Supplementary Materials

1. Supplementary Tables

Supplementary Table 1

Summary of FTD vs. Control Group ICA Comparisons for the SLN and DMN

Comparison			Cluster		Co-ordinates (mm)		
Anatomic region	BA	Side	Size	Peak Z	x	y	z
Increased SLN (FTD > Controls)							
PFC Cluster	9, 10, 11, 32, 44, 45	-	2682	5.27	3	48	39
Superior Occipital	19	R	85	4.48	24	-87	39
Superior Occipital	19	L	52	4.25	-36	-78	45
Caudate Nucleus	-	L	60	4.14	-18	24	6
VMPFC	11	-	186	3.93	0	48	-15
Caudate Nucleus	-	R	72	3.84	15	21	6
Inferior Temporal	20	L	64	3.72	-60	-30	-18
Decreased SLN (Controls > FTD)							
Ventromedial Thalamus	-	L	69	5.36	-9	-18	3
Insula / Putamen	-	L	2448	4.96	-42	0	-12
Middle Cingulate	23	-	447	4.28	-6	-30	30
Superior Temporal	42	R	83	4.19	69	-39	12
Precuneus / Posterior Cingulate	7, 23	-	309	3.99	18	-66	30
Increased DMN (FTD > Controls)							
Middle Insula	-	L	84	4.56	-42	0	12
Angular Gyrus	39	R	148	3.96	54	-57	48
Middle & Anterior Insula	-	R	108	3.92	48	27	3
Anterior Insula	-	L	58	3.89	-45	21	3
Cerebellum	-	R	65	3.87	27	-75	-48
Orbitofrontal Cortex	11	R	76	3.72	30	48	-15
Decreased DMN (Controls > FTD)							
Dorsomedial PFC	32	L	312	3.98	-27	51	21
Anterior Cingulate	24	-	107	3.83	-3	21	33

Supplementary Table 2

Summary of FTD vs. Control Group ICA Comparisons for the SLN Subcomponent Networks

Comparison			Cluster		Co-ordinates (mm)		
Anatomic region	BA	Side	Size	Peak Z	x	y	z
Increased Temporal & Striatum Network (FTD > Controls)							
Inferior Parietal	40	L	138	4.05	-33	-42	57
Decreased Temporal & Striatum Network (Controls > FTD)							
Middle Insula	-	L	48	3.81	-36	3	15
Increased Subgenual Cingulate & VMPFC Network (FTD > Controls)							
Subgenual & VMPFC	11, 25	-	134	3.67	-6	24	-9
Decreased Subgenual Cingulate & VMPFC (Controls > FTD)							
Inferior Parietal	7, 40	R	92	3.98	27	-45	45
Cerebellum	-	R	92	3.79	51	-66	-27
Middle Cingulate	24	-	48	3.55	-9	15	30
Increased Insula & Middle Cingulate Network (FTD > Controls)							
Pulvinar of Thalamus	-	-	51	3.82	-9	-24	18
Decreased Insula & Middle Cingulate (Controls > FTD)							
DLPFC	46	R	48	4.65	33	45	36
Anterior Cingulate	24	-	47	4.08	12	21	24
Increased PFC Network (FTD > Controls)							
Dorsal PFC	9, 32, 46	-	1053	5.06	39	39	15
Orbitofrontal Cortex	47	R	53	4.24	36	45	-9
Caudate Nuclues	-	R	88	4.13	21	24	0
Orbitofrontal Cortex	11	L	89	4.07	-18	54	3
Caudate Nuclues	-	L	68	3.97	-18	24	0
Decreased PFC Network (Controls > FTD)							
Mid Cingulate	23	-	87	3.96	0	-9	42

Supplementary Table 3

Summary of Local Network Changes Associated with FTD

Technique			**Cluster**		**Co-ordinates (mm)**		
Anatomic region	**BA**	**Side**	**Size**	**Peak Z**	**x**	**y**	**z**
Fractional Amplitude of Low Frequency Fluctuations (fALFF)							
Controls > FTD							
Anterior Insula	48	R	344	4.40	38	20	0
Middle Prefrontal Gyrus	46	L	201	4.09	-28	50	8
Regional Homogeneity (REHO)							
Controls > FTD							
Middle Prefrontal Gyrus	46	L	244	5.18	-34	52	10
Middle Prefrontal Gyrus	46	R	273	4.13	30	52	8
Cerebellum	-	L	290	3.96	-34	-52	-50

Supplementary Table 4

Summary of FTD Subtype Differences from the ICA and local network analyses

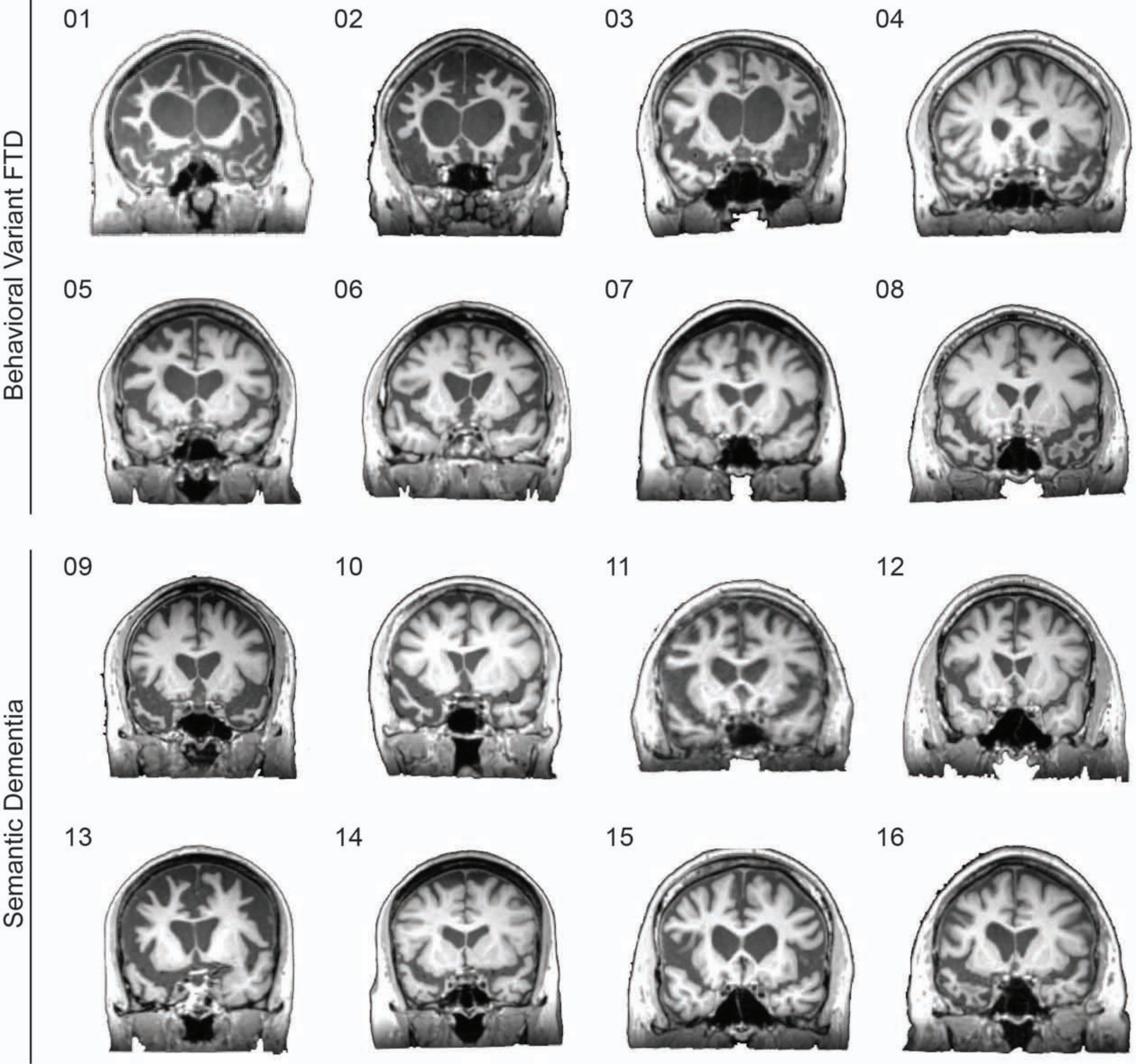
Comparison			**Cluster**		**Co-ordinates (mm)**		
Anatomic region	**BA**	**Side**	**Size**	**Peak Z**	**x**	**y**	**z**
SLN: bvFTD > SD							
DMPFC	9	R	164	3.91	6	60	30
DMPFC	9, 32	L	55	3.70	-15	39	45
Insula & Middle Cingulate Network: SD > bvFTD							
DMPFC	9	R	112	5.07	24	30	51
DMPFC	9, 32	L	60	3.72	-9	36	42
PFC Network: bvFTD > SD							
DMPFC	9	L	53	3.34	-18	39	45
fALFF: SD > bvFTD							
DMPFC	8, 32	R	266	4.42	12	33	48

Supplementary Table 5

Summary of Network - Behavior Correlations

		Behavioral Correlations	
Anatomic Region(s)	**Source Analysis**	**CDR-SB**	**SRI**
FTD Hypoconnectivity (Controls > FTD)			
Limbic Cluster	SLN	-0.30	0.04
DMPFC	DMN	**-0.51**	-0.05
Insula	Temporal Network	*-0.49*	-0.07
Inferior Parietal	Subgenual Network	-0.13	-0.29
Anterior Cingulate	Insula Network	*-0.45*	0.15
Middle Cingulate	PFC Network	-0.37	-0.27
DLPFC	REHO	-0.11	0.17
Insula	fALFF	0.13	0.34
FTD Hyperconnectivity (FTD > Controls)			
Prefrontal	SLN	**0.60**	0.25
Insula	DMN	0.38	0.12
Inferior Parietal	Temporal Network	-0.31	-0.05
Subgenual Cingulate & VMPFC	Subgenual Network	-0.25	**-0.58**
Thalamus	Insula Network	-0.07	0.27
DMPFC	PFC Network	**0.77**	0.13

Note. Correlations in bold are significant at the $p < .05$ level; correlations in italics are marginally significant at the $p < .10$ level.


Behavioral Variant FTD
Semantic Dementia
01
02
03
04
05
06
07
08
09
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11
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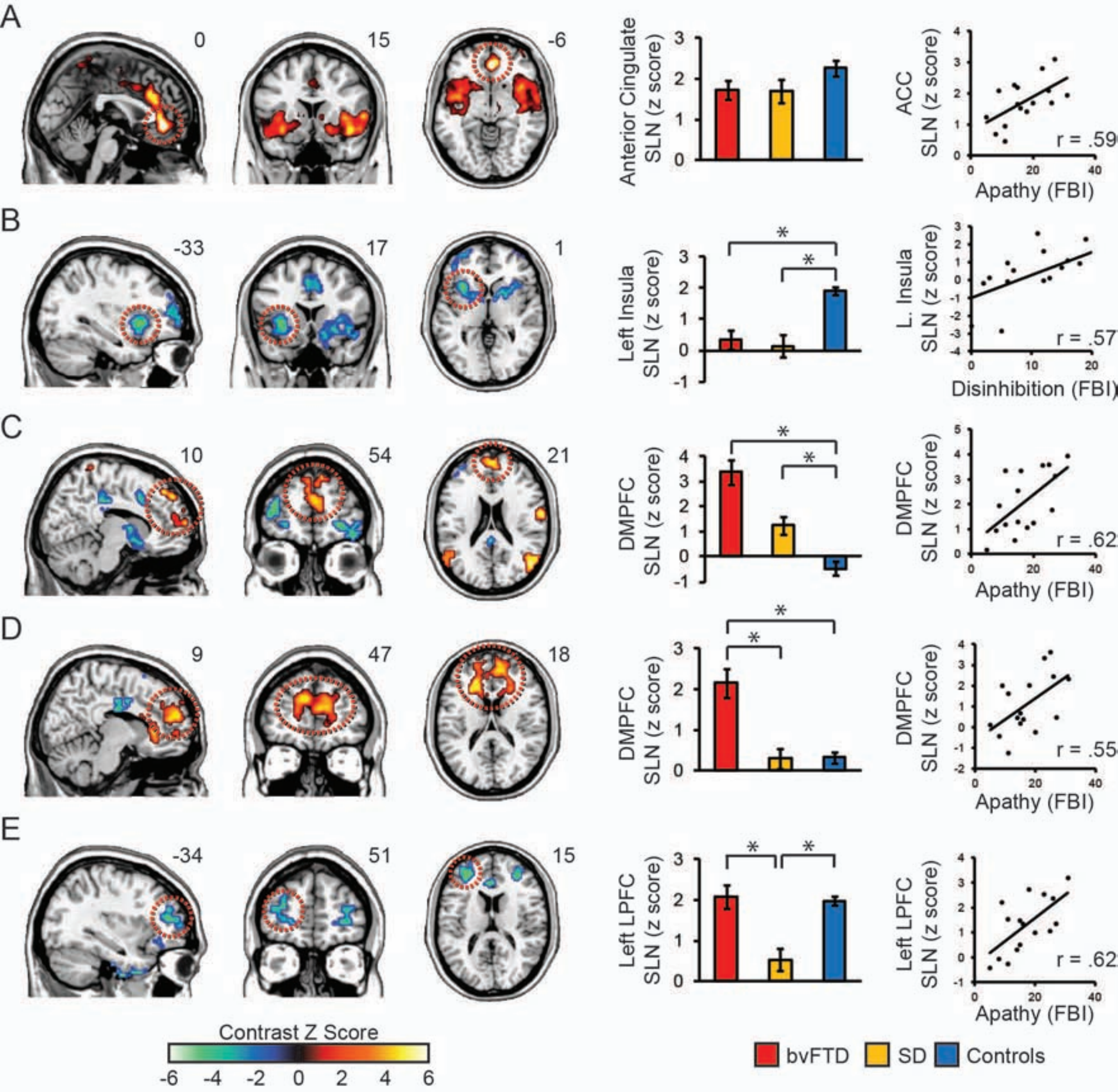
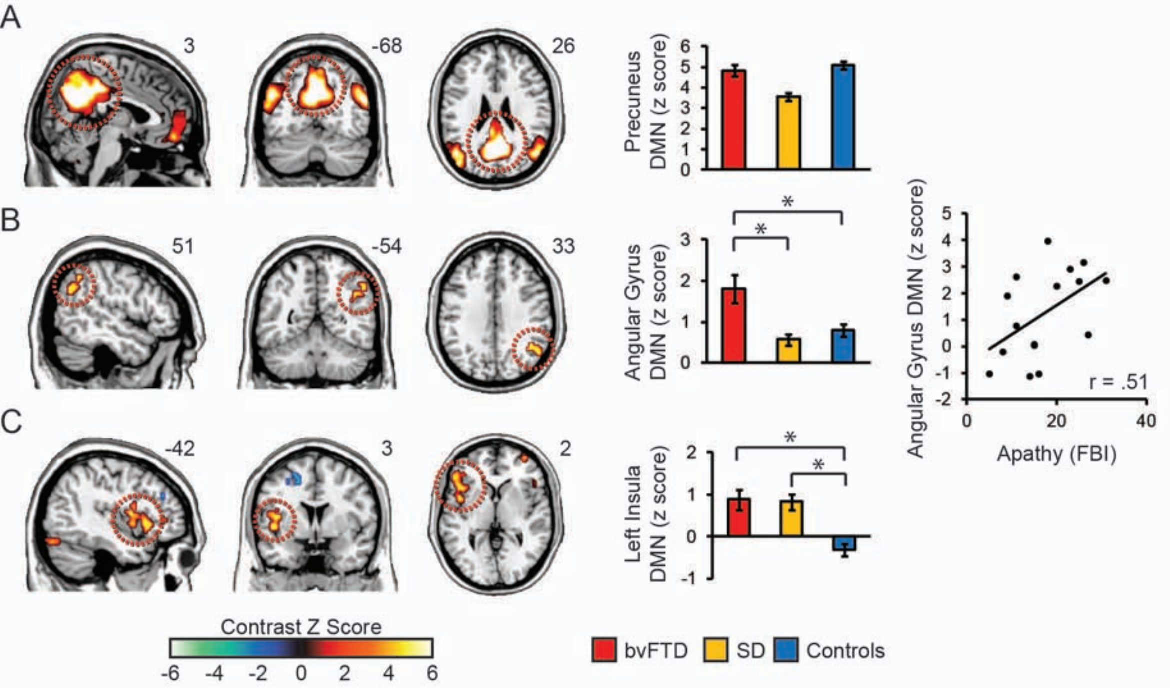
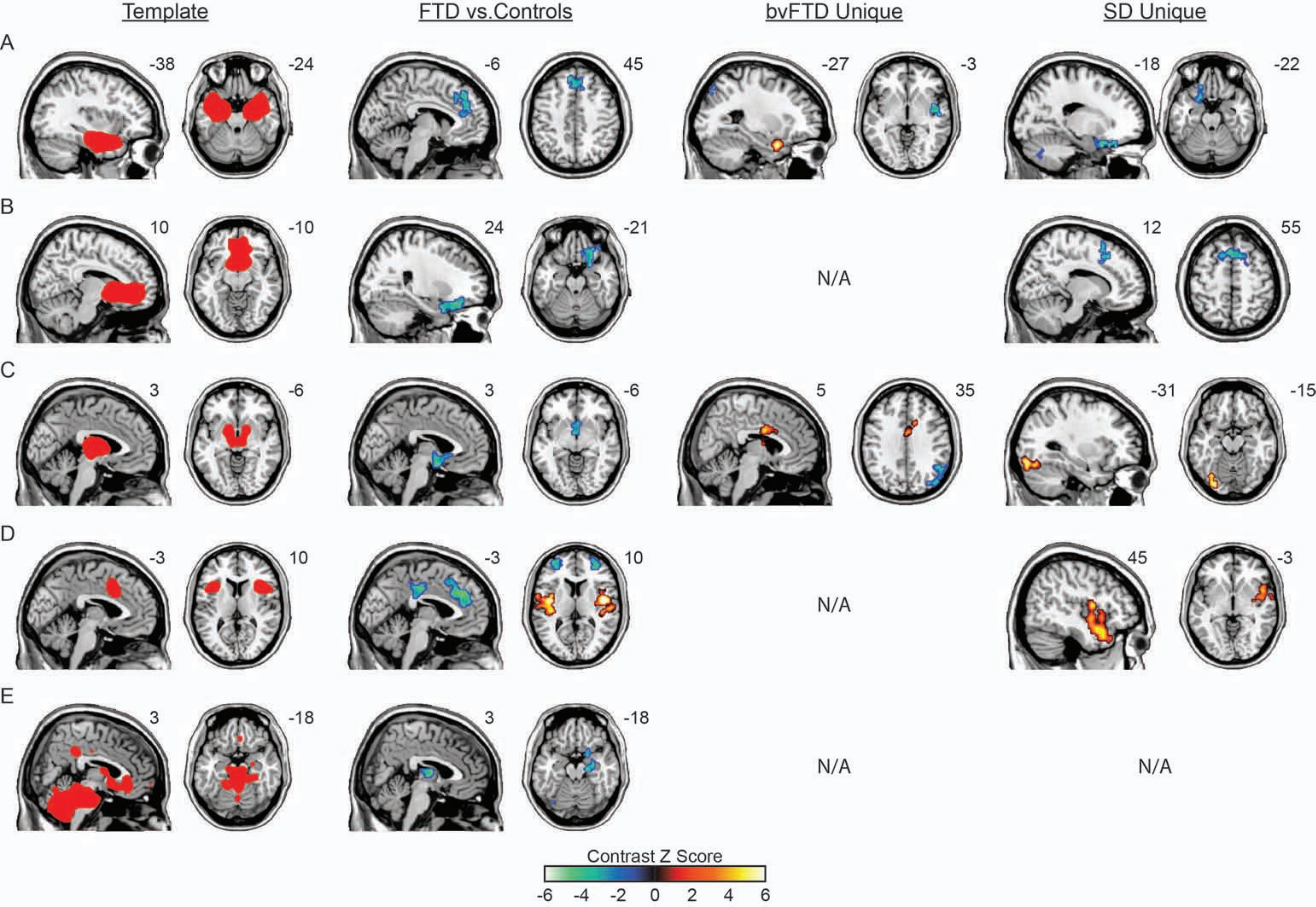
13
14
15
16



A
0
15
-6
Anterior Cingulate SLN (z score)
ACC SLN (z score)
Apathy (FBI)
r = .59
B
-33
17
1
Left Insula SLN (z score)
L. Insula SLN (z score)
Disinhibition (FBI)
r = .57
C
10
54
21
DMPFC SLN (z score)
Apathy (FBI)
r = .62
D
9
47
18
DMPFC SLN (z score)
Apathy (FBI)
r = .55
E
-34
51
15
Left LPFC SLN (z score)
Apathy (FBI)
r = .62
Contrast Z Score
-6 -4 -2 0 2 4 6
bvFTD
SD
Controls



A
3
-68
26
Precuneus DMN (z score)
6
5
4
3
2
1
0
B
51
-54
33
Angular Gyrus DMN (z score)
*
*
3
2
1
0
Angular Gyrus DMN (z score)
5
4
3
2
1
0
-1
-2
0
20
40
Apathy (FBI)
r = .51
C
-42
3
2
Left Insula DMN (z score)
*
*
2
1
0
-1
Contrast Z Score
-6
-4
-2
0
2
4
6
bvFTD
SD
Controls



Template
FTD vs.Controls
bvFTD Unique
SD Unique
A
-38
-24
-6
45
-27
-3
-18
-22
B
10
-10
24
-21
N/A
12
55
C
3
-6
3
-6
5
35
-31
-15
D
-3
10
-3
10
N/A
45
-3
E
3
-18
3
-18
N/A
N/A
Contrast Z Score
-6
-4
-2
0
2
4
6

Supplementary Materials: Partial Least Squares (PLS) Analysis

1. Introduction

This supplementary document details the use of the partial least squares (PLS) analysis technique (McIntosh and Lobaugh, 2004) to replicate the group ICA results discussed in the main text. By employing a multivariate, seed-based approach to generate a complementary pattern of results to the template-matching ICA process, we hope to demonstrate that the connectivity results discussed are not simply idiosyncratic to the technique employed, but instead indicate real patterns within the dataset.

2. Supplementary Methods

To investigate the multivariate detection FTD group and subgroup differences relative to univariate, template-matching ICA techniques, we employed seed-PLS (McIntosh and Lobaugh, 2004), a multivariate analysis technique that identifies group-level spatiotemporal activity patterns maximally correlated with seed region activity. The connectivity assessment investigated DMN and SLN univariate connectivity, using an a priori 'seed' region of interest (ROI) for each network. We used cortical midline structures as seed regions for both networks, as a medial seed would more easily allow for an estimation of bi-hemispheric connectivity. Based on prior literature, for the SLN, an anterior cingulate seed was selected (x=12, y=32, z = 30) (Zhou et al., 2010), while for the DMN a posterior cingulate seed was selected (x=-2, y=-50, z=28) (Grigg and Grady, 2010). The peak REHO and fALFF regions were also included as univariate ROIs, yielding four univariate connectivity ROIs. Individual participant functional connectivity maps were generated for all brain voxels using each of the 4 ROIs as seeds in the REST toolbox and DPARSF. Fisher's Z transformed maps were used to compare correlation estimates at each voxel between FTD and control group participants as well as between the FTD subtypes.

To model low-frequency activity, we adapted methods introduced in a recent study of default network connectivity (Grigg and Grady, 2010). The 165 time points in each participant's resting-state time series were modeled as 33 contiguous "blocks" of 5 consecutive volumes, averaging neural activity across each of the 5 volume (i.e., 10 second) blocks. This averaging technique created an approximate 0.1 Hz low pass filter across the time series, consistent with the temporal filtering techniques applied in the other analysis methods applied in this study. Activity values from the SLN and DMN seeds were then extracted from each of the 33 blocks using 3mm spherical regions of interest. For each of the two seeds, a separate seed-PLS analysis was then performed to create a model that maximized the correlation between the seed region and the rest of the brain. In these analyses the correlation between seed activity and activity in all other brain voxels was determined (i.e., from both the FTD and control groups), and then the pattern of correlation was submitted to singular value decomposition in PLS, modeling the 33 blocks for each of the FTD and control groups, for a total of 66 blocks.

The PLS procedure produces a set of orthogonal latent variables, sets of voxels that maximally correlate across all blocks with the seed region. The first latent variable explains the greatest proportion of seed variance, and was visually inspected to ensure that the seed region was well predicted by the model across the entire resting-state time series. Finally, for each of the two seeds (anterior cingulate SLN and posterior cingulate DMN), a Non-Rotated Behavioral PLS was performed. This analysis contrasted the FTD and control groups with respect to their correlation with seed region activity, showing regions whose seed connectivity significantly differed as a function of FTD status. This was done by specifying a series of contrasts ("1" for FTD patients and "-1" for Controls) for each block in each group. A second Non-Rotated Behavioral PLS was performed to contrast bvFTD and SD FTD subtypes, specifying contrasts ("-1" for bvFTD and "1" for SD) for each block in each subgroup.

To determine a voxel's correlation with the seed region, each voxel receives a salience score that expresses its contribution to the latent variable. Correction for multiple comparisons are not performed in PLS analysis, as all voxels' salience scores are estimated simultaneously and are not the product of multiple comparisons requiring statistical correction. Instead, bootstrap testing was performed to determine the reliability of each voxel: participants were randomly resampled with replacement 1000 times and the standard errors for each voxel's salience score were calculated. The ratio of the salience score to the standard error for each voxel creates a bootstrap ratio, an estimate of how reliably that voxel fits with the latent variable. We set a bootstrap ratio of ≥ 2.0 for establishing the reliability of the seed region correlation pattern, corresponding to a Type-I error p-value of $p < .05$ that matched the corrected p-values of other analyses; a cluster threshold of $k \geq 50$ was also applied to focus on the most powerful regions of seed connectivity.

3. PLS Supplement Results

Separate PLS analyses were run using an anterior cingulate SLN seed and a posterior cingulate DMN seed. For the SLN, anterior cingulate connectivity differed between FTD and Controls: FTD participants displayed greater local connectivity between the SLN seed and the dorsal MPFC relative to Controls, demonstrating enhanced SLN connectivity with regions typically characterized as the executive network. However, relative to Controls, SLN connectivity with limbic regions such as the bilateral insula, thalamus, striatum as well as anterior temporal regions were markedly reduced (PLS Supplementary Figure 1, top). For the DMN, posterior cingulate connectivity also resulted in group differences, with greater FTD connectivity in superior, inferior, and angular parietal regions and the precuneus. However, unlike the ICA analysis, PLS revealed reduced DMN posterior cingulate connectivity in FTD with lateral prefrontal regions (PLS Supplementary Figure 1, bottom; PLS Supplementary Table 1 contains a full list of PLS seed connectivity regions).

Additional non-rotated PLS analyses were conducted using the SLN and DMN seeds within FTD to investigate connectivity differences indicative of FTD subtype. Within patients with FTD, the PLS contrast of the bvFTD and SD subtypes suggested greater anterior cingulate connectivity with the anterior medial PFC (BA 10) in bvFTD, and greater connectivity with the bilateral amygdala, hippocampus, thalamus and ventral cerebellum in SD. The posterior cingulate seed demonstrated greater connectivity with the right angular gyrus and left superior temporal gyrus in bvFTD, and greater connectivity throughout the cerebellum in SD. Images and peak locations for the within FTD PLS analyses are available in PLS Supplementary Figure 2 and PLS Supplementary Table 1.

4. PLS Supplement Discussion

With respect to the comparison of resting-state methods, both the univariate and PLS multivariate analyses revealed similar group connectivity differences. However, the PLS analysis demonstrated additional connectivity differences, consistent with its expectedly greater power to maximize group differences by simultaneously comparing correlation patterns across all participants and groups. Specifically, the PLS analysis identified reduced insula and caudate connectivity with both the salience and default network seeds, rather than only associating such reduced connectivity with the SLN as was observed in the univariate and ICA approaches. This finding serves as a cautionary note against inferring that insula atrophy impacts the SLN alone; rather, the frontotemporal atrophy characterizing FTD may modulate distal network activity as well, perhaps contributing to the greater angular gyrus DMN recruitment observed in FTD. However, despite its greater power to group level connectivity differences with great sensitivity, PLS is limited in its ability to provide meaningful prediction on an individual participant basis. The ICA approach did provide individual ICA component fit scores and peak voxels that were associated with FTD status, which may in turn be useful for the predictive classification of FTD in future research. Thus, while exploring the reliability of ICA and univariate methods for the purposes of clinical prognosis is still an open field of inquiry, the parsimony of investigating a limited number of univariate seed regions may prove to be more tractable in clinical settings.

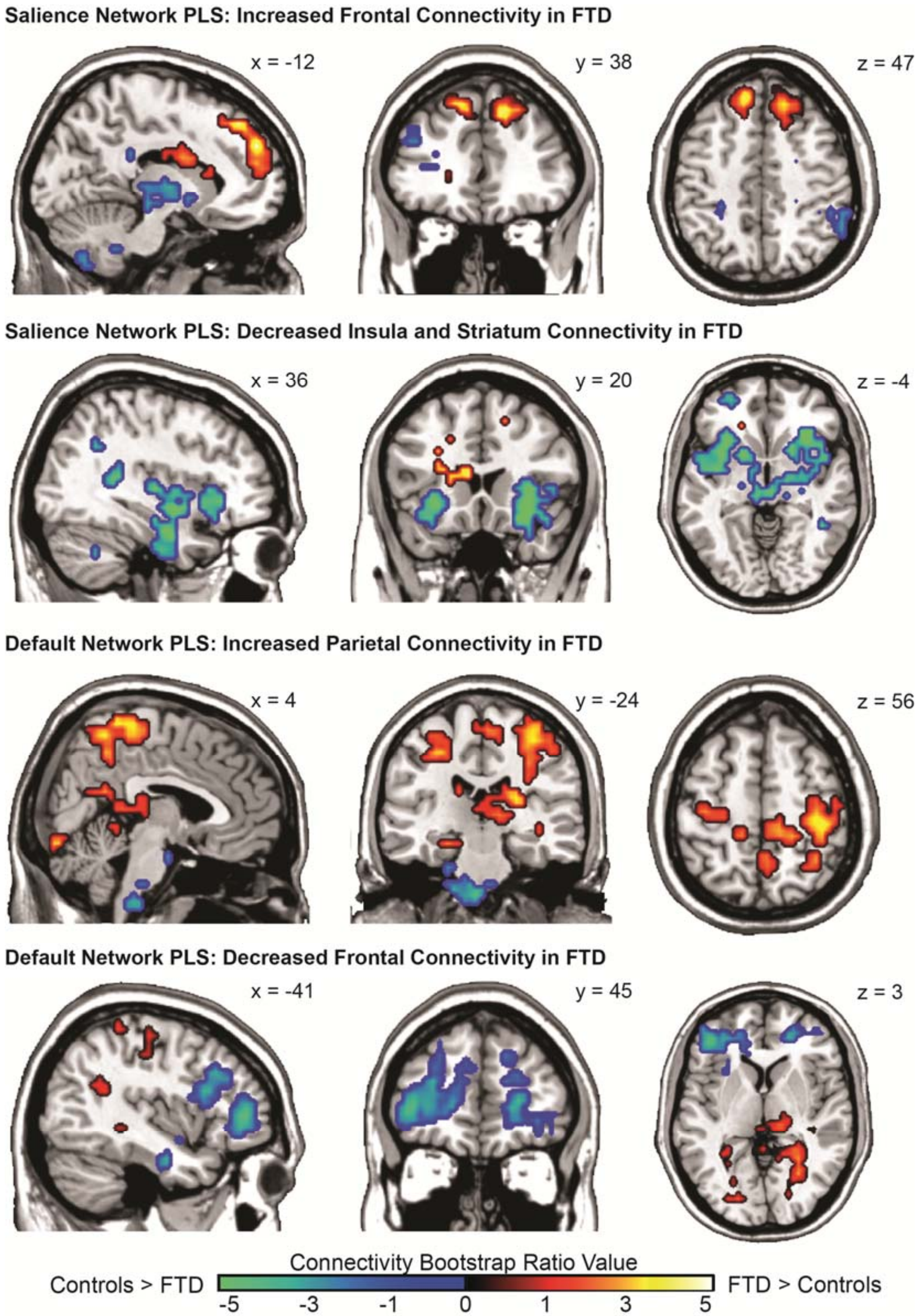
5. PLS Supplement Tables

PLS Supplementary Table 1. *Regions of Between-Group PLS Connectivity Differences*

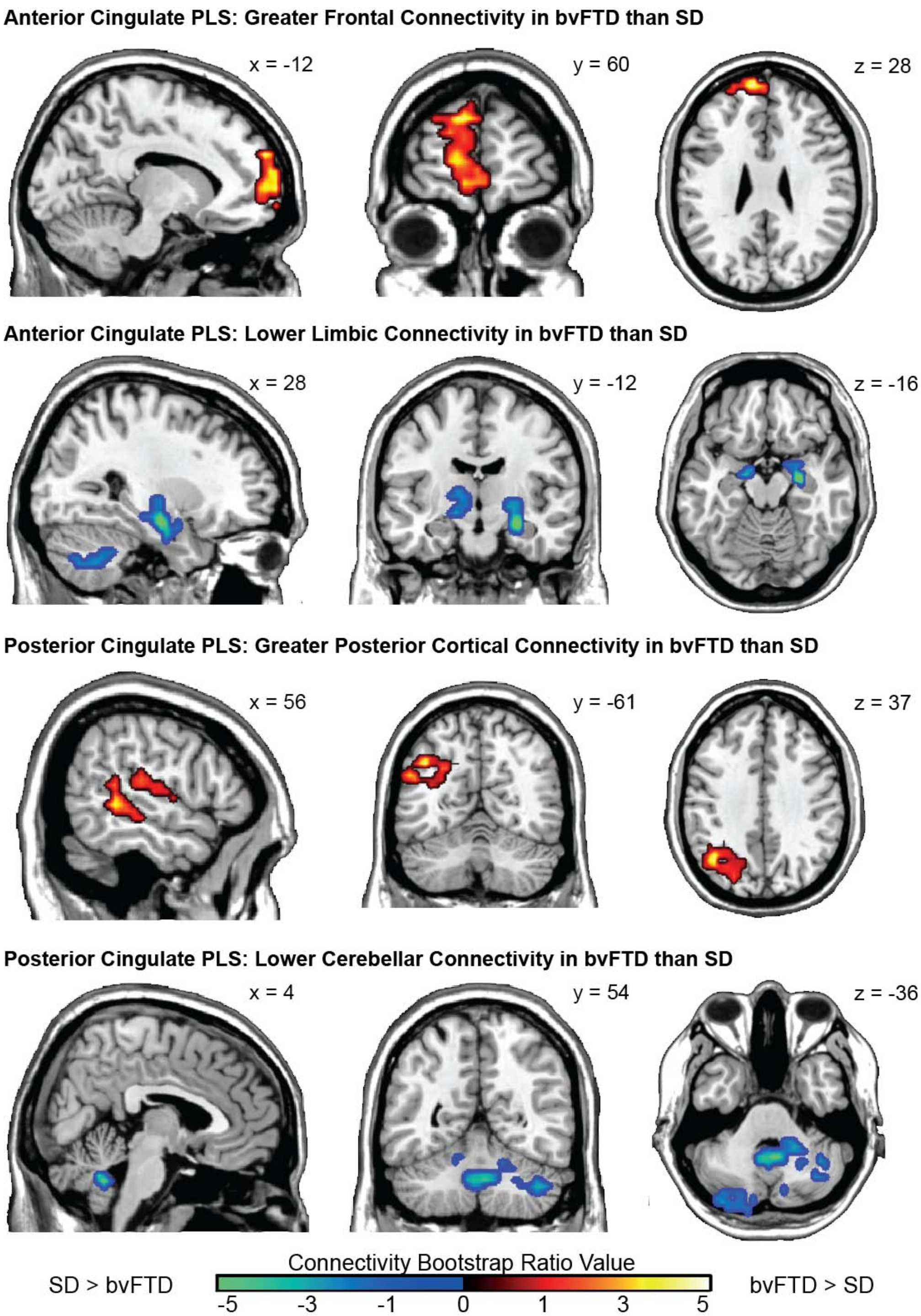
Anatomic region	BA	Side	Cluster Size	Bootstrap Ratio	Co-ordinates (mm) x	y	Z
Salience Network (Anterior Cingulate Seed): FTD vs. Controls							
Dorsomedial Prefrontal Cortex	9 / 10	-	414	5.84	-12	52	32
Caudate Nucleus	-	-	269	4.46	0	12	8
Bilateral Insula & Limbic	48	-	1456	-6.07	28	24	-16
Cerebellum	-	L	311	-5.03	-28	-64	-28
Angular Gyrus	39	L	652	-4.75	-36	-56	28
Lateral and Middle Prefrontal	45 / 46	L	179	-4.74	-36	44	12
Posterior Cingulate	23	R	108	-4.30	16	-68	-52
Middle Temporal	21	R	57	-4.19	44	-48	-4
Salience Network (Anterior Cingulate Seed): bvFTD vs. SD							
Medial Prefrontal Cortex	10	L	165	4.66	-12	60	28
Amygdala / Hippocampus / Thalamus	-	R	54	-5.98	28	-12	-16
Cerebellum	-	L	66	-4.08	-40	-64	-52
Cerebellum	-	R	208	-4.07	40	-60	-44
Hippocampus / Thalamus	-	L	73	-3.55	-16	-8	-16
Default Network (Posterior Cingulate Seed): FTD > Controls							
Somatosensory / Parietal / Parahippocampus	5 / 29 / 23	R	2264	5.98	36	-52	64
Hippocampus	30	L	62	4.18	-24	-28	-16
Pons / Brainstem	-	L	188	-5.04	-8	-20	-48
Anterior Insula / Caudate / Lateral PFC / Middle PFC	48 / 46 / 47 / 32	-	1367	-4.86	-16	56	-8
Inferior Temporal	20	L	67	-4.13	-40	-8	-24
Default Network (Posterior Cingulate Seed): bvFTD vs. SD							
Angular Gyrus	39	L	115	5.04	-40	-64	36
Superior Temporal Gyrus	22	R	104	3.90	56	-40	0
Cerebellum	-	-	80	-4.96	4	-52	-36
Cerebellum	-	R	84	-4.03	44	-56	-40
Cerebellum	-	L	158	-3.85	-8	-80	-20

Negative bootstrap ratio represent regions negatively correlated with the latent variable, i.e., Controls > FTD, or SD > bvFTD.

6. PLS Supplement Figures



Supplementary PLS Figure 1. Between-groups (FTD vs. Controls) PLS Analysis Summary.



Supplementary PLS Figure 2. Within FTD Group Partial Least Squares (PLS) Analysis Summary.

7. PLS Supplement Figure Captions

Supplementary PLS Figure 1. Between-groups (FTD vs. Controls) PLS Analysis Summary. Positive and negative correlates of the anterior cingulate (top two panels) and posterior cingulate (bottom two panels) are displayed. The anterior cingulate demonstrates higher frontal (red) and lower limbic (blue) connectivity in FTD relative to Controls; the posterior cingulate demonstrates higher parietal (red) and lower lateral prefrontal (blue) connectivity in FTD relative to Controls.

Supplementary PLS Figure 2. Within FTD Group Partial Least Squares (PLS) Analysis Summary. Positive and negative correlates of the anterior cingulate (top two panels) and posterior cingulate (bottom two panels). The anterior cingulate demonstrates higher frontal (red) and lower limbic (blue) connectivity in bvFTD relative to SD; the posterior cingulate demonstrates higher parietal (red) and lower cerebellar (blue) connectivity in bvFTD relative to SD.

8. PLS Supplement References

Grigg O, Grady CL. The default network and processing of personally relevant information: converging evidence from task-related modulations and functional connectivity. *Neuropsychologia,* 48 (13):3815-3823, 2010.

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Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, Kramer JH, Weiner M, Miller BL, Seeley WW. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain,* 133 (Pt 5):1352-1367, 2010.