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Research report

Abnormal network connectivity in frontotemporal dementia: Evidence for prefrontal isolation

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ABSTRACT

Introduction: Degraded social function, disinhibition, and stereotypy are defining characteristics of frontotemporal dementia (FTD), manifesting in both the behavioral variant of frontotemporal dementia (bvFTD) and semantic dementia (SD) subtypes. Recent neuroimaging research also associates FTD with alterations in the brain's intrinsic connectivity networks. The present study explored the relationship between neural network connectivity and specific behavioral symptoms in FTD.

Methods: Resting-state functional magnetic resonance imaging was employed to investigate neural network changes in bvFTD and SD. We used independent components analysis (ICA) to examine changes in frontolimbic network connectivity, as well as several metrics of local network strength, such as the fractional amplitude of low-frequency fluctuations, regional homogeneity, and seed-based functional connectivity. For each analysis, we compared each FTD subgroup to healthy controls, characterizing general and subtype-unique network changes. The relationship between abnormal connectivity in FTD and behavior disturbances was explored.

Results: Across multiple analytic approaches, both bvFTD and SD were associated with disrupted frontolimbic connectivity and elevated local connectivity within the prefrontal cortex. Even after controlling for structural atrophy, prefrontal hyperconnectivity was robustly associated with apathy scores. Frontolimbic disconnection was associated with lower disinhibition scores, suggesting that abnormal frontolimbic connectivity contributes to positive symptoms in dementia. Unique to bvFTD, stereotypy was associated with elevated default network connectivity in the right angular gyrus. The behavioral variant was also associated with marginally higher apathy scores and a more diffuse pattern of prefrontal hyperconnectivity than SD.

Conclusions: The present findings support a theory of FTD as a disorder of frontolimbic disconnection leading to unconstrained prefrontal connectivity. Prefrontal

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hyperconnectivity may represent a compensatory response to the absence of affective feedback during the planning and execution of behavior. Increased reliance upon prefrontal processes in isolation from subcortical structures appears to be maladaptive and may drive behavioral withdrawal that is commonly observed in later phases of neurodegeneration.

1. Introduction

Frontotemporal dementia (FTD) includes an array of clinical syndromes characterized by the insidious onset of behavioral disinhibition and/or language impairment with commensurate degeneration of the frontal and anterior temporal lobes. The FTD syndrome consists of multiple subtypes: behavioral disinhibition in the behavioral variant of frontotemporal dementia (bvFTD) is typically associated with anterior foci of atrophy including the frontal lobe and ventral striatum. Language impairment due to progressive non-fluent aphasia and semantic dementia (SD) subtypes is more typically associated with temporal lobe atrophy (Seeley, 2010; Gorno-Tempini et al., 2011; Agosta et al., 2012). However, both behavioral and aphasic variants of FTD are distinguished by deficits in social cognition, motivation, and emotional awareness (Lavenu et al., 1999; Kipps and Hodges, 2006; Zamboni et al., 2008; Kumfor et al., 2011). Specifically, both bvFTD and SD patients exhibit clinically significant levels of emotion dysregulation, reducing the potential for social participation (Snowden et al., 2001; Merrilees et al., 2012). Since FTD selectively impairs affect and behavior regulation while leaving memory and visuospatial skills relatively intact, the study of altered brain function in FTD may clarify the regulatory neural mechanisms that promote adaptive social behavior. Such knowledge may also inform our understanding of FTD pathophysiology, potentially advancing diagnostic methodology and generating ideas for therapeutic intervention.

Progress in relating neurodegeneration to behavioral dysfunction has already been made through examinations of brain structure changes, relating atrophy of the ventral prefrontal cortex (PFC) and anterolimbic regions to symptom severity. In a study spanning several neurodegenerative diseases, disinhibition was associated with atrophy in the orbitofrontal cortex, anterior cingulate, and temporal lobes, whereas executive function was associated with preservation of the dorsal PFC (Krueger et al., 2011). In FTD, atrophy in the PFC and basal ganglia correlated with apathy, while atrophy of anterior limbic regions and temporal cortices correlated with disinhibition (Zamboni et al., 2008). In a bvFTD sample, apathy was associated with atrophy in both the frontal operculum and anterolimbic regions (Eslinger et al., 2012). In a rare functional imaging study of bvFTD, positron emission tomography (PET) imaging was used to link both apathy and disinhibition to reduced metabolic activity in the subgenual cingulate cortex (Peters et al., 2006). Presumably, the atrophy and metabolic decline of these frontal and limbic regions impact communication between brain regions leading to dysregulated behavior, but the functional brain changes underlying behavioral dysfunction have not been identified.

Beyond the revelation of structural differences, neuroimaging has the potential to identify subtle changes to brain networks underlying pathophysiology in processes critical to regulating behavior such as emotion processing (Davidson et al., 2002). However, a major challenge in investigating brain activity changes in FTD, and in dementia research in general, is ensuring patient comprehension and compliance with functional magnetic resonance imaging (fMRI) task paradigms. To this end, resting-state analysis has shown promise in uncovering the mechanisms of FTD and other dementias, as it allows for task-free estimation of the brain's intrinsic connectivity networks during fMRI acquisition (Greicius et al., 2004). Resting-state analysis identifies distinct networks of brain regions between which activity is correlated over time (Biswal et al., 1995; Lowe et al., 1998; Fox and Raichle, 2007), driven by low-frequency fluctuations (~.01–.1 Hz) in the blood oxygen-level dependent (BOLD) signal (Lowe et al., 2000; Cordes et al., 2001). The absence of task requirements has been particularly useful in the assessment of patients with dementia (Rombouts et al., 2005; Greicius, 2008; Koch et al., 2010).

To date there have been very few resting-state studies of FTD. These initial investigations reported pervasive changes to multiple resting-state networks, most notably a weakening of the salience network (SLN), a network bridging the frontal lobes and limbic system, characterized by communication between the anterior cingulate, insula, striatum and amygdala (Seeley et al., 2009; Zhou et al., 2010). Convergent findings have emerged from other imaging techniques: decreased metabolic activity in the SLN has been observed in FTD through ^{18}F-fluorodeoxyglucose PET (FDG-PET) (Peters et al., 2006; Foster et al., 2007; Gabel et al., 2010), and through arterial spin labeling (Du et al., 2006). Atrophy in the anterior insula atrophy is one of the earliest structural biomarkers of behavioral symptoms in FTD (Seeley, 2010), corroborating its significance in this functional network. In healthy individuals, the anterior insula appears to integrate emotional and visceral information into representations of present moment context that guide socially appropriate behavior (Farb et al., 2007; Seeley et al., 2007; Craig, 2009b; Wiech et al., 2010). Frontolimbic disconnection through the anterior insula is therefore a strong candidate mechanism for explaining behavioral symptoms in FTD.

Despite initial evidence of SLN dissolution in FTD, it remains unclear how generalizable these findings are across similar frontolimbic connectivity templates, or whether other intrinsic connectivity network changes also contribute to behavioral symptoms. For instance, Zhou et al. (2010) observed increased resting-state activity of a frontoparietal network, known as the 'default mode network (DMN)'. The DMN is composed of the posterior cingulate, precuneus, medial PFC, and angular gyri, and is associated with autobiographical memory and habitual, self-referential thought (Raichle et al., 2001; Greicius et al., 2003; Buckner et al., 2005). Both SLN and DMN changes may underlie behavioral dysregulation in FTD, as could any number of other local connectivity networks. In two recent meta-analyses