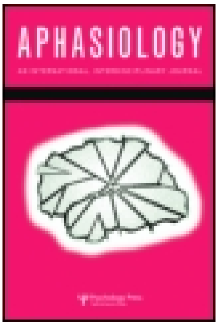

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Grammatical impairments in PPA

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Background: Grammatical impairments are commonly observed in the agrammatic subtype of primary progressive aphasia (PPA-G), whereas grammatical processing is relatively preserved in logopenic (PPA-L) and semantic (PPA-S) subtypes.
Aims: We review research on grammatical deficits in PPA and associated neural mechanisms, with discussion focused on production and comprehension of four aspects of morphosyntactic structure: grammatical morphology, functional categories, verbs and verb argument structure, and complex syntactic structures. We also address assessment of grammatical deficits in PPA, with emphasis on behavioural tests of grammatical processing. Finally, we address research examining the effects of treatment for progressive grammatical impairments.
Main Contribution: PPA-G is associated with grammatical deficits that are evident across linguistic domains in both production and comprehension. PPA-G is associated with damage to regions including the left inferior frontal gyrus and dorsal white matter tracts, which have been linked to impaired comprehension and production of complex sentences. Detailing grammatical deficits in PPA is important for estimating the trajectory of language decline and associated neuropathology. We, therefore, highlight several new assessment tools for examining different aspects of morphosyntactic processing in PPA.
Conclusions: Individuals with PPA-G present with agrammatic deficit patterns distinct from those associated with PPA-L and PPA-S, but similar to those seen in agrammatism resulting from stroke, and patterns of cortical atrophy and white matter changes associated with PPA-G have been identified. Methods for clinical evaluation of agrammatism, focusing on comprehension and production of grammatical morphology, functional categories, verbs and verb argument structure, and complex syntactic structures are recommended and tools for this are emerging in the literature. Further research is needed to investigate the real-time processes underlying grammatical impairments in PPA, as well as the structural and functional neural correlates of grammatical impairments across linguistic domains. Few studies have examined the effects of treatment for grammatical impairments in PPA; research in this area is needed to better understand how (or if) grammatical processing ability can be improved, the potential for spared neural tissue to be recruited to support this and whether the neural connections within

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areas of dysfunctional tissue required for grammatical processing can be enhanced using cortical stimulation.

Keywords: Primary progressive aphasia; Syntax; Morphology; Sentence comprehension; Sentence production.

Three major subtypes of primary progressive aphasia (PPA) have been described in the literature, each associated with characteristic neurolinguistic and neuropathological profiles (Galantucci et al., 2011; Gorno-Tempini et al., 2004, 2008, 2011; Mesulam et al., 2009; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Wilson et al., 2011). According to the current consensus criteria for the classification of PPA subtypes (Gorno-Tempini et al., 2011), one variant of PPA (termed "non-fluent/agrammatic" PPA) is associated with grammatical impairments and/or motor speech deficits, and is typically associated with neural degeneration in left posterior frontal and insular regions as well as damage to dorsal white matter tracts. The second variant, logopenic PPA, is characterised by impaired word retrieval and sentence repetition, with atrophy typically in the left temporo-parietal junction and posterior dorsal white matter tracts and the third variant, semantic PPA, is linked with deficits in object naming and word comprehension and atrophy in the anterior temporal lobes and ventral language tracts. On autopsy, "non-fluent/agrammatic" PPA and the semantic variant of PPA are most frequently linked to frontotemporal lobar degeneration (FTLD), whereas logopenic PPA is associated with Alzheimer Disease pathology (Gorno-Tempini et al., 2008; Mesulam et al., 2008; Rabinovici et al., 2008; Rohrer, Rossor, & Warren, 2012). Therefore, careful subtyping of PPA is clinically important.

In contrast with the terminology proposed in the consensus criteria, we avoid use of the term "non-fluent/agrammatic" (i.e., naPPA) to delineate a subtype of PPA because it does not accurately reflect grammatical ability. The 2011 consensus criteria for naPPA include two core features, either of which is sufficient for classification: (1) agrammatism in language production, and (2) effortful, halting speech with inconsistent speech sound errors. Importantly, however, not all patients with grammatical impairments present with motor deficits, and patients with "pure" motor speech deficits have been reported, who do not evince grammatical impairments (Josephs et al., 2006; Mesulam et al., 2012; Rohrer, Rossor, & Warren, 2010; Wicklund et al., 2014). Further, research has shown that patients with the logopenic variant of PPA may present with either fluent or non-fluent production patterns but, even when speech output is non-fluent, they exhibit at most mild grammatical deficits (Thompson, Ballard, Tait, Weintraub, & Mesulam, 1997; Thompson, Cho, et al., 2012). For example, in the first published paper detailing longitudinal decline in spontaneous speech in PPA, Thompson, Ballard, et al. (1997) analysed language samples collected at one-year intervals over a course of several years (i.e., up to 11 years post symptom onset) from "four subjects presenting with non-fluent primary progressive aphasia" (p. 297). Results showed measurable morphosyntactic impairments and declination over time for three participants (Subjects 1, 3 and 4); however, Subject 2, in spite of his non-fluent production, showed a different deficit pattern: relatively spared morphosyntactic production in the face of significant word retrieval deficits (for both nouns and verbs). Notably, Subject 2 also presented with a motor speech impairment, which worsened over time. Using the Gorno-Tempini et al.

criteria for subtyping this patient, he would today still be diagnosed with "non-fluent/agrammatic" PPA, even though he never showed agrammatic production patterns. Wilson, Galantucci, Tartaglia, and Gorno-Tempini (2012) recently reviewed Subject 2's profile and suggested that he presented with logopenic PPA (confirmed by personal communication with Thompson and Mesulam) (p. 193). Hence, following Mesulam, Thompson, Weintraub and colleagues (e.g., Mesulam et al., 2009, 2012; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013), we use the term *PPA-G* to refer to individuals with grammatical processing impairments. Some of these patients have concomitant motor speech deficits, however, in contrast with the naPPA classification; the PPA-G classification does not include individuals who present with motor speech deficits without grammatical impairments. We also refer to logopenic PPA and semantic PPA as PPA-L and PPA-S, respectively, to maintain terminological consistency with previous work conducted at Northwestern University by Mesulam, Thompson, Weintraub and colleagues (e.g., Mesulam et al., 2009, 2012). Our classifications, although generally equivalent to lvPPA and svPPA, respectively, are generated based on explicit criteria and test performance patterns (i.e., scores on the Northwestern Anagram Test (NAT; Thompson, Weintraub, & Mesulam, 2011; also see Wilson et al., 2011) and on selected items from the Peabody Picture Vocabulary Test- 4th editions (PPVT-4; Dunn & Dunn, 2006)).

In this paper we focus on grammatical processing ability across subtypes of PPA. For a previous review of grammatical processing impairments in PPA, see Wilson et al. (2012). Although grammatical deficits are commonly associated with the agrammatic variant of PPA (though see Graham, Patterson, & Hodges, 2004), some inconsistent findings have been noted regarding specific deficit patterns (see discussion in Graham et al., 2004; Patterson, Graham, Lambon Ralph, & Hodges, 2006; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013). Indeed, some of these inconsistencies may be due to the inclusion of individuals with PPA-L or pure motor speech impairments in the naPPA groups studied. In addition, although the classification criteria for PPA-L and PPA-S include relatively preserved grammatical production, some studies have observed subtle grammatical deficits in these subtypes as well (Meteyard & Patterson, 2009; Wilson, Henry, et al., 2010). In the present paper, we begin by defining the morphosyntactic domains that are affected by grammatical impairments: grammatical morphology, functional categories, verbs and verb argument structure, and complex syntactic structures. We then provide an overview of previous research on grammatical impairments in PPA and their neural correlates. Finally, we discuss options for assessment and clinical management of grammatical deficits.

WHAT IS A GRAMMATICAL DEFICIT?

Grammatical deficits involve impaired production and/or comprehension of the morphosyntactic structure of sentences. There are several components of morphosyntactic structure. *Grammatical morphology* encodes the internal structure of words, including bound inflectional markers of agreement (*They jump* vs. *He jump**s***) and tense/aspect (*They jump* vs. *They jump**ed***). *Functional categories* are closed-class words that serve as heads of functional syntactic phrases, including determiners (***the** cat*), auxiliary verbs (*He **is** jumping*) and complementisers (*Sam thought **that** he left*). In general, verbs play a central role in morphosyntactic processing. In addition to carrying morphological markers of agreement and tense/aspect, the lexical representations of verbs include *verb argument structure*, which specifies syntactic (i.e., subcategorisation) and lexical-semantic (i.e., selectional) restrictions on the phrases (arguments) that are encoded with the verb (e.g., *swim* is intransitive and selects an animate subject). Thus, verb processing is essential to the production and comprehension of simple monoclausal sentences, as well as *complex syntactic structures,* which contain embedded clauses and/or non-canonical argument order (e.g., passive sentences such as *The girl was kissed by the boy*, in which the theme argument precedes the agent). As we review below, PPA-G has been associated with deficits in each of these components of morphosyntactic structure.

Notably, as pointed out above, grammatical impairments are not necessarily associated with deficits in fluency. Non-fluent speech is characterised by slowed rate, disruptions to the flow of speech (e.g., pauses, false starts) and speech sound errors. Although non-fluent speech production is seen in many patients with PPA, grammaticality may or may not be impaired in these patients. In classic stroke-aphasiology, non-fluent speech production is a primary characteristic used to classify Broca's aphasia (Goodglass & Kaplan, 1983), which often is accompanied by deficits in grammatical ability that affect both sentence production and comprehension (Goodglass, 1997; Goodglass et al., 1979; Zurif, Green, Caramazza, & Goodenough, 1976). Hence, the terms non-fluent and Broca's aphasia often are used interchangeably with agrammatic aphasia and implicitly suggest the presence of grammatical deficits (see Thompson & Bastiaanse, 2012). However, research shows that individuals with PPA evince dissociations between fluency and grammatical ability. In an extensive study of narrative speech production in PPA, Thompson, Cho, et al. (2012) found that grammatical ability varies from one variant of PPA to another. However, based on words per minute (WPM) produced (a common marker of fluency) they reported that, of the 37 PPA participants in the study, 27 were non-fluent with WPM at least one standard deviation below the mean for cognitively healthy controls (i.e., 1 SD below 132.2 WPM). This included all the 11 PPA-G participants, 15 of the 20 PPA-L participants and 1 of 6 PPA-S participants. In addition, no significant correlations between speech rate and several measures of grammatical production were found (e.g., proportion of verbs inflected correctly; open:closed ratio, noun:verb ratio, proportion of grammatical sentences) (but see Ash et al., 2009; Gunawardena et al., 2010 who found correlations between speech rate and some measures of grammatical production). Furthermore, evidence is mixed regarding the degree of overlap between the neural substrates of fluency and grammatical production in PPA, as discussed below.

GRAMMATICAL PROCESSING IN PPA

This section summarises previous research on morphosyntactic processing in PPA, organised by linguistic domain: grammatical morphology, functional categories, verbs and verb argument structure, and complex syntactic structures.

Grammatical morphology

Impaired production of grammatical morphology (e.g., verb inflection) has been found in PPA-G. In connected speech samples, these speakers produce fewer verbs with correct inflections compared to cognitively healthy speakers, whereas speakers with PPA-L and PPA-S do not (Thompson, Cho, et al., 2012). In addition, the overall rate of inflected verbs is numerically (though not significantly) lower in speakers with PPA-G than in controls (Knibb, Woollams, Hodges, & Patterson, 2009; Wilson, Henry, et al., 2010), but speakers with PPA-L and PPA-S do not differ from controls (Wilson, Henry, et al., 2010). Across lexical categories, individuals with PPA-G also produce fewer correct grammatical endings than controls (Graham et al., 2004).

In a structured sentence completion task testing production of grammatical morphology (using the Northwestern Assessment of Verb Inflection; Thompson & Lee, experimental version), participants with PPA-G produced fewer correct finite (tensed) verbs compared to those with PPA-L, but the two groups did not differ in accuracy of production of non-finite (non-tensed) verb forms (Thompson, Meltzer-Asscher, et al., 2013). Specifically, speakers with PPA-G correctly produced 67% of finite verbs (vs. 88% production accuracy in PPA-L) and 94% of non-finite verbs (vs. 99% accuracy in PPA-L). A similar pattern was found for participants with stroke-induced agrammatic versus anomic aphasia; agrammatic speakers exhibited greater production difficulty than anomic speakers for finite, but not non-finite verbs. These results suggest that PPA-G is associated with a deficit in verbal morphology production similar to that of stroke-induced agrammatic aphasia, while production of verb morphology in PPA-L and PPA-S is relatively preserved.

PPA-G has also been associated with impaired comprehension of verb morphology. In particular, online sensitivity to morphological violations is impaired. Listeners with PPA-G have shown slowed sensitivity to a range of morphosyntactic agreement violations (e.g., subject–verb, determiner–noun, quantifier–quantified), whereas listeners with PPA-S exhibit intact sensitivity to these violations on the same time course as cognitively healthy controls (Grossman, Rhee, & Moore, 2005). Additionally, listeners with PPA-G show no online sensitivity to tense violations, in contrast to control listeners (Peelle, Cooke, Moore, Vesely, & Grossman, 2007). Given that production of tense morphology is also impaired (Thompson, Meltzer-Asscher, et al., 2013), this suggests a general deficit in representation and/or processing of tense morphology that extends across modalities.

Functional categories

Deficits in functional category production have also been observed in individuals with PPA-G in connected speech samples. Several studies have quantified the overall rate of functional category production through ratios of open class (i.e., content) to closed class (i.e., function) word production, as well as the rate of production of specific functional categories, such as determiners, auxiliaries and pronouns. Results have shown a trend towards higher open:closed (O:C) class ratios in PPA-G (Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010), though these trends did not reach significance in all studies, and in another study (Graham et al., 2004) O:C ratios did not differ between PPA-G and control speakers. This highlights a potential difference between PPA-G and stroke-induced agrammatic aphasia, which is associated with a marked impairment in the rate of closed-class word production (Thompson, Meltzer-Asscher, et al., 2013). However, this apparent difference may, at least in part, reflect the current consensus criteria for the "non-fluent/agrammatic" classification, which includes speakers with and without grammatical impairments.

Furthermore, previous studies suggest that there may be deficits in closed-class word production in PPA-G that are limited to certain functional categories. Wilson, Henry, et al. (2010) found that speakers with PPA-G produce a lower proportion of nouns with determiners than controls (0.89 and 1.00, respectively), whereas those with PPA-L and PPA-S do not (0.97 and 0.99, respectively). Thompson, Ballard, et al. (1997) also reported that three of their "non-fluent" PPA participants evinced impaired production of verbal morphosyntax in spontaneous speech (i.e., production of fewer closed-class words in the verb phrase, production of verb morphology errors (e.g., tense and agreement, etc.)), although Wilson, Henry, et al. (2010) found no differences between any PPA subtype and controls on a measure of auxiliary complexity. Further, it appears that production of pronouns may be intact in PPA-G, in that speakers with PPA-G produce a similar proportion of pronouns (Wilson, Henry, et al., 2010) and pronominal existential subjects (e.g., ***There** is a man here*; Ash et al., 2009) as compared to control speakers.

In contrast to PPA-G, speakers with PPA-S exhibit lower O:C ratios than controls (Thompson, Cho, et al., 2012; also see Wilson, Henry, et al., 2010 who reported a trend in this direction), indicating a deficit in open-, rather than closed-, class word production. Yet another pattern has been observed for PPA-L speakers, who do not statistically differ from controls (Thompson, Cho, et al., 2012; Wilson, Henry, et al., 2010) in open- and closed-class word production. Additionally, speakers with PPA-L and PPA-S produce a higher proportion of pronouns than controls, likely due to deficits in content word retrieval (Ash et al., 2009; Wilson, Henry, et al., 2010). These findings indicate that closed-class word production is relatively preserved in PPA-L and PPA-S. However, closed-class substitution errors occur more frequently in both PPA-G (Knibb et al., 2009) and PPA-S (Meteyard & Patterson, 2009) than in controls.

No studies to our knowledge have examined functional category processing during sentence comprehension in PPA. However, the processing of functional categories as well as grammatical morphology plays a critical role in the comprehension of syntactically complex structures, which is markedly impaired in PPA-G.

Verbs and verb argument structure

A substantial body of evidence indicates that verb production is impaired in PPA-G. Quantitative analyses of connected speech samples have typically reported trends towards impaired verb production in PPA-G, as reflected by higher noun:verb (N:V) ratios than in control speakers (Thompson, Ballard, et al., 1997; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010), although one study found no difference between the two groups (Graham et al., 2004). Speakers with PPA-G also produce fewer verbs, but not nouns, per utterance as compared to cognitively healthy controls (Ash et al., 2009). In addition, PPA-G is associated with verb argument structure production deficits in narrative speech, as reflected by impaired production of verbs with correct argument structure (Thompson, Ballard, et al., 1997; Thompson, Cho, et al., 2012), though another study found that speakers with PPA-G do not differ from controls with respect to the number of arguments produced per verb (Knibb et al., 2009). Verb production deficits are also evident in picture naming tasks. Individuals with PPA-G exhibit more significant impairment in verb (action) naming than in noun (object) naming (Hillis et al., 2006; Hillis, Oh, & Ken, 2004; Hillis, Tuffiash, & Caramazza, 2002; Thompson, Lukic, King, Mesulam & Weintraub, 2012). In addition, these speakers name verbs with simpler argument structures (i.e., intransitive verbs such as *sweep*) more accurately than verbs with more complex argument structures (i.e., transitive verbs such as *carry*) (Thompson, Lukic, et al., 2012), a pattern that is characteristic of agrammatic aphasia resulting from stroke (Kim & Thompson, 2000, 2004; Luzzatti et al., 2002;

Thompson, Lange, Schneider, & Shapiro, 1997; Thompson, Meltzer-Asscher, et al., 2013). However, verb comprehension, like noun comprehension, is largely preserved in PPA-G (Hillis et al., 2006; Thompson, Lukic, et al., 2012), suggesting that the lexical-semantic representations of verbs are intact.

In contrast, speakers with PPA-L and PPA-S do not exhibit specific impairments in verb production or comprehension. Speakers with PPA-L name and comprehend nouns and verbs with approximately equal accuracy (Thompson, Lukic, et al., 2012), and exhibit a trend towards impaired noun production (i.e., lower noun:verb (N:V) ratios as compared to controls) in connected speech samples (Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010). For example, Thompson, Cho, et al. (2012) reported a mean N:V ratio of 0.99 in a group of 20 speakers with PPA-L, as compared to a mean of 1.21 in 13 cognitively healthy speakers; similarly, Wilson, Henry, et al. (2010) found a higher proportion of verbs produced out of all open class items (nouns and verbs) in 11 speakers with PPA-L ($\underline{M}$ = 0.46) than in control speakers ($\underline{M}$ = 0.37). In addition, in a recent study examining pauses in connected speech (i.e., filled pauses (e.g., *um, er*) and unfilled pauses greater than 300 ms in length), we (Mack et al., 2013) found more frequent pauses in pre-noun compared to pre-verb production for individuals with PPA-L, suggesting greater word-retrieval difficulty for nouns than for verbs in this patient group.

Verb-argument structure production is also relatively preserved in PPA-L; speakers with PPA-L produce few verb-argument structure errors in narrative speech (Thompson, Cho, et al., 2012), and intransitive and transitive verbs are named with similar accuracy (Thompson, Lukic, et al., 2012). In PPA-S, production and comprehension of verbs is also relatively preserved, with a marked impairment in noun processing (Hillis et al., 2004, 2006; Thompson, Lukic, et al., 2012). In connected speech samples, N:V ratios are significantly lower in speakers with PPA-S ($\underline{M}$ = 0.74) than in controls ($\underline{M}$ = 1.21), again, indicating impaired noun production (Thompson, Cho, et al., 2012; Wilson, Henry, et al., 2010), and no deficits in verb-argument structure production have been observed (Thompson, Cho, et al., 2012).

Two studies have investigated online processing of verbs during sentence comprehension in PPA, with conflicting results. Peelle et al. (2007) found that listeners with PPA-G show intact sensitivity to thematic violations (e.g., implausible subjects); however, Price and Grossman (2005) found the opposite pattern. That is, their PPA-G participants did not show online sensitivity to thematic violations (e.g., implausible subjects) or transitivity violations (e.g., an intransitive verb combined with a direct object). In addition, Peelle et al. (2007) found impaired sensitivity to morphosyntactic violations (e.g., word class errors, agreement errors), suggesting general verb processing deficits in PPA-G. However, speakers with PPA-S also have shown impaired processing of thematic and transitivity violations (Price & Grossman, 2005). Additional research is needed to identify aspects of online verb processing that are impaired and potential differences in the underlying source of these deficits across subtypes of PPA (i.e., semantic versus syntactic).

Sentence production and comprehension

Sentence production and comprehension is substantially impaired in PPA-G, and relatively mild deficits have also been found in PPA-L. Most quantitative analyses of speech samples have found more grammatical errors in PPA-G than in controls (Knibb et al., 2009; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010) and one study reported a higher rate of grammatical errors in written language samples (Graham et al., 2004). Results are mixed regarding the frequency of morphosyntactic errors in PPA-L. In two studies, we (Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013) found a lower rate of grammatical errors in PPA-L than in PPA-G, with no difference between the PPA-L group and controls. However, Wilson, Henry, et al. (2010) reported that grammatical error rates in PPA-G and PPA-L were both higher than that of age-matched controls.

In addition, the complexity of utterances produced in connected speech samples is reduced in PPA-G and PPA-L. Speakers with PPA-G produce fewer syntactically complex utterances (Ash et al., 2009; Gunawardena et al., 2010; Knibb et al., 2009; Wilson, Henry, et al., 2010) than do cognitively healthy controls, and a reduced rate of embedding has been reported in PPA-L (Wilson, Henry, et al., 2010). In contrast, speakers with PPA-S produce relatively few grammatical errors in connected speech samples (Thompson, Cho, et al., 2012; Wilson, Henry, et al., 2010) as well as a higher rate of embedding than controls (Wilson, Henry, et al., 2010), indicating relatively preserved morphosyntactic production abilities, as well as an apparent tendency to use circumlocution to compensate for lexical-semantic deficits.

Speakers with PPA-G also exhibit deficits in structured sentence production tasks, whereas individuals with PPA-L and PPA-S show relatively unimpaired performance (DeLeon et al., 2012; Thompson, Meltzer-Asscher, et al., 2013). In particular, non-canonical sentences are prone to impairment in PPA-G. Results from a primed sentence production task indicated that while speakers with PPA-G and PPA-L produce canonical sentences (e.g., active sentences, subject *wh*-questions and subject-relative clauses) with comparable accuracy, accuracy is lower in PPA-G than in PPA-L for non-canonical sentences (e.g., passive sentences, object *wh*-questions and object-relative clauses) (Thompson, Meltzer-Asscher, et al., 2013). Specifically, mean production accuracy in PPA-G was 100%, 88% and 80% for active sentences, subject *wh*-questions and subject-relative clauses, respectively; similarly, for the PPA-L participant group accuracy was 97%, 93% and 87% for these canonical forms. Between group differences, however, emerged for the non-canonical forms, production accuracy for PPA-G speakers was 54% for passive sentences, 70% for object *wh*-questions and 32% for object-relative clauses; whereas, for speakers with PPA-L accuracy was 92%, 96% and 68%, respectively, for these more syntactically complex sentences. Non-canonical sentence production deficits in this task have also been observed in stroke-induced agrammatic aphasia (Cho-Reyes & Thompson, 2012; Thompson, Meltzer-Asscher, et al., 2013).

Impaired complex sentence comprehension also is a primary characteristic of PPA-G (Amici et al., 2007; Cooke et al., 2003; Grossman & Moore, 2005; Grossman et al., 1996; Hodges & Patterson, 1996; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Dronkers, et al., 2010), and has also been noted in PPA-L, albeit sentence deficit patterns differ for the two groups (Amici et al., 2007; Gorno-Tempini et al., 2004). One study (Thompson, Meltzer-Asscher, et al., 2013) found greater impairment of non-canonical sentence comprehension in PPA-G than in PPA-L, with no difference between groups in comprehension of canonical forms. A similar pattern was found for stroke-induced agrammatic and anomic aphasia, respectively. However, another study reported numerically poorer non-canonical sentence comprehension in PPA-L than in PPA-G (Amici et al., 2007). These mixed results may be due to deficits in different components of non-canonical sentence processing in the two groups. Wilson et al. (2012) report that, while non-canonical sentence comprehension is generally impaired in PPA-G, listeners with PPA-L exhibit impaired comprehension only of long non-canonical forms. This suggests that sentence comprehension deficits may be largely due to morphosyntactic deficits in PPA-G but verbal working memory deficits may underlie comprehension impairments noted in PPA-L. In PPA-S, sentence comprehension is relatively preserved (Breedin & Saffran, 1999; Gorno-Tempini et al., 2004), though impairments in complex sentence comprehension sometimes emerge as the disease progresses (Grossman & Moore, 2005; Hodges & Patterson, 1996).

NEURAL MECHANISMS OF GRAMMATICAL PROCESSING DEFICITS

In an attempt to understand the neural mechanisms underlying grammatical processing deficits in PPA, we begin with a brief overview of neuroimaging studies examining aspects of grammatical processing in cognitively healthy individuals. Several such studies have investigated the neural correlates of grammatical morphology and functional category processing, with results indicating that processing of inflectional morphology (e.g., tense, agreement) is supported by the left inferior frontal gyrus as well as left motor and premotor regions and posterior parietal regions (Kielar, Milman, Bonakdarpour, & Thompson, 2011; Shapiro, Moo, & Caramazza, 2012; Tyler, Stamatakis, Post, Randall, & Marslen-Wilson, 2005). In addition, one fMRI study (Diaz & McCarthy, 2009) found that left-lateralised inferior frontal, middle temporal and inferior parietal regions support processing of function and content words in isolation.

Neuroimaging studies of word class processing (specifically nouns vs. verbs) have yielded mixed results, which appear to differ depending on fMRI task requirements (see Crepaldi, Berlingeri, Paulesu, & Luzzatti, 2011, for review). However, converging evidence from several investigations implicate posterior perisylvian regions for verb-argument structure processing (see Thompson & Meltzer-Asscher, 2014). In young and older cognitively healthy adults, posterior perisylvian regions, including the middle and superior temporal gyri, as well as the angular and supramarginal gyri are differentially activated by verbs with more as compared to fewer arguments in studies using lexical tasks (Thompson, Bonakdarpour, & Fix, 2010; Thompson et al., 2007; Thompson, Riley, et al., 2013) as well as anomaly detection tasks (e.g., Ben-Shachar, Hendler, Kahn, Ben-Bashat, & Grodzinsky, 2003). In addition, integration of verbs with their arguments has been associated with the left posterior middle and superior temporal gyri (Friederici, 2011; Thompson & Meltzer-Asscher, 2014).

Sentence comprehension in cognitively healthy individuals is also supported by a left-lateralised network that includes the inferior and middle frontal gyri, the middle and superior temporal gyri, and the angular gyrus (see den Ouden et al., 2012; Friederici, 2011; Indefrey, Hellwig, Herzog, Seitz, & Hagoort, 2004; Segaert, Menenti, Weber, Petersson, & Hagoort, 2012; Thompson & Kielar, in press; Thompson, den Ouden, Bonakdarpour, Garibaldi, & Parrish, 2010, and many others). Less is known about the neural basis of grammatical production in cognitively healthy speakers; but again, neuroimaging studies have highlighted the left fronto-temporal-parietal language network for sentence production, in particular inferior frontal regions (Grande et al., 2012; Indefrey et al., 2004; Segaert et al., 2012).

Lesion-deficit correlational studies of patients with stroke-induced agrammatism support these neural activation patterns, although limitations in the interpretation of such studies diminish their contribution to understanding the neural mechanisms of language processing. Patients with agrammatic aphasia resulting from stroke evince lesions in this fronto-temporal-parietal network (i.e., middle cerebral artery lesions involving perisylvian frontal areas, extending posteriorly in many cases). As noted above, many patients with agrammatism resulting from stroke show grammatical deficits across linguistic domains (i.e., grammatical morphology, functional categories, verb argument structure). Sentence comprehension deficits are also a major characteristic of agrammatic aphasia, associated with lesions in the left hemisphere inferior and middle frontal gyri, anterior temporal lobe and temporo-parietal junction (Bates et al., 2003; Caplan et al., 2007; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Magnusdottir et al., 2012; Thothathiri, Kimberg, & Schwartz, 2012). Sentence production deficits are also associated with lesions in these regions (Bates et al., 2003; Borovsky, Saygin, Bates, & Dronkers, 2007), although few (if any) studies have directly examined the neural correlates of morphosyntactic production processes in stroke-induced aphasia.

With regard to PPA, very few studies have correlated grammatical deficits with regions of cortical atrophy, apart from detailing general atrophy patterns associated with PPA variants, which, for PPA-G, reflects a complex of grammatical impairments. In PPA, such impairments have most frequently been linked to atrophy in the left inferior frontal gyrus and neighbouring cortical and subcortical regions. As discussed above, these regions typically undergo atrophy in PPA-G but are relatively unaffected in PPA-L and PPA-S (Gorno-Tempini et al., 2004, 2011; Mesulam et al., 2009, 2012). However, no studies to our knowledge have examined atrophy patterns associated with specific deficits in grammatical morphology, functional categories and/or verbs and verb argument structure. Rather, the few studies examining atrophy patterns associated with specific deficits in grammatical processing in PPA are limited to those focused on sentence comprehension and production.

The left posterior inferior frontal gyrus (IFG) has been correlated with impaired sentence comprehension in mixed-subtype groups of participants with PPA (Amici et al., 2007; Wilson et al., 2011), as well as within a group of participants with PPA-G (Peelle et al., 2008). In fact, impaired sentence comprehension in participants with PPA-G and PPA-S is associated with differential atrophy patterns, with that for PPA-S in the left lateral temporal cortex, which supports lexical-semantic processing (Peelle et al., 2008). These findings suggest that sentence comprehension impairments have different primary underlying sources in PPA-G and PPA-S, namely impaired grammatical processing due to atrophy in the left IFG in PPA-G but impaired lexical-semantic processing due to atrophy in anterior temporal regions in PPA-S. In addition, functional MRI studies have demonstrated that the left IFG is functionally impaired in PPA-G. That is, listeners with PPA-G do not exhibit significant activation in the left posterior IFG in response to complex sentences, as do unimpaired listeners; however, they do show relatively normal patterns of activation in left posterior temporal regions (Cooke et al., 2003; Wilson, Dronkers, et al., 2010). These results suggest that atrophy in the left posterior IFG may be the source of grammatically based comprehension deficits in PPA.

We note, however, that neural activation patterns found in fMRI experiments with PPA are difficult to interpret in that, unlike in stroke-induced lesions when affected neural tissue is destroyed, neurodegenerative disease may affect only particular groups and layers of cells, leaving others relatively intact. Hence, atrophied regions may remain functional, albeit normal processing routines may be altered. For example, Wilson, Dronkers, et al. (2010) investigated the relationship between cortical atrophy and functional activation during a sentence comprehension task in patients with non-fluent PPA. The sentence comprehension task manipulated syntactic complexity (e.g., non-canonical vs. canonical sentences). In an age-matched control group, greater activation was found for non-canonical sentences in regions including the left posterior inferior frontal cortex (IFC) and mid-posterior middle temporal gyrus (MTG). In the non-fluent PPA group, the left IFC was found to be atrophic as well as functionally abnormal; this region was activated during sentence comprehension but was not modulated by syntactic complexity. In contrast, the left mid-posterior MTG was also atrophic but exhibited normal functional activations. These findings illustrate the potential for dissociations between cortical atrophy and functional activation in PPA, and provide further evidence suggesting that the left IFG plays a critical role in supporting grammatical processing in PPA. In addition, activation was also found in left anterior inferior frontal regions that were not active in healthy controls, suggesting recruitment of additional neural tissue for task performance and/or inability to suppress neural activity that is normally inhibited during language processing.

Sentence production deficits in PPA also have been associated with atrophy in the left IFG. Using the Northwestern Anagram Test (NAT; Thompson et al., 2011) to test production of canonical and non-canonical *wh*-questions (i.e., subject and object extracted forms), Rogalski et al. (2011) found IFG atrophy associated with impaired sentence construction. DeLeon et al. (2012) and Wilson et al. (2011) found similar atrophy patterns using an elicited production task to test a range of morphosyntactically simple and complex structures. This region has also been argued to support fluent speech production, although inconsistent findings have been reported in the literature. Based on narrative speech production samples, Wilson, Henry, et al. (2010) found a correlation between impaired grammatical production (measured by the proportion of words in sentences and the number of syntactic errors) as well as reduced grammatical complexity (number of embedded clauses produced) and reduced cortical volume in left frontal regions, including the posterior IFG, superior frontal sulcus and supplementary motor area. In addition, they found that decreased fluency (maximum speech rate) correlated with reduced volume in a largely overlapping set of regions. In another study (Gunawardena et al., 2010), both grammatical complexity (number of complex structures produced) and impaired fluency (WPM) in connected speech samples were associated with atrophy in the left anterior IFG and anterior superior temporal gyrus, with reduced fluency additionally associated with atrophy in left premotor and right inferior frontal regions. In contrast, Rogalski et al. (2011) found distinct neural correlates of impaired grammaticality and fluency; decreased cortical thickness in the left posterior and anterior IFG, supplementary motor area and supramarginal gyrus were associated with impaired grammatical production (non-canonical sentence production on the Northwestern Anagram Test; Thompson et al., 2011), whereas largely distinct regions in the left inferior frontal sulcus and middle frontal gyrus were associated with reduced fluency (mean length of utterance in a narrative speech sample). However, it should be noted that mean length of utterance may reflect not only fluency but grammatical production ability as well.

The role of white matter damage in grammatical impairments

Damage to white matter tracts has also been shown to contribute to grammatical deficits in PPA. Some studies indicate that PPA-G involves damage to the left superior longitudinal fasciculus, a dorsal tract that links posterior temporal and parietal regions to frontal and opercular regions. For example, one study found that dorsal white matter changes were associated with grammatical impairments in PPA (Wilson et al., 2011). The authors reported that reduced fractional anisotropy (a measure of white matter integrity) in the left superior longitudinal fasciculus was correlated with impaired performance on measures of grammatical production and comprehension. These correlations persisted after controlling for grey matter volume in the left posterior IFG, which was also correlated with grammatical impairment. In contrast, there was no correlation between grammatical deficits and fractional anisotropy in ventral tracts, specifically the extreme capsule fibre system and uncinate fasciculus. Other studies support this latter finding in that ventral tracts, including the inferior longitudinal and uncinate fasciculi, may be relatively preserved in PPA-G (Catani et al., 2013; Galantucci et al., 2011; Whitwell et al., 2010). Conversely, PPA-L has been associated with relatively circumscribed white matter changes in the temporoparietal branch of the superior longitudinal fasciculus (Galantucci et al., 2011) and ventral language tracts exhibit significant changes in PPA-S, while dorsal tracts are relatively preserved (Agosta et al., 2010; Catani et al., 2013; Galantucci et al., 2011; Whitwell et al., 2010). That said, there is considerable debate in the literature concerning the role of dorsal and ventral tracts in morphosyntactic processing and language processing in general; see e.g., Catani and Mesulam (2008), Friederici (2009), Griffiths, Marslen-Wilson, Stamatakis, and Tyler (2013), Hickok and Poeppel (2007). Saur et al. (2008), for example, found that sentence comprehension is associated with ventral pathways between prefrontal and middle/inferior temporal cortices. Further, in a recent study, Catani et al. (2013) investigated the relationship between deficits in fluency, lexical-semantic processing and grammatical processing (production of subject- and object-w*h* questions on the Northwestern Anagram Test (NAT); Thompson et al., 2011) and white matter changes in the left uncinate fasciculus and frontal aslant tract; the latter is a dorsal pathway connecting the inferior frontal gyrus to medial frontal regions. Changes in the frontal aslant tract were correlated with impaired fluency, whereas damage to the uncinate fasciculus was associated with impaired lexical-semantic processing. Neither tract was associated with grammatical processing. Further research is needed to fully understand the contribution of dorsal and ventral fibre tracts to grammatical processing in PPA.

EVALUATION AND CLINICAL MANAGEMENT OF GRAMMATICAL ABILITIES IN PPA

Assessment of grammatical deficits

Quantification of grammatical abilities in PPA is important in order to accurately classify individuals with PPA by subtype. This, in turn, is important for estimating the trajectory of language decline and associated neuropathology. It has been reported that 60–70% of cases of PPA that have come to autopsy are attributable to FTLD, with the presence of agrammatism associated with FTLD tauopathy (Knibb, Xuereb, Patterson, & Hodges, 2006; Mesulam et al., 2008). Thus, grammatical deficits may be used as an important clinical marker for inferring the nature of the neuropathology during the lifetime of the patient.

One tool for examining grammatical production abilities in PPA is quantitative analysis of connected speech samples. This method has been used to evaluate production patterns in group studies of PPA (Graham et al., 2004; Knibb et al., 2009; Meteyard & Patterson, 2009; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010) as well as to identify patterns of progressive grammatical impairment in individual speakers (Thompson, Ballard, et al., 1997). This method allows researchers/clinicians to assess the major domains of grammatical production (grammatical morphology, functional categories, verbs and verb argument structure, complex sentence production) using a single task. However, a significant disadvantage of this method is that there is no experimental control over the structures elicited, and therefore the results may not provide a full picture of grammatical ability. Further, linguistic analysis of spontaneous discourse is labour intensive and training is required to identify and code the linguistic forms and structures of interest.

Structured tasks have also been developed to study grammatical production, including the *Northwestern Assessment of Verb Inflection* (NAVI; Thompson & Lee, Experimental version), which examines production of grammatical morphology. Using a sentence completion task, the test evaluates both finite (i.e., present singular (e.g., he *eats*), present plural (e.g., they *eat*), past regular (for regular verbs, e.g., *tickled*) and past irregular (for irregular verbs, e.g., *ate*)) and non-finite (i.e., progressive (e.g., (is) *eating*), and infinitive (e.g., *to eat*)) verb forms. Data derived from use of this test with PPA indicate that it is sensitive to verb inflection deficits in PPA, with different patterns found for PPA-G and PPA-L (see Thompson, Meltzer-Asscher, et al., 2013). In addition, grammatical production deficits in PPA have been assessed using the Northwestern Anagram Test (Thompson et al., 2011), which does not require overt production, and is thus particularly useful for assessing production abilities in speakers with severe apraxia or dysarthria. The elicited production task developed by Goodglass et al. (1972) also has been used to examine sentence deficits in PPA (see DeLeon et al., 2012).

Several tests for examining verb production deficits are available, including the *Verb and Sentence Test* (VAST; Bastiaanse, Edwards, & Rispens, 2002), the *Boston Assessment of Severe Aphasia* (BASA; Helm-Estabrooks, Ramsberger, Morgan, & Nicholas, 1989) and *An Object and Action Naming Battery* (OANB; Druks & Masterson, 2000). However, each of these tests has limitations for the purpose of assessing word class deficits in PPA (and other language impairments). The BASA and OANB assess noun and verb production but not comprehension, and the VAST does not assess noun production or comprehension (see Thompson, Lukic, et al., 2012, for further discussion). The latter is a significant limitation given the importance of N:V ratios to the identification of agrammatic language profiles in PPA-G (Thompson, Ballard, et al., 1997; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013). The *Northwestern Naming Battery* (NNB; Thompson & Weintraub, 2014) evaluates production and comprehension of word class deficits, i.e., nouns and verbs, with a set of items from each word class (matched for frequency and other lexical variables) to derive a N:V ratio. In addition, the NNB examines both transitive and intransitive verb comprehension and production. The *Northwestern Assessment of Verbs and Sentences* (NAVS; Thompson, 2011) also includes subtests to evaluate production and comprehension of verbs that vary with respect to argument structure complexity (i.e., number of arguments, obligatory vs. optional arguments), as well as the ability to produce verbs together with their arguments in sentence context (i.e., the Argument Structure Production Test of the NAVS).

For quantification of sentence comprehension and production abilities, examining both canonical and non-canonical structures is important, since this is what differentiates grammatical from other impairments that can affect sentence processing ability. General aphasia batteries such as the *Western Aphasia Battery-Revised* (WAB-R; Kertesz, 2006) and the *Boston Diagnostic Aphasia Examination* (BDAE; Goodglass & Kaplan, 1983) do not assess production or comprehension of canonical versus non-canonical sentences. Therefore, administration of tests explicitly designed for this purpose is necessary. A few options are available, including the VAST developed by Bastiaanse et al. (2002), which examines several sentential structures across modalities. The Curtiss–Yamada Comprehension Language Evaluation (CYCLE; Curtiss & Yamada, unpublished) also examines comprehension (but not production) of sentences that vary with respect to syntactic complexity (Amici et al., 2007; Gorno-Tempini et al., 2004). Wilson, Dronkers, et al. (2010) and Wilson et al. (2011) used a syntactic comprehension task loosely based on the CYCLE, which was specifically developed for PPA patients in order to reduce lexical processing demands. Another measure for evaluating sentence deficits in PPA is the NAVS (Thompson, 2011), which was standardised with PPA (and stroke-aphasic) patients (Thompson, Meltzer-Asscher, et al., 2013). The NAVS assesses both production and comprehension of the same canonical (actives, subject *wh*-questions, subject-relatives) and non-canonical structures (passives, object *wh*-questions and object-relatives). Production of these forms is tested in the Sentence Production Priming Test (SPPT), whereas comprehension is tested, using the same stimuli, in the Sentence Comprehension Test of the NAVS. Notably, scores derived from the SPPT are highly correlated with those derived from the NAT in patients with PPA (Weintraub et al., 2009); hence, for patients devoid of severe motor speech deficits, we recommend using the NAVS to examine both production and comprehension of canonical and non-canonical sentence forms.

Treatment of grammatical impairments

Few studies evaluating the effects of treatment for PPA have been published, with the majority focused on improving naming and word retrieval deficits (typically objects) and limited to case studies with small cohorts of patients (for a recent review, see Henry et al., 2013). To our knowledge, only three studies have addressed treatment for morphosyntactic deficits in PPA-G. Using a combined verbal plus gestural treatment, Schneider, Thompson, and Luring (1996) showed improved verb morphology (i.e., tensed verb production) in sentence contexts in a woman with PPA, who presented with deficits consistent with PPA-G. In another study, Finocchiaro and colleagues (Finocchiaro et al., 2006) examined the effects of repetitive transcranial magnetic stimulation (rTMS) on verb morphology (i.e., verbs inflected for tense or person) in a 60-year old man with PPA with a selective deficit in verb production accompanied by left fronto-temporal cortical atrophy. Using high-frequency rTMS applied to the left prefrontal cortex, the patient showed improved production of verbs, but not nouns, in sentence completion tasks. Similarly, Cotelli et al. (2012) found that high-frequency rTMS, applied to the dorsolateral prefrontal cortex in either the left or right hemisphere, improved action (verb) compared to object (noun) naming in individuals with PPA-G, but not PPA-S. These results suggest that grammatical abilities in people with PPA may be improved with treatment. However, additional research is needed to replicate the aforementioned effects and to evaluate the effects of treatment for other grammatical impairments in people with PPA (i.e., functional category deficits, sentence comprehension and production deficits, etc.). Two basic questions need to be explored across grammatical domains: (1) can grammatical processing be improved with treatment and/or does treatment slow the decline of grammatical abilities in PPA?, and (2) are behavioural treatment effects boosted by and maintained over time using cortical stimulation?

SUMMARY AND CONCLUSION

This article reviewed research on grammatical deficit patterns seen in individuals with PPA, indicating that grammatical impairments, including grammatical morphology, functional category, verb and verb argument structure, and complex sentence processing deficits, differentiate PPA-G from other PPA subtypes. Importantly, fluency is not directly associated with grammatical impairments. To date, relatively little research has addressed online grammatical processing in PPA. Much has been learned in stroke-aphasia about the nature of grammatical impairments by observing real-time performance, e.g., aspects of the normal processing system that are impaired. Thus, online studies may better inform our understanding of the underlying causes of grammatical deficits in PPA.

The cortical atrophy patterns associated with grammatical deficits (i.e., left posterior frontal, insula and subcortical white matter tracts) also differ from those associated with impairments in other domains of language (e.g., semantic deficits, associated with the anterior temporal region). However, there have been few functional neuroimaging studies of grammatical processing in PPA. Furthermore, there is need for additional structural and functional neuroimaging studies that target other aspects of grammatical processing (e.g., functional categories, grammatical morphology, verbs and verb argument structure).

Because of the importance of identifying grammatical impairments for differential diagnosis of PPA as well as neuropathological trajectories, assessment of grammatical abilities is an essential component of the PPA evaluation. Notably, recently developed assessment tools for this purpose are now available and we recommend their use. Finally, we point out that dearth studies are available for treatment of grammatical deficits in PPA. Research is needed to better understand how (or if) grammatical processing ability can be improved in PPA, the potential for functional (spared) neural tissue to be recruited to support this and whether the neural connections within areas of dysfunctional tissue required for grammatical processing can be enhanced using cortical stimulation.

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