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Elicitation of specific syntactic structures in primary progressive aphasia

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ABSTRACT

Many patients with primary progressive aphasia (PPA) are impaired in syntactic production. Because most previous studies of expressive syntax in PPA have relied on quantitative analysis of connected speech samples, which is a relatively unconstrained task, it is not well understood which specific syntactic structures are most challenging for these patients. We used an elicited syntactic production task to identify which syntactic structures pose difficulties for 31 patients with three variants of PPA: non-fluent/agrammatic, semantic and logopenic. Neurodegenerative and healthy age-matched participants were included as controls. As expected, non-fluent/agrammatic patients made the most syntactic errors. The structures that resulted in the most errors were constructions involving third person singular present agreement, and constructions involving embedded clauses. Deficits on this elicited production task were associated with atrophy of the left posterior inferior frontal gyrus.

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1. Introduction

Primary progressive aphasia (PPA) is a neurodegenerative syndrome in which focal degeneration of language areas leads to progressive language deficits, with other cognitive domains relatively spared (Gorno-Tempini et al., 2011; Mesulam, 1982, 2001). There are three widely recognized variants of PPA. Non-fluent/agrammatic PPA is characterized by agrammatism and/or apraxia of speech (Grossman et al., 1996; Hodges & Patterson, 1996); semantic PPA (also known as semantic dementia) involves deficits in lexical and semantic knowledge (Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Neary, 1989; Warrington, 1975); and logopenic PPA is associated with phonological and word-finding deficits (Gorno-Tempini et al., 2004, 2008). The three variants differ in terms of distribution of atrophy (Gorno-Tempini et al., 2004) and underlying pathologies (Grossman, 2010; Snowden et al., 2011).

Syntactic production and comprehension are impaired in non-fluent/agrammatic PPA and to some extent in logopenic PPA, but are relatively spared in semantic PPA (Gorno-Tempini et al., 2004; Grossman et al., 1996; Hodges & Patterson, 1996; Thompson, Ballard, Tait, Weintraub, & Mesulam, 1997; Wilson, Dronkers, et al., 2010; Wilson, Henry, et al., 2010; Wilson et al., 2011; for review see Wilson, Galantucci, Tartaglia, & Gorno-Tempini, 2012). Assessment of syntactic production is not always straightforward. Most studies that have investigated syntactic production in PPA have done so by quantitative analysis of samples of connected speech (Ash et al., 2006, 2009; Bird, Lambon Ralph, Patterson, & Hodges, 2000; Graham, Patterson, & Hodges, 2004; Gunawardena et al., 2010; 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 et al., 1997; Thompson, Cho, et al., 2012; Wilson, Henry, et al., 2010). While this approach provides rich and comprehensive data, the unconstrained nature of elicited narratives or picture descriptions poses several challenges. Individuals differ in terms of which syntactic structures they will select to tell a narrative or describe a scene. Therefore, it is difficult to determine which particular syntactic structures are difficult for patients, because some patients may attempt challenging structures, resulting in errors, whereas others may produce simplified structures in order to avoid errors (Wilson, Henry, et al., 2010). Furthermore, sometimes when patients make errors, it is not possible to determine the intended structure with certainty.

An alternative approach, which has been employed in just a few studies, is to use elicited production tasks (Thompson, Meltzer-Asscher, et al., 2012; Weintraub et al., 2009). Weintraub et al. (2009) proposed the Northwestern Anagram Test (NAT), which requires that patients assemble words on printed cards to produce sentences describing pictures. The words that are provided (the first few of which are placed for the patient) constrain the sentence that can be produced. Using the NAT, the authors showed that PPA patients perform more poorly on non-canonical syntactic structures—passives, object wh-questions, and object relatives—than

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they do on canonical structures. However PPA patients were not divided according to variants in that study. In a subsequent study, impairments on the NAT were linked to reduced cortical thickness in the left inferior frontal gyrus, ventral sensorimotor cortex, and supramarginal gyrus (Rogalski et al., 2011).

In another study from the same group, Thompson, Meltzer-Asscher, et al. (2012) investigated syntactic production in non-fluent/agrammatic and logopenic patients using two elicitation procedures. In one, the Sentence Production Priming Test (SPPT), the experimenter would describe a picture using a particular sentence structure, and the patient was required to describe another picture using the same structure. In the other, a sentence completion task was used to elicit verbs in various finite or non-finite forms. The authors showed that non-fluent/agrammatic patients have specific difficulties with non-canonical structures such as passives, object wh-questions, and object relatives, and with production of finite verb forms. Their performance was better when they produced canonical structures and non-finite verb forms. In contrast, logopenic patients made comparatively few errors, and did not show the same decrement in performance on non-canonical structures and non-finite verb forms (Thompson, Meltzer-Asscher, et al., 2012).

These elicited production studies have provided valuable data about production of syntactic structures in PPA. However, only a limited range of structures have been investigated so far. Furthermore, the NAT and the SPPT likely make significant demands on executive processes and verbal working memory, which may complicate interpretation. Finally, while Thompson, Meltzer-Asscher, et al. (2012) compared non-fluent/agrammatic and logopenic patients, no study has examined syntactic production using an elicited production procedure in all three PPA variants.

In this study, we investigated syntactic production in the three variants of PPA, using an elicited production task (Goodglass, Gleason, Bernholtz, & Hyde, 1972) to probe production of eleven specific syntactic structures varying in complexity. This simple story completion task is easily understood by patients and appears to make limited demands on other processes. The primary aim of the study was to determine which structures are difficult for patients with PPA. A secondary aim was to identify brain regions where atrophy was predictive of syntactic production deficits as quantified by this elicited production task.

2. Methods

2.1. Participants

Six groups of participants were recruited through the UCSF Memory and Aging Center: three variants of PPA; patients with behavioral variant fronto-temporal dementia (bvFTD); patients with other neurodegenerative diseases (“mixed neurodegenerative”); and healthy age-matched controls. The bvFTD and mixed neurodegenerative groups were included as neurodegenerative control groups. All participants gave written informed consent, and the study was approved by institutional review boards at UCSF and the University of Arizona.

Participants received a comprehensive evaluation including a neurological history and examination, neuropsychological testing, and neuroimaging. Patients were diagnosed with PPA based on recently published criteria (Gorno-Tempini et al., 2011), with bvFTD according to established criteria (Neary et al., 1998), or with other neurodegenerative diseases (see below). The mixed neurodegenerative group were patients whose language was evaluated because they had some language symptoms, but for whom language was not the primary complaint. Additionally, participants were required to be fluent in English, and to have sufficiently preserved language abilities to be able to complete the task.

A total of 58 individuals took part in the study. There were 16 patients with non-fluent/agrammatic PPA, 7 with semantic PPA, 8 with logopenic PPA, 6 with bvFTD, 9 with other neurodegenerative diseases, and 12 healthy age-matched controls. The mixed neurodegenerative group comprised patients who were diagnosed with Alzheimer’s disease ($N = 4$), corticobasal syndrome with suspected Alzheimer’s pathology ($N = 3$), mixed bvFTD and Alzheimer’s disease ($N = 1$), and mixed bvFTD with motor neuron disease ($N = 1$).

Demographic information and neuropsychological data for each group is presented in Table 1. The three PPA variant groups did not differ from one another in terms of age, sex, handedness, education, MMSE, CDR, age of disease onset, or years from first symptom. Because patients who could not complete the task at all were not included, our samples were composed of mild to moderate patients, as reflected in the MMSE and CDR scores.

2.2. Elicited production task

We used an elicited production task described by Goodglass et al. (1972) to determine which common syntactic constructions are spared or impaired in the three variants of PPA. The examiner began the task by informing the patient ‘I will begin a story and ask you to finish it in the most logical and most simple way possible’. A prompt was then read, such as the first item: ‘My friend comes in. I want him to sit down. So I say to him... what?’ The patient then typically responded ‘Sit down’ or similar. This item targets an intransitive imperative. The examiner repeated the prompt once if requested by the patient, but no other directions or prompts were given.

There were 14 targeted structures, each with two items, for a total of 28 items. However the last three structures (the last six items) rarely yielded the intended response, so we did not include those in our analysis. The complete list of prompts for the 11 structures analyzed, along with the intended responses and targeted structures are shown in Table 2.

Participants’ responses were recorded on a Sony camcorder and digitized with VirtualDub, except for one of the patients with non-fluent/agrammatic PPA who was mute and completed the task by writing. Responses were transcribed and coded by two raters (JDL and MB), both of whom were blind to patient diagnosis.

The raters coded: (1) whether the targeted syntactic construction was attempted; (2) if attempted, whether the targeted syntactic structure was produced correctly; (3) presence of any syntactic errors, e.g. missing determiners or inflections (in the target structure or in other parts of the response, regardless of whether the target structure was attempted); (4) presence of any semantic errors, defined as use of words or phrases that were inappropriate for the intended meaning or context (in the target structure or in other parts of the response, regardless of whether the target structure was attempted).

We scored a response as an attempt at the target syntactic structure if it contained all of the required elements for the particular item. For example, for item 10a to be scored as attempted, the response had to be a declarative sentence including a passive in the past tense. If the target syntactic structure was attempted, we recorded it as a correct attempt if it was free of syntactic errors. The response could still be recorded as a correct attempt if it contained semantic errors, phonological paraphasias or distortions.

We also counted the number of words produced by each subject in total. We excluded non-narrative words such as coordinating conjunctions and comments that did not directly address the prompt. We excluded filled pauses, i.e. words such as ‘ah’ or ‘um’. We also excluded false starts, which included partial words that were either followed by production of the word in completed

Table 1
Demographic and neuropsychological data on the participants.

	PPA			bvFTD	Mixed neurodegen.	Normal controls	Sig.
	Non-fluent/ agrammatic	Semantic variant	Logopenic variant				
Demographic							
Age	72.4 (6.7)	66.0 (5.9)	62.9 (8.8)	67.8 (8.4)	64.8 (14.8)	68.3 (3.7)	ns
Sex (M/F)	5/11	3/4	5/3	4/2	6/3	5/7	ns
Handedness (R/L/ambi)	16/0/0*	5/2/0	7/1/0	6/0/0	7/0/2	7/5/0	***
Education	15.3 (3.2)	15.0 (2.1)	16.4 (3.5)	16.0 (2.5)	16.2 (3.5)	18.0 (0.9)	ns
Status							
MMSE (30)t	24.9 (4.2)***	26.6 (2.5)*	25.6 (3.2)*	26.3 (3.5)+	19.6 (8.5)***	29.3 (1.5)	***
CDR Totalf	0.5 (0.3)***	0.5 (0.0)***	0.5 (0.0)***	1.5 (0.5)***	0.9 (0.6)***	0.0 (0.0)	*
Age at disease onset	65.3 (6.2)	56.8 (7.2)	57.9 (8.9)	55.5 (11.1)	54.0 (11.4)[a]	n/a	*
Years from first symptom	4.2 (1.7)	6.7 (2.9)	3.9 (2.0)	8.5 (6.7)	4.8 (3.3)	n/a	+
Language production							
BNT(15)	12.0 (3.2)+	3.7 (3.3)***,a,c	11.5 (2.6)+	12.0 (1.9)	11.1 (3.0)*	14.5 (0.5)	***
Phonemic fluency (D words)	4.8 (2.5)***	4.9 (2.7)***	8.3 (4.6)***	10.3 (6.1)*	6.5 (6.3)***	18.9 (5.3)	***
Semantic fluency (animals)	9.3 (5.0)***	6.0 (3.7)***	10.5 (3.3)***	13.8 (6.7)*	9.1 (6.2)***	23.6 (4.5)	***
Speech fluency (WAB, 10)	7.1 (2.5)°	8.7 (0.8)	9.25 (0.7)	9.7 (0.5)	8.3 (2.2)	n/a	*
Repetition (WAB, 100)	82.8 (13.8)	92.6 (7.8)	73.4 (15.2)[b]	93.2 (5.5)	84.0 (19.4)	n/a	+
Motor speech							
AOS (MSE, 7)†	2.5 (1.8)[b,c]	0.0 (0.0)	0.5 (1.4)	0.0 (0.0)	1.2 (1.7)	n/a	***
Dysarthria rating (MSE, 7)†	2.2 (2.9)	0.0 (0.0)	0.4 (1.1)	1.0 (1.3)	0.4 (0.9)	n/a	+
Language comprehension							
Word recognition (WAB, 60)	59.0 (2.5)	53.9 (6.1)	59.0 (1.8)	60.0 (0.0)	57.6 (4.1)	n/a	*
Sequential commands (WAB, 80)	71.8 (9.3)	75.7 (8.8)	72.5 (8.1)	77.7 (4.1)	68.1 (14.7)	n/a	ns
Syntactic comprehension (CYCLE, 55)	45.2 (7.1)	50.1 (4.5)	44.1 (6.0)	48.0 (8.7)	40.3 (12.8)	n/a	ns
PPTP (52)	48.2 (4.0)	39.0 (7.3)[a,c]	49.3 (1.9)	48.4 (4.8)	43.6 (2.2)	n/a	***
Reading							
PALPA regular words (30)	28.5 (2.2)	27.1 (3.7)	29.1 (0.9)	30.0 (0.0)	29.7 (0.8)	n/a	+
PALPA exception words (30)	26.8 (3.6)	21.1 (5.0)[a,c]	27.9 (2.7)	29.0 (1.4)	29.8 (0.4)	n/a	**
PALPA pseudowords (24)	18.8 (6.2)	20.0 (2.6)	19.9 (2.5)	20.5 (3.5)	20.8 (3.2)	n/a	ns
Visuospatial function							
Modified Rey-Osterrieth copy (17)	14.7 (1.8)	16.0 (0.8)	13.8 (1.7)	15.5 (0.8)	12.1 (3.7)**	15.6 (0.5)	**
Visual memory							
Modified Rey-Osterrieth delay (17)	9.6 (3.6)	10.0 (3.8)	6.4 (1.8)*	8.5 (5.8)	5.9 (5.7)*	11.6 (2.3)	*
Verbal memory							
CVLT-MS trials 1-4	21.3 (7.9)	16.4 (7.7)	19.8 (5.5)	20.8 (8.8)	16.3 (9.6)	n/a	ns
CVLT-MS 30s free recall (10)	6.1 (2.2)	2.3 (2.1)[a]	5.0 (1.9)	4.0 (4.0)	3.8 (3.1)	n/a	*
CVLT-MS 10 min free recall (10)	5.7 (2.3)	1.9 (2.3)[a]	4.3 (1.8)	3.7 (4.2)	2.9 (3.6)	n/a	*
Executive function							
Digit span backwards	3.3 (1.1)***,b	4.9 (1.3)	3.4 (0.9)**	4.2 (1.3)	3.3 (1.4)***	5.7 (1.3)	***
Modified trails (lines per min)	12.3 (10.9)***	23.0 (10.5)*	16.0 (9.5)***	20.1 (12.3)**	12.8 (12.0)***	40.9 (15.6)	***
Calculation (5)	4.6 (1.0)	4.7 (0.5)	3.5 (0.5)**,a	4.7 (0.5)	2.8 (1.5)***	5.0 (0.0)	***

Values shown are mean (standard deviation).
Sig = Omnibus significance; ns = not significant; MMSE = Mini Mental State Exam; CDR = Clinical Dementia Rating; WAB = Western Aphasia Battery; MSE = Motor Speech Evaluation (Wertz, LaPointe, & Rosenbek, 1984); CYCLE = Curtiss-Yamada Comprehensive Language Examination; PALPA = Psycholinguistic Assessments of Language Processing in Aphasia; CVLT-MS = California Verbal Learning Test – Mental Status.
† Tested with nonparametric statistics.
* Significantly impaired relative to normal controls at $p < 0.05$.
** Significantly impaired relative to normal controls at $p < 0.01$.
*** Significantly impaired relative to normal controls at $p < 0.001$.
[a] For the PPA patients only, superscript letters indicate significantly impaired relative to nonfluent/agrammatic at $p < 0.05$.
[b] For the PPA patients only, superscript letters indicate significantly impaired relative to semantic at $p < 0.05$.
[c] For the PPA patients only, superscript letters indicate significantly impaired relative to logopenic at $p < 0.05$.
+ Marginal significance: $p < 0.10$.

form (e.g. 's- sofa') or were abandoned without completion of the word (e.g. 'He sm- well, he laughs'). Contractions such as 'she'll' were counted as one word.

2.3. Statistical analysis

Statistical analysis was performed with R version 2.14.0 (http://www.r-project.org). The six groups were compared using ANOVAs for normally distributed variables, or the Kruskal–Wallis non-parametric test for measures with significant floor or ceiling effects. If the omnibus test was significant, we conducted planned contrasts between each patient group and controls, and between each pair of PPA variants. For ANOVAs, follow-up tests were corrected for multiple comparisons with the default single step procedure implemented in the R program *glht*, whereas non-parametric follow-up tests were Wilcoxon tests performed with *wilcox.exact* and corrected for multiple comparisons using *p-adjust* with Holm's procedure. Performance on specific items was compared using χ^2 tests, with Yates' continuity correction where appropriate.

2.4. Voxel-based morphometry

Structural T1-weighted images were acquired on 1.5T, 3T or 4T Siemens scanners as described previously (Wilson, Dronkers, et al., 2010; Wilson, Henry, et al., 2010). The 12 normal controls were not included. Three patients' scans were not of sufficient quality and so

Table 2
Stimuli used to elicit syntactic structures.

Item	Targeted structure	Prompt scenario	Targeted response
1a	Imperative intransitive	My friend comes in. I want him to sit down. So I say to him... What?	Sit down.
1b	Imperative intransitive	My cousin is at the door. I want him to come in. So I open the door and say... What?	Come in.
2a	Imperative transitive	My little son eats lunch. He has not touched his milk. I want him to drink it. So I say to him... What?	Drink your milk.
2b	Imperative transitive	The grass needs to be cut. I give my son the lawn mower, and I tell him... What?	Mow the grass.
3a	Declarative intransitive with 3sg pres agreement	A baby has a toy. I take the toy away. What happens?	The baby cries.
3b	Declarative intransitive with 3sg pres agreement	The baby smiles. I want the baby to laugh. I tickle the baby. What happens?	The baby laughs.
4a	Declarative transitive with 3sg pres agreement	Dogs always chase cats. A dog is in the street. A cat comes along. What happens?	The dog chases the cat.
4b	Declarative transitive with 3sg pres agreement	Mr. Jones wants to hear the news. The radio is off. What happens?	He turns the radio on.
5a	Declarative ditransitive with 3sg pres agreement	She owes her friend a dollar. She goes to see her friend. She takes out a dollar. What next?	She gives her the dollar.
5b	Declarative ditransitive	My dog is hungry. I get a bone to give to the dog. What next?	I give the dog the bone.
6a	Yes/no interrogative in past tense	John is in his room. He thinks he hears his mother call. So he goes downstairs to see if she called him, and he asks... What?	Did you call me?
6b	Yes/no interrogative in past tense	Mother sent Johnny upstairs to wash and brush his teeth. When he came down, she wondered if he brushed his teeth. She asks... what?	Did you brush your teeth?
7a	Wh interrogative declarative in past tense	Jane can't find her shoes. Her mother has just cleaned the Where did you put my shoes? room. She knows her mother put them somewhere. So she asks... What?	
7b	Wh interrogative declarative in past tense	The father broke the toy. He couldn't fix it. But his son fixed it and the father wondered how. So he asked... What?	How did you fix the toy?
8a	Future intransitive	John works every Saturday. He worked last Saturday, too. And next Saturday... what?	He will work again.
8b	Future transitive	Father smokes his pipe every evening after supper. Supper is just over now. What will happen now?	He will smoke his pipe.
9a	Declarative with embedded small clause	The children were being too noisy. Mother was annoyed. She wanted... what?	... the children to be quiet.
9b	Declarative with embedded small clause	The soldier's gun was dirty. The sergeant was annoyed. So he called the soldier over and told him he wanted... what?	... the soldier to clean the gun.
10a	Passive in past tense	A man was walking on the railroad tracks. A train came along. The man didn't hear it. What happened to him? The man... what?	... was hit by the train.
10b	Passive in past tense	A little girl went too near the angry dog. What happened to her? She... what?	... was bitten.
11a	Comparative	Little Johnny couldn't reach the cookies. He wasn't tall enough. He called his sister and she reached the cookies for him. How come?	She was taller.
11b	Comparative	Mrs. Jones tried to open the jar. She wasn't strong enough. So she called her husband and he did it the first try. How come?	He was stronger.

These stimuli were created by Goodglass et al. (1972).

were excluded (one patient was diagnosed with non-fluent/agrammatic PPA and two with mixed neurodegenerative disease). Therefore there were 43 participants included in this analysis. Images were registered to each other and to Montreal Neurological Institute (MNI) space using SPM5 (Ashburner & Friston, 2005) and DARTEL (Ashburner, 2007). Modulated gray matter and white matter probability maps were scaled by Jacobians, smoothed with a Gaussian kernel of 8 mm full-width at half maximum, then summed together to obtain a map of brain parenchyma.

We correlated percent correct on target structures that were attempted with brain parenchyma probability maps. Covariates of age, sex, total intracranial volume, and scanner type were included in the analysis. The resulting statistical map was thresholded at voxelwise $p < 0.01$, then corrected for multiple comparisons based on cluster size using a permutation method. Specifically, 1000 randomly permuted maps were created, and the largest cluster in each was used to determine the null distribution of maximum cluster size. Permuted maps were masked to include only left hemisphere perisylvian language areas: the left inferior frontal gyrus, pars opercularis and triangularis, the Rolandic operculum, the superior temporal gyrus, and the supramarginal gyrus, based on an anatomical atlas (Tzourio-Mazoyer et al., 2002). This mask was used to increase statistical power, however it should be noted that in the non-permuted analysis of the real data, no regions outside the mask were significantly associated with the syntactic measure. Three additional analyses were also performed including measures of executive function and working memory (digit span backwards, modified trails, and calculation) as covariates.

3. Results

3.1. Number of words produced

The groups produced similar total numbers of words across their responses ($F(5,51) = 1.64$, $p = 0.17$) (Fig. 1a, Table 3). Non-fluent/agrammatic PPA patients produced somewhat fewer words than controls, and semantic PPA patients produced somewhat more, but these differences were not significant.

3.2. Frequency of attempts at targeted structures

The groups differed significantly in the frequency with which they attempted the targeted structures ($F(5,52) = 3.05$, $p = 0.017$) (Fig. 1b, Table 3). Follow-up comparisons revealed that all neurodegenerative groups except for the bvFTD group attempted targeted structures less frequently than healthy controls (non-fluent/agrammatic: $t = 3.39$, $p = 0.0094$; semantic: $t = 2.73$, $p = 0.055$; logopenic: $t = 2.87$, $p = 0.039$; mixed: $t = 2.76$; $p = 0.051$). The three PPA variants did not differ from one another (all $t \leqslant 0.035$) in how often they attempted the targeted structures.

The 22 items differed in the frequency with which participants attempted the targeted structure ($\chi^2(21) = 186.38$, $p < 0.001$) (Fig. 2). While most targeted structures were obtained more than half the time, a few items were particularly unsuccessful: the two items designed to elicit ditransitives (5a and 5b), one of the items intended to elicit an embedded clause (9a), and one intended to elicit a comparative structure (11a).

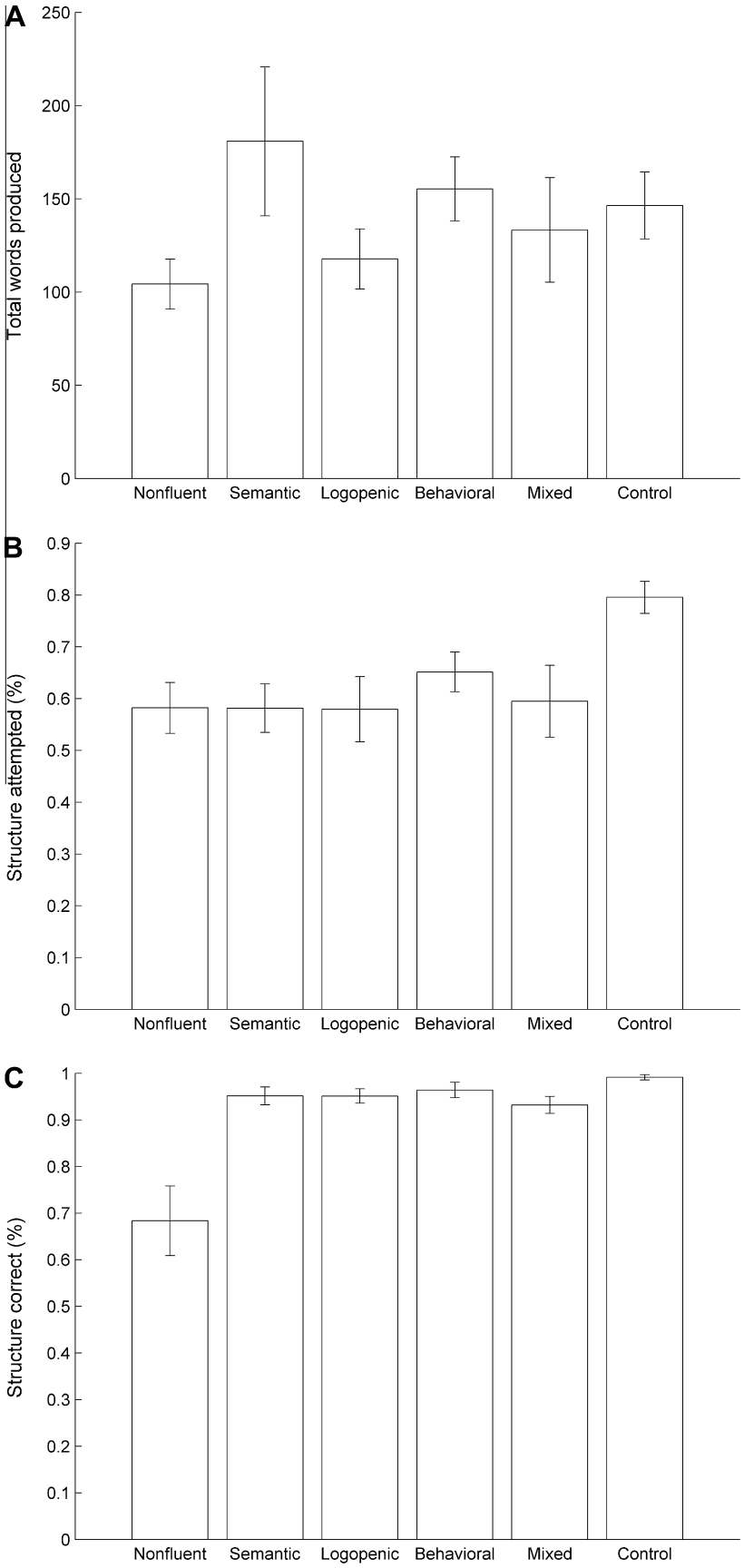

Fig. 1. Responses to the elicited syntactic production task. (A) Total number of words produced. (B) Frequency with which the targeted structures were attempted. (C). Accuracy on the targeted structures, when they were attempted.

Table 3
Responses to the elicited syntactic production task.

	PPA				Mixed neurodegen.	Normal controls	Sig
	Non-fluent/ agrammatic	Semantic variant	Logopenic variant	bvFTD			
Total number of words produced	104.3 (16.6)	180.9 (25.1)	117.8 (23.5)	155.3 (27.2)	133.3 (23.5)	146.4 (19.2)	ns
Targeted structures attempted (%)	58.2 (4.1)**	58.2 (6.2)$^{+}$	58.0 (5.8)*	65.2 (6.7)	59.4 (5.5)$^{+}$	79.5 (4.8)	*
Attempted structures correct (%)	68.4 (4.1)^{***b,c}	95.2 (6.2)	95.1 (5.8)*	96.4 (6.7)	93.2 (5.5)*	99.1 (4.7)	***
Syntactic errors (per hundred words)	7.4 (6.3)^{b,c}	0.7 (0.8)	1.2 (1.0)	0.5 (0.4)	1.4 (1.3)	0.2 (0.4)	***
Semantic errors (per hundred words)	1.0 (1.4)	1.6 (1.8)	1.0 (0.9)	0.7 (1.2)	0.9 (1.0)	0.0 (0.0)	$^{+}$

See caption to Table 1 for explanation of symbols.

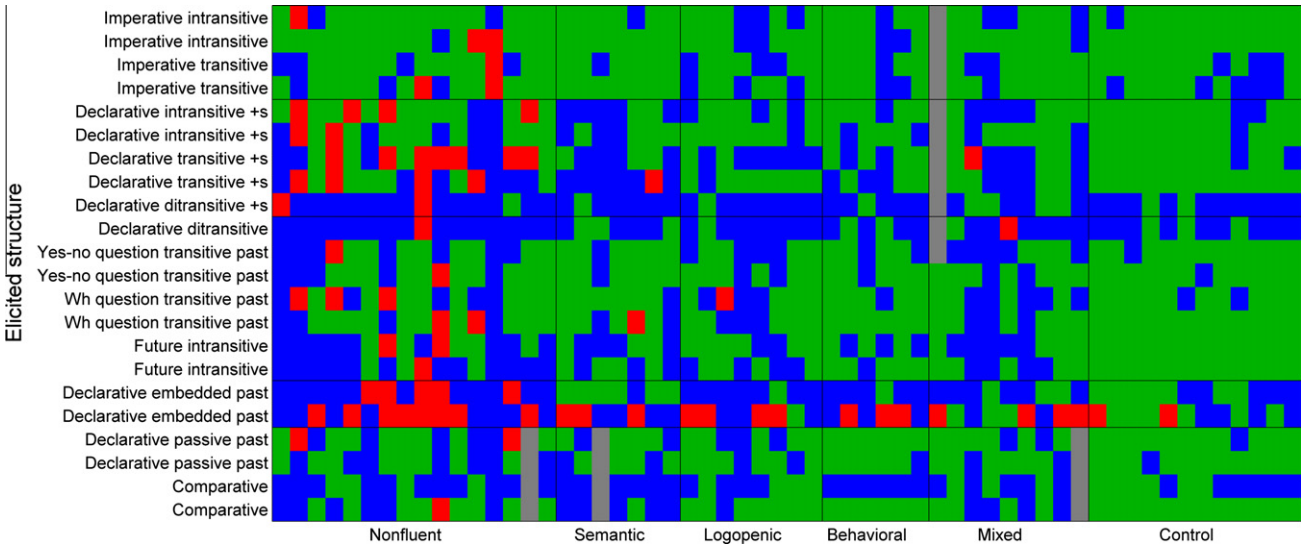

Fig. 2. Item-by-item performance of individual participants. Each participant is represented by a column, and participants are grouped based on diagnosis. Each item is represented by a row, and items are grouped based on similarities obtained in performance, i.e. the constructions requiring 3sg present agreement, and those requiring embeddings, were most difficult for non-fluent/agrammatic patients, so these constructions are set off with horizontal lines. Green: structure was attempted, and correct; Red: structure was attempted, but incorrect; Blue: structure was not attempted (something else was produced); Grey: item was skipped for situational reasons.

For each item, we used a χ^2 test to determine whether the three PPA and two neurodegenerative control groups differed in the frequency with which they attempted the intended structure (we omitted controls because we have already shown that they attempt the targeted structures more frequently in general). We set an alpha criterion of $p < 0.01$ to informally correct for multiple comparisons. No items met this threshold. At an uncorrected threshold of $p < 0.05$, three items showed different distributions: 3a ($p = 0.050$), 9a ($p = 0.030$) and 11b ($p = 0.020$).

3.3. Accuracy on targeted structures

The groups differed significantly in the frequency with which they produced targeted structures correctly, when they did attempt them (Kruskal–Wallis $\chi^2 = 29.41$, $df = 5$, $p < 0.001$) (Fig. 1c, Table 3). Patients with non-fluent/agrammatic PPA were less accurate than controls ($p < 0.001$), logopenic PPA patients were marginally less accurate ($p = 0.068$), and mixed neurodegenerative patients were less accurate ($p = 0.028$). Non-fluent/agrammatic PPA patients were less accurate than semantic ($p = 0.015$) or logopenic ($p = 0.0067$) patients, but semantic and logopenic patients did not differ from one another ($p = 0.79$).

The 22 items differed in the frequency with which participants produced attempted targeted structures correctly ($\chi^2(21) = 193.76$, $p < 0.001$) (Fig. 2). The most challenging structures were the declarative transitive with 3sg agreement (3a), and the two embedded clauses (9a and 9b).

We used sets of chi square tests to determine which items patients with each PPA variant had most difficulty with, applying an alpha criterion of $p < 0.01$ to informally correct for multiple comparisons. Non-fluent patients performed worse than controls on items 3a, 9a and 9b. Inspection of Fig. 2 suggests that 3sg present tense agreement and embeddings posed the most problems for non-fluent patients, followed by wh-questions. There were no items on which semantic or logopenic PPA patients performed significantly worse than controls, though it should be noted that for both groups most errors occurred on item 9b, an embedded clause.

Examples of targeted structures that were attempted but resulted in syntactic errors are shown in Table 4.

3.4. Voxel-based morphometry

Using voxel-based morphometry, we found that the only region where atrophy was significantly predictive of reduced accuracy on targeted structures was the left posterior inferior frontal gyrus, pars opercularis (center of mass: MNI coordinates −53, 12, 13; maximum $t = 3.47$; cluster extent = 3192 mm^3; corrected $p = 0.025$; Fig. 3).

The same region was found to predict reduced accuracy when covariates of executive function and/or working memory were included in the model, however its volume was large enough to survive correction for multiple comparisons only for the calculation covariate (extent = 3648 mm^3); the cluster extent for syntactic accuracy was reduced to 456 mm^3 when digit span backwards was included as a covariate, and 512 mm^3 when modified trails was included as a covariate.

Table 4
Examples of syntactic errors produced by PPA patients.

Item	Targeted response	Actual response	PPA variant
1a	Sit down.	Seat down	Non-fluent/agrammatic
3a	The baby cries.	Baby crying	Non-fluent/agrammatic
3b	The baby laughs.	Laughing	Non-fluent/agrammatic
“	“	He's smiles and he laughs	Non-fluent/agrammatic
4a	The dog chases the cat.	Dog chase that cat	Non-fluent/agrammatic
“	“	Dog chases cats... My dog doesn't	Non-fluent/agrammatic
4b	He turns the radio on.	He turn radio	Non-fluent/agrammatic
5a	She gives her the dollar.	She takes her one the dollar	Non-fluent/agrammatic
6a	Did you call me?	Do you call me?	Non-fluent/agrammatic
6b	Did you brush your teeth?	Brush your teeth?	Non-fluent/agrammatic
7a	Where did you put my shoes?	Where to the shoe?	Non-fluent/agrammatic
“	“	What the closet...where do you put them in the closet?	Non-fluent/agrammatic
7b	How did you fix the toy?	What did you fix it?	Non-fluent/agrammatic
“	“	How do you do the [fɪə] f- fix it at... the the toy?	Non-fluent/agrammatic
8a	He will work again.	Next Saturday work.	Non-fluent/agrammatic
9a	(She wanted) the children to be quiet.	Th- the um... the mother wants to uh [tʃɪld] uh s- silent... stop talking	Non-fluent/agrammatic
“	“	To quiet	Non-fluent/agrammatic
9b	(He wanted) the soldier to clean his gun.	Clean up	Non-fluent/agrammatic
“	“	To clean the gun	Semantic
“	“	To clean all the... rifles... and the... battalion	Logopenic
10a	(The man) was hit by the train	The man the train kill	Non-fluent/agrammatic
“	“	Ran over the train	Non-fluent/agrammatic

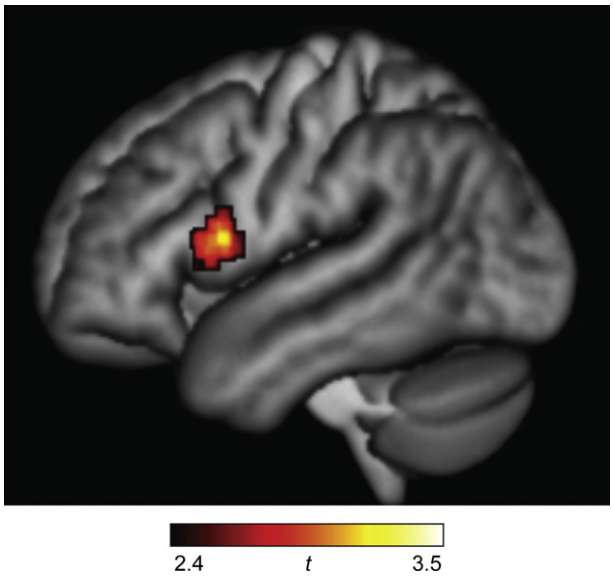

Fig. 3. Voxel-based morphometry. The posterior left inferior frontal gyrus was the only region where atrophy was predictive of decreased accuracy in production of targeted structures ($p < 0.05$, corrected for multiple comparisons).

3.5. Syntactic and semantic errors

We counted syntactic errors irrespective of whether or not the targeted structure was attempted, and divided by the total number of words each participant produced. The groups differed significantly in syntactic errors per word (Kruskal–Wallis $\chi^2 = 34.26$, $df = 5$, $p < 0.001$) (Table 3). Non-fluent/agrammatic PPA patients produced the most errors.

We also counted semantic errors. The groups differed marginally in semantic errors per word (Kruskal–Wallis $\chi^2 = 10.91$, $df = 5$, $p = 0.053$) (Table 3). All patient groups produced some semantic errors, but controls did not produce any.

4. Discussion

Using an elicited production task, we found that all PPA variants, as well as other neurodegenerative patients, produced targeted syntactic structures less frequently than controls. However, the three PPA variants did not differ from one another in the frequency with which they attempted targeted syntactic constructions. When targeted structures were attempted, patients with the non-fluent variant of PPA made more syntactic errors compared to controls and compared to the other PPA variants. Reduced accuracy on production of targeted syntactic structures was associated with atrophy of the left posterior inferior frontal gyrus.

The results of this study are largely consistent with studies that have investigated syntactic production in PPA using quantitative analysis of connected speech (Ash et al., 2006, 2009; Bird et al., 2000; Graham et al., 2004; Gunawardena et al., 2010; Knibb et al., 2009; Meteyard & Patterson, 2009; Orange et al., 1998; Patterson et al., 2006; Patterson & MacDonald, 2006; Rogers & Alarcon, 1998; Thompson et al, 1997; Thompson, Cho, et al., 2012; Wilson, Henry, et al., 2010) and those using constrained production tasks (Thompson, Meltzer-Asscher, et al., 2012; Weintraub et al., 2009). This literature has shown that patients with non-fluent/agrammatic PPA are impaired in syntactic production, whereas only moderate syntactic deficits are found in semantic or logopenic PPA (Meteyard & Patterson, 2009; Thompson, Cho, et al., 2012; Wilson, Henry, et al., 2010). Previous studies have shown that atrophy of left inferior frontal cortex is associated with deficits in the production of syntax (Gunawardena et al., 2010; Rogalski et al., 2011; Wilson, Henry, et al., 2010; Wilson et al., 2012). The left inferior frontal cortex is also functionally abnormal in non-fluent/agrammatic PPA: this region is not modulated by syntactic complexity in these patients as it is in controls (Wilson, Dronkers, et al., 2010). The importance of left inferior frontal cortex for syntactic processing may be associated in part with its role in executive function and/or working memory, though some studies have suggested dissociations between frontal regions important for syntactic and working memory functions (Amici et al., 2007; Makuuchi, Bahlmann, Anwander, & Friederici, 2009). In our study, the extent of the region associated with syntactic production was reduced when measures of executive function and/or working memory were included as covariates, especially the widely used measures of digit span backwards and (modified) trails.

The specific syntactic constructions that we investigated differed considerably in the extent to which they posed difficulties to patients with non-fluent/agrammatic PPA. Some structures were produced accurately by most patients: intransitive and transitive

imperatives, yes/no questions, declarative past tense passives, and comparatives. Of these, the accurate production of passives is most surprising, since previous studies using elicitation tasks have shown poor performance on passive constructions in PPA patients in general (Weintraub et al., 2009) and in non-fluent/agrammatic patients in particular (Thompson, Meltzer-Asscher, et al., 2012). It is noteworthy that the passives elicited in the present study—'(the man) was hit (by the train)' and '(she) was bitten (by the dog)'—are not readily reversible, unlike the passives elicited in these prior studies. Furthermore, participants were not required to produce the subject (since it was already part of the prompt), nor were they required to produce the 'by' phrase, and both of the verbs used have past participles that are homophonous with the past tense (optionally in the case of *bite*).

The structures that proved most difficult were the 3sg present tense marker, and embedded clauses. These results are consistent with Thompson, Meltzer-Asscher, et al. (2012), who found that non-fluent/agrammatic patients are impaired in using 3sg present agreement (61% correct in an elicitation task), and in producing relative clauses. The embedded clauses in the present study were 'small clauses' with infinitive verbs, and these proved difficult not only for non-fluent/agrammatic patients, but for other PPA variants and even other neurodegenerative patients.

In sum, we found that non-fluent/agrammatic patients attempt targeted syntactic structures just as frequently as other PPA variants, but make many more syntactic errors. Constructions differ greatly in the extent to which they are prone to errors, with complex embedded structures and verbal inflection proving the most vulnerable. This information could be useful clinically, since elicitation of just these challenging structures may provide a very quick initial indication as to whether a patient may be agrammatic. However intended structures are not always attempted, and not every agrammatic patient fails on every challenging structure, so it is still important to follow up with a careful assessment of connected speech to confirm the presence or absence of agrammatism.

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