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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 1 (2015) 170-178

Alzheimer's & Dementia

Physiological phenotyping of dementias using emotional sounds

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Abstract

Introduction: Emotional behavioral disturbances are hallmarks of many dementias but their pathophysiology is poorly understood. Here we addressed this issue using the paradigm of emotionally salient sounds.

Methods: Pupil responses and affective valence ratings for nonverbal sounds of varying emotional salience were assessed in patients with behavioral variant frontotemporal dementia (bvFTD) (n = 14), semantic dementia (SD) (n = 10), progressive nonfluent aphasia (PNFA) (n = 12), and AD (n = 10) versus healthy age-matched individuals (n = 26).

Results: Referenced to healthy individuals, overall autonomic reactivity to sound was normal in Alzheimer's disease (AD) but reduced in other syndromes. Patients with bvFTD, SD, and AD showed altered coupling between pupillary and affective behavioral responses to emotionally salient sounds.

Discussion: Emotional sounds are a useful model system for analyzing how dementias affect the processing of salient environmental signals, with implications for defining pathophysiological mechanisms and novel biomarker development.

Keywords: Frontotemporal dementia; Alzheimer's disease; Emotion; Sound; Autonomic; Pupillometry

1. Introduction

Dementias are generally defined by progressive deterioration in cognitive function but often produce less well-characterized alterations in emotional, motivational, and social functions. These alterations are particularly early and significant in behavioral variant frontotemporal dementia (bvFTD) and semantic dementia (SD) within the frontotemporal lobar degeneration (FTLD) spectrum [1–8], and are probably underrecognized in progressive nonfluent-aphasia (PNFA) [9] and Alzheimer's disease (AD) [4,10–12]. However, although emotional disturbances are hallmarks of many dementias and potentially relevant to disease detection, tracking and therapy, the pathophysiology of disturbed emotion in dementia is poorly understood and challenging to measure objectively.

Particularly pertinent to the organization of emotional behaviors is the capacity to identify significant or "salient" objects and events in the external environment and to analyze the consequences of these for the individual's own homeostatic milieu. Emotionally salient stimuli may be linked to basic biological drives and are broadly relevant to social signaling, self-awareness, and reward seeking in a number of dementia syndromes [7,13–17]. Autonomic responses index perceptual, cognitive, and emotional salience of sensory signals and normally require integrated neural network activity [18]. The large-scale brain networks targeted by neurodegenerative proteinopathies [19–21] traverse brain structures previously implicated in emotional salience processing: these include prefrontal and cingulate cortices, insula, mesial temporal and striatolimbic structures that

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http://dx.doi.org/10.1016/j.dadm.2015.02.003

evaluate significant internal and external sensory events, and effector regulatory mechanisms in basal forebrain and dorsal brainstem [8,22,23]. Taken together, this evidence suggests that the detailed characterization of altered autonomic and behavioral responses to emotionally salient stimuli might provide a basis for understanding and measuring the complex behavioral effects of dementia diseases [8].

The domain of nonverbal sounds includes highly salient biological signals that produce autonomic and other physiological effects. Altered processing of nonverbal sounds has been documented in a range of dementia diseases [2,6,24–30]. However, little information is available concerning the physiological correlates of processing nonverbal sounds (or indeed, other sensory stimuli) as salient sensory signals. Although autonomic dysfunction has been described in dementias [31,32], few studies have assessed this systematically in relation to sensory salience coding. Patients with bvFTD and SD have been shown to have either normal or depressed autonomic reactivity to loud tones [13,33] and more complex auditory and multimodal stimuli [34,35] while autonomic reactivity may be retained in AD [33].

Here we took nonverbal sound as a model system to investigate systematically the physiological and behavioral correlates of processing sensory emotional salience in patients with canonical dementia syndromes. We used pupillometry to index autonomic (sympathetic) reactivity: compared with other candidate autonomic indices [36–38], pupil dilatation responses are relatively resistant to disease-associated movement and other artifacts, well preserved to auditory stimuli in healthy older individuals [39], track neural responses closely [23,40,41], and have social behavioral resonance [42,43]. We used affective valence ratings to index the behavioral processing of auditory emotional salience. Three linked experimental hypotheses were tested: first, that dementia syndromes show profiles of altered physiological and affective responses to nonverbal sounds; second, that these syndromic profiles reveal dissociations between autonomic and affective behavioral indices of auditory emotional salience; and finally (and more specifically), these salience signatures stratify dementia syndromes associated with more severe clinical derangements of emotional processing (represented by bvFTD and SD) from clinically associated syndromes with the relative preservation of emotional responses (represented by PNFA and AD).

2. Methods

2.1. Participants

Forty-six patients fulfilling current consensus diagnostic criteria for dementia syndromes (14 bvFTD, 12 PNFA, 10 SD, 10 typical amnestic AD [5,44,45]); and 26 healthy age-matched individuals with no history of neurological or psychiatric illness participated. No participant had a clinical history of hearing loss or pupillary disease or clinical evidence of a mood disorder at the time of participation; to assess any effect from peripheral hearing function on experimental performance, screening pure tone audiometry was conducted in each group using a previously described procedure [46]. Ten patients with bvFTD had a genetic diagnosis (five pathogenic C9orf72 mutations, five MAPT mutations). Cerebrospinal fluid tau and beta-amyloid assays (available for a further 23 patients: six AD, seven bvFTD, four SD, six PNFA) and Florbetapir PET brain imaging (available for nine patients: six SD, three PNFA) further corroborated the clinical diagnoses (CSF total tau: beta-amyloid ratio >1 in all six AD cases and two PNFA cases, ratio <1 in other cases; Florbetapir-PET negative for amyloid deposition in available SD and PNFA cases). At the time of their participation, 18 patients were receiving treatment with acetyl-cholinesterase inhibitors (nine AD, six bvFTD, one SD, two PNFA), 12 with antidepressants (four bvFTD, three SD, three PNFA, two AD), and 2 with neuroleptic agents (both bvFTD).

All participants had a comprehensive assessment of general neuropsychological functions and patients had volumetric brain MRI in support of their syndromic diagnosis. In addition, nonverbal auditory semantic function was assessed in all participants using a novel semantic classification (matching) task on paired sounds that did not require verbal or other cross-modal labeling (see online Supplementary Material). General demographic and neuropsychological data for participant groups are summarized in Table 1. The experimental groups were well matched for age; males were significantly overrepresented in the byFTD group. Mean symptom duration was longer in the bvFTD group than other patient groups, reflecting the wide variation in disease tempo of patients with bvFTD; the syndromic groups were otherwise similar in overall disease stage. Average Mini-Mental State Examination (MMSE) was lower in the SD and AD groups than the healthy control group, but did not differ between patient groups.

All participants gave informed consent in accord with the principles laid down in the Declaration of Helsinki.

2.2. Experimental stimuli and procedures

2.2.1. Sound stimuli

Based on affective valence and identifiability ratings obtained in a pilot experiment on a set of 180 common nonverbal sounds presented to healthy young adults, a subset of highly identifiable (environmental, animal, human, and mechanical) sound stimuli were selected, representing three emotional valence categories: "unpleasant" (e.g., a person spitting, a mosquito), "neutral" (e.g., telephone, throat clearing), and "pleasant" (e.g., baby laughing, stream burbling). Sound valence categories had similar overall identifiability ratings and sounds in each valence category were matched for other psychoacoustic