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Disruption of large-scale neural networks in non-fluent/agrammatic variant primary progressive aphasia associated with frontotemporal degeneration pathology

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ABSTRACT

Non-fluent/agrammatic primary progressive aphasia (naPPA) is a progressive neurodegenerative condition most prominently associated with slowed, effortful speech. A clinical imaging marker of naPPA is disease centered in the left inferior frontal lobe. We used multimodal imaging to assess large-scale neural networks underlying effortful expression in 15 patients with sporadic naPPA due to frontotemporal lobar degeneration (FTLD) spectrum pathology. Effortful speech in these patients is related in part to impaired grammatical processing, and to phonologic speech errors. Gray matter (GM) imaging shows frontal and anterior–superior temporal atrophy, most prominently in the left hemisphere. Diffusion tensor imaging reveals reduced fractional anisotropy in several white matter (WM) tracts mediating projections between left frontal and other GM regions. Regression analyses suggest disruption of three large-scale GM–WM neural networks in naPPA that support fluent, grammatical expression. These findings emphasize the role of large-scale neural networks in language, and demonstrate associated language deficits in naPPA.

1. Introduction

The non-fluent/agrammatic variant of primary progressive aphasia (naPPA), also known as progressive non-fluent aphasia (PNFA), is characterized by effortful, slowed speech that is produced at about one-third the rate of healthy adults. This is accompanied by a disorder of grammar. In oral speech expression, there are grammatical simplifications as well as frank grammatical errors. The presence of a grammatical comprehension deficit emphasizes that this is a central disorder of language that cannot be attributed entirely to a motor impairment. Language output in naPPA also may be characterized by speech errors known as apraxia of speech (AoS). A clinical imaging marker associated with these speech and language characteristics is left frontal gray matter (GM) disease. In this paper, we examine GM and white matter (WM) imaging evidence for disruption of large-scale neural networks underlying the effortful, grammatically-limited speech of patients with sporadic naPPA due to frontotemporal lobar degeneration (FTLD) spectrum pathology.

1.1. Clinical characteristics of naPPA

Current recommendations for identifying naPPA emphasize three clinical features: Effortful speech, a disorder of grammar, and AoS (Gorno-Tempini et al., 2011). While effortful speech has been recognized clinically (Grossman et al., 1996; Snowden, Neary, Mann, Goulding, & Testa, 1992), quantification of slowed speech rate has been documented only recently (Ash et al., 2006, 2009; Rogalski et al., 2011a; Wilson, Henry, et al., 2010). Speech is produced at an average rate of about 45 words per minute (WPM) by naPPA patients in comparison to about 140 WPM for healthy adults. While there are many lengthy pauses in their effortful speech, speech remains significantly slowed even when pauses >2 s duration are taken into consideration (Ash et al., 2009).

Careful analyses have allowed investigators to test several hypotheses about the basis for the slowed, effortful speech found in naPPA. One essential characteristic of speech that is highly correlated with effortfulness is its grammatical characteristics (Ash et al., 2006, 2009; Gunawardena et al., 2010; Rogalski et al., 2011a; Wilson, Henry, et al., 2010). The variety of grammatical forms in sentences is impoverished, and grammatical forms are simplified, with fewer sentences containing features like a subordinate clause or the passive voice. Grammatical simplifications also result in a shortened mean length of utterance (MLU). When syntactic features are produced, they often contain errors.

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Grammatical morphemes may be omitted, particularly free-standing morphemes such as "was" and articles like "a," inappropriate grammatical inflections may be used, and words may be inserted in the incorrect grammatical slot in a sentence.

Evidence that effortful speech in naPPA is not determined entirely by a motor disorder comes at least in part from the observation of grammatical comprehension difficulty in these patients. Impaired grammatical comprehension was first described using a task that is entirely language-based, where a simple question about "who did what to whom" probed brief sentences varying in grammatical complexity (Grossman et al., 1996). In the sentence "Boys that girls kick are unfriendly," for example, naPPA patients often err when asked: "Who did the kicking?" This finding has been replicated more recently in a larger cohort of patients with naPPA (Peelle et al., 2008). These patients also have difficulty pointing to one of several pictures based on a sentence, where selecting the correct picture depends on appreciating the sentence's grammatical structure (Wilson, Dronkers, et al., 2010). Another study used an anagram task to show that naPPA patients have difficulty ordering words printed on cards into a grammatically complex question about a picture (Weintraub et al., 2009). Grammatical difficulties such as this can be used to distinguish naPPA from other PPA variants (Mesulam et al., 2009; Peelle et al., 2008). Moreover, naPPA is a *progressive* disorder of language, and two studies have shown progressive decline of grammatical comprehension in naPPA (Grossman & Moore, 2005; Rogalski et al., 2011b).

Additional evidence consistent with a "central" disorder of grammatical processing difficulty comes from several sources. Measures like those described above are off-line and therefore depend in part on task-related resources. Indeed, neuropsychological studies demonstrate deficits on measures of working memory and executive functioning in naPPA that can compromise task performance (Libon et al., 2007). To deal with these confounds, several investigations minimized task-related resources by examining "on-line" processing of grammatical materials in sentences. One study showed slowed processing of grammatical agreements in subordinate clauses of sentences containing a prepositional phrase that elongates the gap between long-distance, syntactically-dependent words (Grossman, Rhee, & Antiquena, 2005). This study suggested degradation of long-distance grammatical representations in working memory in naPPA. A second study demonstrated insensitivity to lexical grammatical category violations (e.g. a noun occurring in a verb sentential slot) but normal sensitivity to lexical semantic violations (Peelle, Cooke, Moore, Vesely, & Grossman, 2007).

Some naPPA patients also may have a motor disorder contributing to their effortful speech. AoS is a clinical condition involving impaired coordination and planning of the motor articulators. This results in the production of incorrect speech sounds and sequences of sounds that do not occur in the speaker's native language, groping for the correct sound of a word, pauses in the speech stream, and other distortions of speech. This is consistent with the observation that some patients with naPPA have an extrapyramidal disorder such as progressive supranuclear palsy or corticobasal degeneration that can result in poor motor speech control (Josephs, Duffy, et al., 2006), although AoS certainly can occur without a concurrent motor disorder and may be found independently of other disorders of language (Josephs et al., 2012; Rohrer, Rossor, & Warren, 2010b). We noted above the frequent pauses that occur in naPPA speech (Ash et al., 2009), although pauses may occur for a variety of reasons, and we are aware of only one attempt to examine qualitatively distinct speech errors consistent with AoS in naPPA (Ash et al., 2010). This study distinguished between phonetic errors that involve misarticulated speech sounds that are not part of the English speech sound system and therefore are likely to be due to misplacement of the articulators by an impaired motor coordination system; and phonemic errors that are governed by the abstract rules of the phonologic system for representing and combining sounds in language expression and comprehension. The analysis revealed that naPPA patients produce significantly more speech errors than controls, consistent with other observations (Josephs, Duffy, et al., 2006; Rohrer, Rossor, & Warren, 2010a; Rohrer et al., 2010b). However, an overwhelming number of their speech errors are phonemic in nature, qualitatively similar to controls' errors, while only 21% of speech errors in naPPA can be clearly attributed to a motor speech planning disorder because they were distortions that are not part of the English speech sound system. While using these rigorous criteria for subcategorizing speech errors may exclude other examples of AoS, speech errors consistent with AoS certainly occur in naPPA but do not appear to be very common.

1.2. Imaging features of naPPA

What is the neuroanatomic basis for this pattern of language difficulty in sporadic naPPA? There is extensive imaging evidence to suggest that a clinical marker for naPPA is focal disease localized to the left frontal lobe. Several imaging techniques have helped specify the anatomic distribution of disease associated with naPPA. Structural MRI studies have emphasized gray matter (GM) atrophy in the inferior frontal region of the left hemisphere (Gorno-Tempini et al., 2004; Peelle et al., 2008; Rohrer et al., 2009; Sapolsky et al., 2010; Sonty et al., 2003). This typically involves adjacent areas such as frontal operculum and anterior insula, may extend more dorsally and anteriorly into left prefrontal regions, and may encompass superior portions of the left anterior temporal lobe (Gunawardena et al., 2010; Rogalski et al., 2011b). These structural findings are confirmed by functional imaging techniques such as arterial spin labeling (ASL) and positron emission tomography (PET), showing functional deficits in the left inferior frontal lobe, including the frontal operculum and the anterior insula, as well as the anterior–superior temporal lobe (Grossman et al., 1996; Nestor et al., 2003).

Several approaches have been employed to investigate more directly the role of left inferior frontal atrophy in the language deficits of naPPA patients. Regression analyses thus have related grammatical difficulties directly to GM atrophy in left inferior frontal and anterior–superior temporal regions (Gunawardena et al., 2010; Peelle et al., 2008; Rogalski et al., 2011a; Wilson, Dronkers, et al., 2010, Wilson, Henry, et al., 2010). Other work has related speech errors to the left frontal lobe (Ash et al., 2010; Josephs, Duffy, et al., 2006; Rohrer et al., 2010a).

Functional MRI also has been used to assess the neuroanatomic basis for grammatical processing in naPPA. These studies emphasize that disease in left inferior frontal cortex alone does not fully explain the deficits of these patients. In one study, healthy controls and patients with naPPA silently read sentences that feature a complex grammatical structure and a prepositional phrase that lengthens the distance between grammatically linked elements in the sentence (Cooke et al., 2003). Healthy controls activated both ventral portions of the left frontal lobe associated with grammatical processing and dorsal left frontal regions associated with working memory. By comparison, naPPA patients did not activate the ventral frontal region associated with grammatical processing, although they recruited dorsal portions of the left frontal lobe associated with working memory and left posterior–superior temporal regions associated with sentence processing. Another fMRI study showed grammatically simple sentences and grammatically complex sentences to naPPA patients and healthy controls (Wilson, Dronkers, et al., 2010). Controls showed greater left inferior frontal activation during grammatically complex sentences compared to