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ORIGINAL ARTICLE

Taxonomic Interference Associated with Phonemic Paraphasias in Agrammatic Primary Progressive Aphasia

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Abstract

Phonemic paraphasias are thought to reflect phonological (post-semantic) deficits in language production. Here we present evidence that phonemic paraphasias in non-semantic primary progressive aphasia (PPA) may be associated with taxonomic interference. Agrammatic and logopenic PPA patients and control participants performed a word-to-picture visual search task where they matched a stimulus noun to 1 of 16 object pictures as their eye movements were recorded. Participants were subsequently asked to name the same items. We measured taxonomic interference (ratio of time spent viewing related vs. unrelated foils) during the search task for each item. Target items that elicited a phonemic paraphasia during object naming elicited increased taxonomic interference during the search task in agrammatic but not logopenic PPA patients. These results could reflect either very subtle sub-clinical semantic distortions of word representations or partial degradation of specific phonological word forms in agrammatic PPA during both word-to-picture matching (input stage) and picture naming (output stage). The mechanism for phonemic paraphasias in logopenic patients seems to be different and to be operative at the pre-articulatory stage of phonological retrieval. Glucose metabolic imaging suggests that degeneration in the left posterior frontal lobe and left temporo-parietal junction, respectively, might underlie these different patterns of phonemic paraphasia.

Key words: Alzheimer's disease, dementia, eye tracking, interference, phonology

Introduction

Word-finding impairment is a common presenting symptom of aphasia. Object naming failure is a marker of this problem. Successful naming of an object requires the completion of component processes. The object to be named has to be visually identified, the identified object has to be linked to its semantic associations, the "lemma" of the word has to be accessed given those semantic associations, the "lexeme" [a word's phonological code (Kempen and Huijbers 1983)] has to be accessed given the lemma, and finally this lexeme has to be articulated by the motor speech system (Levelt 1992). These processes unfold both serially and in parallel and are interrelated through feedforward and feedback interactions (Mesulam 1998). A failure of any one of these processes results in a failure in object naming. Object naming failures are manifested in several ways. A subject might give no response, say "I don't know," produce a "semantic paraphasia" (a semantically related, but incorrect word, e.g., "rhino" for a picture of a hippo), or produce a "phonemic paraphasia" (an approximation of the correct word with incorrect phonemes, syllabic stress or phoneme order, e.g., saying "sombrado" instead of "sombrero"). Any one of these error types may reflect a degraded lemma or lexeme distinct from motor errors in speech production.

In keeping with the large-scale network theory of language (Mesulam 1990), there is evidence that the phonemic and semantic systems partially overlap and interact with each other. Dell et al. (1997) developed a model in which the phonological and semantic systems continuously interact through reciprocal feedback. This model was largely inspired by the observation that the proportion of "mixed paraphasias"—errors in which an utterance is both phonemically and semantically related to the target (e.g., saying "rat" instead of "cat")—occur at a higher rate than would be expected if phonological and semantic processing acted independently of each other, which had been shown in healthy controls in both continuous speech (Dell and Reich 1981; Harley 1984; del Viso et al. 1991) and object naming (Martin et al. 1989; Brédart and Valentine 1992). Within this model, semantic interference during naming was shown to result in phonemic paraphasias, consistent with cascading activation models of phonemic production when there is difficulty inhibiting semantic competitors (Rapp and Goldrick 2000; Goldrick and Chu 2014). Patterson et al. (1994) found that when semantic dementia patients performed a list recall task, they exhibited phoneme migration across words that the patient did not semantically comprehend, but not across words for which they had preserved comprehension. Similar effects have been observed in healthy controls recalling lists of pseudowords as opposed to real words (Ellis 1980; Treiman and Danis 1988; Jefferies et al. 2006). However, these relationships seem to be quite subtle since patients with severe semantic variant primary progressive aphasia (PPA) (PPA-S; partially overlapping with the syndrome of semantic dementia), who fail to understand even simple words, have no phonological disintegration in speech and can repeat perfectly.

Different variants of PPA are known to have different combinations of phonological and semantic deficits. Progressive neurodegeneration in PPA-S is strongest in the left anterior temporal lobe, resulting in severe semantic deficits characterized by 'blurring' of semantic representations within and eventually across taxonomic boundaries as the deficit gets more severe (Mesulam et al. 2009). This semantic deficit results in severe anomia and semantic paraphasias in naming, however phonological and grammatical functioning of these patients is generally intact. Logopenic variant PPA patients (PPA-L), with progressive neurodegeneration that is strongest in the left posterior temporal lobe and in the temporo-parietal junction (TPJ), exhibit particular difficulty with word finding and verbal repetition (Gorno-Tempini et al. 2008; Mesulam et al. 2012). Single word comprehension in these patients is generally intact, but they do have difficulty in naming, including making phonemic paraphasia errors both in naming and spontaneous speech. Nonfluent variant PPA patients (nfvPPA, also known as agrammatic variant PPA, PPA-G), with progressive neurodegeneration that is strongest in the posterior left frontal lobe, exhibit difficulty in the grammatical production of language, and often in the comprehension of grammar (Grossman 2012; Mesulam et al. 2012). These patients have no clinically consequential difficulty in single word comprehension, but frequently generate phonemic and other apraxic errors when naming objects.

According to interactive cascading models mentioned above (e.g., Dell et al. 1997), phonetic and semantic processing are supposed to be intertwined. In fact, the two PPA variants that display phonemic paraphasias (PPA-G and PPA-L) have been shown to also have subtle but consistent sub-clinical semantic deficits when tested with challenging chronometric tasks (Vandenberghe et al. 2005; Rogalski et al. 2008; Thompson et al. 2012). We therefore structured the current experiment to explore the interrelationship of phonemic errors in naming with semantic interference in a word-to-picture matching task where information processing was documented in real time through eye movement recordings.

Materials and Methods

Participants

This article presents data from 26 PPA patients and 21 healthy controls. All participants were right-handed, native English speakers. The diagnosis of PPA was made using established guidelines, necessitating a progressive language impairment that remained the most salient clinical symptom for at least the first 2 years of the disease (Mesulam 2001; Gorno-Tempini et al. 2011). Semantic variant PPA patients were excluded from this study because of their poor accuracy in performing the task and relative paucity of phonemic paraphasias. The remaining PPA-participants were sorted into nonfluent variant (also known as agrammatic PPA, PPA-G, $n = 14$) and logopenic variant (PPA-L, $n = 12$) groups based on the guidelines described in Gorno-Tempini et al. (2011). Patients where this subtyping was uncertain (e.g., patients who show both moderate agrammatism and severe repetition impairments along with other traits matching both PPA-L and PPA-G profiles) were excluded from analyses comparing across subject groups. Control participants were matched to both PPA groups in age, years of education, and gender. The study was approved by the Institutional Review Board at Northwestern University. All experiments were undertaken with the understanding and written consent of each participant.

Neuropsychological Test Comparisons

The Western Aphasia Battery-Aphasia Quotient (WAB-AQ) was used as a global measure of aphasia severity (Kersetz 2006, Table 2). Participants performed the Peabody Picture Vocabulary Test (PPVT) (Dunn and Dunn 2007) to assess word

Table 1 Group demographic and ancillary neuropsychological test statistics

Variable (max score)	Control ($n = 21$)	PPA-G ($n = 14$)	PPA-L ($n = 12$)
Age	64.7 ± 1.4	66.6 ± 2.0	67.3 ± 2.5
% Female	47.6	71.4[b]	25[b]
Years of education	15.8 ± 0.6	14.6 ± 0.6	15.5 ± 0.7
Rivermead picture recognition (10)	9.6 ± 0.2	9.5 ± 0.3	9.6 ± 0.2
Benton facial recognition (54)	48.2 ± 0.8	46.6 ± 1.3	48.1 ± 1
Judgment of line orientation (20)	16.1 ± 0.7	17.0 ± 0.9	17.9 ± 0.5
WAB repetition (%)	98 ± 1	71 ± 6[a]	58 ± 7[a]
NAT and NAVS-SPPT (nc) (%)	98 ± 1	47 ± 7[a]	60 ± 8[a]
NAVS-SCT (nc) (%)	100 ± 0	81 ± 5[a]	90 ± 3[a]

Note. Values indicate the mean ± standard error of the mean
[a]$P < 0.001$ versus controls
[b]$P < 0.05$ PPA-G versus PPA-L

comprehension. To assess object naming, patients performed the Boston Naming Test (BNT) (Goodglass et al. 2001). Some patients in this assessment made a number of phonemic errors while pronouncing the correct name. To account for this, we present in Table 2 adjusted BNT scores counting phonemic errors as correct responses, following the same definition for phonemic errors used to score responses of the experimental object naming task in this study, described below. Patients performed the picture form of the Pyramids and Palm Trees Test (PPT) (Howard and Patterson 1992) to assess non-verbal visual recognition and knowledge of objects. To assess object recognition in other contexts, participants performed the delayed picture recognition subtest in the Rivermead Behavioural Memory Test (Wilson et al. 2008) and the Benton Facial Recognition Test (Benton et al. 1994, Table 1). To test visuospatial functioning, participants performed the Judgment of Line Orientation Test (Randolph 1998). To assess repetition, participants were asked to repeat the 6 most difficult items in the repetition subset of the Western Aphasia Battery, which were sentences and phrases 4–10 words long. We measured the percentage of words in those items correctly repeated (WAB Repetition) (Kersetz 2006). To assess grammaticality of sentence production, participants performed the Northwestern Anagram Test (NAT) (Weintraub et al. 2009) and the Sentence Production Priming Test (SPPT) of the Northwestern Assessment of Verbs and Sentences (NAVS) (Thompson 2012). We report the average of these scores for non-canonical sentences following convention established in Mesulam (2012). To assess comprehension of grammar, participants performed the Sentence Comprehension Test (SCT) of non-canonical sentences in the NAVS battery (Thompson 2012).

Nonparametric Mann–Whitney U tests were used to test differences in neuropsychological scores between group pairs. Gender proportion was tested with Fisher's Exact Test. Significance levels are indicated in Tables 1 and 2. PPA-L and PPA-G groups did not significantly differ in overall aphasia severity (WAB-AQ). PPA-G, Control, and PPA-L groups did not significantly differ in age or gender, however the PPA-G group had a significantly higher proportion of females than the PPA-L group. There were no significant differences between groups on the Rivermead Behavioural Memory Test, the Benton Facial Recognition test, and the Judgment of Line Orientation test. Although the PPA-L group scored significantly lower than the other groups on the PPT, all three groups showed near-ceiling accuracy on the task (≥95%). Controls, PPA-L, and PPA-G were both considerably impaired relative to controls in the PPVT, the WAB Repetition Test, the NAT & NAVS-SPPT, and the NAVS-SCT, but did not significantly differ from each other in performance on these tests. Both patient groups were highly significantly impaired relative to controls on the BNT, with the PPA-L group being significantly more impaired than the PPA-G group.

Word-to-picture Matching Task

On each trial, participants were given a noun cue presented simultaneously as an auditory word and visually as lowercase text (Fig. 1), facilitating comprehension in the event that a participant has a modality-specific sensory deficit (e.g., Mesulam et al. 2019). The text remained on the screen for 2.5 s, followed by a fixation cross for 0.5 s, after which a search array of 16 standardized grayscale drawings of objects appeared. Participants were asked to touch the drawing corresponding to the stimulus noun. Eye movements and touch responses were recorded After appearing, the search array remained on the screen until the participant made a touch response. This arrangement gave the participants considerable time to comprehend the item before the search array appeared, allowing the dynamics of word-to-picture matching to be better studied. Participants were given no instructions about how they should move their eyes during the task, though they were made aware that their eye movements were being recorded.

The task consisted of 48 trials, with a different target item each trial. Equal numbers of target items were chosen from 4 taxonomic categories (animals, clothes, fruits and vegetables, and manipulable objects). Each array consisted of 1 target item, 7 items from the same semantic category, and 8 items distributed among the remaining 3 semantically unrelated taxonomic categories. The locations of targets, related foils, and unrelated foils were balanced across the 16 array positions. The experiment consisted of 24 trials with high-frequency items and foils, followed by 24 trials with low-frequency items and foils, with no indication to the participants of a change between frequency blocks. This presentation of the easier high-frequency items first was intended to reduce possible frustration participants might have with low frequency items. Word frequency was assessed from the HAL database of the English Lexicon Project (Balota et al. 2007), with a mean of 16 470 (mean log: 8.76) for the high-frequency block and 703 (mean log: 6.22) for the low-frequency block. The targets and foils on each trial were closely matched for psycholinguistic characteristics and visual characteristics of the images we used, as described previously (Seckin et al. 2016a, 2016b).

Table 2 Neuropsychological test and task performance

ID	Type	WAB AQ (%)	BNT60 (%)	PPVT (%)	PPT Pic (%)	% of Word-to-picture matching trials		% of Naming trials		RT (s)		Taxonomic Interference Index	
						Correct	Error	Correct naming	Phonemic paraphasia	Correct naming	Phonemic paraphasia	Correct naming	Phonemic paraphasia
P1	G	66.2	85	92	100	98	2	21	57	3.0	3.0	1.43	1.55
P2	G	78.1	92	97	100	100	0	56	38	4.2	4.5	1.16	1.62
P3	G	80.3	88	92	98	100	0	71	27	4.3	4.8	1.63	2.01
P4	G	78.0	92	97	98	100	0	69	25	4.2	3.3	1.46	1.46
P5	G	68.8	85	83	98	100	0	78	17	3.9	4.4	1.53	2.09
P6	G	81.9	90	97	96	100	0	83	17	6.1	8.0	0.89	1.82
P7	G	69.3	85	89	96	98	2	73	15	6.5	6.4	1.59	2.79
P8	G	86.4	95	97	96	100	0	88	8	5.0	4.9	1.83	0.43
P9	G	87.0	97	100	100	100	0	96	4	4.2	7.0	1.79	2.29
P10	G	80.3	50	92	94	100	0	69	4	2.9	1.5	2.08	1.75
P11	G	NA	93	100	98	100	0	88	4	3.8	3.2	1.35	12.11
P12	G	69.3	60	75	96	100	0	56	4	3.1	2.1	1.13	2.02
P13	G	79.3	73	94	96	100	0	94	2	4.6	4.9	1.27	3.8
P14	G	79.5	70	89	83	91	9	82	0	5.8	3.2	2.07	
Mean ± SEM:		77.3 ± 1.9	83 ± 4[b,d]	92 ± 2[a]	96 ± 1[c]	99 ± 1[d]	1 ± 1	73 ± 5[b,c]	16 ± 4[b]	4.4 ± 0.3[a]	4.4 ± 0.5	1.51 ± 0.09	2.75 ± 0.81
P15	L	75.8	55	81	94	87	13	59	18	4.3	5.6	1.31	0.91
P16	L	64.4	25	86	92	93	7	28	15	3.3	2.4	1.97	1.98
P17	L	70.3	42	97	92	94	6	46	13	3.8	4.7	1.64	1.11
P18	L	83.1	80	89	94	96	4	60	13	3.9	3.6	1.44	1.77
P19	L	75.7	87	83	94	96	4	73	10	3.2	3.3	1.74	1.15
P20	L	70.9	50	89	100	94	6	60	10	5.7	4.4	1.28	1.15
P21	L	70.6	53	78	94	92	8	63	8	5.3	10.8	1.85	1.45
P22	L	72.4	22	94	94	100	0	51	7	4.3	3.1	1.33	0.36
P23	L	89.4	83	94	92	95	5	74	5	3.7	4.9	0.92	1.92
P24	L	92.9	52	86	92	98	2	60	4	5.3	4.4	1.54	0.78
P25	L	81.8	37	81	96	91	9	56	2	4.8	4.6	2.05	0.85
P26	L	97.6	93	100	98	100	0	95	0	3.7		1.87	
Mean ± SEM:		78.7 ± 3.0	57 ± 7[b,d]	88 ± 2[b]	95 ± 1[a,c]	95 ± 1[a,d]	5 ± 1	60 ± 5[b,c]	9 ± 2[b]	4.3 ± 0.2[b]	4.7 ± 0.7	1.58 ± 0.10	1.22 ± 0.15
Controls (n = 21)		NA	97 ± 1	98 ± 0	98 ± 0	99 ± 0	1 ± 0	98 ± 1	1 ± 0	3.3 ± 0.1	3.0 ± 0.4	1.50 ± 0.06	1.18 ± 0.59

Note. BNT scores here have been adjusted to include phonemic errors in that assessment as correct responses [a]$P < 0.01$ versus controls
[b]$P < 0.001$ versus controls
[c]$P < 0.05$ PPA-G versus PPA-L
[d]$P < 0.01$ PPA-G versus PPA-L

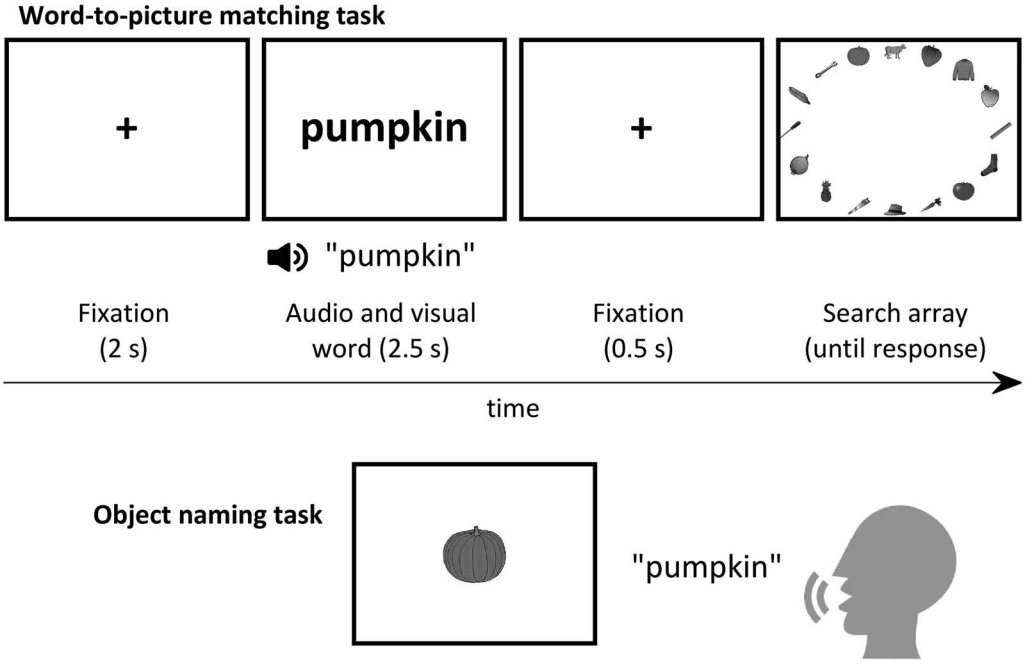

Figure 1. Schematic of the series of events in the word-to-picture matching and object naming tasks.

Word-to-Picture Matching Eye Tracking Procedure

Stimuli were presented and touch responses were recorded using a 20.5 × 11.5 inch touchscreen monitor (Planar PXL2430MW, Planar Systems, Inc., Hillsboro, OR, USA). Eye movements were recorded with an Eyelink 1000 eyetracking system (SR Research, Mississauga, ON, Canada). For most participants, the Eyelink 1000 Tower Mount was used, which measures eye position using a hot mirror, allowing for reaches to the screen to occur without affecting the eye position measurement. For a minority of participants (2 control participants, 2 PPA-G, and 1 PPA-L), a desktop mount was used. The effects described here did not differ between this group and the remaining participants, therefore we combined the groups for analyses. Eye positions were calibrated prior to the recording sessions using nine-point calibration procedures, with five-point calibration procedures used for some participants. Participants rested against a chin and forehead rest to reduce head movements. Participants were seated with the center of their eyes approximately 22 inches from the screen. Before performing the main task, participants practiced the task for 1–3 trials without recording eye movements, using different items from different semantic categories than those used in the main task. Participants with glasses were asked if they could see the practice stimuli accurately and comfortably without glasses. Those that could performed the task without glasses in order to improve eye movement recording quality, while those that could not performed the task with their glasses. The Presentation experimental software package (Neurobehavioral Systems, Inc., Berkeley, CA, USA) was used to present the stimuli.

Object Naming Task

The object naming task was performed only for the items that appeared as targets in the word-to-picture matching task. Participants were shown the same grayscale drawings at the same size that appeared in the array in the word-to-picture matching task, and asked to name the item as quickly as possible. The audio stream of the participants' responses was recorded. Items were presented in a different randomized order than the picture task within frequency blocks, while again presenting the high frequency items before the low frequency items. Advancing to the next item in naming was controlled by the experimenter. Participants were given 20 s or more to produce a response if needed. The naming task was conducted without recording eye movements and with the participants' head free but at the same distance from the monitor as during the word-to-picture matching task. With the exception of 3 control, 4 PPA-G, and 3 PPA-L participants, who were administered the naming task immediately before the word-to-picture matching task, the naming task was administered immediately after the word-to-picture matching task. The effects described here did not differ between these two groups, thus we combined the groups for analyses. E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA, USA) was used to present stimuli and record audio responses.

Audio Response Scoring

Participant naming responses were recorded and scored offline. Responses were sorted into 4 categories: correctly named, phonemic paraphasia, "I don't know"/no response, and semantic paraphasia. The current study focused only on items that were named correctly or with phonemic paraphasias. Two independent raters (MN and SM) listened to each audio response and scored each response into 1 of the 4 categories. Phonemic paraphasias were coded if the word the speaker produced contained well-formed English phonemes that were incorrect for the target word. Phonetic speech errors [i.e., producing sounds that are not well-formed English phonemes (Ash et al. 2010)], motor errors including slurring of speech, and stuttering were not coded as phonemic paraphasias. To consider that the

target word was the word intended to be uttered, ≥50% of the target word phonemes had to present in the utterance (Kiran and Thompson 2003). A semantic paraphasia that happened to contain a phonemic paraphasia was coded as a semantic paraphasia.

About 95% of all recorded responses were initially coded the same between raters. Coders came to a consensus on all disagreements with further trained expert consultation. For a subset of participants, which was the same subset of participants for which the Desktop Mount was used in eye position recordings, audio recordings were not present and the coding was based on the transcription of the investigator during the naming task. The naming task was performed immediately before the word-to-picture matching task for all of these participants. As described before, the effects described here did not differ between this group and the remaining participants, thus we combined the groups for analyses. Coders and investigators during the naming task were blind to each patient's subtype when performing the scoring.

Phonemic paraphasias were coded if the word the speaker produced contained well-formed English phonemes that were incorrect for the target word. Phonetic speech errors [i.e., producing sounds that are not well-formed English phonemes (Ash et al. 2010)], motor errors including slurring of speech, and stuttering were not coded as phonemic paraphasias. To consider that the target word was the word intended to be uttered, ≥50% of the target word phonemes had to present in the utterance (Kiran and Thompson 2003). A semantic paraphasia that happened to contain a phonemic paraphasia was coded as a semantic paraphasia.

Imaging Procedure

We acquired FDG-PET imaging scans of 8 Control, 4 PPA-G, and 4 PPA-L participants. Patients were injected with 8–10 mCi of an 18F FDG tracer (Sofie). 30 min post-injection we then recorded 30 min of emission data with a Siemens Biograph TruePoint PET-CT system (Siemens) while patients quietly rested with their eyes and ears unoccluded. We acquired structural magnetic resonance images (MRI) for the same subjects using a Siemens Trio 3 T scanner (Siemens). Structural MR images were acquired via a T1-weighted 3D MPRAGE sequence (repetition time: 2300 ms; echo time: 2.91 ms; flip angle: 9°; field of view: 256 mm, voxel size: $1 \times 1 \times 1$ mm) at a thickness of 1.0 mm.

Eye Movement Processing

Edf files containing eyetracking data were imported to MATLAB (Mathworks) using the Edf2Mat toolbox, and further processing and analyses were conducted in MATLAB, with the exception that heat maps were produced using the EyeLink DataViewer software (SR Research). The fixation locations for each entire experiment were plotted in two-dimensional screen space and visually inspected post-hoc to ensure data quality. Fixations at the center of the screen (with an eccentricity less than 6° of visual angle) or visibly off of the screen were excluded from analyses.

Using fixation locations and durations, we calculated for each correct trial in the word-to-picture matching task the total time spent viewing semantically related versus unrelated foils. We define the "Taxonomic Interference Index" as the ratio of the time spent viewing related foils divided by the time spent viewing unrelated foils. For each trial condition, the individual values for each foil type were first averaged across trials and then used to calculate the indices for each subject. For plotting, taxonomic interference values were averaged across participants and multiplied by 8/7 in order to account for the fact that there were 7 semantically related foils versus 8 semantically unrelated foils, although this is merely a scaling factor of the absolute result and does not affect any statistical comparisons made.

Statistical Analyses

First, to describe the patterns in each single task, we performed nonparametric Mann–Whitney U rank sum tests between all pairs of subject groups using the mean values of each variable tested for each subject. In the word-to-picture-matching task we tested accuracy, response time (RT) on all correct trials, and taxonomic interference on all correct trials. In the naming task, we tested the proportion of correct items and the proportion of phonemic paraphasias.

To test for an association between phonemic errors and taxonomic interference, we analyzed the taxonomic interference in the word-to-picture matching task on trials that were separated based on the performance of the subject for that item in the naming task. The mean taxonomic interference values per subject per trial group were entered into statistical models along with subject group (Control, PPA-G, and PPA-L) and naming type (Correct naming and Phonemic paraphasias). Because we are ambivalent at this point as to the direction of causality of the potential relationship between taxonomic interference and phonemic paraphasias, we applied two families of models that had different implied causal relationships between these variables.

In one family of models, we applied a standard regression model with taxonomic interference as a dependent variable, and naming type, subject group, and their possible interaction as fixed effects. This family of models implies that the naming type factor led to the different values of taxonomic interference in the word-to-picture matching task. Subject was entered as a random factor and with random slopes and intercepts for naming type across subjects. Within this model, we tested for the simple effect of correct-naming versus phonemic paraphasia items within each subject group. We tested for an interaction contrast of the difference of the effect of correct-naming versus phonemic paraphasia items between PPA-G and PPA-L which was of particular theoretical interest.

In the second family of models, we applied a logistic regression model, with naming type as a dependent variable, and taxonomic interference, subject group, and their possible interaction as fixed effects. This family of models implies that the value of taxonomic interference in the word-to-picture matching task caused the outcome of the different naming types in subjects. Random intercepts for subject were included as a random factor. The model did not converge when random slopes for taxonomic interference across subjects were included, thus these random slopes were not included in the model. Within this model we tested for an interaction contrast of the difference of the effect of taxonomic interference in PPA-G versus PPA-L subjects, as well as the marginal effect of taxonomic interference within each subject group.

Then, to investigate the association between phonemic errors and other task parameters, we applied both sets of models using mean RT and mean accuracy per subject in place of taxonomic interference per subject. Because of the significant

difference in gender between patient groups, we included gender as a controlled fixed effect in all models performed, although we note this had little consequence on the results of the tests.

Frequency-controlled Analyses

To observe if word frequency could explain the results we observed for taxonomic interference, we performed a follow-up analysis controlling for frequency. In this analysis, frequency was added to both families of models as a two-level (high and low frequency block) independent factor with a random intercept of frequency and a random slope of frequency across participants included in the model. In this model, we looked at the same simple effects of naming type and interaction contrasts as we had previously.

Trial-matching Analyses

One item in our experiment might engender higher taxonomic interference indices for all subjects versus that of another item for various reasons. PPA-G subjects might happen to commit more phonemic paraphasias on items that innately have a high taxonomic interference for all subjects. Such a phenomenon would yield a higher taxonomic interference index for phonemic paraphasias in PPA-G without there being a direct link between the commission of a phonemic paraphasia and the altered taxonomic interference index. As a follow up to the effects observed in PPA subjects and in order to show that other subject groups do not show increased taxonomic interference for the items on which PPA-G commit phonemic paraphasias, we performed the following trial-matching simulation analysis.

For each of the 48 items, we first calculated the percentage of naming types (Correct naming, phonemic paraphasia or other) observed across the 14 PPA-G participants. Then across 100 000 iterations, for every item on every subject of each comparison group (controls and PPA-L), we randomly assigned the naming type for that item for that subject using these percentages for each item as the probability of assigning that naming type. For example, if for the item "tiger" PPA-G showed 70% correctly named responses, 20% phonemic paraphasias, and 10% other responses, then for each iteration for each subject in the comparison groups, their naming response for the "tiger" item was simulated to be randomly assigned to those outcomes following those percentages as probabilities. In this manner, the comparison groups on average would be made to artificially follow the same profile of naming responses on each item that the PPA-G showed. These randomly assigned naming types were paired with the real taxonomic interference values for each item and subject in the comparison group, and we calculated for each iteration the mean Taxonomic Interference Index across subjects for correctly named and phonemic paraphasia items in each comparison group following the same procedures during our analyses of the actual data. That taxonomic interference index for each iteration was saved as the outcome of that iteration. We then repeated this procedure 100 000 times, generating a null distribution of the taxonomic interference for correctly named and phonemic paraphasias items. We compared these null distributions to the values actually observed in PPA-G participants to determine the probability that the values in the comparison groups exceed the actual PPA-G values by chance. Specifically, we compared both the overall taxonomic interference on phonemic paraphasia items, as well as the difference in taxonomic interference between correctly-named and phonemic paraphasia items in each iteration. For each comparison group, both tests had the same level of significance, so we report only one p-value.

PET Imaging Analyses

Raw DICOM image files were converted to NIFTI files using SPM12. The registration of each subject's anatomical MRI was then checked against SPM's template PET image. In the SPM Display pane, the origin of each anatomical MRI was reset to the intersection between the anterior and posterior commissure. Then using the default parameters, the FDG-PET images were co-registered to the anatomical MRI. FDG-PET files were realigned and resliced with trilinear interpolation, and then normalized to MNI space with Old Normalize. Finally, all FDG-PET image files were smoothed with an [8 8 8] kernel. Once all files were preprocessed through this pipeline, statistics were run in SPM12. A two sample *t*-test, with control subjects as group 1, a relative threshold of 0.8, implicit masking, and proportional global mean normalization, was run and estimated. The resulting map was thresholded at a z-score of −2 (reflecting less glucose metabolism in the patient group vs. controls) at each voxel.

Results

Task performance variables for each patient and the mean performance for control participants are shown in Figure 2 and Table 2. All subject groups performed the word-to-picture-matching task with high accuracy (>94.6%), however, PPA-L showed a significantly lower percentage of correct trials than both controls ($U = 441$, $P < 0.01$) and PPA-G ($U = 246$, $P < 0.01$). Accuracy did not significantly differ between controls and PPA-G ($U = 348$, $P = 0.24$). In the object-naming task, both PPA-G and PPA-L had a smaller proportion of correctly named items than controls (PPA-G vs. controls: $U = 516.5$, $P < 0.001$; PPA-L vs. controls: $U = 479$, $P < 0.001$), and PPA-L had a smaller proportion of correctly named items than PPA-G ($U = 228$, $P < 0.05$). Both PPA-G and PPA-L had a significantly larger proportion of phonemic paraphasias than controls (PPA-G vs. controls: $U = 245$, $P < 0.001$; PPA-L vs. controls: $U = 252$, $P < 0.001$), but the proportion of phonemic paraphasias between PPA-L and PPA-G was not significantly different ($U = 201.5$, $P = 0.54$). PPA-G and PPA-L had longer RTs on correct items than controls (PPA-G vs. controls: $U = 286$, $P < 0.01$; PPA-L vs. controls: $U = 258$, $P < 0.001$), although RTs did not significantly differ between PPA-G and PPA-L ($U = 190$, $P = 0.98$). The taxonomic interference index on all correct word-to-picture-matching trials did not significantly differ between any groups (PPA-G vs. controls: $U = 366$, $P = 0.70$; PPA-L vs. controls: $U = 331$, $P = 0.34$; PPA-G vs. PPA-L: $U = 180$, $P = 0.66$). These analyses show that PPA-L are modestly impaired in terms of accuracy in word-to-picture matching, but with a small effect size (94.6% correct vs. 98.7% correct for controls and 99.1% correct for PPA-G). Both patient groups are impaired in naming relative to controls, and both patient groups show similar proportions of phonemic paraphasias in naming. Overall PPA-G and PPA-L groups perform the word-to-picture matching task similarly to controls, albeit somewhat slower.

Heat maps, for example, trials in each participant group with some different naming outcomes for the target items are shown in Figure 3. Example audio files of these naming

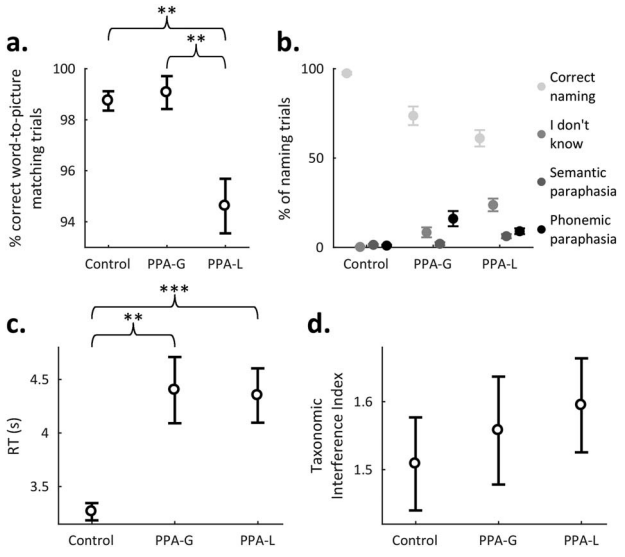

Figure 2. Overall task performance. Plots show for each participant group: (*a*) the percent of correct trials overall in the word-to-picture matching task, (*b*) the percent of naming responses overall for each participant group, (*c*) the RT on correct trials in the word-to-picture matching task, (*d*) the taxonomic interference index (see Methods: Eye Movement Processing) on correct trials in the word-to-picture matching task. This is the ratio of time spent viewing distractors in the same semantic category as the target item divided by the time spent viewing distractors of different semantic categories than the target. A value of 1 indicates an equal propensity to view related versus unrelated foils. PPA-L are modestly impaired in terms of accuracy in word-to-picture matching, but with a small effect size. Both patient groups are impaired in naming, but show similar proportions of phonemic paraphasias relative to each other. Overall, both patient groups perform the word-to-picture matching task similarly to controls, albeit somewhat slower. Error bars show the standard error of the mean. $^{**}P < 0.01$, $^{***}P < 0.001$.

response are available in the Supplementary Materials. P2 (a PPA-G patient) uttered "gui-ter"(/gaɪtɜ/) when trying to name the target item "tiger". During word to-picture matching for that item (Fig. 3, bottom-middle), she spent extra time looking at the zebra while also looking at the horse, elephant, cow, lion, and cat (all semantically related foils), while only looking at the wrench and near the corn among the semantically unrelated foils. Conversely, she properly pronounced the word "hat" during object naming, and during word-to-picture matching for that item (Fig. 3, top-middle) she viewed the glove, vest and shoe (semantically related foils) while also viewing the skunk, cow, and pumpkin (semantically unrelated foils), resulting in a mixture of semantically related and unrelated items viewed at a similar ratio to other participants. P17 (a PPA-L patient) uttered "ba-na-moh"(/bænʌməʊ/) when trying to name the target item "banana", and during word-to-picture matching for that item (Fig. 3, bottom-right) he viewed related foils (carrot and apple) versus unrelated foils (spoon, tie, screwdriver, bear) at a similar ratio as he did for "hammer", which he correctly pronounced during naming (Fig. 3, top-right; related foils viewed: wrench, ax, scissors; unrelated foils viewed: pants, dress, shirt).

To quantify this effect across trials and subjects, we plotted the Taxonomic Interference Index for phonemic paraphasia trials relative to correct naming trials (Fig. 4). The standard regression model showed that PPA-G showed increased taxonomic interference for phonemic paraphasia items relative to correctly named items ($F(1,67) = 4.73$, $P < 0.05$), but controls and PPA-L did not (controls: $F(1,67) = 0.09$, $P = 0.76$; PPA-L: $F(1,67) = 0.36$, $P = 0.55$). An interaction contrast revealed that the effect of a phonemic paraphasia on taxonomic interference was significantly more positive in PPA-G versus PPA-L ($F(1,67) = 4.14$, $P < 0.05$). The logistic regression model revealed that the marginal effect of taxonomic interference for PPA-G was significantly positive ($F(1,67) = 4.72$, $P < 0.05$), but this marginal effect was not significant for PPA-L or controls (controls: $F(1,67) = 0.40$, $P = 0.53$; PPA-L: $F(1,67) = 1.13$, $P = 0.39$). The interaction contrast of the effects of taxonomic interference and subject group between PPA-G and PPA-L was significant ($F(1,67) = 6.25$, $P < 0.05$), reflecting that taxonomic interference had more of a positive effect on the likelihood of a phonemic paraphasia in PPA-G versus PPA-L.

There were no significant differences in the proportion of correct word-to-picture-matching trials on phonemic paraphasia items versus correctly-named items (controls: $F(1,67) = 0.11$, $P = 0.74$; PPA-G: $F(1,67) = 0.02$, $P = 0.89$; PPA-L: $F(1,67) = 0.16$, $P = 0.69$), or in the interaction of this effect between PPA-G and PPA-L ($F(1,67) = 0.15$, $P = 0.70$). The logistic regression model using accuracy found no significant effects (controls: $F(1,67) = 0.04$, $P = 0.85$; PPA-G: $F(1,67) = 0.14$, $P = 0.71$; PPA-L: $F(1,67) = 0.06$, $P = 0.80$; PPA-G vs. PPA-L: $F(1,67) = 0.20$, $P = 0.68$). Thus although PPA-L were a bit less accurate overall, their errors were not associated with their commission of a phonemic paraphasia.

There were no significant differences in RT between correct-naming and phonemic paraphasia items in any subject group (controls: $F(1,67) = 0.05$, $P = 0.83$; PPA-G: $F(1,67) = 0.27$, $P = 0.61$; PPA-L: $F(1,67) = 0.70$, $P = 0.41$) and no significant interactions of this RT difference between PPA-G and PPA-L ($F(1,67) = 0.07$, $P = 0.79$). The logistic regression model using RT found no significant effects (controls: $F(1,67) = 0.44$, $P = 0.51$; PPA-G: $F(1,67) < 0.01$, $P = 0.98$; PPA-L: $F(1,67) = 0.47$, $P = 0.50$; PPA-G vs. PPA-L: $F(1,67) = 0.24$, $P = 0.62$).

Frequency-controlled Analyses

Given our study design, this increased taxonomic interference for PPA-G subjects on phonemic paraphasia items could result from a hidden effect of word frequency. This would occur, for example, if PPA-G patients showed an increased proportion of phonemic paraphasias in the low-frequency block coupled with increased semantic blurring on all trials regardless of naming performance in that same block. To investigate this, we plotted the Taxonomic Interference Index and the proportion of naming type trials separately for the high and low frequency blocks for each participant group (Fig. 5*a*,*b*). Importantly, PPA-G's show increased taxonomic interference on phonemic paraphasia items for both high and low frequency items. The Taxonomic Interference Index difference between phonemic paraphasia and correctly named items in PPA-G's remained significant when controlling for frequency ($F(1,127) = 5.08$, $P < 0.05$), and remained not significant in controls ($F(1,127) = 0.08$, $P = 0.77$) and PPA-L ($F(1,127) = 0.21$, $P = 0.65$). The interaction contrast of the different phonemic paraphasia effect for PPA-G versus PPA-L when controlling for word frequency remained significant ($F(1,127) = 4.25$, $P < 0.05$). In the logistic regression model while controlling for word frequency, this interaction was significant ($F(1,127) = 4.05$, $P < 0.05$). The marginal effect of taxonomic interference for PPA-G was significant ($F(1,127) = 4.92$, $P < 0.05$) but not for Controls ($F(1,127) = 1.18$, $P = 0.28$) or PPA-L ($F(1,127) = 0.89$, $P = 0.35$).

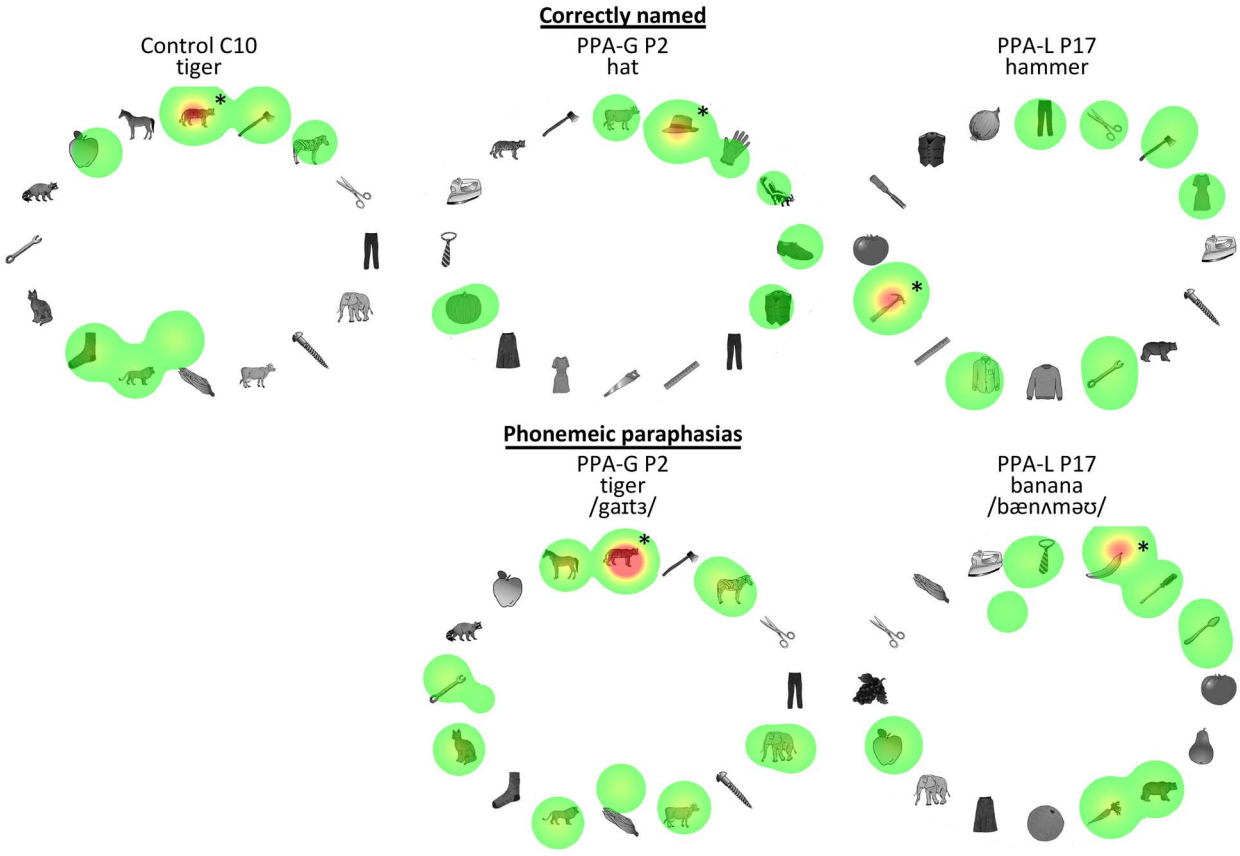

Figure 3. Eyetracking example trials in patient groups and controls. Illustrative heat maps are shown reflecting the relative amount of time spent viewing each item for the three different participant groups. Asterisks indicate the correct chosen item for each map. Many distractors of the same semantic category are viewed by the PPA-G patient in the example where they commit a phonemic paraphasia during naming.

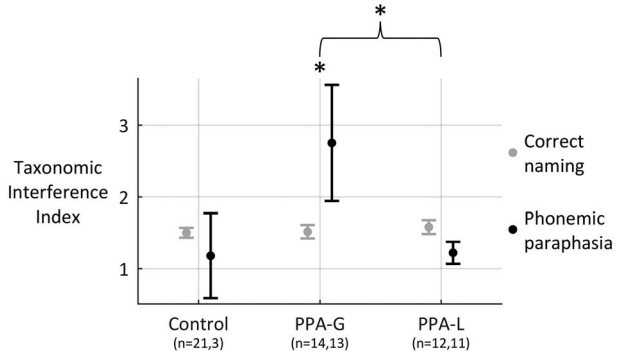

Figure 4. Taxonomic interference in patient groups and controls. Plots show the taxonomic interference index (see Methods: Eye Movement Processing) in correctly answered trials in the word-to-picture matching task, with trials grouped based on how the participant named the target item picture in a serially-performed object naming task (light grey: correctly-named items; black: phonemic paraphasia items). The numbers of participants in each group with at least one correct-naming or phonemic paraphasia item, respectively, is listed below the plot. Asterisks reflect a significant difference between correct-naming and phonemic paraphasia items within the corresponding participant group, and the bracketed asterisk reflects a significant interaction contrast of this effect between groups. PPA-G showed increased taxonomic interference for phonemic paraphasia items, with a larger increase for these items relative to PPA-L. Error bars show the standard error of the mean. $*P < 0.05$.

Trial-matching Analyses

Furthermore, if the items that elicited phonemic paraphasias in PPA-G's also elicited higher taxonomic interference in all groups, this could lead to the results observed without there being an underlying direct relation between taxonomic interference and phonemic paraphasias. To test this, we performed a trial-matching simulation analysis (see Materials and Methods: Trial-matching Analysis) in which naming types per item were randomly assigned to the comparison groups (Control and PPA-L) following the same proportion in which they were actually observed in PPA-G participants. Results in Figure 6 show that the taxonomic interference for phonemic paraphasia items in PPA-G, as well as the difference in taxonomic interference between phonemic paraphasia and correctly named items, were both significantly higher in PPA-G data than the trial-matched items in both controls (Simulation, see Methods: Trial-matching Analyses, $P < 0.01$) and PPA-L patients (Simulation, $P < 0.05$). This suggests a direct relation between phonemic paraphasias and taxonomic interference in PPA-G's.

PET Imaging Analyses

To quantify the cortical locations damaged in our patient samples, we performed analyses of PET glucose metabolism imaging for a subsample of participants from whom these data were recorded (Fig. 7). Relative to controls, PPA-G patients show

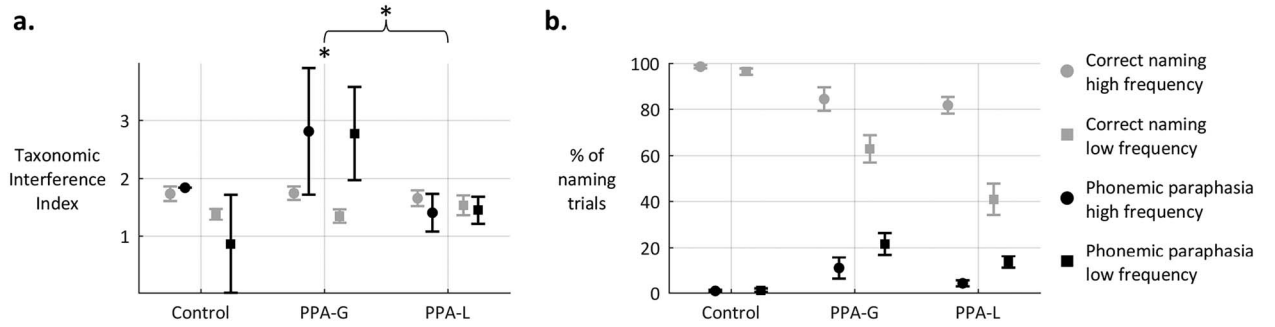

Figure 5. Taxonomic interference in patient groups and controls when controlling for frequency. (*a*) The taxonomic interference index is shown for each participant group with circles and squares showing data in the high- and low-frequency blocks, respectively. Error bars show the standard error of the mean. Asterisks reflect a significant difference between correct naming and phonemic paraphasia items within the corresponding participant group when accounting for effects of frequency, and bracketed asterisks reflect a significant interaction contrast of this effect across groups when accounting for frequency. *$P < 0.05$. (*b*) The proportion of each naming type trial for each frequency block and participant group. The connection between phonemic paraphasias and taxonomic interference in PPA-G is not explained by word frequency.

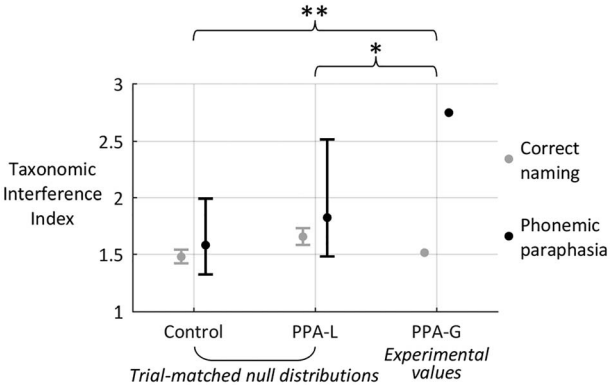

Figure 6. Trial-matching analyses. Error bars show the 95% confidence interval for control participants and PPA-L patients when the correct naming and phonemic paraphasia labels were randomly assigned across participants to follow the same frequencies per item that were experimentally observed in the PPA-G patients. Dots for PPA-G reflect the actual experimental values, to be compared against the other subject group values. Asterisks significance of the PPA-G phonemic paraphasia taxonomic interference index relative to the randomly trial-matched null distribution in the other respective groups. The connection between phonemic paraphasias and taxonomic interference in PPA-G is not explained by item effects. *$P < 0.05$, **$P < 0.01$.

glucose hypometabolism primarily in the posterior frontal regions in the left hemisphere, including portions of the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), and superior frontal gyrus (SFG). They also show hypometabolism in the right SFG and MFG, and right superior parietal cortex. The PPA-L group shows peak hypometabolism in the left temporoparietal junction (TPJ), and elevated hypometabolism in the left posterior and middle portions of the superior temporal gyrus (STG) and middle temporal gyrus (MTG) and left inferior parietal lobule. They also show hypometabolism in the left posterior frontal cortex, but less than PPA-G, and a small region of significance in the right supramarginal gyrus. These results are generally consistent with the distribution of atrophy in PPA-G and PPA-L (Mesulam et al. 2012).

Discussion

PPA-G but not PPA-L patients showed increased taxonomic interference in a word-to-picture matching task for stimuli that elicited phonemic paraphasias during confrontation naming. Control participants made very few phonemic paraphasias, but did not appear to show increased taxonomic interference on those few trials. PPA-G showed increased taxonomic interference for phonemically misnamed items during the word-to-picture matching task for both high and low frequency words. The same items that elicited phonemic paraphasias in PPA-G did not exhibit increased taxonomic interference among either control or PPA-L participants. The interference effect is therefore linked to the phonemic paraphasia rather than any intrinsic requirement of processing for the target item. PET imaging on a subset of patients showed that glucose hypometabolism was present primarily in the left posterior frontal regions in PPA-G and in the left TPJ and posterior STG and MTG in PPA-L.

The taxonomic interference effect we have shown in PPA-G may give the initial impression that phonemic paraphasias in these patients may also have a latent semantic component. This interpretation is consistent with the logistic regression model of our analyses, in which taxonomic interference is the cause of a phonemic paraphasia. There is indeed a vast literature on the interactions between grammar and phonology (Patterson et al. 1994; Dell et al. 1997), and on the semantic functions of the left IFG (Petersen et al. 1988; Fiez 1997; Poldrack et al. 1999; Wagner et al. 2000, 2001; Binder et al. 2009; Reilly et al. 2011; Anderson et al. 2018). Nonetheless, our finding that the taxonomic interference is associated with phonemic paraphasias in PPA-G but not PPA-L is difficult to explain in any simple way since neither subtype experiences consequential semantic impairments in everyday life and since the very subtle semantic interference effects that have been documented are quite comparable in PPA-G and PPA-L (Vandenberghe et al. 2005; Rogalski et al. 2008; Thompson et al. 2012). We would therefore like to propose an alternative explanation suggesting that the taxonomic interference in PPA-G may reflect an apperceptive rather than semantic mechanism. This is based on clinical aphasia patterns indicating that the IFG has a general role in encoding and decoding the sequential organization of words and sentences. At the output stage, dysfunction of this route leads to impairments of word articulation (requiring the sequencing of phonemes) and syntax (requiring the sequencing of words into a meaning-appropriate sentence). At the input stage, patients with IFG lesions are known to have deficits in understanding the meaning of noncanonical sentences where the sequencing of words is atypical (Caramazza

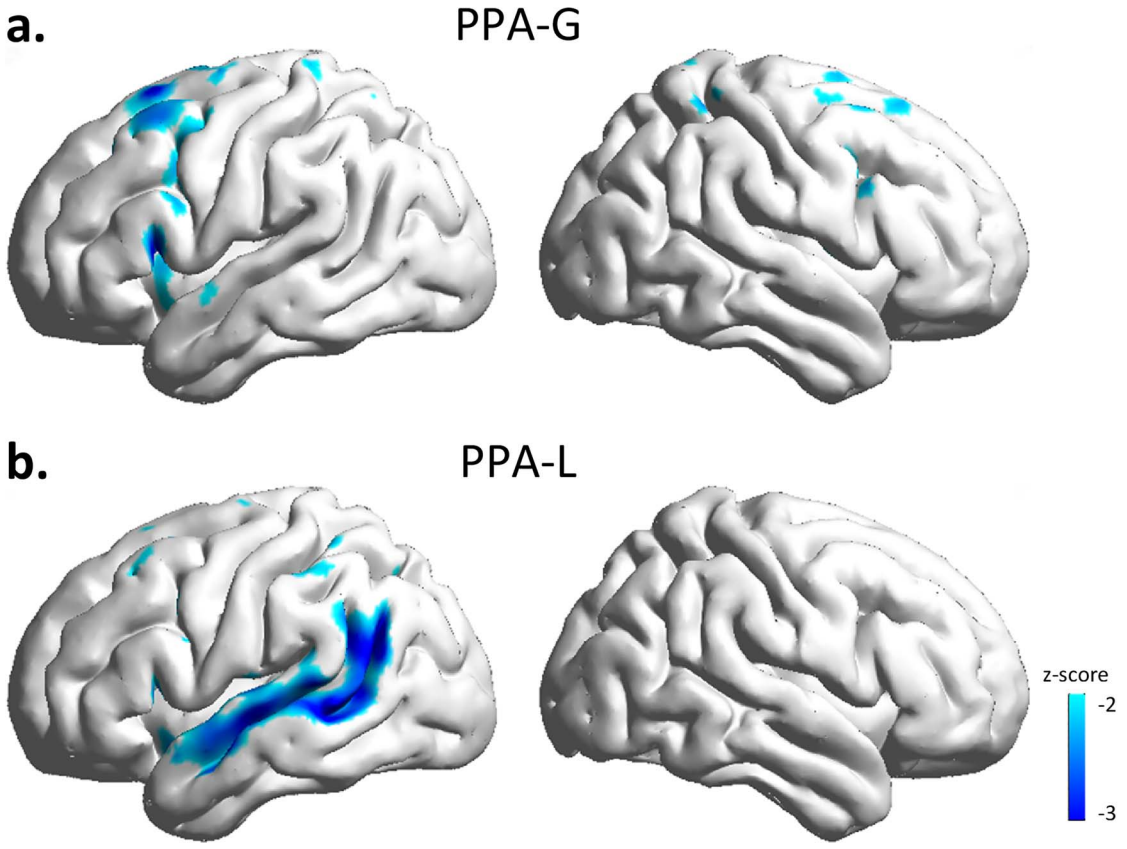

Figure 7. PET imaging analysis. (*a*) Glucose hypometabolism in PPA-G. Results show locations of significant glucose hypometabolism in a subsample of PPA-G patients ($n = 4$) relative to controls participants ($n = 8$) for which this imaging was available. (*b*) Glucose hypometabolism in PPA-L. Results show locations of significant glucose hypometabolism in a subsample of PPA-L patients ($n = 4$) relative to controls participants for which this imaging was available. Voxels where hypometabolism was significant, where the color reflects the uncorrected *z*-score at each voxel according to the colorbar. PPA-G patients show glucose hypometabolism primarily in left posterior frontal regions, with some regions of significance in the right frontal and superior parietal regions. PPA-L patients primarily show significant glucose hypometabolism in the left TPJ, and mid-to-posterior regions of the left STG and MTG.

and Zurif 1976; Peelle et al. 2008; Grossman 2012). Along this line of reasoning, it is conceivable that IFG lesions would also interfere with the perceptual encoding of the phonemes that constitute words, which is supported by functional imaging data in healthy subjects (Burton et al. 2000; Rogers and Davis 2017). In fact prior investigations have shown that PPA-G but not PPA-L is associated with impaired phonological facilitation effects (Mack et al. 2013). It is therefore conceivable that the findings of this experiment reflect a partial degradation of phonological word forms in agrammatic PPA during both word-to-picture matching (input stage) and picture naming (output stage). This interpretation suggests that in PPA-G, taxonomic interference may be the "consequence" of an apperceptive barrier for particular words, consistent with the standard regression model in our analyses.

Items that are semantically similar tend to be visually similar. This is more apparent for animals than for the other groups in this experiment. We cannot rule out the contribution of shape similarity to the taxonomic interference effect we measured. However, in a separate analysis the effects described here were present both for animals and for the other categories where visual similarity is much less conspicuous.

Additional experiments will be needed to further characterize the mechanisms underlying the taxonomic interference effect we detected in the phonemic paraphasias of PPA-G and to determine their relationships to phonology, semantics, perceptual similarity, and the IFG. In contrast to PPA-G, the phonemic paraphasias in PPA-L were not associated with the taxonomic interference effect and may reflect impaired phonological retrieval, a process closely allied to the proposed functionality of the left temporoparietal junction (Gorno-Tempini et al. 2008; Pillay et al. 2014). The single most important outcome of this study is the demonstration of heterogeneity in the mechanisms underlying phonemic paraphasias, some associated with taxonomic interference and some not.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Notes

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