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Functional neuroanatomy of speech signal decoding in primary progressive aphasias

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ABSTRACT

The pathophysiology of primary progressive aphasias remains poorly understood. Here, we addressed this issue using activation fMRI in a cohort of 27 patients with primary progressive aphasia (nonfluent, semantic, and logopenic variants) versus 15 healthy controls. Participants listened passively to sequences of spoken syllables in which we manipulated 3-key auditory speech signal characteristics: temporal regularity, phonemic spectral structure, and pitch sequence entropy. Relative to healthy controls, nonfluent variant patients showed reduced activation of medial Heschl's gyrus in response to any auditory stimulation and reduced activation of anterior cingulate to temporal irregularity. Semantic variant patients had relatively reduced activation of caudate and anterior cingulate in response to increased entropy. Logopenic variant patients showed reduced activation of posterior superior temporal cortex to phonemic spectral structure. Taken together, our findings suggest that impaired processing of core speech signal attributes may drive particular progressive aphasia syndromes and could index a generic physiological mechanism of reduced computational efficiency relevant to all these syndromes, with implications for development of new biomarkers and therapeutic interventions.

1. Introduction

The primary progressive aphasias (PPAs) have collectively helped established the paradigm of selective neural vulnerability to neurodegenerative pathologies (Mesulam, 1982; Mesulam et al., 2014). These disorders have been characterized as 'language-led dementias', comprising 3 canonical syndromes (Gorno-Tempini et al., 2011): nonfluent variant PPA (nfvPPA), presenting with impaired speech production and/or agrammatism; semantic variant PPA (svPPA), presenting with impaired single-word comprehension and vocabulary loss due to progressive erosion of semantic memory; and logopenic variant PPA (lvPPA), presenting with word-finding difficulty and impaired auditory verbal working memory. These syndromes have separable though partly overlapping neuroanatomical and pathological substrates: nfvPPA principally targets a peri-Sylvian brain network and svPPA an anterior temporal lobe network and both syndromes are generally underpinned by non-Alzheimer proteinopathies in the frontotemporal lobar degeneration spectrum (Grossman, 2012; Hodges and Patterson, 2007; Rohrer et al., 2011); whereas lvPPA targets a network centered on the temporo-parietal junction and is most often underpinned by Alzheimer pathology (Gorno-Tempini et al., 2008; Rabinovici et al., 2008; Rohrer et al., 2010).

The pathophysiological basis of PPA remains to be fully defined (Grossman, 2012; Mesulam et al., 2014). Language impairment is the dominant clinical consideration in PPA and enshrined in current consensus diagnostic criteria (Gorno-Tempini et al., 2011). However, a substantial proportion of cases of PPA do not fall clearly into current diagnostic categories, whereas similar linguistic deficits may be prominent in other dementia syndromes such as bvFTD (Hardy et al., 2015; Rohrer and Warren, 2016). A number of studies have documented profiles of nonverbal auditory deficits associated with PPA syndromes (Bozeat et al., 2000; Fletcher et al., 2015; Golden et al.,

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2015, 2016; Goll et al., 2010, 2011; Grube et al., 2016; Hailstone et al., 2011, 2012; Hardy et al., 2016; Rohrer et al., 2012). Indeed, presentations with word deafness and auditory agnosia have been well-attested since the earliest descriptions of PPA (Fletcher et al., 2013; Mesulam, 1982; Serieux, 1893; Uttner et al., 2006). This is likely to reflect shared neural resources for processing speech and other complex auditory signals, consistent with evidence in the healthy brain (Binder et al., 2000; Goll et al., 2012; Griffiths and Warren, 2002; Hardy et al., 2016; Warren and Griffiths, 2003). It has been proposed that generic deficits of auditory signal processing may be intrinsic to PPA syndromes and could underpin neurolinguistic impairment in these syndromes (Goll et al., 2010; Grube et al., 2016).

Functional MRI (fMRI) has delineated altered (including compensatory) patterns of cerebral activation in PPA cohorts relative to healthy controls (Goll et al., 2012; Nelissen et al., 2011; Vandenbulcke et al., 2005; Wilson et al., 2010, 2016). However, this technique has not been used previously to identify fundamental mechanisms of abnormal information processing in PPA. Here, we used activation fMRI to deconstruct the functional neuroanatomy of speech perception in PPA into component neural mechanisms that process core attributes of speech signals. We studied a cohort of patients representing all major PPA syndromes in relation to healthy older individuals. In experimental stimuli based on sequences of spoken syllables, we manipulated 3 generic auditory speech signal characteristics relevant to previously documented neurolinguistic deficits in PPA syndromes: temporal regularity, phonemic structure (presence of intelligible phonemes), and average signal information content (entropy).

Analysis of temporal structure is crucial for speech segmentation (and therefore lexical access) in healthy individuals (Dilley and McAuley, 2008; Dilley et al., 2010) and vulnerable particularly in nfvPPA (Grube et al., 2016). In this experiment, we varied syllabic timing such that the interval between syllables was either regular (isochronous) or irregular (anisochronous). Phonemes are the smallest intelligible units of spoken language and constitute a special category of auditory 'objects' (Griffiths and Warren, 2004), defined by specific combinations of spectrotemporal acoustic features: phonemic processing deficits are prominent in lvPPA and nfvPPA (Hailstone et al., 2012; Hardy et al., 2015; Henry et al., 2016; Rohrer et al., 2010). Here, we manipulated higher-order spectral structure that distinguishes natural (intelligible) phonemes from complex synthetic (unintelligible) speech-like sounds (Blesser, 1972), to target a universal neural mechanism of phoneme detection relevant to any language. 'Entropy' is a concept derived from information theory describing the average amount of information carried by any signal (Overath et al., 2007): it measures signal unpredictability, in the sense that an unpredictable signal is less 'redundant' and therefore conveys more information (henceforth in this article, we use information in this technical sense). We manipulated the information content (entropy) of our experimental stimuli by varying the predictability of pitch patterns across successive syllables in a sequence, a generic characteristic related to speech prosody but not bound to the prosodic conventions of any particular language. Deficits of pitch pattern processing have been documented in all major PPA syndromes (Golden et al., 2015, 2016; Hsieh et al., 2011; Rohrer et al., 2012): however, the experimental manipulation used here (unlike those previously employed) was designed to index a brain mechanism responsible for computing the overall statistics of an auditory object (the 'melody' of the syllable sequence). An analogous computational mechanism has been invoked to account for the profile of evolving object recognition deficits across sensory modalities in svPPA (Lambon Ralph et al., 2010).

To assess the effect of PPA syndromes on these generic mechanisms of speech signal analysis relatively uncontaminated by executive, working memory or other extraneous task demands (Hickok and Poeppel, 2007; Rauschecker and Scott, 2009), we adopted a passive listening fMRI paradigm with 'sparse' image acquisition (presentation of auditory stimuli interleaved with scanner noise). We hypothesized that PPA syndromes would have separable functional neuroanatomical signatures of abnormal speech signal decoding relative to healthy older individuals. Based on available evidence in PPA and in the healthy brain, we further hypothesized that nfvPPA and lvPPA would show abnormal processing of speech signal isochrony and phonemic structure (Grube et al., 2016; Hailstone et al., 2012; Hardy et al., 2015; Henry et al., 2016; Rohrer et al., 2010), whereas svPPA would show abnormal processing of entropy as an auditory object statistic (Golden et al., 2015; Hsieh et al., 2011; Lambon Ralph et al., 2010). Finally, we hypothesized that the functional substrates of isochrony and entropy processing would lie within a distributed network including posterior temporal, cingulate and striatal structures, previously implicated in the analysis of auditory regularity and predictability (Cope et al., 2014; Griffiths and Warren, 2002; Ide et al., 2013; Overath et al., 2007); whereas the substrate of phoneme processing would lie within superior temporal cortex, previously implicated in the analysis of phonemic structure (Hickok and Poeppel, 2007; Liberman and Mattingly, 1989; Rauschecker and Scott, 2009; Scott et al., 2000).

2. Materials and methods

2.1. Participants

The patient cohort comprised 12 patients with nfvPPA (5 female; mean age 70.9 years), 9 patients with svPPA (3 female; mean age 62.3 years), and 6 patients with lvPPA (2 female; mean age 62.7 years), each fulfilling consensus criteria for the respective syndromic diagnosis (Gorno-Tempini et al., 2011) and recruited via a specialist cognitive disorders clinic. Brain magnetic resonance imaging (MRI) findings corroborated the syndromic diagnosis in each case; no patient had radiological evidence of significant comorbid cerebrovascular damage. Cerebrospinal fluid tau/abeta profiles were available for 5 of the 6 patients with lvPPA, all of which were consistent with Alzheimer's pathology based on local reference ranges (total tau: beta-amyloid$_{1-42}$ ratio >1). Fifteen healthy older individuals (8 female; mean age 68.8 $\pm$ 4.5 years) with no history of neurological or psychiatric illness also participated. All participants had a comprehensive general neuropsychological assessment. Demographic, clinical, and neuropsychological characteristics of participant groups are summarized in Table 1. Peripheral hearing function was assessed in all participants using pure tone audiometry (procedural details in Supplementary Material on-line).

All participants gave informed consent, and the ethical approval for the study was granted by the National Hospital for Neurology and Neurosurgery and University College London Research Ethics Committees, following Declaration of Helsinki guidelines.

2.2. Experimental stimuli

The stimuli presented in the fMRI experiment were based on sequences of spoken syllables comprising consonant-vowel or vowel-consonant phoneme combinations, recorded in a standard Southern English accent by a young adult male speaker. The syllables 'af', 'ba', 'da', 'mo', 'om', 'or', 'po', and 'ro' were selected for high intelligibility and identifiability, based on pilot testing in 5 young adult listeners in our laboratory. In MATLAB R2012a (https://uk.mathworks.com/), recorded syllables were each edited to duration 240 msec and concatenated with random ordering into