Neurobiology of Aging 34 (2013) 1687–1699

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

White matter tract signatures of the progressive aphasias

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ARTICLE INFO

Article history:
Received 30 July 2012
Received in revised form 30 October 2012
Accepted 3 December 2012
Available online 9 January 2013

Keywords:
Primary progressive aphasia
DTI
Networks
White matter

ABSTRACT

The primary progressive aphasias (PPA) are a heterogeneous group of language-led neurodegenerative diseases resulting from large-scale brain network degeneration. White matter (WM) pathways bind networks together, and might therefore hold information about PPA pathogenesis. Here we used diffusion tensor imaging and tract-based spatial statistics to compare WM tract changes between PPA syndromes and with respect to Alzheimer's disease and healthy controls in 33 patients with PPA (13 nonfluent/agrammatic PPA); 10 logopenic variant PPA; and 10 semantic variant PPA. Nonfluent/agrammatic PPA was associated with predominantly left-sided and anterior tract alterations including uncinate fasciculus (UF) and subcortical projections; semantic variant PPA with bilateral alterations in inferior longitudinal fasciculus and UF; and logopenic variant PPA with bilateral but predominantly left-sided alterations in inferior longitudinal fasciculus, UF, superior longitudinal fasciculus, and subcortical projections. Tract alterations were more extensive than gray matter alterations, and the extent of alteration across tracts and PPA syndromes varied between diffusivity metrics. These WM signatures of PPA syndromes illustrate the selective vulnerability of brain language networks in these diseases and might have some pathologic specificity.

1. Introduction

The primary progressive aphasias (PPA) or 'language-led dementias' are important on clinical and neurobiological grounds (Gorno-Tempini et al., 2011; Grossman, 2010; Rohrer et al., 2010c). Clinically, PPA is associated with the selective but relentless erosion of language functions; and neurobiologically PPA illustrates regional vulnerability of brain language systems to neurodegenerative pathologies that are collectively characterized by abnormal protein accumulation. The spectrum of PPA is clinically, anatomically, and pathologically heterogeneous (Grossman, 2010). The canonical PPA syndromes comprise semantic variant PPA (sv-PPA), characterized by impaired knowledge of the meaning of words and objects in association with focal predominantly left anterior temporal lobe atrophy; nonfluent/agrammatic variant PPA (nv-PPA), characterized by speech production failure with apraxia of speech and/or agrammatism, associated with predominantly left-sided peri-Sylvian atrophy; and logopenic variant PPA (lv-PPA), characterized by prolonged word-finding pauses and impaired phonological memory without agrammatism, associated with predominantly left-sided temporo-parietal atrophy (Gorno-Tempini et al., 2011; Rohrer et al., 2009, 2010b).

Despite the recent formulation of new consensus diagnostic criteria for PPA (Gorno-Tempini et al., 2011), substantial nosological difficulties remain (Knibb et al., 2006). These include the frequent occurrence of overlap syndromes, clinicoanatomical convergence between syndromic subtypes and pathological heterogeneity (Rogalski et al., 2011a; Rohrer et al., 2008, 2011). A recent wealth of genetic and neuropathological data has enabled certain clinical PPA phenotypes to be correlated with particular pathological substrates: for example, sv-PPA is predominantly associated with TAR DNA-binding protein 43 (TDP-43) type C pathology and lv-PPA with Alzheimer's disease (AD) pathology (Grossman, 2010; Rohrer et al., 2011; Whitwell and Josephs, 2011). However, despite these advances, predicting tissue pathology or indeed making an accurate clinical diagnosis remains challenging for the diseases in the PPA spectrum. This is compounded by a paucity of robust in vivo biomarkers to detect disease onset and track disease progression. These issues in turn present challenges for planning future trials of disease-modifying therapies in PPA: such trials are likely to target specific pathologies and to seek to initiate treatments early in the disease course to minimize cognitive decline.

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http://dx.doi.org/10.1016/j.neurobiolaging.2012.12.002

The recent identification of changes in large-scale intrinsic connectivity networks associated with neurodegenerative disease syndromes (Greicius et al., 2004; Seeley et al., 2009) suggests a potentially powerful framework for understanding the regionally-specific but distributed effects of PPA diseases. White matter (WM) tracts bind cortical hubs within neural networks, and WM tract changes are therefore likely to hold important information about brain network disintegration in neurodegenerative pathologies. However, though substantial evidence has been amassed concerning regional cortical profiles of PPA (Gorno-Tempini et al., 2004; Josephs et al., 2006; Mummery et al., 2000; Pereira et al., 2009; Rohrer et al., 2009, 2010b), relatively little information is available concerning changes in WM tracts within brain language networks produced by neurodegenerative disease (Agosta et al., 2010; Whitwell et al., 2010; Zhang et al., 2009). Previous WM tract studies in PPA (Acosta-Cabronero et al., 2011; Agosta et al., 2010, 2011; Galantucci et al., 2011; Schwindt et al., 2011) have shown considerable anatomic and methodological variability. There remain few detailed comparisons between PPA subtypes and other neurodegenerative diseases, and between gray matter (GM) and WM changes in these diseases. Besides facilitating diagnosis and tracking of PPA (Larsson et al., 2004; Schmierer et al., 2007) identification of WM tract signatures of PPA syndromes might improve our understanding of the pathophysiology of network disintegration in these diseases and could yield important insights into the molecular organization of vulnerable language networks (Raj et al., 2012; Warren et al., 2012; Zhou et al., 2012).

Here we set out to identify profiles of white matter tract degeneration in each of the canonical clinical subtypes of PPA using diffusion tensor imaging (DTI) with several diffusivity metrics and an anatomically unrestricted tract-based statistical approach. We hypothesized that characteristic signatures of WM tract degeneration underpin each PPA subtype within the distributed language network. We further hypothesized that these signatures distinguish PPA syndromes from each other and from other neurodegenerative diseases, in line with a core role for specific network disintegration in the pathogenesis of PPA.

2. Methods

2.1. Subjects

Consecutive patients fulfilling current consensus criteria (Gorno-Tempini et al., 2011) for a diagnosis of PPA were recruited from the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery. Subjects underwent a structured clinical and neurolinguistic assessment and structural magnetic resonance imaging (MRI) to exclude significant WM disease or other focal cerebral lesions. For purposes of syndrome definition, a general neuropsychological assessment using standardized tests was performed. Behavioral tests are described in more detail in the Supplementary data (see "Description of behavioural tests"). Demographic and neuropsychological data were analyzed statistically in STATA 10 (Statacorp) using Student *t* test and Wilcoxin rank-sum tests of significance. In addition, cerebrospinal fluid (CSF) data (if available) were analyzed to assess the extent to which particular syndromes were likely to have underlying AD (versus non-AD) pathology. Total CSF tau (a measure of neuronal loss, as a nonspecific accompaniment of neurodegeneration) and CSF amyloid-beta$_{1-42}$ (Aß$_{1-42}$; a measure of amyloid deposition specific for AD pathology) were measured (Innotest platforms, Innogenetics, Ghent, Belgium). Local reference ranges for tau and Aß$_{1-42}$ were used to assess the likelihood of underlying AD versus non-AD pathologies; cases deemed to have probable underlying AD pathology had tau >307 pg/mL and Aß$_{1-42}$ <325 pg/mL (cutoffs derived from local data with 85% sensitivity for AD).

Ethical approval for the study was obtained from the local institutional ethics committee and all subjects gave written informed consent to participate in accordance with the Declaration of Helsinki.

2.2. MRI acquisition

Brain MRI data were acquired for all subjects on a Siemens Trio 3T MRI scanner using a 32-channel phased array head-coil (Siemens, Erlangen, Germany). Two 64-direction DTI sequences were acquired with a single shot, spin-echo echo planar imaging sequence (field of view: 240 mm; matrix: 96 × 96; yielding an isotropic voxel size of 2.5 × 2.5 × 2.5 mm; 55 contiguous axial slices; repetition time: 6800 ms; echo time: 91 ms; b value: 1000 s/mm^2), augmented with parallel imaging acceleration to reduce susceptibility artifact. Nine sequences without diffusion weighting were acquired (b = 0 s/mm^2). A sagittal 3-D magnetization prepared rapid gradient echo T1 weighted volumetric MRI (echo time/repetition time/inversion time = 2.9/2200/900 ms, dimensions of 256 × 256 × 208, voxel size of 1.1 × 1.1 × 1.1 mm) and a coronal fluid-attenuated inversion recovery sequence were acquired. For all subjects, volumetric MRI, DTI, and fluid-attenuated inversion recovery sequences were assessed visually in all planes to ensure adequate coverage and to exclude artifacts, unexpected pathology, or significant motion.

2.3. Diffusion image analysis

Raw diffusion weighted images were affine-aligned to the first corresponding b0 image using a linear image registration tool (FLIRT v5.5) within the FMRIB Software Library (FSL v4.1.5) (Cook et al., 2006; Smith et al., 2004). DTI volumes were then combined for tensor fitting using CAMINO and the tensor eigenvalues (λ1, λ2, and λ3; where axial diffusivity, AX = λ1), radial diffusivity (RD = (λ2 + λ3)/2), trace diffusivity, (TR = λ1 + λ2 + λ3) and fractional anisotropy (FA) were extracted at each voxel. After tensor fitting, images were processed with the tract-based spatial statistics pipeline (TBSS v1.1) (Smith et al., 2006). A general linear model was created incorporating disease group membership as the factor of interest and nuisance covariates of age, sex, disease duration (as a measure of disease severity), and total intracranial volume, calculated by summing GM, WM, and CSF acquired from segmentation of the structural images (using SPM8, as described below). The same model was fitted separately to FA, RD, AX, and TR and each PPA subgroup was contrasted with the healthy and disease control groups and with each of the other PPA subgroups. Statistical analysis was implemented using the permutation-based (nonparametric) 'randomize' tool within FSL with 5000 permutations generated for each test. A significance threshold ($p < 0.05$) was applied after correction for multiple comparisons using family-wise error (FWE) correction with threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009). Significant results were projected onto a study-specific mean brain registered to standard (Montreal Neurological Institute; MNI) space. To provide accurate anatomic localization a series of tract-specific masks were applied to the significant whole brain results. Masks reflected the anatomic location of major white matter structures generated using a previously published probabilistic WM tract atlas (Mori et al., 2004). A probability threshold of >20% was deemed acceptable in defining the boundaries for each mask. In total 14 masks were generated which included right and left inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF), anterior thalamic radiation (ATR), cingulum bundle (CB),