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A physiological signature of sound meaning in dementia

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ABSTRACT

The meaning of sensory objects is often behaviourally and biologically salient and decoding of semantic salience is potentially vulnerable in dementia. However, it remains unclear how sensory semantic processing is linked to physiological mechanisms for coding object salience and how that linkage is affected by neurodegenerative diseases. Here we addressed this issue using the paradigm of complex sounds. We used pupillometry to compare physiological responses to real versus synthetic nonverbal sounds in patients with canonical dementia syndromes (behavioural variant frontotemporal dementia – bvFTD, semantic dementia – SD; progressive nonfluent aphasia – PNFA; typical Alzheimer's disease – AD) relative to healthy older individuals. Nonverbal auditory semantic competence was assessed using a novel within-modality sound classification task and neuroanatomical associations of pupillary responses were assessed using voxel-based morphometry (VBM) of patients' brain MR images. After taking affective stimulus factors into account, patients with SD and AD showed significantly increased pupil responses to real versus synthetic sounds relative to healthy controls. The bvFTD, SD and AD groups had a nonverbal auditory semantic deficit relative to healthy controls and nonverbal auditory semantic performance was inversely correlated with the magnitude of the enhanced pupil response to real versus synthetic sounds across the patient cohort. A region of interest analysis demonstrated neuroanatomical associations of overall pupil reactivity and differential pupil reactivity to sound semantic content in superior colliculus and left anterior temporal cortex respectively. Our findings suggest that autonomic coding of auditory semantic ambiguity in the setting of a damaged semantic system may constitute a novel physiological signature of neurodegenerative diseases.

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1. Introduction

Disambiguation of potentially relevant, 'salient' stimuli from the busy multisensory background is accomplished efficiently and largely automatically by the healthy brain. However, successful processing of sensory salience depends on a number of subprocesses: these include accurate parsing of the sensory environment, representation of particular sensory objects, assignment of emotional and reward value, and linkage to physiological and motor effector mechanisms that govern an appropriate behavioural response (Beissner, Meissner, Bar, & Napadow, 2013; Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Kirsch, Boucsein, & Baltissen, 1995; Zhou & Seeley, 2014). Each of these subprocesses entails complex neural computations that are likely a priori to be vulnerable to the effects of neurodegenerative pathologies. The canonical syndromes of frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) are associated with altered emotional, physiological and behavioural responses to salient sensory signals (Fletcher, Downey, et al., 2015a, in press; Fletcher, Nicholas, et al., 2015c, 2015d; Hoefer et al., 2008; Zhou & Seeley, 2014). These are most strikingly exemplified by the phenotypes of disrupted hedonic valuation and aberrant reward processing that characterise FTLD (Fletcher, Downey, et al., 2015a; Perry et al., 2014), though AD may also produce abnormalities of sensory salience coding (Fletcher, Downey, et al., 2015a, in press; Fletcher, Nicholas, et al., 2015c, 2015d). Such abnormalities further suggest a physiological substrate for the higher order disturbances of emotional and social cognition that frequently accompany these diseases (Downey et al., 2015; Kumfor & Piguet, 2012; Omar et al., 2011; Warren, Rohrer, & Rossor, 2013; Woolley et al., 2015), with implications for biomarker development and management strategies.

The salience of a sensory signal generally depends on attribution of its meaning and this is well illustrated in the often ambiguous realm of sounds. Perceptually similar sound sources can have very different biological implications (compare, for example, the rumble of thunder and the growl of a large predator). Auditory salience cues such as loudness, movement (looming) and affective valence are coded physiologically in pupillary and other autonomic responses (Fletcher, Nicholas, et al., 2015c, 2015d; Neuhoff, 2001) mediated by distributed cortico-subcortical brain networks (Beissner et al., 2013; Critchley et al., 2000; Mueller-Pfeiffer et al., 2014). In addition to these well recognised examples, auditory semantic ambiguity is also a candidate salience cue: there is a biological imperative to resolve the identity of potentially meaningful sounds, and the ability to do this efficiently and accurately is likely to have conferred survival and reproductive advantages during human evolution. In this context, 'potentially meaningful' sounds would include naturally occurring, spectrotemporally complex sounds sharing perceptual characteristics with animal (including conspecific) vocalisations. It might be predicted that the processing of such sounds would engage brain mechanisms for coding salience, particularly under adverse listening conditions where the identity of the sound source is difficult to determine. Coding such ambiguous sounds for salience would direct attentional and behavioural resources to the sound source so that its identity can be determined rapidly with an appropriate behavioural response. From a clinical perspective, diseases of the auditory pathways tend to render sounds more difficult to identify and 'adverse listening conditions' might also be produced by brain diseases that degrade central mechanisms of auditory semantic analysis: in this situation, the perceptual features of sounds will be coded more or less accurately but sounds will be ambiguous (and therefore, potentially salient) because the attribution of meaning to auditory percepts is impaired. However, it has not been established whether semantically significant or semantically ambiguous sounds have physiological salience correlates. In particular, the interaction of semantic and salience mechanisms has not been explored in neurodegenerative diseases that that might disrupt these mechanisms differentially.

Here we investigated physiological and neuroanatomical correlates of this putative 'semantic salience' response in a cohort of patients representing canonical dementia syndromes (semantic dementia – SD; behavioural variant frontotemporal dementia – bvFTD; progressive nonfluent aphasia – PNFA; typical amnestic AD) relative to healthy older controls. We studied patients representing a range of dementia syndromes in order to assess the extent to which putative salience responses might differentiate or transcend syndromic categories. Semantic deficits are not restricted to a particular syndrome: while SD is the paradigmatic disorder of the human semantic system (Lambon Ralph, Sage, Jones, & Mayberry, 2010), less severe or less consistent auditory and other semantic deficits have been documented in each of the other neurodegenerative syndromes included here (Golden et al., 2015; Goll, Crutch, Loo, et al., 2010, Goll et al., 2011; Hardy et al., 2015; Hsieh, Hornberger, Piguet, & Hodges, 2011). Moreover, these diseases have been shown to have distinct profiles of pupil reactivity to salient sounds (Fletcher, Nicholas, et al., 2015c, 2015d). We measured pupil responses to sounds that varied in semantic content, constituting two sound conditions: real nonverbal sounds with prior semantic associations and synthetic sounds that lacked any such associations. Pupil responses in these two sound conditions were compared and assessed in relation to nonverbal auditory semantic function in each group. Neuroanatomical correlates were determined using voxel-based morphometry (VBM) of patients' brain MR images. We hypothesised that healthy older individuals would show larger pupil responses to real than synthetic sounds and that the magnitude of this difference would vary inversely with nonverbal auditory semantic function across the patient cohort. In particular, we hypothesised an exaggerated pupil response to real sounds in the SD group, as severely degraded sound identification in these patients would preclude disambiguation of these potentially salient sound sources. We further hypothesised an anatomical correlate of this semantic salience response in anterior temporal cortex previously implicated in auditory semantic analysis (Golden et al., 2015; Goll, Ridgway, Crutch, Theunissen, & Warren, 2012; Hsieh et al., 2011) and in the central autonomic control network previously implicated in programming physiological salience responses (Critchley et al., 2000; Wang, Boehnke, Itti, & Munoz, 2014; Wang, Boehnke, White, & Munoz, 2012; Zhou & Seeley, 2014).