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Brain Network Organization and Social Executive Performance in Frontotemporal Dementia

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Abstract

Objectives: Behavioral variant frontotemporal dementia (bvFTD) is characterized by early atrophy in the frontotemporoinsular regions. These regions overlap with networks that are engaged in social cognition-executive functions, two hallmarks deficits of bvFTD. We examine (i) whether Network Centrality (a graph theory metric that measures how important a node is in a brain network) in the frontotemporoinsular network is disrupted in bvFTD, and (ii) the level of involvement of this network in social-executive performance. **Methods:** Patients with probable bvFTD, healthy controls, and frontoinsular stroke patients underwent functional MRI resting-state recordings and completed social-executive behavioral measures. **Results:** Relative to the controls and the stroke group, the bvFTD patients presented decreased Network Centrality. In addition, this measure was associated with social cognition and executive functions. To test the specificity of these results for the Network Centrality of the frontotemporoinsular network, we assessed the main areas from six resting-state networks. No group differences or behavioral associations were found in these networks. Finally, Network Centrality and behavior distinguished bvFTD patients from the other groups with a high classification rate. **Conclusions:** bvFTD selectively affects Network Centrality in the frontotemporoinsular network, which is associated with high-level social and executive profile. (*JINS*, 2016, *22*, 250–262)

Keywords: Functional connectivity, Graph theory analysis, Frontoinsular stroke, Neurodegenerative disease, f MRI resting-state, Node centrality

INTRODUCTION

Behavioral variant frontotemporal dementia (bvFTD) is characterized by early brain atrophy in the frontotemporoinsular regions (Piguet, Hornberger, Mioshi, & Hodges, 2011; Rascovsky et al., 2011). These regions overlap with networks that are engaged in high-level processes, such as emotion recognition, social inference [e.g., theory of mind (ToM)], and executive functions (Ibanez & Manes, 2012; Kennedy & Adolphs, 2012; Stanley & Adolphs, 2013). Several reports have associated bvFTD-specific neurodegeneration with deficits in such social-executive domains (Possin et al., 2013; Torralva, Roca, Gleichgerrcht, Lopez, & Manes, 2009); and previous studies have shown that the disruption of long-distance networks (Pievani, de Haan, Wu, Seeley, & Frisoni, 2011) provides information about behavioral symptoms (Farb et al., 2013), executive functions

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(Agosta et al., 2013), and disease progression (Day et al., 2013) in bvFTD. However, no single study has assessed the network centrality of the frontotemporoinsular network and its potential association with social-executive impairments.

Here, we seek to determine whether connectivity properties of the frontotemporoinsular network were associated with social-executive performance. Our analysis was based on the use of Graph Connectivity Metrics, which constitute a sensitive approach to study neurodegeneration (Pievani et al., 2011). We selected the Network Centrality (NC), a local metric which indicates the importance of a node in the global context of a network (Freeman, 1977). NC is a sensitive metric for bvFTD (Agosta et al., 2013) and, compared to other local metrics (e.g., clustering coefficient or degree), offers rich data about the relations between a network's properties and observed symptoms and behaviors (Goch et al., 2014; Zuo et al., 2012). Global connectivity metrics (such as characteristic path length or average clustering coefficient) were not used because they do not provide local network information (Sporns, 2014). Thus, they are unsuitable to evaluate whether behavioral impairments are associated with deficits in specific nodes.

We assessed whether the frontotemporoinsular network's centrality was altered in bvFTD, and examined whether this centrality measure was associated with social-executive performance. To this end, we used three control steps. First, we included frontoinsular stroke patients as a disease control group to test whether the NC properties of the frontotemporoinsular network in bvFTD were specific to neurodegeneration. Frontal stroke patients present important similarities with the clinical symptoms of bvFTD (Mesulam, 1986), such as distractibility and personality changes. However, opposed to bvFTD, frontal lobe patients show high cognitive variability, ranging from almost totally preserved to impaired performance in multiple domains, including social cognition (Ibanez & Manes, 2012; Mesulam, 1986). Studies comparing patients with neurodegenerative diseases and stroke lesions provide valuable insights into such common patterns (Baez et al., 2014; Lambon Ralph, Cipolotti, Manes, & Patterson, 2010). By comparing two groups of patients with similar clinical manifestations but different neuropathology, we aimed to evaluate whether NC results are specific to bvFTD degeneration or common to a broad range of neurological conditions. Second, to determine whether NC alterations were specific to the frontotemporinsular network, we also considered the integrity of selected anatomical regions from six well-characterized resting-state networks.

Finally, to challenge the distinctive association between the NC of the frontotemporoinsular network and social-executive performance, we also considered the association between NC and a general cognitive measure, which assess other domains than social-executive performance.

In sum, our aims were (i) to assess the NC of the frontotemporoinsular network in bvFTD, (ii) to evaluate whether NC is associated with social-executive profile, and (iii) to determine the contributions of this metric (together with behavioral deficits) in identifying bvFTD. We hypothesized that the NC of the frontotemporoinsular network would discriminate bvFTD patients from controls, and from stroke patients, and that it would be associated with social-executive performance.

MATERIALS AND METHODS

Network Centrality analyses

Participants

We recruited 14 patients who fulfilled the revised criteria for probable bvFTD (Rascovsky et al., 2011). These patients presented with prominent changes in personality and social behavior, which were verified by their caregivers. They underwent a clinical standard examination for accurate diagnosis at the Institute of Cognitive Neurology (INECO). This includes an extensive battery of neurological, neuropsychiatric, and neuropsychological assessments, and a MRI-SPECT. The diagnoses were made by a group of bvFTD experts (F.M. and T.T.). All patients showed frontal atrophy on MRI, and frontal hypoperfusion on SPECT, when available. They were all in the early/mild stages of the disease and did not fulfill criteria for specific psychiatric disorders. Patients who primarily presented with language deficits were excluded.

We also formed a control group of 12 age- and education-matched participants with no history of psychiatric or neurological disease (Table 1A). In addition, we recruited 10 frontoinsular stroke patients (Figure 2A) as a disease control group for complementary comparisons that were also assessed with the institutional standard examination. They were evaluated at least 6 month after suffering the stroke (time needed for the stability of the lesion extension and the clinical symptoms presentation).

All participants underwent a 10-min functional MRI (fMRI) resting protocol. They provided signed informed consent in accordance with the Declaration of Helsinki. The study's protocol was approved by the institutional Ethics Committee.

FMRI preprocessing and connectivity analysis

FMRI acquisition. Functional images were acquired on a Philips Intera 1.5T with a conventional head coil. Thirty-three axial slices (5-mm thick) were acquired parallel to the plane connecting the anterior and posterior commissures and covering the whole brain (repetition time = 2777 ms, echo time = 50 ms, flip angle = 90, image matrix = 64 × 64 mm). The fMRI acquisition lasted 10 min and we obtained 209 functional brain images for each subject. The participants were instructed to think about their daily routines (e.g., the activities performed that day since waking or what they were going to do for the rest of the day), to keep their eyes closed and to avoid moving and falling asleep (Sedeño et al., 2014).

fMRI preprocessing. Functional data were preprocessed using statistical parametric mapping software (SPM8; http://fil.ion.ucl.ac.uk/spm). Echo-planar imaging (EPI) images

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Table 1. Demographic and behavioral statistical results

	bvFTD	Controls	Stroke	$\chi 2$	*p*	*Post hoc* comparison (Tukey's HSD)
A. Demographics						
Gender	5 F: 9 M	5 F: 7 M	2 F:8 M	1.27	.53	
				F	*p*	
Age (years)	66.42 (6.83)	62.58 (6.30)	54.50 (9.80);	7.26	<.01*	bvFTD-Stroke <.01 Controls-stroke = .04
Education (years)	14.71 (4.02)	15.50 (2.64)	17.00 (2.70)	1.76	.18	—
B. Social-executive evaluation						
MMSE	25.50 (3.87)	29.08 (1.44)	28.8 (1.09)	4.18	03*	bvFTD-Controls <.01 bvFTD-Stroke = .03
EF	53.92 (20.53)	85.55 (4.57)	78.00 (16.72)	13.27	<.01*	bvFTD-Controls <.01 bvFTD-Stroke <.01
ER	60.55 (16.85)	85.41 (6.89)	80.00 (16.95)	12.42	<.01*	bvFTD-Controls <.01 bvFTD-Stroke <.01
ToM	41.02 (12.93)	73.38 (8.97)	68.33 (9.74)	25.50	<.01*	bvFTD-Controls <.01 bvFTD-Stroke <.01
SCS	49.00 (12.98)	79.40 (5.74)	79.86 (2.49)	25.27	<.01*	bvFTD-Controls <.01 bvFTD-Stroke <.01
SEP	50.02 (12.54)	81.45 (4.53)	81.57 (3.47)	30.27	<.01*	bvFTD-Controls <.01 bvFTD-Stroke <.01

Note. Mean (*SD*).
*Significant differences.
EF = executive functions; ER = emotion recognition; ToM = theory of mind; NC = Network Centrality; MMSE = Mini-Mental Status Examination; SCS = Social Cognition score; SEP = Social-Executive Performance.

were slice-time corrected, aligned to the mean volume of the session scanning, normalized (using the SPM8 default EPI template) and smoothed (using an 8-mm full-width half-maximum Gaussian kernel), following the same procedures previously described by our group (Barttfeld et al., 2012, 2013; Sedeno et al., 2014) (Figure 1A–C). The final spatial resolution of the images was $2 \times 2 \times 2$ mm.

Motion parameters showed no movements greater than 3 mm or rotation movements higher than 3° of rotation (Supekar & Menon, 2012). We also compared the mean translational and mean rotational parameters among groups using a mixed repeated-measures analysis of variance (ANOVA) test, with a within-subject factor (the two motion parameters) and a between-subject factor (group). No parameter effects [$F(1,33) = 1.12$; $p = .29$] or parameter x group interaction [$F(2,33) = .63$; $p = .53$] were observed, indicating no significant differences in motion parameters among groups. In addition, we did not find any significant correlation between motion parameters and the main results at the group level (Supplementary Data 1A).

To partially correct and remove low-frequency drifts from the MR scanner, we applied a band-pass filter between 0.078 and 0.35 Hz using the Resting-State fMRI Data Analysis Toolkit (REST, http://resting-fmri.sourceforge.net/). Finally, applying these software, we regressed out the following items: (i) the six motion parameters, (ii) the average signals acquired form spherical ROIS in the ventricular cerebrospinal fluid (CSF) and white matter (WM), and (iii) the signal averaged over the whole brain (global signal) (Van Dijk, Sabuncu, & Buckner, 2012). This last procedural step was performed to remove the potential variance introduced by spurious sources (Figure 1D).

Correlation matrices for wavelet connectivity analysis. Based on the Automated Anatomical Labeling (AAL)-Atlas (Tzourio-Mazoyer et al., 2002), mean time courses were extracted by averaging the BOLD signal of all voxels contained in each of the 116 regions of interest (ROIs). Wavelet analysis was used to construct a 116-node functional connectivity network for each subject from these time series, based on slow frequency components (0.01 to 0.05 Hz) (Supekar, Menon, Rubin, Musen, & Greicius, 2008). We followed the same procedures described by Supekar et al. (2008), which have been previously used and detailed in studies of our group (Barttfeld et al., 2012, 2013; Sedeno et al., 2014) (Figure 1E).

Graph theory analysis: Network Centrality (NC). NC measures the number of shortest paths that pass through a node and links the other node pairs across the network (Freeman, 1977). It indicates the importance of a node for efficient communication and integration across a network (Freeman, 1977). Several studies have already used NC (also called "betweenness centrality") to identify changed connections in disconnections syndromes (Agosta et al., 2013; Buckner et al., 2009; Goch et al., 2014; Seo et al., 2013). In our study, we calculated the average NC across regions within different networks to characterize the central role of each network in the overall system's dynamics.

To calculate NC, we converted functional weighted correlation matrices into binary undirected ones. Because

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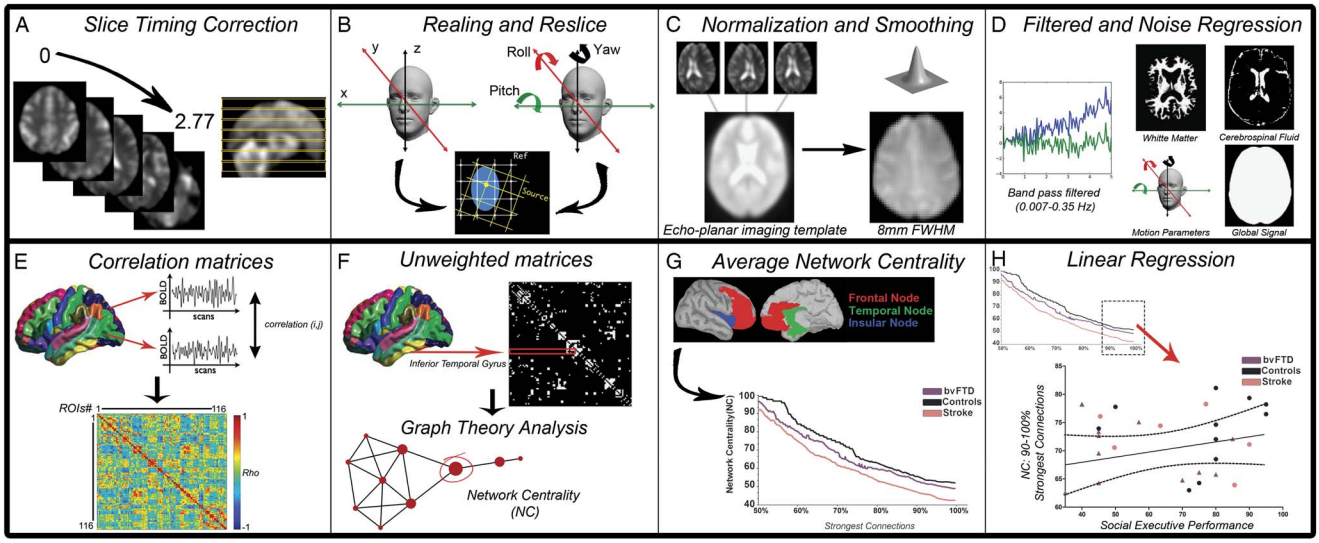


Fig. 1. Functional MRI preprocessing and graph connectivity metrics. *Preprocessing.* **A,B:** Images were slice-time corrected and aligned to the mean volume of the scanning session. **C:** Data were normalized to a SPM8 default echo-planar imaging template and then smoothed. **D:** A band-pass filter was applied to correct and extract low-frequency drifts. Next, the images were regressed out by motion parameters, cerebrospinal fluid (CSF), white matter (WM), and global brain signals. **E:** Mean time series were extracted by averaging BOLD voxel signals in each region of interest (ROI), and then wavelet analysis was applied to construct correlation matrices of slow frequencies (0.01 to 0.05 Hz). *Graph Connectivity Metrics analysis.* **F:** Network Centrality (NC) was calculated based on a series of undirected graphs, with different numbers of positive connections (ranging from 50 to 100% of the connections of correlation matrices). **G:** We analyzed the average NC of a frontotemporoinsular network (and the main areas of six resting-state networks, see Figure 3 and Supplementary Data 2 for details related to the anatomical atlas and brain areas included in these networks) of the different undirected graphs in the range of 50 to 100% of positive connections with a cluster-based permutation test (see the Statistical Analysis section). **H:** We conducted simple linear regression analyses to explore whether social cognition and executive performances were partially associated by the averaged NC results from the 90 to 100% of positive connections (in these, differences were more consistent across comparisons).

network metrics depend both on network structure and size, a group comparison of the groups should be performed on networks of equal size (de Haan et al., 2009). Thus, if the samples have metric results calculated on matrices of the same size of connections, the network differences might reflect differences in graph structure (de Haan et al., 2009). To achieve this goal, we used the number of links (ROIs that are positively correlated) in weighted matrices as a cutoff to create a series of undirected graphs with different proportions of positive connections (global network density) (de Haan et al., 2009; He, Chen, & Evans, 2008; Tian, Wang, Yan, & He, 2011; Yao et al., 2010).

The BCT toolbox (Sporns & Zwi, 2004) was used to calculate the averaged NC across nodes within the fronto-temporoinsular network (bilateral as well as left and right sides). This network involves the main areas of early degeneration that are the frontal paralimbic network, which includes the anterior cingulate cortex (ACC), anterior insula, frontal pole, amygdala, and striatum (Ibanez & Manes, 2012; Piguet et al., 2011; Rascovsky et al., 2011; Rosen et al., 2002; Seeley et al., 2008). In addition, this early degeneration pattern have been associated with specific bvFTD social cognition impairments (Couto et al., 2013).

Then, we examined whether NC results in bvFTD were specific to its atrophy areas or represented a property of all long-range connections. To this end, we evaluated the averaged NC of the main anatomical regions from six resting-state networks (the default mode, the cingulo-opercular, the frontoparietal, the sensorimotor, the visual and the cerebellar networks). The anatomical regions corresponding to each network were selected from the AAL-Atlas according to previous reports (Beckmann, DeLuca, Devlin, & Smith, 2005; Damoiseaux et al., 2006; Kalcher et al., 2012; Smith et al., 2009; van den Heuvel, Mandl, & Hulshoff Pol, 2008) (Supplementary Data 3).

There are no established criteria to select relevant undirected graphs for examining metric results. Here, we explored the networks' configuration in the range of 50 to 100% of positive connections to allow comparability with a previous graph theory study in bvFTD (Agosta et al., 2013), which revealed topological abnormalities in the patients' more densely connected networks. Note that, by establishing the 50% of connections as the lower limit, we avoided the inclusion of networks with disconnected nodes (Agosta et al., 2013; Supekar et al., 2008). Finally, we have also corroborated that these networks presented a small-world organization (Supplementary Data 1B).

One bvFTD patient and one stroke patient were eliminated from the NC analysis because they presented metric values 2 *SD*s above the mean of their respective groups.

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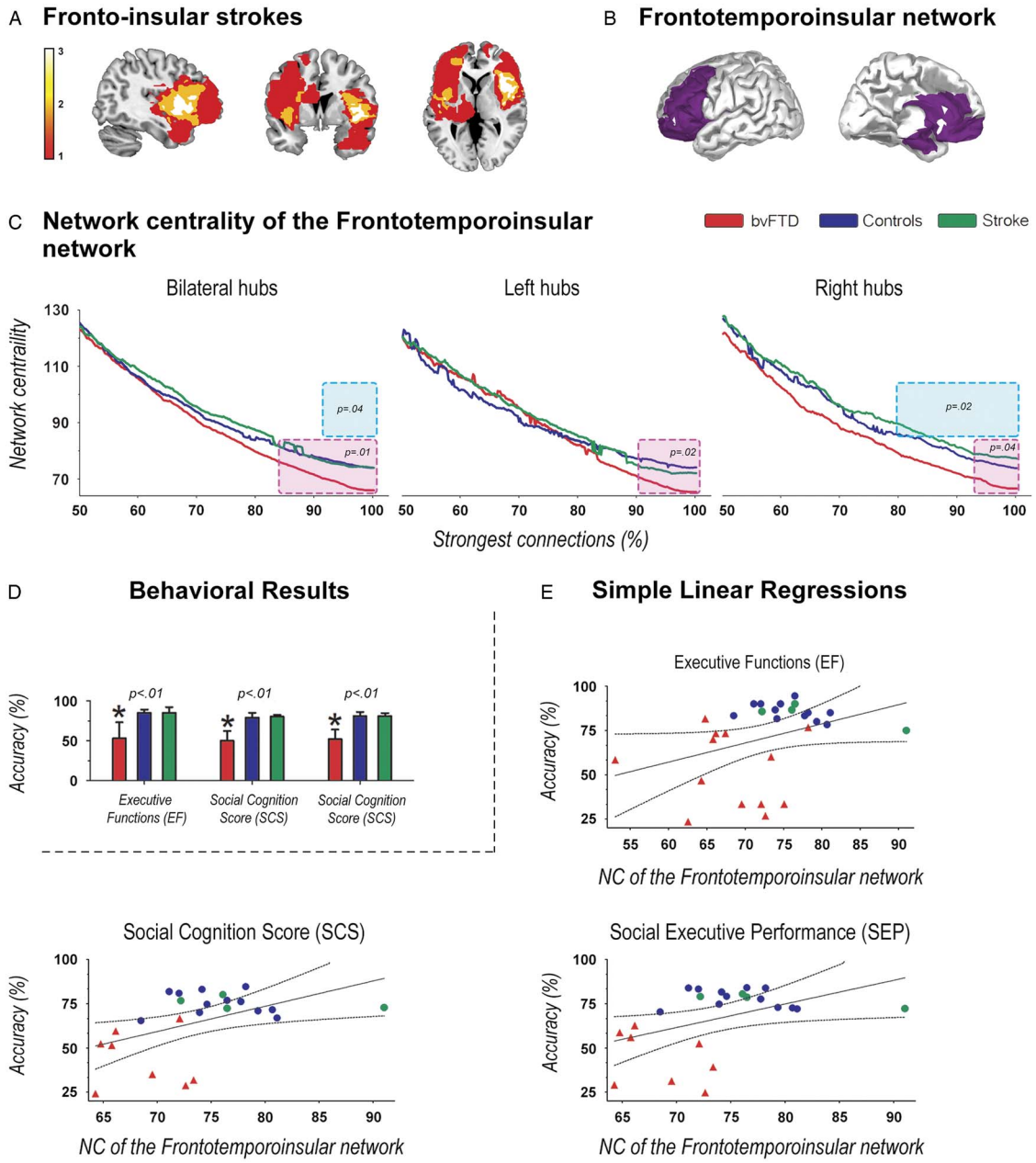


Fig. 2. A: Frontal and insular structures that were injured in stroke patients. The colormap indicates lesions overlapping across the group: red refers to areas affected by the lesion of only one subject, while white shows injured areas shared by three patients. **B:** Regions of interest included in the frontotemporoinsular network were based on Tzourio-Mazoyer's (2002) Automated Anatomical Labeling (AAL)-Atlas (see Supplementary Data 3). **C:** Pink boxes indicate the clusters were the bvFTD patients presented decreased NC compared to controls. Light blue boxes indicate the clusters were bvFTD patients showed decreased NC compared to the frontoinsular stroke group. No significant differences were found between controls and the last sample in the centrality of the frontotemporoinsular network. **D:** Compared with controls and stroke patients, bvFTD patients showed impairments in executive functions (EF), Social Cognition Score (SCS), and Social-Executive Performance (SEP) measures. No differences were found between controls and stroke patients. **E:** The NC of the bilateral frontotemporoinsular network was associated with participants' performance in executive functions, SCS, and SEP.

Behavioral Assessment

Participants

A sub-sample of the participants completed general cognitive, executive function, and social cognition tasks. This sub-sample encompassed 14 bvFTD patients (nine of whom carried out the emotion recognition task), four frontoinsular stroke patients, and 12 controls. The results thus obtained, alongside the NC results from the 90 to 100% of positive connections (where differences were more consistent across comparisons, Figure 2C), were used for simple linear regression and classification analysis.

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General cognitive state

The Mini-Mental State Examination (MMSE) (Butman, Allegri, Harris, & Drake, 2000) is a clinical screening instrument that evaluates the general cognitive state of subjects and is used in bvFTD (Chow, Hynan, & Lipton, 2006; Rascovsky et al., 2005). It comprises questions that assess orientation, memory, attention, and language.

Executive functions evaluation

The INECO Frontal Screening (IFS) (Torralva et al., 2009) is a sensitive battery to detect executive dysfunction in patients with dementia (Gleichgerrcht, Roca, Manes, & Torralva, 2011; Torralva et al., 2009). It includes the following subtests: motor programming, conflicting instructions, motor inhibitory control, numerical working memory, verbal working memory, spatial working memory, abstraction capacity, and verbal inhibitory control.

Social cognition

Emotion recognition. The Awareness of Social Inference Test (TASIT) (McDonald, Flanagan, Rollins, & Kinch, 2003) involves videotaped vignettes of everyday social interactions, which have been proven useful for detecting subtle deficits in bvFTD patients (Kipps, Nestor, Acosta-Cabronero, Arnold, & Hodges, 2009). This task introduces contextual cues (e.g., prosody, facial movement, and gestures) and additional processing demands (e.g., adequate speed of information processing, selective attention, and social reasoning) that are not taxed when viewing static displays. We only considered part 1, termed the emotion evaluation test (EET), which assesses recognition of spontaneous emotional expression (fearful, surprised, sad, angry, and disgusted). We selected this because it is affected at the initial stages of bvFTD regardless of the degree of atrophy (Kumfor et al., 2014). In the EET, speaker demeanor combined with the social situation indicates the emotional meaning. It comprises a series of 20 short (15–60 s) videotaped vignettes of trained actors interacting in everyday situations. After viewing each scene, the participant is instructed to choose (from a forced-choice list) the emotion expressed by the focused actor.

Social inferences (Theory of Mind, ToM). The Reading the Mind in the Eyes Test (RMET) assesses emotional inference aspects of ToM (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997) and is a sensitive task used to evaluate bvFTD patients (Torralva et al., 2009). It is a computerized and validated test that consists of 36 pictures of the eye region of a face. Given four words, the participants are asked to choose the best word that describes what the person in each photograph is thinking or feeling.

Global scores

Based on a similar strategy of previous studies that have found bvFTD patients to be impaired in emotion recognition and ToM (Kipps et al., 2009; Torralva et al., 2009), we constructed a global Social Cognition Score (SCS) to evaluate the global performance of participants and also to analyze the association of this performance with the NC results. The SCS combines the percent of correct answers from the TASIT and RMET.

In addition, given that the interrelationship between social cognition and executive functions plays an important role in the clinical presentation and symptomatology of bvFTD (Eslinger, Moore, Anderson, & Grossman, 2011; Possin et al., 2013), we derived another score that indexes the global Social-Executive Performance (SEP) of the participants and combines the IFS, TASIT, and RMET scores. We also tested whether the SEP was associated with NC results.

Statistical Analysis

Demographic information was compared among groups using ANOVA tests, and Pearson chi-square (χ^2) was used for gender.

To reduce the impact of the multiple comparison problem on the analysis of NC, we have used a modified version of the cluster-based permutation test proposed by Maris et al. (Maris & Oostenveld, 2007). This analysis was implemented using the FieldTrip Toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) and it has been previously applied to analyze multiple thresholds in graph theory (Sanz-Arigita et al., 2010). In this, the statistical metric of the original data was computed with two-tailed independent samples *t* tests. Afterward, the *t*-values were combined into connected sets based on their adjacency, and cluster-level statistics were calculated by taking the sum of the *t*-values within each cluster. The data were later permutated by applying 5000 permutation draws to generate a histogram. Then, we used the Monte-Carlo estimation of the permutation *p*-value, which is the proportion of random partitions in which the observed test statistic is larger than the value drawn from the permutation distribution. If this *p*-value is smaller than the critical alpha-level of .05, then the data can be concluded to reveal significant differences. This method offers a straightforward solution to the multiple comparisons problem and does not depend on multiple comparisons correction or assumptions about the normal distribution of the data (Nichols & Holmes, 2002).

Given age differences between groups (Table 1A), we decided to perform an analysis of covariance test adjusted for age for the analyses of NC (Supplementary Data 1D), as well as for the social-executive comparisons (regarding the last, we reported only those effects that remained significant after covarying).

Simple linear regression analyses were used to explore whether the behavioral tasks and the global scores were partially associated by NC in the frontotemporoinsular, and whether global scores were associated with the main areas of the resting-state networks.

A k-means-like (MacQueen, 1967) analysis (a vector discretization method) was used to test whether NC and SEP

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discriminated the bvFTD patients from controls and from stroke patients. This involves computing a centroid for each group by averaging corresponding data. Centroids were calculated for two groups: one encompassed by bvFTD patients and the other composed by controls and stroke patients. Then, a predicted group for an individual would be given by the closest centroid. This conservative approach (it only considers averages, disregarding information about cluster shapes) is appropriate because, given our sample size, averages should be reasonably robust, but cluster shapes may not be so. Note that this observation concerns the predictive power of the aforementioned variables, not the properties of an optimal classifier, which could be the object of further research. Once again, because of sample size, a leave-one-out cross-validation approach proved reasonable to determine whether classifier performance would generalize well to new data.

To corroborate classification results, we applied a different and independent method: the nearest neighbors' classification method (Altman, 1992), selecting three neighbors as parameter for the analysis. In this, a data point is compared to its three closest neighbors and is assigned to the most common class among them (in our case we had two: bvFTD patients and the other two groups). From the outputs of this classification method, we calculated the sensitivity and specificity for bvFTD from this combination of the NC of the frontotemporoinsular network and the SEP.

RESULTS

Network Centrality

Compared to controls and stroke patients, the bvFTD group exhibited significantly decreased NC in the bilateral and right side of the frontotemporoinsular network. Significant differences were also observed on the left side, but only relative to controls (Table 2A; Figure 2C). Differences among groups remained the same after adjusting for age (Supplementary Data 1D).

Five of the six resting state-networks used as control comparisons presented no group differences. The only exception was the cingulo-opercular network, which revealed significant decreased NC in stroke patients relative to controls (Figure 3; Supplementary Data 1C).

Finally, the effect sizes of all significant differences reported in NC were above 0.8, indicating large differences among groups.

Behavioral Assessment

Relative to controls and stroke patients, bvFTD patients obtained significantly lower scores in their general cognitive state, executive functions, emotion recognition and ToM. The same was true of global SCS and SEP scores (Table 1B; Figure 2D; Supplementary Data 1E).

NC Contribution to Behavioral Performance

NC in the bilateral frontotemporoinsular network was associated with SCS and SEP (Table 2B; Figure 2E). The right hemisphere nodes (but not the left ones) were also related to performance in both the SCS and SEP. With regard to behavioral tasks, the bilateral and right NC significantly contributed to emotion recognition, whereas the right side was also associated with executive functions performance. Left nodes of this network were marginally related to ToM accuracy (Table 2B; Supplementary Data 1F). These results were significant even when a stroke patient that presented extreme values (Figure 2E) was excluded from the analysis (Supplementary Data 1F).

To evaluate the association between social-executive impairments and specific frontotemporoinsular network hubs in bvFTD, we conducted additional regression analyses considering only this group. The main network was divided into frontal, temporal, and insular regions. We found that (i) increased NC in the left insular nodes was related to impairments in emotion recognition and SCS, and (ii) the right frontal nodes were marginally associated with ToM impairments (Supplementary Data 1F).

No associations were found between the NC of the frontotemporoinsular network and MMSE results. This was true when considering bilateral regions as well as left and right sides alone (Table 2B). Moreover, none of the six resting-state networks analyzed was associated with the subjects' social-executive profiles (SCS and SEP) (Supplementary Data 1F).

Group Discrimination Based on NC and SEP

The k-means-like model had a 100% correct classification rate (24 of 24). Thus, it should generalize well to new data because of two factors: the parameter count was low and a leave-one-out cross-validation yielded 95% correct classification rate [23 of 24 models, although over-fitting limitations should be considered (Nestor, 2013)].

In addition, the nearest neighbors' classification analysis yielded a high sensitivity (100%) and high specificity (100%) for discriminating bvFTD from controls.

To establish whether our classification model was biased by the inclusion of both the stroke and the control groups, we re-ran these discrimination analyses excluding the stroke patients. The results remained the same, that is, bvFTD and controls were successfully discriminated (Supplementary Data 1G)

Finally, as patients were assessed with sensitive behavioral tasks, we performed a logistic regression only with NC to evaluate the classification power of this individual variable (as in the classification methods, we considered controls and stroke patients as a single group). In this, NC of bilateral frontotemporoinsular network was found to be a remarkably good predictor (pseudo-R2 = .40) of bvFTD, with a reduction of 1 point in NC being associated to a 1.40 increase in the odds of FTD (Supplementary Data 1H).

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Table 2. NC and regression analysis

	Cluster network range	Mean (*SD*) controls	Mean (*SD*) bvFTD	Cluster *t*	*p*	Cohen's *d*
A. Network Centrality of the frontotemporoinsular network						
Controls versus bvFTD						
Bilateral hubs	85 to 100%	76.72 (3.87)	69.68 (6.65)	228.84	.01*	1.34
Right hubs	94 to 100%	77.39 (6.44)	70.26 (9.05)	70.55	.04*	.96
Left hubs	90 to 100%	75.44 (5.12)	67.36 (8.07)	140.54	.02*	1.25
Stroke versus bvFTD						
Bilateral hubs	92 to 100%	74.70 (7.10)	67.38 (6.51)	99.24	.04*	1.07
Right hubs	80 to 100%	82.09 (9.66)	72.19 (9.18)	254.75	.02*	1.05

B. NC contribution to behavioral performance					
Frontotemporoinsular network	Behavioral performance	*F*	*p*	β	R^2
Bilateral hubs	EF	3.86	.06[a]	.35	.12
	ER	4.47	.04*	.41	.17
	ToM	4.13	.05[a]	.37	.13
	SCS	6.77	.02*	.48	.23
	SEP	5.04	.03*	.43	.18
	MMSE	2.12	.15	.27	.07
Right hubs	EF	5.58	.02*	.41	.17
	ER	8.27	<.01*	.52	.27
	ToM	1.66	.20	.24	.06
	SCS	8.89	<.01*	.53	.28
	SEP	7.92	.01*	.51	.26
	MMSE	1.97	.17	.26	.07
Left hubs	EF	0.69	.41	.15	.02
	ER	0.32	.57	.12	.01
	ToM	3.90	.06[a]	.36	.13
	SCS	1.69	.29	.22	.05
	SEP	0.58	.45	.16	.02
	MMSE	1.14	.29	.20	.04

Note. Mean (*SD*).
[a]Tendency differences.
*Significant differences.
EF = executive functions; ER = emotion recognition; ToM = theory of mind. NC = Network Centrality; MMSE = Mini-Mental Status Examination; SCS = Social Cognition score; SEP = Social-Executive Performance.

DISCUSSION

To our knowledge, this report is the first to show abnormal NC in the frontotemporoinsular connectivity of bvFTD patients and its association with social-executive performance.

Frontotemporoinsular Centrality in bvFTD

First, as compared with controls and stroke patients, bvFTD patients showed reduced NC of the frontotemporoinsular network. This finding aligns with previous evidence of centrality alterations in frontoinsular hubs (Agosta et al., 2013) and confirms the sensitivity of Graph Connectivity Metrics for bvFTD (Pievani et al., 2011). Moreover, such centrality alterations were absent in stroke patients. Thus, both groups of patients presented a similar frontoinsular affectation but with a different impact in the network centrality. The neurodegenerative process in bvFTD shows a specific alteration of frontotempoinsular connections that is consistent with its pattern of atrophy. Brain lesions, on the other hand, present centrality deficits circumscribed to the specific injured areas (cingulo-opercular network, see below), probably triggered by hypoconnectivity of the affected regions (Garcia-Cordero et al., 2015).

This difference in the involvement of brain networks is associated with distinct groups' social-executive profile. While bvFTD exhibits larger deficits in all the behavioral tasks, the stroke patients, according to the variability of their performance (Ibanez & Manes, 2012; Mesulam, 1986) have similar results than the controls. In this way, despite that some similar areas are compromised in both neurological diseases (as the insular regions), the particular pathogenic processes of each one generates different patterns of connectivity alterations. Thus, our results suggest that the centrality alterations of the frontotemporoinsular network

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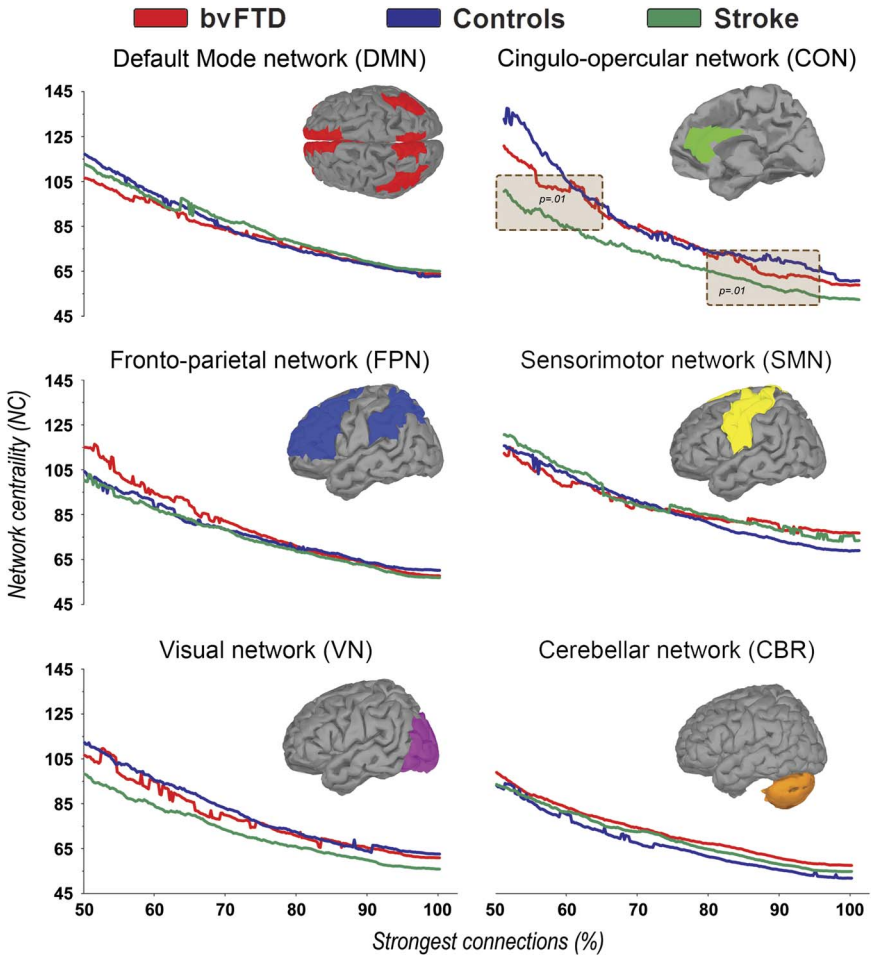


Fig. 3. NC of the main anatomical areas from six resting-state networks. Brown boxes indicate the clusters were the frontoinsular stroke patients presented decreased Network Centrality (NC) compared to controls. Significant differences were found only in the cingulo-opercular (CON) between these two samples. No significant differences were observed in the main anatomical areas of the other resting-state networks among groups (see Supplementary Data 1C).

are a distinctive connectivity hallmark of neurodegeneration in bvFTD.

Importantly, this NC decrease in bvFTD was specific to the frontotemporoinsular network. This is consistent with previous studies reporting connectivity abnormalities of the salience network (SN) in bvFTD, although none of them applied a graph theory approach (Day et al., 2013; Filippi et al., 2013; Whitwell et al., 2011; Zhou et al., 2010). The impaired areas included in these studies as part of the SN involved the insular cortex, the ACC, the right superior temporal pole, the dorsolateral frontal lobe, the hypothalamus, the amygdala, and the striatum. Some of these regions are part of the frontotemporoinsular network that was found altered in our bvFTD sample. Thus, our results support the potential biomarker status of these networks. Indeed, connectivity alterations in bvFTD revealed by NC analyses engaged a widespread frontotemporoinsular network that overlaps with its pattern of early atrophy. Thus, our study illustrates the benefits of using graph theory analyses to examine the neurological correlates of cognitive performance in clinical populations.

We also found a significant NC alteration of the cingulo-opercular network in stroke patients relative to controls. While ours seems to be the first connectivity report of patients with frontoinsular lesions using graph methods, such alteration was expected given that the cingulo-opercular network comprises regions which are mainly damaged in this stroke sample (namely, insula and ACC). Future research focused on stroke patients' deficits could shed broader light on the sensitivity of this network. A promising avenue is the exploration of possible alterations in long-range coupling among networks due to post-lesion compensatory effects and readjustments of functional connections in remotes sites (Grefkes & Fink, 2014; Sporns, 2014).

To summarize, the selective alteration of frontotemporoinsular NC, only present in bvFTD and restricted to this network, is consistent with (i) several volumetric studies that have described a fronotemporoinsular pattern of atrophy in this disease, and (ii) their association with specific social cognition impairments (Couto et al., 2013; Rosen et al., 2002; Seeley et al., 2008).

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Social-Executive Performance and Long-Distance Networks in bvFTD

The frontotemporoinsular NC was associated with the participants' social-executive profiles. This supports the view that high-level cognitive domains, particularly social cognition and related executive functions, depend on distributed frontotemporoinsular regions (particularly in right-sided areas) (Ibanez & Manes, 2012; Kennedy & Adolphs, 2012; Stanley & Adolphs, 2013). The specific involvement of this network in social-executive performance is further underscored by the null association among these behavioral domains and resting-state networks. Additionally, the lack of associations between the frontotemporoinsular NC and the MMSE (which assesses basic-level cognitive processes, such as orientation, attention, and memory) supports the specific involvement of this network in high-level social-executive performance (Ibanez & Manes, 2012). Thus, by showing that similar network activity contributed to performance in both executive functions and social cognition, our results also corroborate the relationship between such domains.

Several studies have demonstrated this link between executive functions and social cognition (Decety, 2011; Singer, 2006; Singer & Lamm, 2009). Working memory, selective attention, and inhibitory control (Decety, 2011; Rankin, Kramer, & Miller, 2005; Singer, 2006; Singer & Lamm, 2009) are particularly associated with the cognitive aspects of ToM. Specifically, inferring the intentionality of others requires the inhibition of one's own perspective and the simultaneous appraisal of contextual cues (Rankin et al., 2005). Additionally, brain regions that are relevant for executive functions, such as the prefrontal dorsolateral cortex, ACC, premotor cortex, parietal inferior cortex, orbitofrontal cortex, partially overlap and interact with areas involved in socio-affective responses (e.g., the ACC cortex, insula, and amygdala) (Singer & Lamm, 2009). Thus, the intertwining of executive functions and social cognition is not unexpected in bvFTD patients given that both domains are usually affected (Possin et al., 2013). This is in the same vein that the association we found between the frontotemporoinsular NC and the performance in both executive functions and social cognition.

In addition, increased NC in the left insular and right frontal hubs in the bvFTD group was associated with the patients' social cognition impairments. Disease-specific compensatory or abnormally increased activity of these regions may modify the network's centrality and compromise social cognition processes. Although speculative, this interpretation aligns with the increased connectivity observed in the bvFTD patients in the left insular (Day et al., 2013; Farb et al., 2013) and right frontal (Rytty et al., 2013) hubs. Moreover, it clarifies the elusive association between bvFTD-specific atrophy and social cognition impairments. Thus, the present findings confirm executive functions and social cognition impairments in bvFTD (Possin et al., 2013; Torralva et al., 2009) while showing that these deficits are associated with frontotemporoinsular NC.

Finally, both frontotemporoinsular NC and social-executive performance were able to distinguish bvFTD patients from the other two groups (with a high classification rate). In addition, we have shown that NC discriminates patients individually (Supplementary Data 1H). Although behavioral measures seem enough to classify patients in our sample, it must be considered that: (i) these measures were selected "*a priori*", based on their sensitivity for bvFTD; (ii) social-executive performance is strongly associated with NC; and (iii) this centrality measure also has a high classification ratio on its own. These findings highlight the potential contributions of combining behavioral and connectivity measures in future studies with larger samples (Pievani et al., 2011).

LIMITATIONS AND FURTHER ASSESSMENT

Although our patient sample size was larger than those in other bvFTD connectivity reports (Day et al., 2013; Garcia-Cordero et al., 2015), future studies should include even larger groups. While the sample of vascular patients was also small, we considered it only for complementary comparisons. Note, however, that smaller group sizes have been used in recent functional connectivity studies (Day et al., 2013; Farb et al., 2013; Sajjadi et al., 2013).

In addition, bvFTD is not an anatomically homogeneous syndrome (Kril, Macdonald, Patel, Png, & Halliday, 2005; Rascovsky et al., 2011; Whitwell et al., 2009). We have overcome this issue by analyzing the principal atrophy areas reported, thus maintaining consistency across subjects. Further studies with larger sample sizes should consider: (i) perform functional connectivity analyses for bvFTD patient samples featuring distinct atrophy patterns, and (ii) other FTD subtypes to disentangle whether each subtype presents a particular pattern of connectivity deficits. Future research should likewise consider additional social-executive measures.

Another limitation is that we focused only on NC from binary matrices. While this measure may be implemented considering weighted graphs (Brandes, 2001), algorithms used to such end do not measure the same network properties (Opsahl, Agneessens, & Skvoretz, 2010) as the ones presently considered. While the algorithm for binary matrices highlights the number of connections between nodes, the other ones ascribe more importance to the ties' weight (a node with few connections and with high weights would have greater NC than a node with more connections but with low weights). Currently, most graph theory studies assessing NC in dementia are based on the binary approach (Agosta et al., 2013; Baggio et al., 2014; Brier et al., 2014; Li, Qin, Chen, & Li, 2013; Liu et al., 2012; Xiang, Guo, Cao, Liang, & Chen, 2013). Future studies should analyze the impact of each method on network properties of bvFTD and other neurodegenerative diseases.

Finally, to corroborate the discrimination power of NC, it would be useful to compare this metric with node-segregation and network-integration metrics.

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CONCLUSION

The combination of theoretical models (social cognition network approaches), clinical evidence (bvFTD brain abnormalities and specific impaired performance), and recent mathematical developments (network science) represents a promising approach to increase our understanding of the neural networks engaged in social-cognitive process affected by bvFTD.

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Supplementary Materials

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1355617715000703.

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