CORTEX 74 (2016) 149–157

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Behavioural neurology

Two insular regions are differentially involved in behavioral variant FTD and nonfluent/agrammatic variant PPA

Maria Luisa Mandelli [a,*], *Paolo Vitali* [b], *Miguel Santos* [a], *Maya Henry* [c], *Kelly Gola* [a], *Lynne Rosenberg* [a], *Nina Dronkers* [d,e], *Bruce Miller* [a], *William W. Seeley* [a,f] *and Maria Luisa Gorno-Tempini* [a]

[a] *Department of Neurology, Memory and Aging Center, University of California San Francisco, San Francisco, CA, United States*

[b] *Division of Neurology, Department of Medicine, Centre hospitalier de l'Université de Montreal (CHUM), Montreal, Canada*

[c] *Department of Communication Sciences and Disorders, University of Texas, Austin, United States*

[d] *Center for Aphasia and Related Disorders, VA Northern California Health Care System, Martinez, CA, United States*

[e] *Department of Neurology, University of California, Davis, United States*

[f] *Department of Pathology, University of California, San Francisco, United States*

ARTICLE INFO

Article history:
Received 18 April 2015
Reviewed 6 July 2015
Revised 3 September 2015
Accepted 13 October 2015
Action editor Peter Garrard
Published online 14 November 2015

Keywords:
Primary progressive aphasia
Behavioral variant frontotemporal dementia
Insula
Speech production
Voxel-based morphometry
Apraxia of speech

ABSTRACT

The non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA) and the behavioral variant frontotemporal dementia (bvFTD) are focal neurodegenerative disorders belonging to the FTD-spectrum clinical syndromes. NfvPPA is characterized by effortful speech and/or agrammatism and left frontal atrophy, while bvFTD is characterized by social–emotional dysfunction often accompanied by right-lateralized frontal damage. Despite their contrasting clinical presentations, both disorders show prominent left anterior insula atrophy. We investigated differential patterns of insular sub-region atrophy in nfvPPA and bvFTD. Based on knowledge of insular connectivity and physiology, we hypothesized that the left superior precentral region of the dorsal anterior insula (SPGI) would be more atrophic in nvfPPA due to its critical role in motor speech, whereas the ventral anterior region would be more atrophied in bvFTD reflecting its known role in social –emotional–autonomic functions. Early stage nfvPPA and bvFTD patients matched for disease severity, age, gender and education and healthy controls participated in the study. Detailed clinical history, neurological examination, neuropsychological screening evaluation, and high-resolution T1-weighted brain magnetic resonance imaging (MRI) were collected. Voxel-based morphometry (VBM) was applied to perform group comparisons across the whole brain and in bilateral insula region of interest (ROI). Correlation analyses between insular sub-region atrophy and relevant clinical features were performed. Whole brain group comparisons between nfvPPA and bvFTD showed the expected predominantly left or right anterior insular atrophy pattern. ROI analysis of bilateral insula showed that

* *Corresponding author*. UCSF Memory and Aging Center, Department of Neurology, University of California San Francisco, Sandler Neurosciences Center, 675 Nelson rising Lane, Suite 190, Box 1207, San Francisco, CA 94143-1207, United States.
E-mail address: MariaLuisa.Mandelli@ucsf.edu (M.L. Mandelli).

http://dx.doi.org/10.1016/j.cortex.2015.10.012

the left SPGI was significantly more atrophied in nfvPPA compared to bvFTD, while the bilateral ventral anterior and right dorsal anterior insula sub-regions were more atrophied in bvFTD than nfvPPA.

Only left SPGI volume correlated with speech production abilities, while left and right ventral anterior insula volumes correlated with ratings of aberrant eating behavior.

These two FTD clinical variants show different patterns of insular sub-region atrophy in the left precentral dorsal anterior and bilateral ventral anterior regions, providing further evidence for the role of these sub-regions in speech production and social–emotional function.

1. Introduction

Frontotemporal dementia (FTD) is a heterogeneous group of neurodegenerative diseases characterized by atrophy of frontal, temporal, and insular brain regions. Clinically, FTD manifests either with prominent behavioral and personality changes (behavioral variant, bvFTD; Neary et al., 1998; Rascovsky et al., 2011) or with isolated language impairments (primary progressive aphasia, PPA; Mesulam, 1982, 2001).

The non-fluent/agrammatic variant PPA (nfvPPA) is characterized by agrammatism and/or effortful, halting speech consistent with apraxia of speech (AOS) (Gorno-Tempini et al., 2011; Grossman et al., 1996; Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007). Imaging studies in nfvPPA patients have shown left-lateralized atrophy mostly in the posterior frontal lobe, including Broca's area and premotor cortex, as well as in the anterior insula (Gorno-Tempini et al., 2004; Josephs et al., 2006; Nestor et al., 2003; Rogalski et al., 2011; Rohrer et al., 2009).

BvFTD is characterized by prominent progressive changes in personality and social–emotional function. Typical symptoms include disinhibition, altered eating behavior, loss of empathy, apathy, compulsivity and emotional dysregulation. Aberrant eating behavior is one of the most common and distinctive symptoms of bvFTD (Bozeat, Gregory, Ralph, & Hodges, 2000). It occurs in over 80% of bvFTD patients over the course of the disease (Piguet, Hornberger, Shelley, Kipps, & Hodges, 2009) and is characterized by gluttonous and indiscriminant food consumption (Shinagawa et al. 2009; Snowden et al., 2001). BvFTD neuroimaging studies have shown areas of atrophy in the ventromedial and posterior orbital frontal cortex, as well as the anterior insula and anterior cingulate cortex, striatum, and amygdala bilaterally but often more prominently on the right (Boccardi et al., 2005; Franceschi et al., 2005; Ibach et al., 2004; Rosen et al., 2002; Schroeter, Raczka, Neumann, & Yves von Cramon, 2007).

Despite the broad clinical and anatomical differences between bvFTD and nfvPPA, both disorders share regions of focal neurodegeneration in the insulae. Recent evidence highlights differential roles of anterior insular sub-regions in sensory-motor, cognitive, control and attentional, and behavioral functions (Deen, Pitskel, & Pelphrey, 2011; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Mutschler et al., 2009; Nelson et al., 2010; Touroutoglou, Hollenbeck, Dickerson, & Feldman Barrett, 2012). We predicted that the left superior precentral region of the dorsal anterior insula (SPGI), previously implicated in motor speech planning (Dronkers, 1996), would be most involved in nfvPPA, whereas the ventral anterior insula, previously linked to social–emotional and autonomic functions (Wooley et al., 2007), would be more atrophied in bvFTD. To test these hypotheses, we compared the patterns of MRI-based regional gray matter (GM) atrophy between early-stage nfvPPA and bvFTD. In particular, we investigated distinct subregions of the insulae to isolate specific foci of focal GM atrophy associated with each clinical presentation. Correlation analyses between these specific sub-regional volumes and relevant clinical scores were performed.

2. Material and methods

2.1. Subjects

We searched the University of California San Francisco (UCSF) Memory and Aging Center (MAC) database for patients who met the following inclusion criteria: a research diagnosis of bvFTD or nfvPPA, a high-resolution magnetic resonance imaging (MRI), and a Clinical Dementia Rating (CDR) score ≤ 1 (Morris, 1993) within 6 months of first diagnosis. Detailed clinical history, neurological examination, and neuropsychological screening were conducted as previously described (Rosen et al., 2002). NfvPPA patients also underwent a detailed speech and language evaluation (Gorno-Tempini et al., 2004). Recent research clinical criteria for bvFTD and nfvPPA were applied (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Eighty-eight patients met these initial inclusion criteria (40 nfvPPA and 48 bvFTD) but the groups significantly differed in age, gender and CDR. For this reason, we then matched the two groups of patients, seeking comparable distributions of age, gender, disease severity (CDR total and sum-of-boxes scores and Mini-Mental State Examination) and sample size. The resulting study population included 25 nfvPPA and 23 bvFTD patients (Table 1). Fifty healthy volunteers matched to the patient groups according to age, gender, education, and handedness were recruited as controls for the imaging analysis. An additional cohort of healthy subjects ($n = 34$) who received the language battery were used as controls for the