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Research report

Functional network connectivity in the behavioral variant of frontotemporal dementia

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ABSTRACT

Introduction: The aim of this study was to investigate, using resting state (RS) functional magnetic resonance imaging (fMRI), the functional connectivity within and among brain networks in patients with the behavioral variant of frontotemporal dementia (bvFTD), compared with healthy controls and patients with probable Alzheimer's disease (pAD).

Methods: Twelve bvFTD patients were compared with 30 controls and 18 pAD patients. Functional connectivity within the salience, default mode (DMN), executive (EXN), attention/working memory (ATT/WM), and dorsal attentional networks was assessed using independent component analysis. The temporal associations among RS networks (RSNs) were explored using the functional network connectivity toolbox.

Results: A decreased dorsal salience network (DSN) connectivity, mainly involving the anterior cingulum, was observed in bvFTD versus controls and pAD. BvFTD was also characterized by a decreased ventral salience network connectivity in the basal ganglia, and divergent connectivity effects versus controls in the dorsolateral prefrontal cortex (decreased) and precuneus (enhanced) within the right ATT/WM network. The dorsal attentional network had a decreased connectivity with the DMN and EXN in bvFTD versus controls, and a decreased connectivity with the DSN versus pAD.

Conclusions: RSN functional abnormalities occur in bvFTD, involving not only the salience network, but also the DMN and fronto-parietal network associated with ATT and WM modulation. The pattern of functional changes differs from that seen in pAD. The altered

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interactions among RSN observed in bvFTD and pAD may provide a new venue to explore the functional correlates of cognitive abnormalities in neurodegenerative and psychiatric disorders.

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1. Introduction

The behavioral variant of frontotemporal dementia (bvFTD) and Alzheimer's disease (AD) are the two most common causes of dementia among patients less than 65 years of age (Ratnavalli et al., 2002). BvFTD presents with marked changes in emotion processing, personal and social conduct, and decision making. These deficits occur in concert with early, focal degeneration of the anterior cingulate cortex (ACC) and frontoinsular cortex, as well as the dorsomedial prefrontal cortex, striatum, and thalamus (Seeley et al., 2008). In contrast, AD patients are characterized clinically by an early memory loss, and the earliest pathology in AD involves the hippocampus and entorhinal cortex, gradually extending to the posterior temporal, lateral parietal regions and posterior cingulate cortex (PCC) (Thompson et al., 2001).

The analysis of functional connectivity of the resting state (RS) (Biswal et al., 1995) [i.e., RS functional magnetic resonance imaging (fMRI)], which is easy to obtain and does not suffer from performance confounds in the case of cognitively impaired individuals, has been largely used to elucidate brain functional organization in AD patients (Filippi and Agosta, 2011). In AD, brain atrophy and β-amyloid deposition occur mainly in the brain regions part of the default mode network (DMN), i.e., the PCC/precuneus, lateral parietal cortex, medial temporal lobe (MTL), and medial frontal cortex. These regions are active at rest, and deactivated during cognitively demanding tasks (Greicius et al., 2003). Disruption of DMN regions in AD has been consistently reported in RS MRI studies (Greicius et al., 2004; Wang et al., 2006; Zhang et al., 2010, 2009a). Early DMN functional disruption in AD involves the MTL and PCC/precuneus (Qi et al., 2010; Sorg et al., 2007), subsequently worsening and extending to the lateral parietal and medial frontal regions with increasing disease severity. In addition to a reduced DMN connectivity (Zhang et al., 2010), an increased functional connectivity between fronto-parietal regions has also been reported in these patients (Agosta et al., 2012; Qi et al., 2010; Zhang et al., 2009a).

To this date, only a few studies investigated the functional connectivity of the brain networks in bvFTD (Whitwell et al., 2011; Zhou et al., 2010). The most consistent RS fMRI feature in bvFTD (Whitwell et al., 2011; Zhou et al., 2010) is a reduced connectivity within a large-scale network, the so-called "salience" network, that includes the ACC, orbitofrontal-insular cortices, and subcortical structures, and which is related to socially-emotionally relevant information processing (Seeley et al., 2007). The functional connectivity patterns found in the DMN from bvFTD patients have been less consistent, with some authors reporting enhanced connectivity within parietal DMN regions (Whitwell et al., 2011; Zhou et al., 2010) and others reporting a reduced DMN connectivity (Whitwell et al., 2011), similar to that seen in AD. Furthermore, whether RS networks (RSNs) other than the salience network and DMN are affected by bvFTD, and whether these abnormalities differ from those seen in AD have not been investigated yet.

In this study, we used RS fMRI to assess the functional connectivity within RSN related to cognition, i.e., the salience (Seeley et al., 2007), DMN (Greicius et al., 2003), executive (EXN) (Seeley et al., 2008), asymmetric attention/working memory (ATT/WM) (Damoiseaux et al., 2006), and dorsal attentional (Fox et al., 2005) networks, in bvFTD patients relative to healthy elderly controls and probable AD (pAD) patients. In addition, we used a novel approach to quantify the relationships among such RSN (Jafri et al., 2008). We hypothesized that patients with bvFTD would not only experience an altered functional connectivity within RSN related to emotional processing and executive/attentional functions, but also a defective integration among them, and that such abnormalities differ from those observed in AD patients.

2. Methods

2.1. Subjects

Right-handed (Oldfield, 1971) patients with a diagnosis of probable bvFTD and pAD (McKhann et al., 2011; Rascovsky et al., 2011) were recruited consecutively at the San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy. According to established criteria (McKhann et al., 2011; Rascovsky et al., 2011), the diagnoses of probable bvFTD and pAD were based on a comprehensive evaluation including neurological history and examination, neuropsychological testing, structural routine MRI, and functional neuroimaging [i.e., ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) or single photon emission computed tomography (SPECT) with Technetium-99m-bicisate ethyl cysteinate dimer]. Clinical assessment was performed by experienced neurologists blinded to MRI. History was taken with a structured interview from patients' relatives. In a sample of patients, cerebrospinal fluid (CSF) and genetic analysis were also available and were used to support the clinical diagnosis. Right-handed (Oldfield, 1971) healthy controls (HCs) were recruited among the spouses of patients and by word of mouth. Controls underwent a multidimensional assessment, including neurological and neuropsychological evaluation, and were included in the study only when the results were fully normal. Potential patients and controls were excluded if they had: family history of dementia; significant medical illnesses or substance abuse that could interfere with cognitive functioning; any other major systemic, psychiatric or neurological illnesses; and other causes of focal or diffuse brain damage, including lacunae and other evidence of extensive cerebrovascular disease at routine MRI. Approval was received from local ethical standards committee on

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