Brain & Language 125 (2013) 245–252

Contents lists available at SciVerse ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Distinct regional anatomic and functional correlates of neurodegenerative apraxia of speech and aphasia: An MRI and FDG-PET study

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ARTICLE INFO

Article history:
Accepted 6 February 2013
Available online 28 March 2013

Keywords:
Apraxia of speech
Aphasia
Atrophy
Broca's area
Premotor cortex
Hypometabolism

ABSTRACT

Progressive apraxia of speech (AOS) can result from neurodegenerative disease and can occur in isolation or in the presence of agrammatic aphasia. We aimed to determine the neuroanatomical and metabolic correlates of progressive AOS and aphasia. Thirty-six prospectively recruited subjects with progressive AOS or agrammatic aphasia, or both, underwent the Western Aphasia Battery (WAB) and Token Test to assess aphasia, an AOS rating scale (ASRS), 3T MRI and 18-F fluorodeoxyglucose (FDG) PET. Correlations between clinical measures and imaging were assessed. The only region that correlated to ASRS was left superior premotor volume. In contrast, WAB and Token Test correlated with hypometabolism and volume of a network of left hemisphere regions, including pars triangularis, pars opercularis, pars orbitalis, middle frontal gyrus, superior temporal gyrus, precentral gyrus and inferior parietal lobe. Progressive agrammatic aphasia and AOS have non-overlapping regional correlations, suggesting that these are dissociable clinical features that have different neuroanatomical underpinnings.

1. Introduction

Apraxia of speech (AOS) is a motor speech disorder in which subjects have impaired planning or programming of movements for accurate production of syllables across words, or within multisyllabic words (Duffy, 2005, 2006; McNeil, Doyle, & Wambaugh, 2000). It is characterized by slow rate, articulatory distortions, distorted sound substitutions, segmentation of syllables in multisyllabic words or across words, and articulatory groping and trial and error articulatory movements. In the progressive form, AOS can be the sole presenting symptom of a neurodegenerative disease (primary progressive apraxia of speech, PPAOS (Josephs et al., 2012)), but AOS can also co-occur with agrammatic aphasia (Gorno-Tempini et al., 2004; Hart, Beach, & Taylor, 1997; Josephs et al., 2005, 2006; Knibb, Woollams, Hodges, & Patterson, 2009). Subjects who present with both AOS and agrammatic aphasia display grammatical errors in speech and writing and impairments in comprehending syntactically complex sentences (Gorno-Tempini et al., 2011).

Neuroimaging studies in subjects with mixed AOS and agrammatic aphasia have found atrophy on MRI and hypometabolism on 18-F fluorodeoxyglucose (FDG) PET in the left medial and lateral posterior frontal cortex, involving inferior, middle and superior frontal gyri, and the left insula and temporal lobe (Gorno-Tempini et al., 2004; Josephs et al., 2006, 2010; Nestor et al., 2003; Rabinovici et al., 2008). In contrast, more focal abnormalities in the superior aspects of the premotor cortex have been observed in PPAOS without any aphasia (Josephs et al., 2012). These studies therefore suggest that AOS is associated with abnormalities in superior premotor cortex, while agrammatic aphasia is more likely to be associated with abnormalities in the inferior frontal cortex, namely Broca's area. This study aimed to test this hypothesis by examining direct correlations between measures of AOS severity and measures of aphasia severity and regional atrophy and hypometabolism in a large cohort of subjects with varying degrees of these clinical features.

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http://dx.doi.org/10.1016/j.bandl.2013.02.005

2. Methods

2.1. Subjects

A total of 36 subjects with AOS, agrammatic aphasia, or both AOS and agrammatic aphasia were included in this study. All subjects were recruited from the Department of Neurology into a prospective speech and language based disorder study between July 1st 2010 and June 31th 2012. All subjects underwent detailed speech and language examination by one of two speech-language pathologists (JRD or EAS), neurological evaluation, volumetric MRI and FDG-PET. All subjects had video and audio recordings of their formal speech and language assessment, as well as general conversation. The presence of AOS and agrammatic aphasia were determined by consensus between both speech-language pathologists based on review of the video and audio recordings, and performance on speech and language testing. Of the 36 subjects in the study, 18 subjects had both AOS and agrammatic aphasia, 17 subjects had only AOS and hence met criteria for PPAOS, and one subject had agrammatic aphasia without AOS. Of the 19 subjects with agrammatic aphasia, nine met recent clinical criteria for the agrammatic variant of primary progressive aphasia (PPA) (Gorno-Tempini et al., 2011). The remaining ten subjects did not meet criteria for the agrammatic variant of PPA because the severity of AOS was worse than the severity of agrammatic aphasia. The criteria for PPA state that deficits in language, and not deficits in the motoric formation of words, must be the most prominent clinical feature early in the disease (Mesulam, 1982, 2003). Imaging findings in 12 of the 17 PPAOS subjects have previously been published (Josephs et al., 2012). Subjects with aphasia not characterized by agrammatic spoken or written language output, for example those meeting criteria for semantic variant of PPA or logopenic variant of PPA, (Gorno-Tempini et al., 2011) were not included in this study. Subjects with concurrent illnesses that could account for the language deficits, subjects meeting criteria for another neurodegenerative disorder, or subjects where MRI was contraindicated, were excluded.

2.2. Speech and language testing

Language assessments performed in this cohort have been previously described in detail (Josephs et al., 2012) and included The Western Aphasia Battery (WAB), revised (Kertesz, 2007), Part 1, plus several writing subtests from Part 2, and a 22-item version of Part V of DeRenzi and Vignolo's Token Test (De Renzi & Vignolo, 1962); other measures of language ability were also obtained, but are not reported here. Imaging associations with the WAB Aphasia Quotient (AQ) and Token Test were assessed. These tests were chosen since the WAB AQ provides a global measure of aphasia severity and the Token Test provides a measure of relatively complex sentence comprehension that includes a requirement for processing of grammatic and syntactic relationships (e.g. after picking up the green square, touch the white circle; touch-with the blue circle-the red square); both are appropriate for assessing agrammatic aphasia. The clinical judgment concerning the presence of agrammatism was based primarily on the presence of deficiencies in sentence length and grammar/syntax/morphology in the WAB Spontaneous Speech (conversational questions and picture description) and/or Writing Output subtests of the WAB. The Token Test was not used solely to designate subjects as agrammatic but was important as a determiner of the presence of aphasia and as a measure of complex sentence comprehension.

The severity of AOS was measured using an AOS rating scale (ASRS) which assesses the prevalence/prominence of 16 features characteristic of AOS (Josephs et al., 2012). Items included in the ASRS provided a description of AOS characteristics and quantitative index of severity. Ratings for each feature were based on the following scale: 0 = not present; 1 = detectable but not frequent; 2 = frequent but not pervasive; 3 = nearly always evident but not marked in severity; 4 = nearly always evident and marked in severity, resulting in a total possible score of 64.

The study was approved by the Mayo Clinic IRB and all subjects were consented for enrollment.

2.3. MRI and PET image acquisition

All subjects underwent a standardized MRI imaging protocol at 3.0 T, that included a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE/T1, 2300/3/900 ms; flip angle 8°, 26-cm FOV; 256×256 in-plane matrix with a phase FOV of 0.94, slice thickness of 1.2 mm, in-plane resolution of 1.0 mm). All MRI scans underwent pre-processing correction for gradient non linearity (Jovicich et al., 2006) and intensity non-uniformity (Sled, Zijdenbos, & Evans, 1998). FDG-PET scans were acquired within one day of the MRI and were acquired using a PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin) operating in 3D mode. Subjects were injected with 366–399 MBq of ^{18}F-FDG in a dimly lit room with minimal auditory stimulation. Subjects were imaged after 30–38 min, for an 8-min image acquisition consisting of four 2-min dynamic frames. A low-dose CT of the brain was used for attenuation correction. Emission data were reconstructed into a 128×128 matrix with 256-mm FOV, pixel size of 2 mm and 4.25 mm section thickness.

2.4. MRI and PET image analysis

An atlas-based parcellation technique was employed using SPM5 and the automated anatomic labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) in order to generate grey matter volumes and mean FDG uptake values for a number of specific regions-of-interest, selected in order to assess different aspects of the language network (Turken & Dronkers, 2011). We assessed the left and right pars opercularis and pars triangularis that are considered to constitute Broca's area, the pars orbitalis, the middle frontal gyrus, supplemental motor area, precentral gyrus, insula, superior temporal gyrus and the inferior parietal lobe. In addition, since the premotor cortex has been implicated in PPAOS (Josephs et al., 2012), we manually placed a focal ROI in the superior lateral premotor cortex. It was necessary to manually place this ROI because the AAL atlas does not include a specific premotor cortex ROI; the premotor cortex is instead part of a much larger superior frontal ROI that includes prefrontal cortex. Left and right hemisphere values were assessed separately.

In order to generate regional volumes from the MRI, all subject MRIs and the AAL atlas were spatially normalized to a customized template using the unified segmentation tool in SPM5 (Ashburner & Friston, 2005). The customized template was created using 200 healthy controls and 200 subjects with dementia. Then for each subject, the inverse transformation was applied to the atlas in custom template space in order to warp the atlas to the subjects native anatomical space, and each native-space MRI was segmented into grey matter, white matter, and CSF. The grey matter probability maps for each subject were thresholded to create a binary mask, and were multiplied by the native-space AAL atlas, to generate a custom grey matter atlas for each subject, parcellated into different ROIs. Total intracranial volume (TIV) was measured and used to normalize regional grey matter volumes for differences in head size. In order to generate regional uptake values from the FDG-PET, the FDG-PET images were co-registered to the MPRAGE for each subject using six degrees-of-freedom rigid registration with a mutual information cost function. The native-space custom grey