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Auditory conflict and congruence in frontotemporal dementia

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ABSTRACT

Impaired analysis of signal conflict and congruence may contribute to diverse socio-emotional symptoms in frontotemporal dementias, however the underlying mechanisms have not been defined. Here we addressed this issue in patients with behavioural variant frontotemporal dementia (bvFTD; n = 19) and semantic dementia (SD; n = 10) relative to healthy older individuals (n = 20). We created auditory scenes in which semantic and emotional congruity of constituent sounds were independently probed; associated tasks controlled for auditory perceptual similarity, scene parsing and semantic competence. Neuroanatomical correlates of auditory congruity processing were assessed using voxel-based morphometry. Relative to healthy controls, both the bvFTD and SD groups had impaired semantic and emotional congruity processing (after taking auditory control task performance into account) and reduced affective integration of sounds into scenes. Grey matter correlates of auditory semantic congruity processing were identified in distributed regions encompassing prefrontal, parieto-temporal and insular areas and correlates of auditory emotional congruity in partly overlapping temporal, insular and striatal regions. Our findings suggest that decoding of auditory signal relatedness may probe a generic cognitive mechanism and neural architecture underpinning frontotemporal dementia syndromes.

1. Introduction

Natural sensory environments or scenes often convey a cacophonous mixture of signals. Successful decoding of such scenes depends on resolution of the sensory mixture to enable a coherent behavioural and emotional response. Competing or conflicting signals present an important challenge to this enterprise. Signal conflict (simultaneous activation of incompatible or divergent representations or associations, Botvinick et al., 2001) often requires modification of behavioural goals; an appropriate behavioural response depends on detecting the salient signal mismatch and decoding its semantic and emotional significance. Equally, accurate determination of signal similarities and congruence is essential to establish regularities in the environment that can guide future adaptive behaviours. Analysis of signal 'relatedness' (conflict versus congruence) and conflict resolution are integral to complex decision making and emotional responses, particularly in social contexts (Chan et al., 2012; Clark et al., 2015b; Moran et al., 2004).

In neurobiological terms, behavioural responses to sensory signal relatedness reflect the operation of hierarchically organised generative models (Cohen, 2014; Nazimek et al., 2013; Silvetti et al., 2014). These models form predictions about the environment based on current and previous sensory experience, detect unexpected or 'surprising' events as prediction errors and adjust behavioural output to minimise those errors (Friston, 2009; Moran et al., 2004). The underlying neural computations engage large-scale brain networks: these networks encompass posterior cortical areas that parse sensory traffic into component objects; medial fronto-parietal cortices that direct and control attention and the detection of salient sensory events according to behavioural context; antero-medial temporal areas that store previously learned knowledge and schemas about sensory objects and regularities; insular and prefrontal cortices that implement and assess violations in rule-based algorithms; and striatal and other subcortical structures that code emotional and physiological value (Christensen et al., 2011; Cohen, 2014; Dieguez-Risco et al., 2015; Dzafic et al., 2016; Gauvin et al., 2016; Groussard et al., 2010; Henderson et al., 2016; Jakuszeit et al., 2013; Klasen et al., 2011; Merkel et al., 2015; Michelon et al., 2003; Nazimek et al., 2013; Remy et al., 2014; Ridderinkhof et al., 2004; Rosenbloom et al., 2012; Silvetti et al., 2014; Watanabe et al., 2014), Within this distributed circuitry, separable mechanisms have been identified for the processing of semantic and affective congruence

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(Dieguez-Risco et al., 2015) and for elementary versus more abstract levels of incongruity decoding (Paavilainen, 2013).

On clinical as well as neuroanatomical grounds, abnormal processing of conflict and congruence is a candidate generic mechanism of disease phenotypes in the frontotemporal dementias (Warren et al., 2013). These diseases collectively constitute an important cause of young onset dementia and manifest clinically with diverse deficits of semantic, emotional and social signal decoding, particularly in the syndromes of behavioural variant frontotemporal dementia (bvFTD) and semantic dementia (SD) (Downey et al., 2015; Fumagalli and Priori, 2012; Irish et al., 2014; Kipps et al., 2009; Piwnica-Worms et al., 2010; Snowden et al., 2003; St Jacques et al., 2015; Warren et al., 2013). Although bvFTD is defined by early, prominent behavioural and emotional impairments while SD is defined by progressive, pan-modal impairment of semantic memory, these two syndromes substantially overlap, both clinically and neuroanatomically (Gorno-Tempini et al., 2011; Hodges and Patterson, 2007; Rascovsky et al., 2011; Warren et al., 2013). Key deficits in both syndromes may reflect impaired integration of context and perspective taking (Ibanez and Manes, 2012). Inability to reconcile different perspectives may contribute more specifically to loss of empathy and theory of mind (Baez et al., 2014; Irish et al., 2014; Kipps et al., 2009), reduced self-awareness (Sturm et al., 2013), aberrant resolution of moral and social dilemmas (Carr et al., 2015; Eslinger et al., 2007) and abnormally polarised behaviours (Clark and Warren, 2016). Defective recruitment of stored social and semantic schemas may reduce adherence to social regularities (Zahn et al., 2007) while impaired ability to modify behaviour in response to 'surprising' events may contribute to dysfunctional reward seeking and valuation (Dalton et al., 2012; Perry et al., 2014). Abnormal conflict monitoring has been documented early in bvFTD (Krueger et al., 2009) and it remains uncertain as to what extent this reflects more general executive dysfunction (Seer et al., 2015). Neuroanatomically, the candidate network substrates for processing signal relatedness overlap key areas of disease involvement in bvFTD and SD (Fletcher and Warren, 2011; Hodges and Patterson, 2007; Perry et al., 2014; Warren et al., 2013). Despite much clinical and neurobiological interest, fundamental or generic models and mechanisms that can capture the clinical and neuroanatomical heterogeneity of frontotemporal dementia are largely lacking. There would be considerable interest in identifying a model system that reflects important clinical deficits in these diseases, while at the same time allowing those deficits to be more easily understood, measured and tracked, with a view to the development and evaluation of therapies.

Nonverbal sound is one such attractive model sensory system, with particular resonance for frontotemporal dementia and the potentially unifying theme of abnormal conflict and congruence signalling. Signal prediction and detection of violated predictions are likely to be intrinsic to the analysis of auditory scenes, in line with the commonplace observation that sound events (such as 'things that go bump in the night') are often ambiguous and require active contextual decoding to prepare an appropriate behavioural response (Fletcher et al., 2016). The requirements for disambiguating competing sound sources, tracking of sound sources dynamically over time and linking sound percepts to stored semantic and emotional associations all impose heavy computational demands on neural processing mechanisms. Moreover, the fronto-temporo-parietal and subcortical brain networks that instantiate these mechanisms are selectively targeted by the disease process in frontotemporal dementias (Hardy et al., 2017; Warren et al., 2013). One might therefore predict abnormalities of sound signal decoding in these diseases and indeed, a range of a auditory deficits have been described, ranging from impaired electrophysiological responses to acoustic oddballs (Hughes et al., 2013) to complex cognitive and behavioural phenotypes (Downey et al., 2015; Fletcher et al., 2015a, 2016, 2015b; Hardy et al., 2016). Many of these phenotypic features might arise from impaired integration of auditory signals and impaired processing of signal mismatch. However, the relevant cognitive and neuroanatomical mechanisms have not been defined.

Here we addressed the processing of signal conflict and congruence in auditory environments in two canonical syndromes of frontotemporal dementia, bvFTD and SD relative to healthy older individuals. We designed a novel behavioural paradigm requiring decisions about auditory 'scenes', each comprising two competing sound sources in which the congruity or incongruity of the sources was varied along semantic (identity relatedness) and affective (emotional relatedness) dimensions independently. We constructed 'model' scenes that would simulate naturalistic processing of the kind entailed by real world listening while still allowing explicit manipulation of the stimulus parameters of interest. The stimulus dimensions of semantic and emotional congruity were anticipated to be particularly vulnerable to the target syndromes, based on an extensive clinical and neuropsychological literature in auditory and other cognitive domains (Hardy et al., 2017; Hodges and Patterson, 2007; Warren et al., 2013). Structural neuroanatomical associations of experimental task performance were assessed using voxel-based morphometry in the patient cohort.

We hypothesised firstly that both bvFTD and SD (relative to healthy older individuals) would be associated with impaired detection and affective valuation of auditory signal relatedness, given that these syndromes show qualitatively similar semantic and affective deficits when required to integrate information from social and other complex auditory signals (Downey et al., 2015; Fletcher et al., 2015a, 2016, 2015b; Hodges and Patterson, 2007; Rascovsky et al., 2007; Warren et al., 2013). We further hypothesised that these deficits would be evident after taking into account background auditory perceptual and general cognitive competence. We anticipated that the decoding of both semantic and affective auditory relatedness would have a neuroanatomical correlate in anterior temporal and insula cortical 'hubs' for processing signal salience based on prior expectations (Christensen et al., 2011; Groussard et al., 2010; Merkel et al., 2015; Nazimek et al., 2013; Remy et al., 2014; Watanabe et al., 2014). Finally, we hypothesised that the analysis of auditory semantic congruence would have an additional correlate in fronto-parietal cortices previously linked to processing of rule violations and conflict resolution (Chan et al., 2012; Groussard et al., 2010; Henderson et al., 2016; Jakuszeit et al., 2013; Paavilainen, 2013; Remy et al., 2014; Ridderinkhof et al., 2004; Rosenbloom et al., 2012; Strelnikov et al., 2006); while the analysis of auditory emotional congruence would have an additional subcortical correlate in striatal and mesial temporal structures previously linked to the processing of emotional congruence and associated reward value (Dzafic et al., 2016; Klasen et al., 2011; Schultz, 2013).

2. Methods

2.1. Participant groups

Twenty-nine consecutive patients fulfilling current consensus criteria for bvFTD ((Rascovsky et al., 2011); n = 19, mean age 64 years (standard deviation 7.2 years), three female) or SD ((Gorno-Tempini et al., 2011); n = 10, mean age 66.2 (6.3) years, four female) were recruited via a tertiary specialist cognitive clinic; 20 healthy older individuals (mean age 68.8 (5.3) years, 11 female) with no history of neurological or psychiatric illness also participated. None of the participants had a history of clinically relevant hearing loss. Demographic and general neuropsychological characteristics of the study cohort are summarised in Table 1. Syndromic diagnoses in the patient groups were corroborated with a comprehensive general neuropsychological assessment (Table 1). Genetic screening of the whole patient cohort revealed pathogenic mutations in eight patients in the bvFTD group (five *MAPT,* three *C9orf72*); no other pathogenic mutations were identified. CSF examination was performed in six patients with sporadic bvFTD and in five patients with SD: profiles of CSF neurodegeneration markers in these cases provided no evidence for underlying AD pathology based on local laboratory reference ranges (i.e., no patient had total CSF tau: