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Individual differences in socioemotional sensitivity are an index of salience network function

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ABSTRACT

Connectivity in intrinsically connected networks (ICNs) may predict individual differences in cognition and behavior. The drastic alterations in socioemotional awareness of patients with behavioral variant frontotemporal dementia (bvFTD) are presumed to arise from changes in one such ICN, the salience network (SN). We examined how individual differences in SN connectivity are reflected in overt social behavior in healthy individuals and patients, both to provide neuroscientific insight into this key brain–behavior relationship, and to provide a practical tool to diagnose patients with early bvFTD. We measured SN functional connectivity and socioemotional sensitivity in 65 healthy older adults and 103 patients in the earliest stage [Clinical Dementia Rating (CDR) Scale score $\leq$1] of five neurodegenerative diseases [14 bvFTD, 29 Alzheimer's disease (AD), 20 progressive supranuclear palsy (PSP), 21 semantic variant primary progressive aphasia (svPPA), and 19 non-fluent variant primary progressive aphasia (nfvPPA)]. All participants underwent resting-state functional imaging and an informant described their responsiveness to subtle emotional expressions using the Revised Self-Monitoring Scale (RSMS). Higher functional connectivity in the SN, predominantly between the right anterior insula (AI) and both "hub" cortical and "interoceptive" subcortical nodes, predicted socioemotional sensitivity among healthy individuals, showing that socioemotional sensitivity is a behavioral marker of SN function, and particularly of right AI functional connectivity. The continuity of this relationship in both healthy and neurologically affected individuals highlights the role of socioemotional sensitivity as an early diagnostic marker of SN connectivity. Clinically, this is particularly important for identification of patients in the earliest stage of bvFTD, where the SN is selectively vulnerable.

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1. Introduction

A heterogeneous group of neurodegenerative disease syndromes is associated with fronto-insular and temporal degeneration, with behavioral variant frontotemporal dementia (bvFTD) syndrome accounting for up to 50% of these cases (Johnson et al., 2005; Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011). The earliest symptoms of bvFTD are deficits in personal and social conduct, emotion, and insight (Neary et al., 1998; Rosen et al., 2002), often in the context of otherwise preserved cognitive and motor functioning. Consequently, initial clinical diagnosis of patients with bvFTD relies entirely on the assessment of patients' social and emotional symptoms (Rascovsky et al., 2011). However, bvFTD patients are almost never identified until their disease is well past the initial stages. As a result of their emotional and behavioral symptoms, bvFTD patients often are mistaken for patients with a late onset psychiatric disorder, and may spend years under psychiatric care before receiving a correct neurodegenerative diagnosis (Khan et al., 2012; Woolley, Khan, Murthy, Miller, & Rankin, 2011). Thus, to ensure early and accurate clinical diagnosis of bvFTD patients, particularly in the stage before expensive and technically demanding brain imaging is ordered, it is necessary to identify and validate tests that not only measure characteristic patterns of bvFTD social dysfunction, but which also directly reflect changes to the specific brain circuits that degenerate in bvFTD (Shany-Ur et al., 2014; Sollberger et al., 2009). Also, because the earliest symptoms result from altered functional connectivity that precedes structural atrophy (Lee et al., 2014; Whitwell et al., 2011), tests proven to correlate with functional changes will be more diagnostically powerful.

Resting-state functional magnetic resonance imaging (rs-fMRI) studies in healthy participants have revealed a set of highly reproducible intrinsically connected functional networks (ICNs), including the salience (SN) (Seeley et al., 2007), the default-mode (DMN) (Greicius, Srivastava, Reiss, & Menon, 2004), and the sensorimotor (SMN) (Zielinski, Gennatas, Zhou, & Seeley, 2010) network. These ICNs perform specific socioemotional, cognitive, and sensorimotor functions (Yeo et al., 2011), and are affected differently by distinct neurodegenerative disease syndromes (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). The SN works to integrate and interpret interoceptive, autonomic signals, and adjust arousal and attention on the basis of perceived relevance. This network is the site of earliest dysfunction in mild and even prodromal (Dopper et al., 2013; Seeley et al., 2008; Whitwell et al., 2011) bvFTD. The key node within the SN is the right anterior insula (AI), which integrates highly processed sensory stimuli with homeostatic, affective, motivational, and hedonic information, much of which arises from subcortical SN nodes, including the dorsomedial thalamus (dmTH), hypothalamus (HT), amygdala (AMY), and midbrain periaqueductal gray (PAG) (Seeley et al., 2007). This interoceptive information provides a fundamental basis for the awareness of and sensitivity to self- and other-related emotions (Craig, 2009). Consequently, the altered socioemotional awareness of bvFTD patients likely reflects early changes in particular connectivity patterns between the right AI and both cortical [left AI, anterior cingulate cortex (ACC)] and subcortical SN nodes, leading to a failure to integrate basic interoceptive information into a full-blown emotional experience and response (Craig, 2002, 2009).

The primary aim of the present study was to identify whether individual differences in SN connectivity, and specific patterns of connectivity between cortical and subcortical SN nodes, predict socioemotional sensitivity and responsiveness to subtle emotional expressions. Though we predicted that this brain–behavior relationship could be observed in healthy individuals, we wished to account for the possibility of small effect sizes in this exploratory analysis. Thus, in order to ensure adequate variance to detect this relationship, we enriched our healthy control sample with individuals with very early neurodegenerative disease, who were likely to show below normal levels of SN connectivity and socioemotional sensitivity, thereby increasing variance for the regression models. We hypothesized that socioemotional sensitivity would be related to connectivity in the SN, but not to connectivity in two "control" networks, the DMN and SMN, in this enriched (controls + patients) sample. We selected the DMN and SMN as our "control" networks because DMN connectivity corresponds to efficiency of memory processing (Greicius et al., 2004), and because we assumed that the SMN is neither related to socioemotional sensitivity nor to memory. We also expected that connectivity primarily between the right AI and both cortical and subcortical SN nodes would significantly predict socioemotional sensitivity in this full sample. As secondary, exploratory analyses, taking into consideration that our subgroups were likely underpowered due to their small sample size, we investigated whether these relationships were independently detectable in any of the diagnostic subgroups, including healthy controls.

2. Material and methods

2.1. Participants

One hundred and sixty eight participants were enrolled in the study. Participants included 65 healthy older controls (NC) and 103 patients diagnosed with one of five neurodegenerative disease syndromes: 14 patients were diagnosed with bvFTD (Rascovsky et al., 2011), 29 met NINCDS-ADRDA criteria Alzheimer's disease (AD) (McKhann et al., 2011), 20 were diagnosed with progressive supranuclear palsy (PSP) (Litvan et al., 1996), 21 had semantic variant primary progressive aphasia (svPPA) (Gorno-Tempini et al., 2011), and 19 were diagnosed with non-fluent variant primary progressive aphasia (nfvPPA) (Gorno-Tempini et al., 2011). Patients' diagnoses were determined by a multidisciplinary team of neurologists, neuropsychologists, and nurses, following thorough neurological, neuroimaging, and neuropsychological assessments. Patients were required to have Clinical Dementia Rating (CDR), Mini-Mental State Examination (MMSE), Revised Self-Monitoring Scale (RSMS) informant questionnaire, and neuropsychological scores obtained within 90 days of structural and functional imaging scanning. Only patients who were very early in disease progression (CDR score ≤ 1) were included. All participants were required to have valid functional imaging scans, and to obtain the final number of 168 participants, 35