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Distinctive pathological mechanisms involved in primary progressive aphasias

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ABSTRACT

Primary progressive aphasia (PPA) comprises a heterogeneous group of neurodegenerative conditions that can be classified in three cliniconeuroanatomic syndromes. Limited information exists, however, about patterns of neuropathologic spreading and microscopic changes underpinning each syndrome. We performed an analysis of a longitudinal in vivo cohort and a postmortem PPA cohort to investigate neurodegeneration over time and to quantify microscopic changes in key language brain areas. The longitudinal analyses demonstrated distinctive patterns of topological extension of brain atrophy. Although semantic variant (sv-PPA) showed an eccentric pattern, nonfluent and/or agrammatic (nfv-PPA) and logopenic (lv-PPA) variants showed additional multifocal extension. The quantitative pathology showed that sv-PPA had neuronal loss and thinning in BA 38, whereas nfv-PPA showed thinning in BA 44/45 and evidence of microscopic involvement in BA 40/22. Although lv-PPA showed neuronal loss focused on BA 40/22, imaging results demonstrated widespread left-sided brain atrophy. These analyses provide an account of the pathologic process whereby each variant has stereotypical patterns of brain atrophy extension, which is largely determined by the specific pathologic type.

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1. Introduction

It is well established that the language network can be selectively targeted by neurodegeneration and causes progressive, albeit circumscribed, language deterioration (Mesulam, 1982). This condition, formally known as primary progressive aphasia (PPA) (Mesulam, 2001), can be caused by different pathologies, each of which tends to exhibit specific patterns of linguistic deficits and a characteristic distribution of brain atrophy. Based on the presence of core language and speech deficits, current international consensus criteria propose three clinical variants: semantic (sv-PPA), nonfluent and/or agrammatic (nfv-PPA), and logopenic (lv-PPA) (Gorno-Tempini et al., 2011). Cases with semantic variant display marked anomia and difficulties in recognizing words, objects, people, and tunes, deficits attributed to degradation of semantic representations (Hodges et al., 2010; Hsieh et al., 2011). By contrast, cases with nfv-PPA show preservation of semantic knowledge but effortful

speech, loss of prosody, and articulatory errors, all of which result from disruption of motor planning or speech execution (Croot et al., 2012; Josephs et al., 2013b) or, alternatively, present with morphosyntactical deficits and omission of function words leading to agrammatism and oversimplification of language output (Wilson et al., 2010a, 2010b). In contrast to the other variants, logopenic variant (lv-PPA) cases display relative preservation of semantic representations and motor aspects of speech, but instead they show marked word-finding difficulties, anomia and striking difficulties in sentence repetition (Gorno-Tempini et al., 2004, 2008).

Evidence from neuroimaging studies implicates distinct left hemispheric brain regions as responsible for the core language deficits in each of the variants of PPA. In sv-PPA, the temporal pole (BA 38) is strongly correlated with semantic processing (Mesulam et al., 2009; Mummery et al., 2000). Reduced speech fluency in nfv-PPA is correlated with cortical thinning in the left inferior frontal cortex (BA 44/45) (Gunawardena et al., 2010; Sapolsky et al., 2010; Wilson et al., 2010a, 2013b). The deficits of impaired naming and reduced sentence repetition in lv-PPA have been correlated with cortical thinning in the supramarginal gyrus (BA 40) and superior temporal gyrus (BA 22), respectively (Leyton et al., 2012). In

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accordance with these language and neuroanatomic relations, current criteria establish imaging-supported diagnostic findings whereby brain atrophy in each variant tends to be focused on those key anatomic regions (Gorno-Tempini et al., 2011).

Although most sv-PPA cases demonstrate transactive response DNA-binding protein of 43 KDa (TDP-43) positive inclusions (Chare et al., 2014; Harris et al., 2013; Hodges et al., 2010), a large proportion of nfv-PPA cases show tau positive inclusions (Chare et al., 2014; Harris et al., 2013; Josephs et al., 2006), and lv-PPA cases are strongly associated with Alzheimer pathology (Chare et al., 2014; Harris et al., 2013; Mesulam et al., 2008). These clinical, neuroanatomic, and pathologic relations, however, are not strict, and a proportion of cases reveal unexpected associations. The lack of clinicopathologic correlation is particularly problematic in Alzheimer's disease (AD), although present in most lv-PPA cases, it can also be found in the other variants, especially nfv-PPA (Chare et al., 2014; Harris et al., 2013; Mesulam et al., 2014, 2008).

It has been argued that a major source of discrepancy stems from the insufficiently specific diagnostic criteria (Sajjadi et al., 2012), but it is possible that a more diffuse pathologic involvement associated with AD causes more pervasive language deficits with less defined and more overlapping linguistic syndromes than those observed in other PPA variants. In keeping with this argument, unclassifiable PPA cases with mixed linguistic deficits are more likely to have Alzheimer pathology (Mesulam et al., 2014; Sajjadi et al., 2014).

Although there have been a number of quantitative imaging studies comparing the PPA variants (Gorno-Tempini et al., 2004; Mesulam et al., 2012; Rohrer et al., 2009; Sapolsky et al., 2010; Wicklund et al., 2014), relatively little is known about the distribution of pathology observed in the three variants of PPA. Quantitative pathology methods could contribute to understanding clinical–pathologic discrepancies, as these methods can detect microscopic changes overlooked by structural imaging methods. Although structural imaging studies estimate the severity of atrophy irrespective of pathologic changes, quantitative pathology provides a direct estimation of neuronal loss by quantifying neuronal densities and cortical thicknesses as well as the anatomic distribution of specific pathologic markers, such as amyloid plaques and neurofibrillary tangles. Another issue hindering our understanding is the progressive nature of neurodegeneration. A clear syndrome-pathologic delineation at onset can become blurred as pathology propagates throughout the language network (Rohrer et al., 2012). The characterization of anatomic changes over time can contribute to deciphering the biological behavior of each variant. Although imaging evidence shows that neurodegeneration gradually erodes the language network irrespective of the specific pathology (Rogalski et al., 2011), pathologic evidence suggests that each pathologic subtype follows a stereotypic pattern of progression (Braak and Braak, 1991; Brettschneider et al., 2014). In view of this conflicting evidence, this study aimed to analyze the pattern of progression of atrophy in a clinical cohort, combined with quantitative pathologic data obtained from a postmortem sample of PPA. As such, our primary goal was to analyze changes in neuronal density and cortical thickness of the core regions affected in each PPA variant. The pathologic study was complemented with the analysis of cortical thickness of those regions in the in vivo cohort. A secondary goal was to track structural changes in the longitudinal cohort to estimate the pattern of progression in each variant.

2. Materials and methods

2.1. Participants

2.1.1. In vivo cohort
Consecutive participants enrolled at Frontier between July 2008 and September 2014 with clinical diagnosis of primary progressive aphasia (PPA) (Mesulam, 2001) and at least one annual follow-up was selected. Cases were classified in any of the three clinical variants of primary progressive aphasia according to current consensus criteria (Gorno-Tempini et al., 2011) based on a semi-structured language assessment, Primary Progressive Aphasia Scale, detailed elsewhere (Leyton et al., 2011). We excluded (1) participants with limited English proficiency (proficiency was defined as those who had English as a second language and had lived and worked in an English speaking country for over 10 years); (2) participants with advanced disease who were essentially mute or had Addenbrooke Cognitive Examination revised (Mioshi et al., 2006) under 50; (3) participants who developed concomitant motor neuron disease, significant extrapyramidal features or had a past history of stroke, epilepsy, alcoholism, or significant traumatic brain injury; (4) participants with abnormalities on MRI brain scan, other than atrophy; (5) participants without an adequate MRI. As a result, 39 (sv-PPA = 13, nfv-PPA = 16, lv-PPA = 10) patients were included in the study. Healthy control subjects (n = 15) with at least one annual follow-up were selected from the volunteer panel of Frontier and matched case by case so that all groups could have equivalent gender distribution ($X^2_{(3)}$ = 2.6, p = 0.5), age (overall mean ±standard deviation, 68.0 ± 7.9, $F_{(3,53)}$= 2,5 p = 0.07), level of education (13.5 ± 3.1 years, $F_{(3,53)}$ = 0.2, p = 0.9), and time elapsed between baseline and follow-up visits (1.8 ± 0.7 years, $F_{(3,53)}$ = 1.1, p = 0.37). The study received approval from the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales Human Research Ethics committees.

2.1.2. Postmortem cohort
Brain samples of participants with initial clinical diagnosis of PPA were sourced from two brain banks, Cambridge (n = 19) and Sydney (n = 3), with consent from the families for tissue donation at death and institutional ethics approvals. Patients were diagnosed in life by an experienced clinician after a medical interview, an informant history, and when it was available, cognitive testing. This clinical information was then analyzed so that all cases could be retrospectively classified into any of the clinical variants defined by current criteria (Gorno-Tempini et al., 2011) as described previously (Chare et al., 2014). As a result, the pathologic sample was classified in 7 lv-PPA, 7 nfv-PPA, and 8 sv-PPA cases, plus 7 normal controls, all of which were matched for age ($F_{(3,28)}$ = 0.3, p = 0.9) and sex distribution ($\chi^2_{(3)}$ = 4.3, p = 0.2). The postmortem interval of the whole pathologic sample was 23 h on average (range: 4–72 h; mean ±standard deviation for controls = 15 ± 7; for sv-PPA = 28 ± 21; for nfv-PPA = 20 ± 18 and for lv-PPA=30 ± 21, $F_{(3,25)}$ = 1.0, p = 0.4). Demographic features of both cohorts are displayed in Table 1.

2.2. Neuropsychological and language assessment

Participants in the in vivo cohort underwent a thorough clinical examination, routine neuropsychologic and language evaluation. The neuropsychological evaluation included Addenbrooke Cognitive Examination revised (Mioshi et al., 2006), which is a cognitive screening test that assesses attention, orientation, memory, verbal fluency, language, and visuospatial abilities. Other neuropsychological tasks included the verbal and/or auditory digit span task from the WAIS-III (Wilde et al., 2004); Trail Making Test, time for Trial A and Trial B (Reitan, 1955); Rey-Osterrieth Complex Figure Task, scores for copy and retrieval after 3 minutes (Meyers and Meyers, 1995), were included. Finally, a letter fluency task was scored as the total number of words produced for F, A, and S combined (Controlled Oral Word Association Test) (Strauss and Esther, 2006). Language tasks included the Sydney Language Battery, which is a single-word battery comprised a set of 30 colored pictures to be named, word comprehension, repetition of