Functional Connectivity From Disease Epicenters in Frontotemporal Dementia

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Study Question
What is the brain architectural distribution of rearrangements in functional connectivity from disease epicenters across clinical presentations of the frontotemporal dementia (FTD) spectrum?

What Is Known and What This Paper Adds
MRI connectomics has demonstrated a close relationship between brain connectivity networks and atrophy accumulation in FTD disorders, supporting a “network-based” spread model of pathologic protein deposits. However, most previous studies have assessed connectivity abnormalities on a whole-brain scale, without discerning between direct and indirect connections with the disease epicenter. Stepwise functional connectivity (SFC) assesses functional connectivity modifications at different link-step distances from a seed region of interest, thus helping to discriminate between alterations of one step (direct) and longer distance (indirect) connections. This study’s results show an interplay between decreased and increased functional connectivity alterations.

Figure
Stepwise Functional Connectivity Alterations in bvFTD

Cortical and subcortical differences between bvFTD patients and age-matched healthy controls in stepwise functional connectivity of the left anterior insula, identified as disease epicenter (red-yellow = lower functional connectivity, blue-green = higher functional connectivity). bvFTD = behavioral variant of frontotemporal dementia.
connectivity with the disease epicenter, affecting both direct and indirect connections, characterizing each FTD clinical variant.

Methods
For this cross-sectional study, 64 patients (mean age, SD: 65.9, 7.9; % female: 40.6%) with behavioral variant of FTD (bvFTD), 34 (mean age, SD: 69.0, 8.3; % female: 65.7%) with nonfluent variant of primary progressive aphasia (nfvPPA), and 36 (mean age, SD: 66.9, 8.3; % female: 50%) with semantic variant PPA (svPPA) were recruited between October 2009 and April 2021 through the Neurology Unit of San Raffaele Hospital in Milan (Italy), together with 94 age-matched and sex-matched healthy controls. All subjects underwent brain 3T MRI scans. The peaks of atrophy of each variant (i.e., disease epicenters) were identified using voxel-based morphometry in an independent cohort of 42 FTD cases with high confidence of FTLD pathology, as provided by the Mayo Clinic in Rochester, MN. These were used as seed regions for SFC analyses in the Milan cohort to compare connectivity in regions directly and indirectly connected to the epicenters between patient groups and controls. Correlations between SFC architecture in controls and atrophy patterns in patients with FTD were tested.

Results and Study Limitations
SFC analyses showed extensive reductions of functional connectivity in brain regions with direct and indirect connections with the respective seed regions in the 3 main clinical FTD variants. Patients with FTD also showed more localized connectivity increases involving either short-range direct connections (i.e., 1 step-link distance) or more distant indirect connections (i.e., 2–4 step-link distance) (Figure). The interplay between locally increased direct connectivity and longer-range functional disconnection was most evident for bvFTD and nfvPPA. In the case of svPPA, a significant correlation between the healthy SFC architecture from the disease epicenter in the inferior temporal gyrus and the regional distribution of atrophy in patients was demonstrated ($r = 0.29, p = 0.03$). These findings provide fundamental evidence supporting the notion of FTD variants as “disconnection syndromes,” opening promising perspectives to understand the physiopathologic underpinnings of disease progression through brain networks. This study’s limitations include its cross-sectional design, which did not allow to draw strong conclusions regarding the evolution of observed increased/decreased connectivity nor its maladaptive or compensatory role, and the use of amyloid-PET negativity to support high confidence of FTLD pathology, when postmortem confirmation was not available.

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