



Research report

Auditory hedonic phenotypes in dementia: A behavioural and neuroanatomical analysis

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ABSTRACT

Patients with dementia may exhibit abnormally altered liking for environmental sounds and music but such altered auditory hedonic responses have not been studied systematically. Here we addressed this issue in a cohort of 73 patients representing major canonical dementia syndromes (behavioural variant frontotemporal dementia (bvFTD), semantic dementia (SD), progressive nonfluent aphasia (PNFA) amnesic Alzheimer's disease (AD)) using a semi-structured caregiver behavioural questionnaire and voxel-based morphometry (VBM) of patients' brain MR images. Behavioural responses signalling abnormal aversion to environmental sounds, aversion to music or heightened pleasure in music ('musicophilia') occurred in around half of the cohort but showed clear syndromic and genetic segregation, occurring in most patients with bvFTD but infrequently in PNFA and more commonly in association with MAPT than C9orf72 mutations. Aversion to sounds was the exclusive auditory phenotype in AD whereas more complex phenotypes including musicophilia were common in bvFTD and SD. Auditory hedonic alterations correlated with grey matter loss in a common, distributed, right-lateralised network including antero-mesial temporal lobe, insula, anterior cingulate and nucleus accumbens. Our findings suggest that abnormalities of auditory hedonic processing are a significant issue in common dementias. Sounds may constitute a novel probe of brain mechanisms for emotional salience coding that are targeted by neurodegenerative disease.

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1. Introduction

Altered emotional responsiveness to salient sensory stimuli is a key issue in neurodegenerative diseases. From a clinical perspective, emotional dysregulation is likely to contribute to a wide spectrum of symptoms that impact the lives of patients

and their caregivers: examples range from abnormal responses to thermoregulatory and other basic homeostatic signals (Ahmed et al., 2014) to pathological seeking of rewarding stimuli such as food, sex or drugs (Perry et al., 2014; Whitwell et al., 2007; Woolley et al., 2007) and derangements of complex social behaviours (Clark, Downey, Golden, et al., 2014; Mahoney, Rohrer, Omar, Rossor, & Warren, 2011; Sturm et al., 2013).

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From a neurobiological perspective, such dysfunction illuminates critical neural mechanisms mediated by brain networks that are targeted by neurodegenerative pathologies (Zhou & Seeley, 2014). Altered emotional responses are a hallmark of diseases in the frontotemporal lobar degeneration (FTLD) spectrum, particularly in association with the syndromes led by behavioural disintegration (behavioural variant frontotemporal dementia, bvFTD) and semantic disintegration (semantic dementia, SD) (Duval et al., 2012; Hodges & Patterson, 2007; Rankin et al., 2009; Rohrer & Warren, 2010; Snowden et al., 2001). However, emotional disturbances may also be significant in other FTLD syndromes such as progressive nonfluent aphasia (PNFA) (Kumfor et al., 2011; Rohrer & Warren, 2011; Rohrer, Sauter, Scott, Rossor, & Warren, 2012) and with other neurodegenerative pathologies, notably Alzheimer's disease (AD) (Sturm et al., 2013). This phenotypic overlap reflects the involvement in these diseases of distributed fronto-temporal, parietal and subcortical circuitry previously implicated in the representation, decoding and evaluation of salient stimuli (Sescousse, Caldu, Segura, & Dreher, 2013).

In contrast to the better characterised phenotypes of language, perceptual and executive impairment, phenotypes of altered emotional responsiveness are difficult to capture using standard neuropsychological instruments and remain poorly defined in the dementias. This reflects the inherently complex organisation of emotional behaviour, which is often only partly accessible to explicit cognitive decoding and relies intimately on subjective states of emotional awareness or affect. Besides neuropsychological and psychophysical procedures, a complete characterisation of affective responses in patients with dementia requires detailed analysis of output behaviours, particularly those signalling pleasure or aversion. Furthermore, it is necessary to sample a wide range of stimuli and behaviours, as alterations of affective processing in neurodegenerative diseases may extend to categories of stimuli that lack primary biological reward value. The auditory domain is a particularly promising vehicle with which to explore affective abnormalities in these diseases, since sound encompasses a broad continuum of sensory signals ranging from the highly biologically or perceptually salient to the banal to the richly symbolic. A key example of the last is music: this essential abstract stimulus has been shown to engage reward circuitry extensively in the healthy brain (Blood & Zatorre, 2001; Blood, Zatorre, Bermudez, & Evans, 1999; Koelsch, 2014; Menon & Levitin, 2005; Salimpoor et al., 2013; Salimpoor, Zald, Zatorre, Dagher & McIntosh, 2015) and musical pleasure is associated with powerful autonomic responses (Gewe, Nagel, Kopiez, & Altenmüller, 2005). Musical pleasure is likely to depend heavily on factors such as familiarity, pattern recognition and predictability based on past experience (Koelsch, 2014; Salimpoor et al., 2015; Zatorre & Salimpoor, 2013): the integrative neural computations required are likely to be vulnerable in the dementias. Music may become the object of obsessional interest or 'musicophilia' in neurodegenerative syndromes (Fletcher, Downey, Witoonpanich, & Warren, 2013), and more generic abnormalities of affective responsiveness to hedonically neutral sounds also occur: for example, a substantial proportion of patients with SD exhibit increased sensitivity and aversion to everyday environmental noises (Mahoney, Rohrer, Goll, et al.,

2011). As the symptom profile of SD encompasses both heightened pleasure in music and aversion to environmental sounds, it is evident that changes in auditory hedonic responsiveness produced by neurodegenerative syndromes are likely to be complex and bi-directional. Neuroanatomical correlates of these symptoms have been described in auditory cortical and subcortical pathways, antero-mesial temporal and frontal reward circuitry (Fletcher et al., 2013; Mahoney, Rohrer, Goll, et al., 2011; Mahoney, Rohrer, Omar, Rossor & Warren, 2011). More generic alterations in affective and autonomic responses to emotional sounds have been described in various dementia syndromes (Fletcher et al., *in press-a*, *in press-b*). These observations underline the potential of sound to probe brain networks that mediate affective responses and are targeted by neurodegenerative diseases. However, phenotypes of altered affective response to sound and their brain bases have not been studied systematically across dementia syndromes.

Here we addressed this issue in cohorts of patients representing major canonical syndromes of FTLD and AD. Altered hedonic responses to nonverbal sound – increased pleasure, anhedonia or aversion to environmental sounds and music – in these diseases were indexed from patients' verbal and nonverbal behaviours, as recorded using a semi-structured caregiver questionnaire. The questionnaire also recorded any alterations in patients' sweet food preferences, in order to assess hedonic responses of sounds in relation to a hedonic behaviour that is commonly affected in dementia but linked to a primary biological reward (Perry et al., 2014; Whitwell et al., 2007; Woolley et al., 2007). Structural neuroanatomical substrates of abnormal auditory hedonic responses were assessed using voxel-based morphometry (VBM) of patients' brain MR images. Based on previous clinical evidence, we hypothesised that these neurodegenerative syndromes would produce a complex of auditory hedonic abnormalities with bi-directional shifts in the valuation of particular sound categories (environmental sound and music); and that such abnormalities would be more common in the syndromes of bvFTD and SD than other neurodegenerative syndromes, and would correlate with altered sweet food preference. We further hypothesised that altered auditory hedonic responsiveness would be associated with grey matter changes in a distributed brain network including areas previously implicated in encoding the affective salience of sounds and other sensory signals (in particular, insula and anterior cingulate cortex: Zhou & Seeley, 2014), evaluating their affective meaning (in particular, antero-mesial temporal lobe: Omar et al., 2011; Hsieh, Hornberger, Piguet, & Hodges, 2012) and representing their reward value (in particular, ventral striatum: Sescousse et al., 2013).

2. Methods

2.1. Patient characteristics

A cohort of 73 patients was recruited over a three-year interval via a tertiary cognitive disorders clinic. The cohort comprised 56 patients with a syndrome of FTLD (bvFTD, $n = 22$; SD, $n = 19$; PNFA, $n = 15$) and 17 patients with amnesic AD. All were diagnosed by an experienced cognitive neurologist and

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