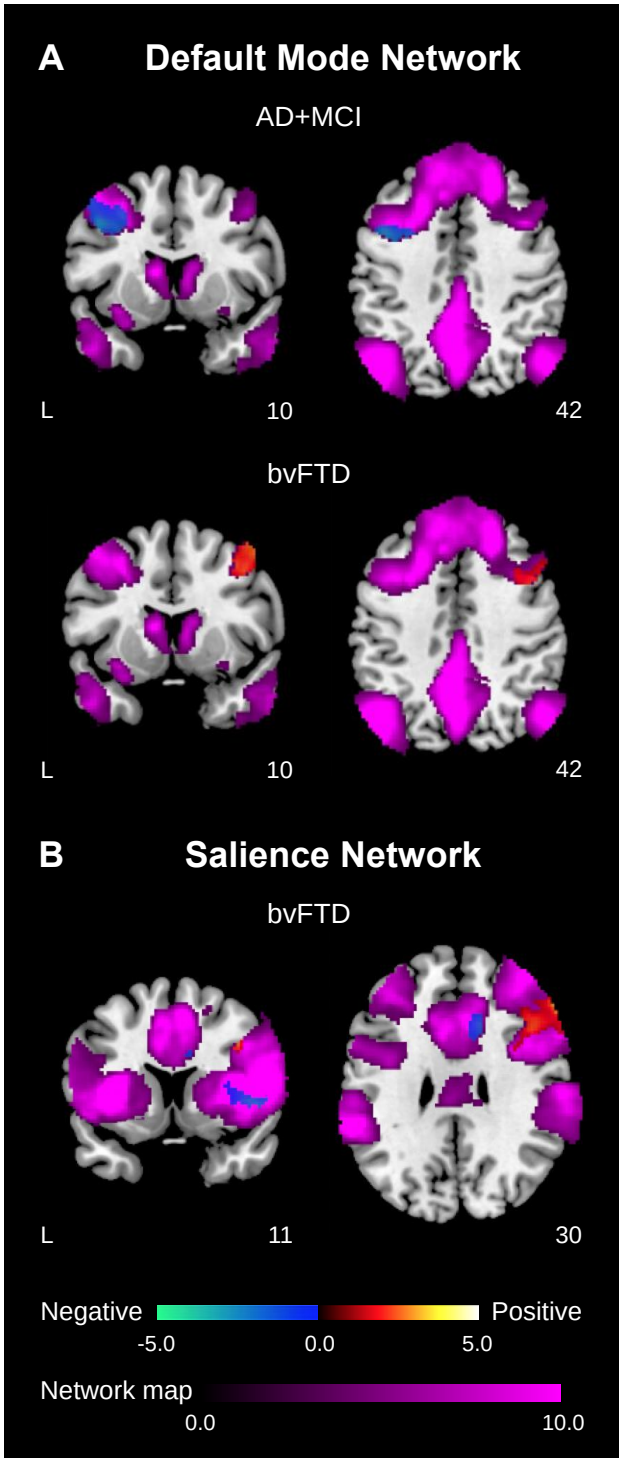
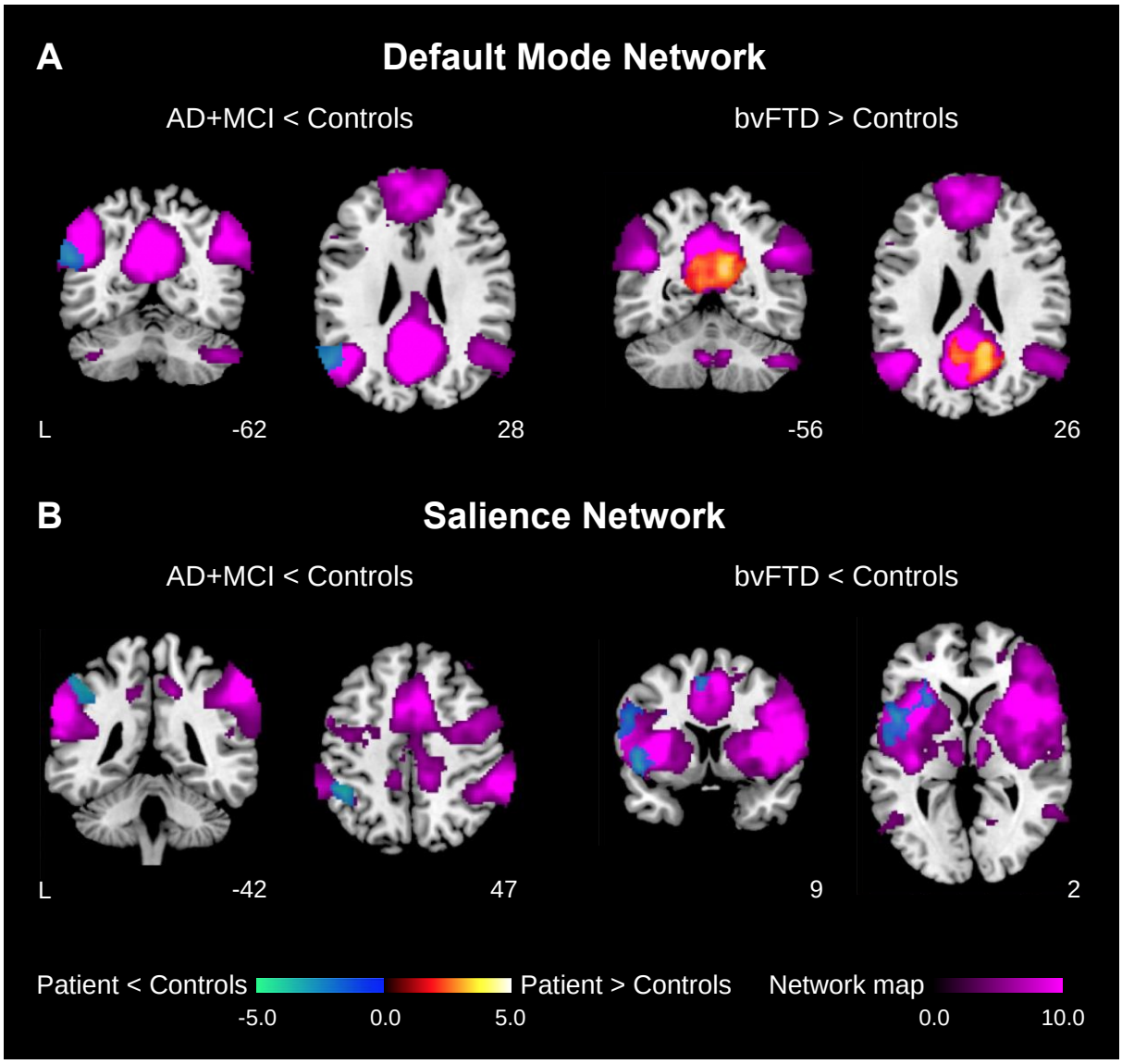
Supplementary Material

Plasma Neurofilament Light Relates to Divergent Default and Salience Network Connectivity in Alzheimer's Disease and Behavioral Variant Frontotemporal Dementia



Supplementary Figure 1. Differential associations between voxelwise functional connectivity maps and plasma NfL in AD+MCI and bvFTD patients using preprocessed fMRI images where bandpass filtering was performed after nuisance signal regression. Group functional connectivity association maps, indicating brain clusters showing negative (cool color) or positive (hot color) associations between plasma NfL and functional connectivity of (A) default mode or (B) salience networks in AD+MCI and bvFTD patients, are overlaid on their respective group network masks generated from cognitively normal controls (purple color). Both maps are displayed on the Montreal Neurological Institute template brain. A) Consistent with the original findings, higher plasma NfL was associated with lower default mode network functional connectivity of the left posterior cingulate cortex to the left dorsolateral prefrontal cortex in AD+MCI patients, and higher default mode network functional connectivity of the left posterior cingulate cortex to the right dorsolateral prefrontal cortex in bvFTD patients. B) Likewise, higher plasma NfL was associated with lower salience network functional connectivity of the right anterior insula to several clusters covering the right insula, frontal gyrus, putamen, middle and anterior cingulate cortex, and higher salience network functional connectivity of the right anterior insula to the right inferior and middle frontal gyrus in bvFTD patients. NfL, neurofilament light; FC, functional connectivity; AD, Alzheimer's disease; MCI, mild cognitive impairment; bvFTD; behavioral variant frontotemporal dementia; fMRI, functional magnetic resonance imaging.



Supplementary Figure 2. Differences in voxelwise functional connectivity between patient groups and controls. Group functional connectivity difference maps, depicting brain clusters that show significantly higher (hot color) or lower (cool color) (A) default mode and (B) salience network functional connectivity in AD+MCI and bvFTD patients compared to cognitively normal controls. Consistent with previous findings, (A) AD+MCI patients showed lower default mode network connectivity of the left posterior cingulate cortex to the left angular gyrus/middle temporal gyrus compared to controls, while bvFTD patients showed higher default mode network connectivity of the left posterior cingulate cortex to the bilateral precuneus/calcarine gyrus/posterior cingulate cortex relative to controls. By comparison, compared to controls, (B) bvFTD patients showed lower salience network connectivity of the right anterior insula to several regions including the left insula, frontal gyrus, superior temporal gyrus, rolandic operculum, precentral gyrus and supplementary motor area, while AD+MCI patients showed lower salience network connectivity of the right anterior insula to the left inferior parietal and angular gyrus, which is not a key region of the salience network (the cluster is located within the control network of an independent functional brain atlas [1]). AD, Alzheimer's disease; MCI, mild cognitive impairment; bvFTD; behavioral variant frontotemporal dementia.

Supplementary Table 1. Clusters showing significant negative FC-NfL association and significant group difference in FC-NfL association between AD+MCI and bvFTD patients after controlling for voxelwise grey matter volumes

Nature of significant association with plasma NfL	Cluster						Difference in FC-NfL association (AD+MCI < bvFTD)			
	Regions	Size (voxels)	Peak T	X (mm)	Y (mm)	Z (mm)	Unstd. coeff.	SE	t	p
Default mode network seed: Left posterior cingulate cortex (X = -7, Y = -43, Z = 33)										
Negative association in AD+MCI	Left DLPFC	183	4.53	-44	10	42	0.361	0.144	2.50	0.016*
Salience network seed: Right anterior insula (X = 35, Y = 24, Z = 5)										
Negative association in bvFTD	Right INS/IFGoperc/PUT/ROL/ TPOsup/PAL	1090	6.93	59	16	-7	-0.372	0.144	-2.58	0.013*
	Right IFGtriang/MFG/DCG/CAU/ACG	714	4.88	49	38	8	-0.343	0.131	-2.62	0.012*

Coordinates shown are in Montreal Neurological Institute normalized space (thresholded at the uncorrected TFCE threshold of $p < 0.01$ and cluster size of 100 voxels). NfL, neurofilament light; AD, Alzheimer's disease; MCI, mild cognitive impairment; bvFTD, behavioral variant frontotemporal dementia; Unstd. coeff., unstandardized coefficient; SE, standard error; DLPFC, dorsolateral prefrontal cortex; INS, insula; IFGoperc, inferior frontal gyrus, opercular part; PUT, lenticular nucleus, putamen; ROL, rolandic operculum; TPOsup, temporal pole: superior temporal gyrus; PAL, lenticular nucleus, pallidum; IFGtriang, inferior frontal gyrus, triangular part; MFG, middle frontal gyrus; DCG, median cingulate and paracingulate gyri; CAU, caudate nucleus; ACG, anterior cingulate and paracingulate gyri.

Supplementary Table 2. Similarities in plasma NfL-functional connectivity associations of AD+MCI and bvFTD patients between the original analyses and the new analyses (using preprocessed fMRI images where bandpass filtering was performed after nuisance signal regression)

Group	Nature of association	Cluster						Cluster present in original analysis?
		Regions	Size (voxels)	Peak T	X (mm)	Y (mm)	Z (mm)	
Default mode network seed: Left posterior cingulate cortex (X = -7, Y = -43, Z = 33)								
AD+MCI	Negative	Left DLPFC	321	3.04	-44	11	38	Yes
bvFTD	Positive	Right DLPFC	371	2.78	48	11	55	Yes[1]
Salience network seed: Right anterior insula (X = 35, Y = 24, Z = 5)								
bvFTD	Positive	Right IFGtriang/ IFGoperc/MFG	745	4.55	54	19	35	Yes
bvFTD	Negative	Right INS/IFGoperc/ PUT	246	3.33	49	4	-1	Yes[2]
		Right IFGtriang/ MFG/INS	123	1.84	31	34	9	Yes[2]
		Right DCG/ACG	95	2.36	14	21	33	Yes[2]

[1]Cluster was present in the original analysis but did not meet the cluster size threshold of 500 voxels. [2]All three clusters (cluster sizes of 246, 123, and 95 voxels respectively) showing negative association between functional connectivity and plasma NfL in bvFTD patients overlapped with the cluster (cluster size of 2824 voxels) in the original analysis. Coordinates shown are in Montreal Neurological Institute normalized space (thresholded at the uncorrected TFCE threshold of $p < 0.01$ and cluster size of 300 voxels). NfL, neurofilament light; AD, Alzheimer's disease; MCI, mild cognitive impairment; bvFTD, behavioral variant frontotemporal dementia; DLPFC, dorsolateral prefrontal cortex; IFGtriang, inferior frontal gyrus, triangular part; IFGoperc, inferior frontal gyrus, opercular part; MFG, middle frontal gyrus; INS, insula; PUT, lenticular nucleus, putamen; DCG, median cingulate and paracingulate gyri; ACG, anterior cingulate and paracingulate gyri.

Supplementary Table 3. Association between neuropsychological assessment scores and functional connectivity of select 4 mm spherical regions-of-interest in AD+MCI and bvFTD patients

Group	Nature of significant association with plasma NfL	4 mm spherical regions-of-interest	Association with neuropsychological assessment scores					
			Assessment	n	Unstd. coeff.	SE	t	p
Default mode network seed: Left posterior cingulate cortex (X = -7, Y = -43, Z = 33)								
AD+MCI	Negative association in AD+MCI	Left DLPFC (Peak t: 3.43) (MNI coordinates: -44, 8, 40)	MMSE	38	8.11	5.74	1.41	0.168
			MoCA	38	13.82	5.80	2.38	0.024*
			CDR SOB	16	-13.31	5.15	-2.59	0.032*
			NPI total severity	22	3.24	3.45	0.94	0.363
			NPI total caregiver distress	22	0.44	4.56	0.10	0.925
		Left DLPFC (Peak t: 2.71) (MNI coordinates: -32, 11, 34)	MMSE	38	8.48	6.42	1.32	0.197
			MoCA	38	12.59	6.67	1.89	0.069
			CDR SOB	16	-15.50	4.39	-3.53	0.008*
			NPI total severity	22	4.21	4.55	0.93	0.369
			NPI total caregiver distress	22	3.70	5.93	0.62	0.542
Salience network seed: Right anterior insula (X = 35, Y = 24, Z = 5)								
bvFTD	Negative association in bvFTD	Right PUT (Peak t: 4.29) (MNI coordinates: 29, -6, 2)	MMSE	16	16.58	13.46	1.23	0.246
			MoCA	16	22.70	14.89	1.52	0.158
			FTLD-CDR SOB	14	-14.85	8.06	-1.84	0.103
			NPI total severity	13	11.52	15.87	0.73	0.491
			NPI total caregiver distress	13	22.15	26.23	0.84	0.426
		Right TPOsup (Peak t: 4.12) (MNI coordinates: 59, 16, -7)	MMSE	16	12.50	12.35	1.01	0.335
			MoCA	16	13.25	14.23	0.93	0.374
			FTLD-CDR SOB	14	-15.11	6.87	-2.20	0.059
			NPI total severity	13	19.59	21.85	0.90	0.400
			NPI total caregiver distress	13	48.51	33.95	1.43	0.196
		Right INS (Peak t: 3.89) (MNI coordinates: 41, 10, -9)	MMSE	16	1.09	16.82	0.06	0.950
			MoCA	16	2.00	19.24	0.10	0.919
			FTLD-CDR SOB	14	-18.48	9.20	-2.01	0.080
			NPI total severity	13	12.06	15.67	0.77	0.467
			NPI total caregiver distress	13	32.86	24.30	1.35	0.218

'*' represents significant association between functional connectivity and neuropsychological assessment scores ($p < 0.05$). AD, Alzheimer's disease; MCI, mild cognitive impairment; bvFTD, behavioral variant frontotemporal dementia; NfL, neurofilament light; Unstd. coeff., unstandardized coefficient; SE, standard error; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; CDR SOB, Clinical Dementia Rating sum-of-boxes score; FTLD-CDR SOB, Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating sum-of-boxes score; NPI, neuropsychiatric inventory; DLPFC, dorsolateral prefrontal cortex; PUT, lenticular nucleus, putamen; TPOsup, temporal pole: superior temporal gyrus; INS, insula.

Supplementary Table 4. Clusters showing significant functional connectivity differences in AD+MCI and bvFTD patients compared to controls

Contrast	Cluster					
	Regions	**Size (voxels)**	**Peak T**	**X (mm)**	**Y (mm)**	**Z (mm)**
Default mode network seed: Left posterior cingulate cortex (X = -7, Y = -43, Z = 33)						
AD+MCI < Controls	Left ANG, MTG, SMG	438	3.66	-55	-59	26
bvFTD > Controls	Bilateral PCUN, CAL, PCG, CUN	1800	4.75	11	-53	23
Salience network seed: Right anterior insula (X = 35, Y = 24, Z = 5)						
AD+MCI < Controls	Left IPL, ANG	467	3.97	-49	-44	49
bvFTD < Controls	Left INS, STG, ROL, IFGoperc, TPOsup, ORBinf, IFGtriang	961	3.95	-47	10	-6
	Left PreCG, IFGoperc	531	3.25	-55	5	18
	Left SMA, SFGmed, DCG	465	3.80	-10	21	41

Coordinates shown are in Montreal Neurological Institute normalized space (thresholded at the uncorrected TFCE threshold of $p < 0.01$ and cluster size of 400 voxels). AD, Alzheimer's disease; MCI, mild cognitive impairment; bvFTD, behavioral variant frontotemporal dementia; ANG, angular gyrus; MTG, middle temporal gyrus; SMG, supramarginal gyrus; PCUN, precuneus; CAL, calcarine fissure and surrounding cortex; PCG, posterior cingulate gyrus; CUN, cuneus; IPL, inferior parietal, but supramarginal and angular gyri; INS, insula; STG, superior temporal gyrus; ROL, rolandic operculum; IFGoperc, inferior frontal gyrus, opercular part; TPOsup, temporal pole: superior temporal gyrus; ORBinf, inferior frontal gyrus, orbital part; IFGtriang, inferior frontal gyrus, triangular part; PreCG, precentral gyrus; SMA, supplementary motor area; SFGmed, superior frontal gyrus, medial; DCG, median cingulate and paracingulate gyri.

Supplementary Table 5. Overlap of clusters showing significant plasma NfL-functional connectivity associations with the networks of an independent functional brain atlas [1]

Group	Nature of association	Cluster	Percentage overlap (%) with networks of an independent brain atlas[1] [1]
Default mode network seed: Left posterior cingulate cortex (X = -7, Y = -43, Z = 33)			
AD+MCI	Negative	Left DLPFC	Default network (23.37%) Control network (6.53%) Other networks (0%)
Salience network seed: Right anterior insula (X = 35, Y = 24, Z = 5)			
bvFTD	Positive	Right IFGtriang/ IFGoperc/MFG	Control network (54.56%) Default network (0.56%) Other networks (0%)
	Negative	Right MFG/INS/ IFGtriang/IFGoperc/ PUT/ACG/DCG/ROL	Salience/ventral attention network (31.91%) Control network (2.69%) Somatomotor network (1.49%) Default network (0.39%)

[1]The brain atlas can be downloaded here: https://github.com/ThomasYeoLab/CBIG/blob/master/stable_projects/brain_parcellation/Yeo2011_fcMRI_clustering/1000subjects_reference/Yeo_JNeurophysiol11_SplitLabels/MNI152/Yeo2011_17Networks_N1000.split_components.FSL_MNI152_2mm.nii.gz. Percentage overlap (%) with a particular network of the independent brain atlas is computed as: (number of voxels in the cluster that overlapped with a particular network of the atlas*100)/(total number of voxels in the cluster). NfL, neurofilament light; AD, Alzheimer's disease; MCI, mild cognitive impairment; bvFTD, behavioural variant frontotemporal dementia; DLPFC, dorsolateral prefrontal cortex; IFGtriang, inferior frontal gyrus, triangular part; IFGoperc, inferior frontal gyrus, opercular part; MFG, middle frontal gyrus; INS, insula; PUT, lenticular nucleus, putamen; ACG, anterior cingulate and paracingulate gyri; DCG, median cingulate and paracingulate gyri; ROL, rolandic operculum.

REFERENCES

[1] Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, Fischl B, Liu H, Buckner RL (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* **106**, 1125-1165.