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White matter tract signatures of impaired social cognition in frontotemporal lobar degeneration

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ABSTRACT

Impairments of social cognition are often leading features in frontotemporal lobar degeneration (FTLD) and likely to reflect large-scale brain network disintegration. However, the neuroanatomical basis of impaired social cognition in FTLD and the role of white matter connections have not been defined. Here we assessed social cognition in a cohort of patients representing two core syndromes of FTLD, behavioural variant frontotemporal dementia (bvFTD; n = 29) and semantic variant primary progressive aphasia (svPPA; n = 15), relative to healthy older individuals (n = 37) using two components of the Awareness of Social Inference Test, canonical emotion identification and sarcasm identification. Diffusion tensor imaging (DTI) was used to derive white matter tract correlates of social cognition performance and compared with the distribution of grey matter atrophy on voxel-based morphometry. The bvFTD and svPPA groups showed comparably severe deficits for identification of canonical emotions and sarcasm, and these deficits were correlated with distributed and overlapping white matter tract alterations particularly affecting frontotemporal connections in the right cerebral hemisphere. The most robust DTI associations were identified in white matter tracts linking cognitive and evaluative processing with emotional responses: anterior thalamic radiation, fornix (emotion identification) and uncinate fasciculus (sarcasm identification). DTI associations of impaired social cognition were more consistent than corresponding grey matter associations. These findings delineate a brain network substrate for the social impairment that characterises FTLD syndromes. The findings further suggest that DTI can generate sensitive and functionally relevant indexes of white matter damage in FTLD, with potential to transcend conventional syndrome boundaries.

1. Introduction

Frontotemporal lobar degeneration (FTLD) refers to a heterogeneous group of non-Alzheimer dementias collectively characterised by progressive atrophy of the frontal and temporal lobes and presenting with insidious disintegration of social behaviour or language (Ratnavalli et al., 2002; Rosen et al., 2005; Hodges and Patterson, 2007; Kipps et al., 2009; Rohrer and Warren, 2010; Omar et al., 2011; Rascovsky et al., 2011; Gorno-Tempini et al., 2011; Rohrer et al., 2011; Whitwell and Josephs, 2011; McGinnis, 2012; Warren et al., 2013a). These diseases collectively constitute a common cause of young-onset 'frontotemporal dementia' (Ratnavalli et al., 2002), pose substantial problems of nosology and diagnosis, and highlight the fundamental neurobiological problem of selective neurodegeneration.

These challenges are well illustrated by the canonical FTLD syndromes of behavioural variant frontotemporal dementia (bvFTD) and the semantic variant of primary progressive aphasia (svPPA, or semantic dementia). Clinically, bvFTD characteristically manifests with progressive behavioural deterioration leading to severe social dysfunction that may be misdiagnosed as a primary psychiatric disorder (Rosen et al., 2005; Kipps et al., 2009; Omar et al., 2011; Rascovsky et al., 2011), while svPPA presents with progressive erosion of semantic memory manifesting as loss of knowledge about words, objects and concepts, typically with supervening behavioural and personality changes later in the course (Hodges and Patterson, 2007; Rohrer and Warren, 2010; Gorno-Tempini et al., 2011). Both syndromes potentially hold unique insights into the neurobiology of social cognition and the impact of disease on its critical brain substrates. Emerging structural and functional neuroimaging evidence has implicated specific large-scale brain networks in the pathogenesis of bvFTD and svPPA: in the

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case of bvFTD, a 'salience' network that processes emotionally significant internal and external stimuli including social signals (Seeley et al., 2009; Zhou et al., 2010) and links distributed brain regions including the prefrontal cortex, orbitofrontal cortex, anterior cingulate, and insula; and in the case of svPPA, a 'semantic' network that associates multimodal sensory and symbolic data with meaning, instantiated in the anterior temporal and inferior frontal lobes (Hodges and Patterson, 2007; Fletcher and Warren, 2011). Differential involvement of these networks may provide candidate brain substrates for social cognition deficits in these syndromes (Seeley et al., 2009; Zhou et al., 2010, 2012; Irish et al., 2011; Raj et al., 2012).

Social cognition is a multi-dimensional and still poorly understood aspect of human brain function (Zahn et al., 2007; Adolphs, 2009; Kennedy and Adolphs, 2012; Olson et al., 2013); it typically entails emotional, semantic, mnestic and evaluative processing of sensory signals, and yet specialised brain systems underpinning social cognition have been inferred from evidence in the healthy brain and in disease states, suggesting that it might be a useful paradigm for detecting and tracking the clinical course of diseases in the FTLD spectrum. Indeed, the multidimensionality of social cognition is reflected in the diverse deficits described in bvFTD, including multimodal recognition of canonical emotions (Omar et al., 2011; Kumfor et al., 2013), empathic concern and perspective taking (Rankin et al., 2005; Mahoney et al., 2011), mentalising (Le Bouc et al., 2012; Downey et al., 2013), perception of humour and sarcasm (Snowden et al., 2003; Kipps et al., 2009), affective decision making (Torralva et al., 2007), moral reasoning (Chiong et al., 2013) and conceptualising self in relation to others (Irish et al., 2011). Although social cognition deficits in svPPA are less widely documented, a number of studies have reported similar abnormalities of social functioning in these patients (Rankin et al., 2009; Zahn et al., 2009; Duval et al., 2012).

The processing of sarcasm is an attractive model for probing component processes of social cognition that are vulnerable in FTLD syndromes (Kipps et al., 2009; Rankin et al., 2009). Sarcasm exemplifies a familiar and relatively simple paralinguistic cue that must be processed according to social context in order to understand the verbal message; as a stimulus feature, sarcastic intent is straightforward to manipulate and its detection can be reliably assessed (McDonald et al., 2006). Improved understanding of the brain mechanisms of sarcasm processing and social dysfunction more generally could potentially facilitate earlier and more accurate diagnosis and symptom management in FTLD and ultimately, evaluation of therapies in clinical trials. The overlapping phenomenology of interpersonal difficulties exhibited by patients with bvFTD and svPPA might reflect underlying neural substrates that are at least partly shared, consistent with convergent profiles of regional brain damage in these syndromes (McGinnis, 2012; Warren et al., 2013b); and impaired detection of sarcasm has been shown to predict and to track progression in bvFTD (Kipps et al., 2009; Kumfor et al., 2014). Impaired understanding of sarcasm has been linked to damage involving distributed neural networks including the ventro-medial prefrontal cortex, orbitofrontal cortex, anterior temporal lobes and their connections, also implicated in processing sarcasm and other social signals in the healthy brain (Zahn et al., 2007; Adolphs, 2009; Carrington and Bailey, 2009; Kipps et al., 2009; Davis et al., 2015).

This work contributes to a growing body of evidence associating particular social cognition deficits with regional brain damage in FTLD (Mahoney et al., 2011; Le Bouc et al., 2012; Chiong et al., 2013; Rankin et al., 2009; Zahn et al., 2009; Moll et al., 2011). To date, however, neuroanatomical correlative studies have focussed essentially on grey matter alterations: if (as neuroimaging work in the healthy brain strongly suggests), the processes that underpin social cognition are distributed across brain networks, then techniques that can assess structural and functional connections between individual brain regions will be required in order to delineate fully the brain mechanisms that support social cognition and the effects of disease. This is particularly relevant to neurodegenerative diseases such as FTLD that are inherently network-based (Warren et al., 2013b). White matter tracts bind brain networks, and techniques such as diffusion tensor imaging (DTI) can assess the microstructural integrity of white matter connections and correlate these with clinical deficits (Whitwell et al., 2010; Agosta et al., 2012; Mahoney et al., 2013; Tovar-Moll et al., 2014). DTI has been shown to detect white matter alterations in genetically mediated FTLD prior to the onset of symptoms or cortical atrophy, suggesting a potential role as a sensitive disease biomarker (Dopper et al., 2013).

Here we investigated white matter correlates of social cognition impairment in bvFTD and svPPA using DTI. We correlated DTI metrics with indices of canonical emotion identification (a key component of social signal coding) and sarcasm identification (a model of everyday social signal interpretation) in naturalistic vignettes. DTI data were analysed using a tract-based spatial statistics (TBSS) processing pipeline that makes minimal prior assumptions about key sites of disease involvement and is therefore relatively anatomically unbiased. White matter alterations were correlated with the distribution of grey matter atrophy assessed using voxel-based morphometry (VBM). We hypothesised that white matter alterations would target pathways binding the distributed fronto-temporal and limbic networks previously implicated in neuroimaging studies of social cognition in the healthy brain and in neurodegenerative disease. We further hypothesised that white matter signatures of impaired social cognition would constitute 'transsyndromic' substrates for the overlapping behavioural deficits that characterise the bvFTD and svPPA syndromes clinically. DTI measures of axial (AX), radial (RD) and total (trace, TR) diffusivity and fractional anisotropy (FA) were assessed in parallel, given previous work suggesting that different DTI measures may constitute relatively specific indices of structural or functional integrity in white matter pathways (Acosta-Cabronero et al., 2010; Whitwell et al., 2010; Agosta et al., 2012; Mahoney et al., 2013, 2014).

2. Methods

2.1. Participants

Twenty-nine patients fulfilling consensus criteria for probable or definite bvFTD (Rascovsky et al., 2011) and 15 patients fulfilling consensus criteria for svPPA (Gorno-Tempini et al., 2011) were recruited from a specialist cognitive disorders clinic (details summarised in Table 1). Thirty-seven healthy older individuals with no history of neurological or psychiatric illness also participated. All participants underwent a structured clinical evaluation and an assessment of general neuropsychological functions covering general intellect, memory, semantic, linguistic, executive and perceptual domains (Table 1; see also Supplementary material on-line). Informed consent was obtained for all participants and the study was approved by the local Research Ethics Committee under Declaration of Helsinki guidelines.

2.2. Assessment of social cognition

The Awareness of Social Inference Test (TASIT) (McDonald et al., 2006) was used to assess participants' ability to identify basic emotions and sarcastic intent in social situations. This test has been widely used as a measure of social cognition performance in clinical contexts and requires interpretation of posed but relatively naturalistic social scenarios. We administered an abbreviated TASIT comprising emotion identification and sarcasm identification subtests derived from the first portions of the respective subtests in the full TASIT. In the emotion identification subtest, 14 audio-visual video vignettes (each 15–20 s duration) conveying either a positive (surprised, happy), neutral or negative (anger, disgust, sadness or anxiety) emotional valence were presented in randomised order; the task on each trial was to decide which emotion was dominantly portrayed in a seven-alternative forced-choice procedure. In the sarcasm identification subtest, nine video vignettes were