Original Investigation

Salience Network Resting-State Activity
Prediction of Frontotemporal Dementia Progression

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IMPORTANCE Noninvasive measures of activity within intrinsic brain networks may be clinically relevant, providing a marker of neurodegenerative disease and predicting clinical behaviors.

OBJECTIVE To correlate baseline resting-state measures within the salience network and changes in behavior among patients with frontotemporal dementia.

DESIGN Baseline resting-state functional magnetic resonance imaging data and longitudinal clinical measures were obtained from prospectively accrued patients during 8 weeks.

SETTING Tertiary academic care center specializing in the assessment and management of patients with neurodegenerative disease.

PARTICIPANTS Fifteen patients with clinically diagnosed frontotemporal dementia (5 behavioral variant and 10 semantic dementia).

MAIN OUTCOMES AND MEASURES Baseline resting-state functional magnetic resonance imaging data measured within regions of interest were regressed on serial behavioral measures from prospectively accrued patients with frontotemporal dementia to determine the ability of baseline resting-state activity to account for changes in behavior.

RESULTS Low-frequency fluctuations in the left insula significantly predicted changes in Frontal Behavioral Inventory scores (standard $\beta = 0.51$, $P = .049$), accounting for 28% of the change variance. The trend was driven by changes in measures of apathy independent of dementia severity.

CONCLUSION AND RELEVANCE Baseline measures of salience network connectivity involving the left insula may predict behavioral changes in patients with frontotemporal dementia.

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Advances in functional neuroimaging have provided a window into the brain's intrinsic connectivity, leading to the discovery of the salience network (SLN), composed of the anterior cingulate, insula, striatum, and amygdala. The SLN is activated in healthy patients during tasks requiring attentional selection, task switching, and self-regulation of behavior[1] and is an important neural substrate in frontotemporal dementia (FTD),[2] with dysfunction confirmed on histopathology[3] and resting-state functional magnetic resonance (fMR) imaging.[1,2] Within the SLN, the insula has emerged as a nodal point of particular importance for frontolimbic function and dysfunction.[2] Supporting this assertion, insular atrophy is recognized as one of the earliest structural biomarkers in behavioral variant FTD (bvFTD) and semantic dementia,[3,4] with insular loss correlated with worsening behavioral inventory scores[5] and progressive accumulation of FTD-associated pathologic inclusions within insular von Economo neurons and Fork cells.[6,7]

Abnormal activity within intrinsic brain networks may be clinically relevant, indicative of neurodegenerative disease.[1,2] Resting-state fMR imaging may provide a noninvasive biomarker for the diagnosis and longitudinal monitoring of patients with FTD. However, it remains to be determined whether this emerging technique can be used to identify patterns of network disruption in patients before the development of changes on clinical examination or structural neuroimaging. We explored the ability of baseline resting-state connectivity measures to predict behavioral changes in participants with bvFTD and semantic dementia during 8 weeks.

Table 1. Demographic and Clinical Characteristics of Study Patients

Variable	bvFTD Group (n = 5)	Semantic Dementia Group (n = 10)	*P* Value[a]
Age, mean (SD), y	62.6 (4.2)	59.1 (8.9)	.42
Male sex, No. (%)	2 (40)	6 (60)	.44[b]
Education, mean (SD), y	16.6 (2.2)	16.6 (2.8)	>.99
Duration of illness, mean (SD), y	5.4 (4.2)	3.9 (2.2)	.37
Clinical Dementia Rating, mean (SD), sum of boxes score	1.8 (1.3)	1.3 (0.7)	.29
FBI, mean (SD), total score			
Baseline	29.6 (16.9)	25.0 (9.9)	.51
8 wk	29.8 (15.8)	23.6 (9.1)	.35
% Change	3.8 (22.9)	−3.6 (6.5)	.34

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; FBI, Frontal Behavioral Inventory.

[a] Two independent-samples *t* test, assuming equal variance (unless otherwise indicated).

[b] χ^2_1.

Methods

All procedures were approved by institutional ethics boards. Written informed consent was obtained from patients or their substitute decision makers. Baseline resting-state fMR imaging data were collected from 15 patients with clinically diagnosed FTD (5 bvFTD and 10 semantic dementia[8]) before initiation of study medication as part of the protocol for a prospective open-label clinical trial. Details concerning study recruitment have been published previously.[9] In the present study, the subtype diagnosis for 2 patients has been amended from bvFTD to semantic dementia because symptoms of the semantic variant of primary progressive aphasia manifested after clinical trial completion. Control participants were not explicitly recruited for the open-label trial; however, resting-state data were available from 16 age-matched healthy volunteers enlisted for a parallel study and were included in comparison analyses.[1] Control participants did not differ from the patients in age, sex, or educational status. The term *frontotemporal dementia* refers herein to both the bvFTD and semantic dementia subtypes of FTD.

Behavioral measures were obtained at baseline and at 8 weeks from patients with FTD using the Frontal Behavioral Inventory (FBI) total score (with apathy and disinhibition subscores)[10] and the more global Clinical Dementia Rating.[11] Patients with FTD received the clinical intervention, memantine hydrochloride (10 mg), twice daily.

The fMR imaging protocol directed participants to lie with eyes closed during image acquisition. Data were preprocessed using a computer program (Data Processing Assistant for Resting-State fMRI; www.restfmri.net). To identify SLN hubs for our analysis, we compared resting-state activity in patients with FTD with that of healthy control subjects and selected regions of interest (ROIs) based on areas of maximal group distinction. Three ROIs were identified, including the right and left insulae and the medial anterior cingulate cortex extending into both hemispheres (eTable 1 in the Supplement).[1]

Resting-state activity within the right insula, left insula, and anterior cingulate ROIs was separately assessed using 2 distinct measures of voxelwise signal power and homogeneity. Signal power was measured using fractional amplitude of low-frequency fluctuation (fALFF),[12] a voxelwise ratio between low-frequency power (ie, 0.01-0.1 Hz) and the broader-frequency spectrum of resting-state activity (ie, 0-0.25 Hz). The fALFF reported for an ROI is the first eigenvariate of the fALFF scores from all voxels within that region. Fractional amplitude of low-frequency fluctuation has emerged as a functional measure of local signal strength of connections within neural networks, providing a measure of integrity (ie, health) of individual nodal points within a network. On the other hand, regional homogeneity (REHO) provides a measure of local coherence in the brain, calculated as the cross-correlation between each voxel and its neighbors, reflecting coherence within an ROI.[13] When applied to analysis of the spontaneous low-frequency fluctuations observed during the resting state, REHO is argued to represent local brain network integrity.[14] Changes in fALFF and REHO within SLN structures can reliably discriminate patients having neurodegenerative disease from healthy control subjects.[1,2]

A forward linear regression analysis used baseline resting-state scores (REHO and fALFF) within ROIs to predict percentage change on behavioral scales at the end of 8 weeks. Before the forward regression, baseline FBI total scores were entered as a first step in the model to control for variation in initial symptom severity. A predictor variable was selected for inclusion in the model if it improved the model fit at a significance level of $P < .05$. Post hoc linear regression was performed to quantify the extent to which baseline resting-state activity predicted behavioral change in patients with FTD. Analyses were performed using statistical software (IBM SPSS Statistics 20; IBM Corporation).

Results

Table 1 lists demographic and clinical characteristics of the patients; all had dementia of mild to moderate severity. The groups with bvFTD and semantic dementia did not differ in clinical or demographic measures. Changes in patients' FBI scores were heterogeneous across 8 weeks, without discernible improvement or degradation (**Table 2**). Resting-state measures within the left insula differentiated controls from patients with semantic dementia and bvFTD (**Figure**).

Forward linear regression for the entire sample revealed a predictive relationship between fALFFs in the left insula and

Table 2. Frontal Behavioral Inventory (FBI) Baseline Scores and Percentage Change at 8 Weeks for Individual Patients

	FBI Total Score		FBI Apathy Subscore		FBI Disinhibition Subscore	
Patient No.	Baseline	% Change, Mean (SD)	Baseline	% Change, Mean (SD)	Baseline	% Change, Mean (SD)
bvFTD Group						
003	**32**	−2 (−6.3)	25	0	7	−2 (−28.6)
004	**49**	1 (2.0)	31	2 (6.4)	18	−1 (−5.5)
006	**42**	−4 (−9.5)	23	−4 (−17.4)	19	0
018	**9**	−1 (−11.1)	9	−1 (−11.1)	0	0
026	**16**	7 (4.4)	11	7 (63.6)	5	0
Semantic Dementia Group						
002	**33**	−4 (−12.1)	27	−2 (−7.4)	6	−2 (−33.3)
005	**14**	−1 (−7.1)	8	0	6	−1 (−16.7)
007	**33**	−3 (−9.1)	18	0	15	−3 (−20.0)
011	**17**	0	15	0	2	0
015	**26**	1 (4.3)	15	3 (20.0)	11	−5 (−45.5)
019	**26**	1 (3.8)	14	0	12	1 (8.3)
020	**41**	−1 (−2.4)	20	−1 (−5.0)	21	0
021	**23**	0	11	0	12	0
022	**8**	0	5	0	3	0
028	**29**	−4 (−13.8)	16	−6 (−37.5)	13	2 (15.4)

Abbreviation: bvFTD, behavioral variant frontotemporal dementia.

changes in behaviors captured with the FBI total scores (standard β = 0.51, P = .049) (eTable 2 in the Supplement). Higher left insular fALFF activity predicted an interval worsening (increase) in FBI scores, accounting for 28% of the change variance (Figure). The trend seemed to be driven by alterations in the FBI apathy subscores. Left insula fALFF predicted increases in the apathy subscores (standard β = 0.66, P = .006). Right insula resting-state measures did not independently predict changes in overall FBI scores; however, after controlling for left fALFF, right fALFF measures improved predictions of changes in the apathy subscores, while higher right insula fALFF identified those least likely to experience increases in the apathy subscores (standard β = −0.49, P = .03). Neither insular REHO nor resting-state measures within the anterior cingulate cortex accounted for changes in behavior. In addition, no correlation was observed between baseline resting-state measures and duration of illness, global Clinical Dementia Rating, or the magnitude of FBI scores (eTable 3 in the Supplement).

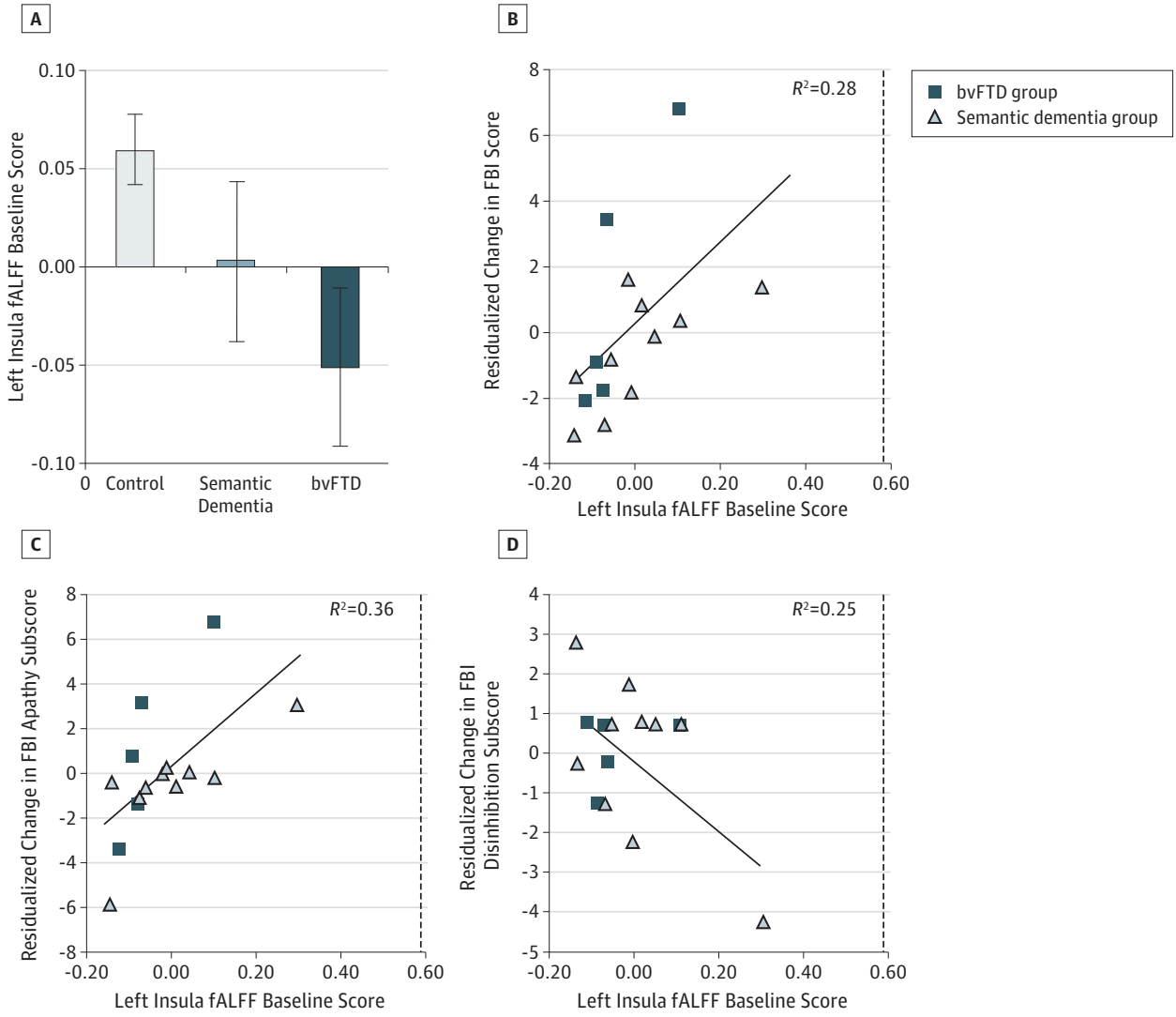
To confirm the generalization of these findings to FTD subtypes, we repeated the regression analysis separately for patients with bvFTD and semantic dementia. The results were more robust for the bvFTD group: baseline fluctuations in low-frequency resting-state activity in the left insula strongly predicted increases in the FBI (standard β = 1.02, P = .03, R^2 = 0.80), especially increases in the apathy subscores (standard β = 1.07, P = .04, R^2 = 0.85) (eTable 4 in the Supplement). A similar correlation with left fALFF activity was observed in the semantic dementia group (standard β = 0.61, P = .04, R^2 = 0.37), including apathy subscores (standard β = 0.72, P = .02, R^2 = 0.52) (eTable 5 in the Supplement). Correlations were confirmed with parametric and nonparametric statistical measures (eTable 6 in the Supplement), suggesting that the described relationship was not driven by outliers.

Discussion

Patterns of connectivity within and between SLN structures reliably distinguish patients with FTD from healthy control subjects[1] and from patients with Alzheimer disease.[2] The results of this study corroborate the importance of the insula within the SLN, suggesting that baseline measures of SLN connectivity involving the left insula may predict changes in behavior in patients with FTD, as measured with the FBI. Measures of low-frequency signal within the left insula did not serve as an indicator of disease severity because no association was observed between baseline measures of resting-state activity and clinical features or measures of disease severity at the time of entry into the trial.

Rapid behavioral change early in the course of FTD is a well-described yet poorly understood clinical phenomenon.[15] This effect is not seen in patients with Alzheimer disease,[15] suggesting that accelerated functional decline in FTD may be explained by a model of neurodegenerative disease that emphasizes breakdown of network connectivity, preceding structural changes detected on standard neuroimaging. The pattern of breakdown is presumed to be distinct from that seen in Alzheimer disease, accounting for differences in clinical progression and facilitating differentiation between FTD and Alzheimer disease with resting-state measures.[2,3] In line with this, the increased tonic signaling measured within the left insula of study patients may reflect a compensatory response resulting from loss of regional connections. Similar increases are recorded in the mean firing rate of neurons within the subthalamic nuclei of patients with Parkinson disease undergoing deep brain electrode implantation,[16] suggesting that hyperactive neuronal discharges in the subthalamic nucleus are as-

Figure. Left Insula Fractional Amplitude of Low-frequency Fluctuation (fALFF) Scores and Symptom Change



A, Identification of left insula fALFF in patients having behavioral variant frontotemporal dementia (bvFTD) or semantic dementia vs healthy control subjects. B, Patient Frontal Behavioral Inventory (FBI) changes during 8 weeks and fALFF measures. The line represents the regression for the entire group (n = 15). The FBI change scores are residualized, controlling for baseline FBI scores. C, The FBI apathy subscore changes during 8 weeks and fALFF measures. D, The FBI disinhibition subscore changes and fALFF measures. Dashed vertical line indicates the mean fALFF activity measured in the control group.

sociated with motor dysfunction. The magnitude of resting-state activity measured within the SLN of our patients with FTD was less than that measured in healthy controls, emphasizing the importance of interpreting resting-state measures relative to other patients with FTD. In our study, a relative increase in fALFFs was predictive of behavioral worsening during as short a period as the next 8 weeks in patients with FTD. Within this population, measures of fALFFs within the left insula may provide a marker of a dysregulated network at greatest risk of collapse. An alternate explanation for the observed correlations may be that higher left insula resting-state activity selected for patients with a less advanced clinical stage of dementia, identifying those with preserved behavioral functions and the greatest potential for change (ie, the most to lose). However, no correlation was found between resting-state activity and clinical measures approximating disease severity, favoring the assertion that resting-state measures may predict behavioral change independent of assessable clinical measures. Resting-state measures may provide a functional neuroimaging correlate for the precipitous behavioral decline detailed in FTD,[15] permitting evaluation of the role of SLN dysfunction in this process.

Anterior insular atrophy is reported early in the course of bvFTD, with the extent of right hemisphere involvement exceeding that of the left on structural neuroimaging.[17] Correspondingly, fALFFs are reduced in the right insula of patients having bvFTD and semantic dementia compared with controls.[1] Extending these findings, higher right insula fALFF seemed protective against worsening of apathy in patients with FTD (after controlling for left fALFF activity). Relative preservation of right insula fALFFs may be protective against behavioral decline. The contributions of dysfunc-

tion within right and left SLNs to the FTD phenotype are deserving of further study.

The small sample size in this study likely limited the ability to draw correlations between resting-state measures and behavior. No significant changes in behavioral measures were reported across the 8-week study period for the total sample, the bvFTD group, or the semantic dementia group, indicating that a longer study with a larger sample might be more informative. In addition, all patients received memantine hydrochloride. However, it is unlikely that open-label use of memantine significantly altered behavior given the published randomized control trial that demonstrated no effect in patients with FTD,[18] as well as the finding that FBI scores did not improve during the open-label trial study period.[9] Future studies could control for medication use and include more resting-state measurements during the course of the illness. Eight weeks may be too short a time to detect clinically significant changes in network connectivity.

Limitations notwithstanding, the results of this analysis expand on prior studies. Resting-state measures of neural connectivity may provide a noninvasive means of assessing network functioning in neurodegenerative disease.

ARTICLE INFORMATION

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Acquisition of data: Pollock, Chow.
Analysis and interpretation of data: Day, Farb, Tang-Wai, Masellis, Black, Freedman, Chow.
Drafting of the manuscript: Day, Farb, Chow.
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Statistical analysis: Day, Farb.
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