Region	Sham (n=12) Mean ± SE	Active Treatment (n=24) Mean ± SE	p
Bankssts	1.25±0.08	1.33±0.07	0.408
Caudal Anterior Cingulate	1.11±0.10	1.19±0.05	0.460
Caudal Middle Frontal	1.28±0.10	1.27±0.05	0.951
Cingulate Lobe	1.27±0.09	1.32±0.05	0.651
Cuneus	1.37±0.12	1.34±0.06	0.860
Entorhinal	1.24±0.11	1.29±0.07	0.674
Frontal Lobe	1.33±0.09	1.36±0.05	0.760
Frontal Pole	2.31±0.14	2.34±0.08	0.856
Fusiform	1.20±0.08	1.27±0.05	0.494
Inferior Parietal	1.27±0.08	1.33±0.06	0.594
Inferior Temporal	1.17±0.06	1.25±0.05	0.296
Insula	1.70±0.12	1.73±0.06	0.813
Insula Lobe	1.69±0.12	1.72±0.06	0.798
Isthmus Cingulate	1.49±0.09	1.47±0.05	0.809
Lateral Occipital	1.19±0.08	1.20±0.04	0.936
Lateral Orbitofrontal	1.58±0.11	1.56±0.05	0.863
Left Cingulate Lobe	1.27±0.09	1.32±0.05	0.643
Left Frontal Lobe	1.32±0.09	1.35±0.05	0.761
Left Insula Lobe	1.71±0.12	1.74±0.06	0.811
Left Occipital Lobe	1.27±0.07	1.29±0.05	0.826
Left Parietal Lobe	1.23±0.09	1.28±0.05	0.628
Left Temporal Lobe	1.26±0.07	1.31±0.05	0.650
Lingual	1.35±0.08	1.41±0.06	0.538
Medial Orbitofrontal	1.59±0.09	1.59±0.05	0.974
Middle Temporal	1.26±0.07	1.28±0.05	0.849
Occipital Lobe	1.25±0.08	1.26±0.05	0.877
Paracentral	1.28±0.09	1.33±0.05	0.632
Parahippocampal	1.02±0.08	1.14±0.06	0.284
Parietal Lobe	1.27±0.09	1.32±0.05	0.587
Pars Opercularis	1.25±0.08	1.27±0.06	0.784
Pars Orbitalis	1.81±0.14	1.81±0.06	0.973
Pars Triangularis	1.48±0.09	1.44±0.04	0.676
Pericalcarine	1.19±0.07	1.19±0.06	0.980
Postcentral	1.29±0.11	1.32±0.05	0.836
Posterior Cingulate	1.24±0.09	1.34±0.05	0.370
Precentral	1.33±0.09	1.35±0.04	0.786
Precuneus	1.26±0.11	1.34±0.05	0.547
Right Cingulate Lobe	1.27±0.09	1.32±0.05	0.671
Right Frontal Lobe	1.34±0.09	1.37±0.05	0.761
Right Insula Lobe	1.67±0.12	1.70±0.06	0.794
Right Occipital Lobe	1.23±0.08	1.24±0.05	0.924

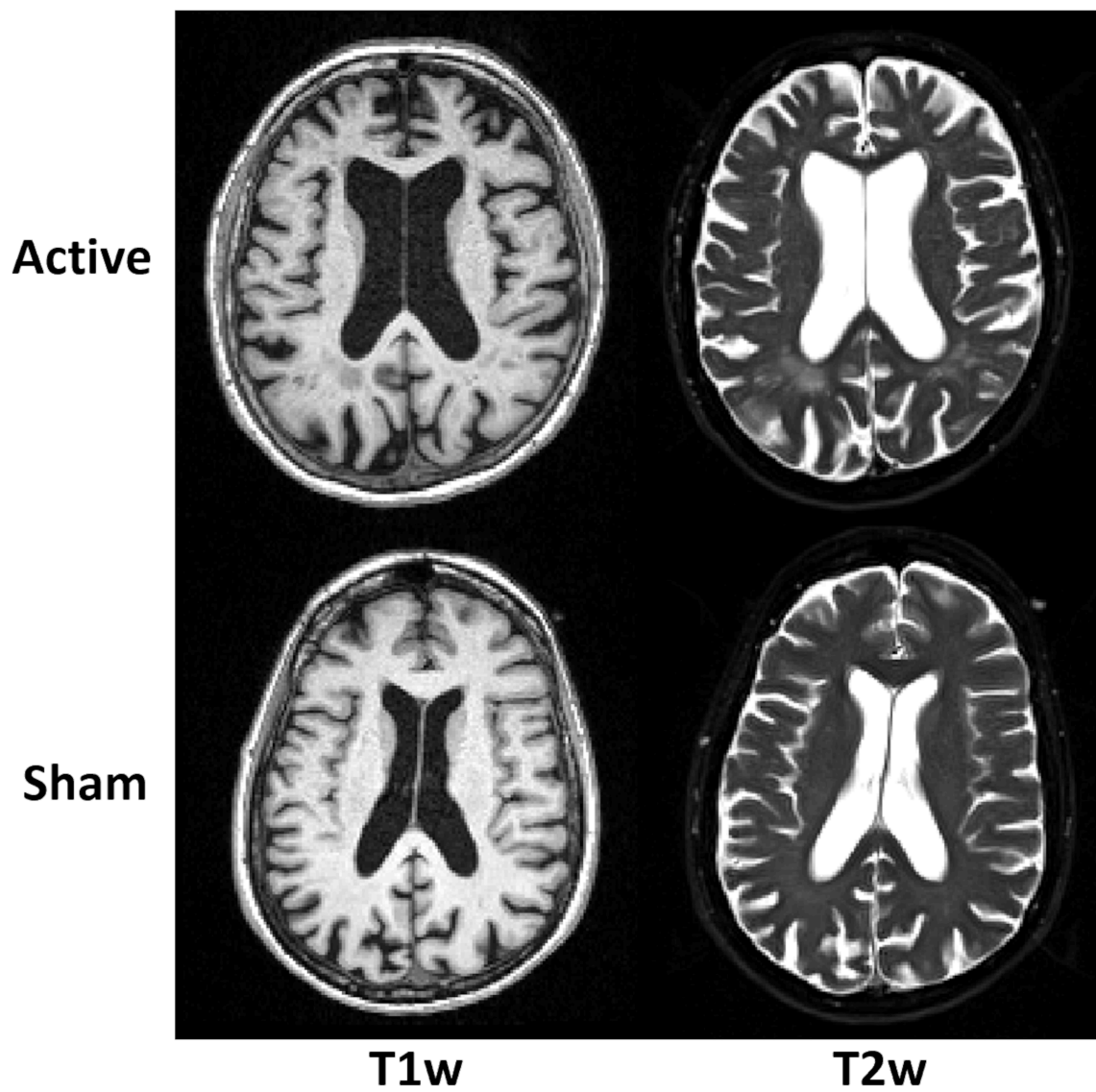
Right Parietal Lobe	1.31±0.09	1.37±0.05	0.554
Right Temporal Lobe	1.27±0.08	1.32±0.05	0.596
Rostral Anterior Cingulate	1.21±0.09	1.24±0.05	0.825
Rostral Middle Frontal	1.29±0.09	1.31±0.05	0.892
Superior Frontal	1.21±0.08	1.30±0.05	0.390
Superior Parietal	1.11±0.07	1.18±0.05	0.446
Superior Temporal	1.48±0.10	1.46±0.05	0.902
Supramarginal	1.52±0.10	1.56±0.06	0.727
Temporal Lobe	1.26±0.08	1.31±0.05	0.619
Temporal Pole	1.43±0.09	1.34±0.05	0.446
Transverse Temporal	1.59±0.11	1.61±0.07	0.871

Supplementary Table 3. Comparison of p values and adjusted p values of white matter volume changes from baseline for a 6-month period. Raw p values and adjusted p values, using Benjamini-Hochberg procedure (FDR), are shown. For FDR, an assumption of independence between subregions within a lobe is made. Two subregions that have p values less than 0.05 have FDR Corrected p values greater than 0.05. Light orange shaded areas for $p < 0.01$, light green shaded areas for $0.01 \leq p < 0.05$, and light-yellow shaded areas for $0.05 \leq p < 0.1$.

Lobe	p	FDR Corrected p
Frontal		
Caudal Middle Frontal	0.049*	0.154
Frontal Pole	0.576	0.634
Lateral Orbitofrontal	0.91	0.91
Medial Orbitofrontal	0.093	0.17
Paracentral	0.056	0.154
Pars Opercularis	0.434	0.53
Pars Orbitalis	0.114	0.179
Pars Triangularis	0.004**	0.044*
Precentral	0.05	0.154
Rostral Middle Frontal	0.085	0.17
Superior Frontal	0.352	0.484
Temporal		
Bankssts	0.749	0.843
Entorhinal	0.001**	0.009**
Fusiform	0.064	0.222
Inferior Temporal	0.074	0.222
Middle Temporal	0.27	0.486
Parahippocampal	0.631	0.843
Superior Temporal	0.109	0.245
Temporal Pole	0.881	0.881
Transverse Temporal	0.683	0.843
Parietal		
Inferior Parietal	0.254	0.318
Postcentral	0.012*	0.06
Precuneus	0.091	0.185
Superior Parietal	0.393	0.393
Supramarginal	0.111	0.185
Occipital		
Cuneus	0.009**	0.02*
Lateral Occipital	0.01*	0.02*
Lingual	0.064	0.085
Pericalcarine	0.69	0.69
Cingulate		
Caudal Anterior Cingulate	0.868	0.868
Isthmus Cingulate	0.752	0.868
Posterior Cingulate	0.263	0.526
Rostral Anterior Cingulate	0.071	0.284

Supplementary Table 4. Comparison of p values and adjusted p values of LS Mean T1w/T2w ratio changes from baseline for a 6-month period. Raw p values and adjusted p values, using Benjamini-Hochberg procedure (FDR), are shown. For FDR, an assumption of independence between subregions within a lobe is made. Two subregions that have p values less than 0.05 have FDR Corrected p values greater than 0.05. Light orange shaded areas for $p < 0.01$, light green shaded areas for $0.01 \leq p < 0.05$ and light-yellow shaded areas for $0.05 \leq p < 0.1$.

Lobe	p	FDR Corrected p
Frontal		
Caudal Middle Frontal	0.053	0.081
Frontal Pole	0.211	0.211
Lateral Orbitofrontal	0.211	0.211
Medial Orbitofrontal	0.059	0.081
Paracentral	0.014*	0.044*
Pars Opercularis	0.122	0.149
Pars Orbitalis	0.044*	0.081
Pars Triangularis	0.004**	0.044*
Precentral	0.016*	0.044*
Rostral Middle Frontal	0.014*	0.044*
Superior Frontal	0.058	0.081
Temporal		
Bankssts	0.277	0.312
Entorhinal	0.003**	0.027*
Fusiform	0.018*	0.081
Inferior Temporal	0.104	0.187
Middle Temporal	0.23	0.296
Parahippocampal	0.178	0.267
Superior Temporal	0.071	0.184
Temporal Pole	0.082	0.184
Transverse Temporal	0.66	0.66
Parietal		
Inferior Parietal	0.024*	0.03*
Postcentral	0.005**	0.025*
Precuneus	0.023*	0.03*
Superior Parietal	0.067	0.067
Supramarginal	0.014*	0.03*
Occipital		
Cuneus	0.023*	0.04*
Lateral Occipital	0.008**	0.032*
Lingual	0.03*	0.04*
Pericalcarine	0.287	0.287
Cingulate		
Caudal Anterior Cingulate	0.186	0.186
Isthmus Cingulate	0.184	0.186
Posterior Cingulate	0.067	0.134
Rostral Anterior Cingulate	0.056	0.134



Supplementary Figure 1. T1w and T2w MRI images of a sample active treatment participant (top row) and a sham participant (bottom row). The images are shown in neurological convention.