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Tracking the development of agrammatic aphasia: A tensor-based morphometry study

Jennifer L. Whitwell [a,*], *Joseph R. Duffy* [b], *Mary M. Machulda* [c], *Heather M. Clark* [b], *Edythe A. Strand* [b], *Matthew L. Senjem* [a,d], *Jeffrey L. Gunter* [a,d], *Anthony J. Spychalla* [a], *Ronald C. Petersen* [e], *Clifford R. Jack Jr.*[a] *and Keith A. Josephs* [e,f]

[a] *Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[b] *Department of Neurology (Speech Pathology), Mayo Clinic, Rochester, MN, USA*
[c] *Department of Psychiatry & Psychology (Neuropsychology), Mayo Clinic, Rochester, MN, USA*
[d] *Department of Information Technology, Mayo Clinic, Rochester, MN, USA*
[e] *Department of Neurology (Behavioral Neurology), Mayo Clinic, Rochester, MN, USA*
[f] *Department of Neurology (Movement Disorders), Mayo Clinic, Rochester, MN, USA*

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ABSTRACT

Agrammatic aphasia can be observed in neurodegenerative disorders and has been traditionally linked with damage to Broca's area, although there have been disagreements concerning whether damage to Broca's area is necessary or sufficient for the development of agrammatism. We aimed to investigate the neuroanatomical correlates of the emergence of agrammatic aphasia utilizing a unique cohort of patients with primary progressive apraxia of speech (PPAOS) that did not have agrammatism at baseline but developed agrammatic aphasia over time. Twenty PPAOS patients were recruited and underwent detailed speech/language assessments and 3T MRI at two visits, approximately two years apart. None of the patients showed evidence of agrammatism in writing or speech at baseline. Eight patients developed aphasia at follow-up (progressors) and 12 did not (non-progressors). Tensor-based morphometry utilizing symmetric normalization (SyN) was used to assess patterns of grey matter atrophy and voxel-based morphometry was used to assess patterns of grey matter loss at baseline. The progressors were younger at onset and more likely to show distorted sound substitutions or additions compared to non-progressors. Both groups showed change over time in premotor and motor cortices, posterior frontal lobe, basal ganglia, thalamus and midbrain, but the progressors showed greater rates of atrophy in left pars triangularis, thalamus and putamen compared to non-progressors. The progressors also showed greater grey matter loss in pars triangularis and putamen at baseline. This cohort provided a unique opportunity to assess the anatomical changes that accompany the development of agrammatic aphasia. The results suggest that

* *Corresponding author*. Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA.
E-mail address: whitwell.jennifer@mayo.edu (J.L. Whitwell).
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damage to a network of regions including Broca's area, thalamus and basal ganglia are responsible for the development of agrammatic aphasia in PPAOS. Clinical and neuroimaging abnormalities were also present before the onset of agrammatism that could help improve prognosis in these subjects.

1. Introduction

Agrammatic aphasia can be observed in neurodegenerative disorders and is characterized by grammatical errors in speech or writing and impairments in comprehending syntactically complex sentences (Thompson & Mack, 2014). Early stroke studies associated the presence of agrammatic aphasia with damage to Broca's area, located in the left inferior frontal lobe (Broca, 1865; Geschwind, 1970), although there have been disagreements in the literature concerning whether damage to Broca's area is necessary or sufficient for the development of agrammatic aphasia (Fridriksson, Fillmore, Guo, & Rorden, 2015; Marie, 1906). Patients have been reported with agrammatic aphasia that do not have strokes affecting Broca's area, and, conversely, patients have been reported with strokes in Broca's area that do not have agrammatism (Fridriksson et al., 2015; Marie, 1906; Yang, Zhao, Wang, Chen, & Zhang, 2008). Several stroke studies have suggested that damage to other structures, including the insula, parietal lobe, superior temporal lobe, thalamus and basal ganglia are also important in the development of agrammatism (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007; Jodzio, Gasecki, Drumm, Lass, & Nyka, 2003; Mohr et al., 1978; Yang et al., 2008).

Structural neuroimaging has also been used to try to pinpoint the anatomic correlate of agrammatic aphasia in neurodegenerative disorders. These studies have typically assessed patterns of atrophy in groups that have the agrammatic variant of primary progressive aphasia (Gorno-Tempini et al., 2004; Grossman et al., 2013; Josephs et al., 2013, 2006; Rohrer et al., 2009), and a couple of studies have examined correlations between clinical measures of agrammatic aphasia severity and grey matter volume (Amici et al., 2007; Whitwell, Duffy, Strand, Xia, et al., 2013). The latter approach identified correlates in Broca's area, but also in the middle and superior frontal gyri and even temporal regions (Amici et al., 2007; Whitwell, Duffy, Strand, Xia, et al., 2013). The weakness of these approaches is that patients with agrammatic aphasia often have other clinical features, such as apraxia of speech (Josephs et al., 2006) or parkinsonism (Graff-Radford, Duffy, Strand, & Josephs, 2012; Josephs et al., 2006; Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005), and hence it can be difficult to disentangle the possible causal relationships between anatomy and these different clinical features. In addition, the patients in these studies already had well established agrammatic aphasia and so it has not been possible to assess the changes in the brain that occur before symptom onset or at the time of development of agrammatic aphasia.

Primary progressive apraxia of speech (PPAOS) is a neurodegenerative motor speech disorder characterized by isolated apraxia of speech (J. R. Duffy, 2013), in the absence of agrammatic aphasia (Josephs et al., 2012); however, we have recently demonstrated that some patients with PPAOS develop agrammatic aphasia over time, while in others apraxia of speech remains the sole feature (Josephs et al., 2014). Thus, patients with PPAOS provide a unique opportunity to study the emergence of agrammatic aphasia. The aim of this study was, therefore, to study a cohort of PPAOS subjects that had been followed longitudinally to assess the neuroimaging changes that accompany the development of agrammatic aphasia when it occurs. A comparison of PPAOS subjects that develop agrammatic aphasia to those that do not allowed us to identify regions specifically associated with the development of aphasia, rather than general worsening of other clinical features. We have shown that patients with PPAOS demonstrate a relatively focal pattern of atrophy, with grey and white matter loss observed in the supplementary motor area and superior lateral premotor regions (Josephs et al., 2013, 2012; Whitwell, Duffy, Strand, Machulda, et al., 2013). Hence, we hypothesized that the development of agrammatic aphasia in PPAOS would be associated with a spread of disease from superior premotor regions into inferior frontal regions, including Broca's area.

2. Materials and methods

2.1. *Subjects*

A cohort of 20 subjects with PPAOS underwent two serial MRIs with an interval of approximately two years. All subjects had been recruited into a cross-sectional National Institute of Health (NIH) funded grant and had been given a diagnosis of PPAOS at their first, i.e., baseline, research visit after undergoing an extensive speech and language battery, as previously described (Josephs et al., 2012). Subjects were diagnosed with PPAOS if the dominant presenting sign was apraxia of speech and any other nonspeech neurological or aphasia characteristics were considered absent or, at most, equivocal. Dysarthria was not an exclusionary problem unless it was judged as more severe than PPAOS at initial assessment. Diagnosis was made after review of video and audio recordings and speech and language test scores by two speech-language pathologists. All subjects returned for follow-up as soon as possible as part of another NIH-funded longitudinal grant. All subjects underwent an identical neurological evaluation, speech and language examination and volumetric head MRI at both baseline and follow-up. All MRI scans were performed within two days of the neurological and speech and language examinations for every subject. The video and audio recordings and speech and language test scores from the follow-up assessments were