

## The neural basis of syntactic deficits in primary progressive aphasia

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### ABSTRACT

Patients with primary progressive aphasia (PPA) vary considerably in terms of which brain regions are impacted, as well as in the extent to which syntactic processing is impaired. Here we review the literature on the neural basis of syntactic deficits in PPA. Structural and functional imaging studies have most consistently associated syntactic deficits with damage to left inferior frontal cortex. Posterior perisylvian regions have been implicated in some studies. Damage to the superior longitudinal fasciculus, including its arcuate component, has been linked with syntactic deficits, even after gray matter atrophy is taken into account. These findings suggest that syntactic processing depends on left frontal and posterior perisylvian regions, as well as intact connectivity between them. In contrast, anterior temporal regions, and the ventral tracts that link frontal and temporal language regions, appear to be less important for syntax, since they are damaged in many PPA patients with spared syntactic processing.

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### 1. Introduction

In primary progressive aphasia (PPA), degeneration of dominant hemisphere language regions leads to progressive language deficits, with relative sparing of other cognitive functions (Gorno-Tempini et al., 2011; Mesulam, 1982, 2001). There is considerable variability in which specific regions are affected. Consequently, individuals with PPA vary greatly in the extent to which different aspects of language, such as syntactic processing, are impacted. The aim of this paper is to provide a brief review of the literature on the neural basis of syntactic deficits in PPA.

There are three widely recognized variants of PPA: non-fluent, semantic and logopenic (Gorno-Tempini et al., 2004, 2011). Non-fluent PPA is characterized by agrammatism and/or apraxia of speech (Grossman et al., 1996; Hodges & Patterson, 1996). In this review, we use the term *non-fluent* to refer to a clinically defined variant (Gorno-Tempini et al., 2011); it is important to note that the traditional concept of fluency is multifactorial and does not always provide a good basis for classifying PPA patients (Thompson et al., 2012a; Wilson et al., 2010b). In semantic PPA (for which diagnostic criteria mostly overlap with those for semantic dementia; Neary et al., 1998), loss of lexical and semantic knowledge is the most salient feature (Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Neary, 1989; Warrington, 1975). Logopenic

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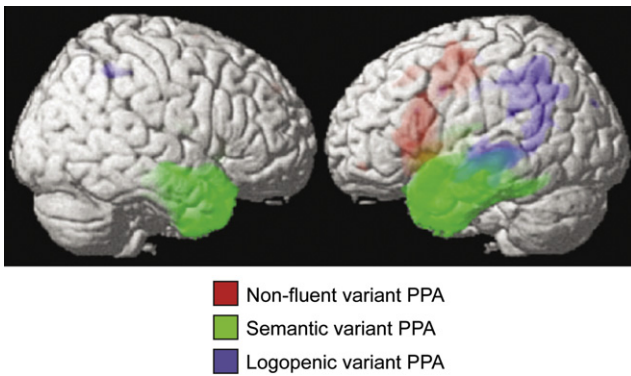
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PPA is characterized by phonological and word-finding problems (Gorno-Tempini et al., 2004, 2008; Henry & Gorno-Tempini, 2010). Each variant has a characteristic pattern of atrophy (Fig. 1) (Gorno-Tempini et al., 2004), and each variant is associated with different likelihoods of underlying pathologies (Davies et al., 2005; Josephs et al., 2008; Mesulam et al., 2008; Snowden, Neary, & Mann, 2007; Snowden et al., 2011; see Grossman (2010) and Henry, Wilson, and Rapcsak (2012) for review).

In this review, we begin with a brief discussion of syntactic deficits and how they are typically assessed in PPA. Then we examine the nature and extent of syntactic deficits, if any, along with structural and metabolic imaging findings for each of the three variants in turn. We then discuss morphometric studies that have examined relationships between atrophy and syntactic deficits irrespective of variant. These studies are particularly important because there is considerable heterogeneity among patients diagnosed with each variant, and furthermore, the progressive nature of PPA implies that patients' language functioning changes significantly over time (Kertesz, Davidson, McCabe, Takagi, & Munoz, 2003). We then discuss functional imaging and diffusion tensor imaging studies, before concluding with a summary of the brain areas linked to syntactic deficits in PPA, and suggestions for future directions.

### 2. Assessment of syntactic deficits in PPA

We define syntactic processing as the ability to implicitly generate hierarchically structured representations of sentences, and to use function words and inflectional morphology to express



**Fig. 1.** Characteristic patterns of atrophy in the three variants of PPA. Voxel-based morphometry was used to identify regions where each variant showed volume loss relative to controls ( $p < 0.05$ , corrected for multiple comparisons). Reprinted (with modifications) from Gorno-Tempini et al. (2004).

grammatical categories such as number, definiteness, tense and aspect. Syntactic deficits can be defined as limitations in syntactic processing, which may be manifest in production, in comprehension, or most typically, in both production and comprehension. Core syntactic deficits would by definition affect both production and comprehension, and across a population of PPA patients, deficits in the production and comprehension of syntax are highly correlated (Wilson et al., 2011). However dissociations between production and comprehension may occur in principle, reflecting either impairments in peripheral processes, or partially distinct neural substrates for the production and comprehension of syntax.

Two patterns of syntactic production deficits are often recognized in the aphasiology literature: agrammatic and paragrammatic. The core features of agrammatic speech are omissions of function words and morphemes, reduced complexity of syntactic forms, and ungrammatical utterances, whereas paragrammatic speech is characterized by “unacceptable juxtapositions of phrases and misuse of words” (Goodglass, Christiansen, & Gallagher, 1994, p. 598). We consider both patterns to be indicative of syntactic deficits, though the underlying causes may be different (Goodglass, Christiansen, & Gallagher, 1993).

In PPA, syntactic production has most commonly been assessed by quantitative analysis of connected speech samples (Ash et al., 2006, 2009; Bird, Lambon Ralph, Patterson, & Hodges, 2000; Graham, Patterson, & Hodges, 2004; Knibb, Woollams, Hodges, & Patterson, 2009; Meteyard & Patterson, 2009; Orange, Kertesz, & Peacock, 1998; Patterson, Graham, Lambon Ralph, & Hodges, 2006; Patterson & MacDonald, 2006; Rogers & Alarcon, 1998; Thompson, Ballard, Tait, Weintraub, & Mesulam, 1997; Thompson et al., 2012a; Wilson et al., 2010b). This approach provides a rich description of a patient’s capacity to correctly produce syntactic structures, but it has several disadvantages. One is that it is relatively unconstrained, so patients may differ in the extent to which they attempt structures that may be challenging. Therefore the same degree of syntactic impairment could result in syntactic errors in one patient, but simplified utterances in another (Wilson et al., 2010b). To circumvent this limitation, several recent studies have used constrained speech production tasks in which targeted sentence structures are primed or elicited (DeLeon et al., submitted for publication; Thompson et al., in press). The second limitation of connected speech analysis is that motor speech deficits are often prominent in non-fluent PPA and can complicate the quantification of syntactic deficits; indeed, some patients are mute and cannot produce connected speech at all. To assess syntax in patients without intact speech production, Weintraub et al. (2009) have proposed the Northwestern Anagram Test, in which patients are

asked to assemble printed words to describe pictures. Some patients performed better on this test than they did on a constrained speech production task, revealing a greater command of sentence structure than was otherwise apparent (Weintraub et al., 2009).

Syntactic comprehension has most often been assessed with sentence-picture matching tasks, in which the patient hears (or reads) a sentence and has to select a matching picture from an array containing foils. Examples include the Test for Reception of Grammar (Bishop, 1983) and the Curtiss-Yamada Comprehension Language Examination (Curtiss and Yamada, unpublished test). However some of the tests that have been used were not designed for patients with PPA. They contain lexical items that can be challenging for patients with semantic PPA in particular, and they require choices among multiple possible responses, making considerable demands on working memory and executive processes. We have proposed a sentence-picture matching task that uses only high-frequency lexical items and has only one foil per item, making it more suitable for patients with PPA (Wilson et al., 2010a, 2011). Another approach that may also reduce executive demands is to present a sentence, then ask patients a probe question that tests syntactic comprehension (Grossman, Rhee, & Moore, 2005).

Even optimized versions of “offline” tasks such as these make considerable demands on working memory and executive processes, which can complicate interpretation of observed deficits. Moreover, syntactic processing takes place rapidly in real time, and many aspects can therefore only be studied in real time (Friederici, 2002). Several researchers have employed online tasks with PPA patients (Grossman et al., 2005; Peelle, Cooke, Moore, Vesely, & Grossman, 2007; Tyler, Moss, Patterson, & Hodges, 1997). For instance, in normal participants, detection of a target word is slower immediately following a syntactic violation (Marslen-Wilson & Tyler, 1980). This and similar paradigms have been used to investigate abnormal syntactic processing in PPA patients (Grossman et al., 2005; Peelle et al., 2007; Tyler et al., 1997), with the advantage that there is less of an impact of other processes such as working memory and executive function.

### 3. Non-fluent variant PPA

#### 3.1. Syntax in non-fluent PPA

Early clinical studies reported that non-fluent PPA patients produce agrammatic speech (Grossman et al., 1996; Hodges & Patterson, 1996; Mesulam, 1982; Snowden, Neary, Mann, Goulding, & Testa, 1992; Weintraub, Rubin, & Mesulam, 1990). These early studies typically classified PPA patients as fluent versus non-fluent, potentially including in the non-fluent group patients who would now be classified as logopenic. Recent studies have mostly recognized three variants, permitting more specific findings relating to each variant. A detailed picture of syntactic production deficits in non-fluent PPA has emerged from a number of studies that have quantified syntactic structures produced and syntactic errors in connected speech samples (Ash et al., 2006, 2009; Graham et al., 2004; Knibb et al., 2009; Patterson et al., 2006; Thompson et al., 1997, 2012a; Wilson et al., 2010b). These studies have shown that utterances produced by many non-fluent PPA patients are characterized by omissions of grammatical words and morphemes such as determiners, auxiliaries and verbal inflections, reduced access to verbs, incorrect argument structures, and decreased utterance length and complexity. All of these features become more severe as the disease progresses (Thompson et al., 1997). Elicited syntactic production studies have supported these findings, revealing particular difficulties with inflectional morphology, embeddings, and passive constructions (DeLeon et al., submitted for publication; Thompson et al., in press).

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