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Affective mentalizing and brain activity at rest in the behavioral variant of frontotemporal dementia

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ABSTRACT

Background: bvFTD patients display an impairment in the attribution of cognitive and affective states to others, reflecting GM atrophy in brain regions associated with social cognition, such as amygdala, superior temporal cortex and posterior insula. Distinctive patterns of abnormal brain functioning at rest have been reported in bvFTD, but their relationship with defective attribution of affective states has not been investigated.
Objective: To investigate the relationship among resting-state brain activity, gray matter (GM) atrophy and the attribution of mental states in the behavioral variant of fronto-temporal degeneration (bvFTD).
Methods: We compared 12 bvFTD patients with 30 age- and education-matched healthy controls on a) performance in a task requiring the attribution of affective vs. cognitive mental states; b) metrics of resting-state activity in known functional networks; and c) the relationship between task-performances and resting-state metrics. In addition, we assessed a connection between abnormal resting-state metrics and GM atrophy.
Results: Compared with controls, bvFTD patients showed a reduction of intra-network coherent activity in several components, as well as decreased strength of activation in networks related to attentional processing. Anomalous resting-state activity involved networks which also displayed a significant reduction of GM density. In patients, compared with controls, higher affective mentalizing performance correlated with stronger functional connectivity between medial prefrontal sectors of the default-mode and attentional/performance monitoring networks, as well as with increased coherent activity in components of the executive, sensorimotor and fronto-limbic networks.
Conclusions: Some of the observed effects may reflect specific compensatory mechanisms for the atrophic changes involving regions in charge of affective mentalizing. The analysis of specific resting-state networks thus highlights an intermediate level of analysis between abnormal brain structure and impaired behavioral performance in bvFTD, reflecting both dysfunction and compensation mechanisms.

1. Introduction

The behavioral variant of frontotemporal dementia (bvFTD) is the most common clinical syndrome within the frontotemporal lobar degeneration (FTLD) spectrum, accounting for about half of all FTLD cases (Piguet et al., 2011). Along with Alzheimer's disease (AD), it is the most common cause of early-onset neurodegenerative dementia (Piguet et al., 2011). Neuropathological and imaging studies suggest that specific neural systems are affected by dementias (Zhou and Seeley, 2014). In bvFTD, the neurodegenerative process specifically targets brain regions associated with the processing of social and affective

Abbreviations: bvFTD, behavioral variant of frontotemporal dementia; FTLD, frontotemporal lobar degeneration; AD, Alzheimer's disease; ToM, theory of mind; BOLD, blood-oxygen-level-dependent; GM, gray matter; SPM, statistical parametric mapping; FDR, false discovery rate; MANCOVAN, multivariate analysis of covariance; VBM, voxel based morphometry; RSNs, resting-state networks; rs-*f*MRI, resting-state fMRI; aDMN, anterior default mode network; pDMN, posterior default mode network; MMSE, Mini-Mental State Examination; SET, story-based empathy task; EA, emotion attribution; IA, intention attribution; CI, causal inferences; gICA, group independent component analysis; PCA, principal component analysis.

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stimuli (Seeley et al., 2008; Irish et al., 2011). Crucial clinical manifestations, indeed, are changes in personality, interpersonal conduct and emotional control, associated, in the early stages of the disease, with a relative preservation of cognitive performance on standard neuropsychological measures (Cerami and Cappa, 2013). In particular, loss of sympathy and/or empathy is a key feature for the differential diagnosis of bvFTD (Rascovsky et al., 2011). Several studies provided behavioral evidence of early impairments of social cognition, involving emotion recognition, empathy, as well as the correct attribution of mental states to other individuals (i.e. mentalizing, or "theory of mind" (ToM); Elamin et al., 2012). The objective assessment of socio-affective abilities may thus provide crucial cues to the diagnosis of this dementia subtype (Torralva et al., 2009; Gleichgerrcht et al., 2010).

At the neural level, the impairment of social cognition in bvFTD reflects a selective vulnerability of limbic and fronto-insular networks (Kim et al., 2012), characterizing the disease since its earliest stage (Seeley et al., 2008) (see Ibañez and Manes (2012) for a recent proposal on the role of these networks in processing social contextual effects). Only a few studies, however, have directly investigated the connection between the multiple facets of social cognition and the underlying neural impairment in bvFTD (Elamin et al., 2012). At the structural brain level, we have recently shown that, in bvFTD patients, a selective deficit in the ability to attribute affective states (as compared to cognitive states such as intentions) reflects gray matter atrophy in key nodes of the "social brain" (Adolphs, 2009; Frith, 2007; Lieberman, 2007)", such as amygdala, superior temporal cortex and posterior insula (Cerami et al., 2014a). Here we aim to complement this neuroanatomical evidence by relating the empathic deficit displayed by bvFTD patients to possible abnormal patterns in their resting-state brain activity.

Starting from the observation of synchronous, low-frequency, fluctuations of BOLD activity shown by specific regions at rest (Biswal et al., 1995), the investigation of so-called resting-state networks (RSNs) has provided critical information on intrinsic (i.e. task-free) brain activity, both in health and in pathological conditions (e.g. Biswal et al., 2010). Abnormalities in such an intrinsic functional brain architecture (i.e. connectome; Smith et al., 2013), and their relationship with impaired cognition and behavior, have been also investigated in dementia (Seeley et al., 2009), and particularly in AD. The phenotypical characterization of dementia may greatly benefit from non-invasive measures of intrinsic brain activity at rest, which, complementing research on the neuropathology and genetics of different types of dementia, may provide an additional biomarker of specific neurodegenerative disease, endowed with prognostic potentialities (Greicius and Kimmel, 2012; Pievani et al., 2014). In the last years, several studies have taken advantage of resting-state *f*MRI (rs-*f*MRI) to investigate a relationship between intrinsic brain activity and performance in tasks which require extensive patient cooperation (Khanna et al., 2015). This is a powerful method to assess patients with behavioral disorders, which may have difficulty in performing a task within an MR scanner.

Compared with a wide literature on rs-*f*MRI in AD, bvFTD has been less frequently investigated (Agosta et al., 2013; Filippi et al., 2013; Rytty et al., 2013; Whitwell et al., 2011; Zhou et al., 2010). The available studies highlighted distinctive patterns of abnormal brain functioning at rest, in particular altered activity and reduced connectivity within the attentional "salience" network and the anterior components of the default mode network (aDMN) (Seeley et al., 2007a), including key structures for socio-affective processing such as limbic and fronto-insular regions, alongside increased functional connectivity within the posterior default mode network (pDMN) (Zhou and Seeley, 2014). This pattern, opposite to that typically observed in AD dementia subtype (i.e. disrupted connectivity in the pDMN alongside increased connectivity in the salience network; Zhou et al., 2010), is consistent with the impairments in self-projection, insight and meta-cognition observed in bvFTD patients (Irish et al., 2011; Rankin et al., 2006). To date, however, no study has directly related anomalous resting-state metrics to impaired affective mentalizing in bvFTD patients.

To fill this gap, in the present study we compared resting-state brain activity, as well as its relationship with the ability to attribute affective vs. cognitive mental states to others, between bvFTD patients and age/education-matched healthy controls. Based on our previous data (Cerami et al., 2014a) we predicted that the bvFTD deficit in the attribution of affective vs. cognitive states would be specifically related to anomalous resting-state brain activity, involving in particular fronto-medial and fronto-limbic RSNs. In addition, we also investigated the relationship between functional (resting-state) and morphometric (GM density) levels of analysis, under the hypothesis that anomalous resting-state activity in specific networks, related to specific social cognition deficits, may reflect the presence of gray matter atrophy.

2. Materials and methods

2.1. Subjects

Within a larger sample (Cerami et al., 2014a) of patients fulfilling clinical criteria for probable bvFTD (Rascovsky et al., 2011), 12 patients (9 men, 3 women; mean age = 63.11 years; standard deviation (SD) = 7.17; Clinical Dementia Rating (CDR) scale ≤ 1) were enrolled for this rs-*f*MRI study. Patients were consecutively recruited from the Neurorehabilitation Unit (Department of Clinical Neurosciences) at San Raffaele Hospital (Milan, Italy), and evaluated by a team of experienced behavioral neurologists and neuropsychologists. Their resting-state brain activity and task-performance (see below) were compared with those obtained in 30 age- and education-matched healthy controls (18 men, 12 women; mean age = 58.84 years; SD = 7.30) (see Table 1).

Besides the main experimental task, all subjects underwent a structured clinical interview, a full neurological examination, a standard neuropsychological battery including measures of logical-reasoning, attention and executive functioning (i.e. Digit Span forward and backward, Raven's Progressive Matrices, Attentional Matrices) and a neurobehavioral assessment (i.e. Neuropsychiatric Inventory and Frontal Behavioral Inventory). Instrumental data, including neurophysiological (i.e. EEG) and neuroimaging (i.e. conventional brain MRI and/or brain [^{18}F]FDG-PET), were also collected for each patient to support the clinical diagnosis. The exclusion criteria were a Mini-Mental State Examination (MMSE) raw score below 21/30 and a Clinical Dementia Rating (CDR) scale global score above 1.

Healthy controls were recruited at local senior community centers. Their inclusion criteria were the absence of any neuropsychiatric disorder, a normal neurological examination, a CDR = 0, MMSE raw score ≥28/30, and verbal and visuo-spatial delayed memory performance ≥25th percentile. There were no significant differences between bvFTD and controls in age or educational level (Table 1). A chi-square test confirmed that the distribution of males and females was not significantly different across patients and controls ($Chi^2(1) = 0.162$, $p = 0.688$).

All subjects, or their informants/caregivers, gave informed consent to the experimental procedure, which was approved by the local Ethical Committee.

2.2. Experimental task

Participants were administered a non-verbal cartoon task (Story-based Empathy Task, SET; Cerami et al., 2014a,b; Dodich et al., 2015) assessing the correct attribution of mental states to other individuals, and namely their intentions vs. affective states (see Fig. 1). The task lasts 15/20 min and includes two main experimental conditions, i.e. identifying affective states (emotion attribution, EA) or intentions (intention attribution, IA). A third "control" condition, devoid of social components, is aimed to assess the ability to infer physical causal