Introduction

Progressive aphasia is a disorder in which individuals suffer from a gradual decline in language functions as a result of degenerative neurological disease. Individuals with progressive aphasia present with focal language deficits while other cognitive functions remain relatively spared. This behavioral profile is due to an underlying pattern of cortical atrophy that preferentially affects language cortex. Individuals with progressive aphasia may present with a nonfluent, fluent/semantic, or logopenic language profile, each of which has been associated with a distinct pattern of cortical atrophy (Amici et al., 2006). The nonfluent variant shows atrophy of the left frontal lobe (Kertesz, Davidson, McCabe, Takagi, & Munoz, 2003; Gorno-Tempini et al., 2004) as well as the left insula (Nestor et al., 2003); fluent progressive aphasia, or semantic dementia, is associated with atrophy of the anterior temporal lobe, particularly in the left hemisphere (Hodges et al., 1992; Mummery et al., 2000); and the logopenic variant is characterized by atrophy in left temporo-parietal cortex (Gorno-Tempini et al., 2004; 2008).

As is the case in aphasia resulting from stroke, any of several critical language processing domains may be affected in progressive aphasia, including syntax, semantics, phonology, and orthography. In stroke-induced aphasia, traditional lesion mapping approaches have provided important insight into the localization of the individual cortical regions supporting these domains. Specifically, left anterior and posterior perisylvian cortex has been implicated in syntactic and phonological aspects of language processing, whereas left extrasylvian cortical regions have been implicated in lexical-semantic and orthographic functions. The goal of the present study was to seek converging evidence for the role of left hemisphere cortical regions in these language processing domains using voxel-based imaging techniques in individuals with progressive aphasia.

Method

Eleven individuals with progressive aphasia as well as 15 demographically-matched normal controls were included in the study (see Table 1). Participants with progressive aphasia presented with aphasia with relative sparing of other cognitive functions. Language profiles included nonfluent, semantic dementia (SD), and logopenic variants. Mean age for the patient group was 72.1 (7.9) and average time post onset of symptoms was 4.8 (2.4) years. Normal controls were free from neurological or psychological illness, with a mean age of 67.8 (8.5), which did not differ significantly from the patient group ($p=.20$). Individuals in the patient group were administered a comprehensive language battery that included subtests in each of four language domains: syntax, semantics, phonology, and orthography (see Table 2). All participants underwent high-resolution T1-weighted structural MRI scanning within one month of behavioral testing.

Composite scores for the syntax, semantics, and phonology were derived by averaging percent correct across subtests in each domain. For written language, a derived measure was calculated for each individual by averaging irregular word performance across reading and spelling, averaging nonword performance across both modalities, and subtracting the latter score from the former: *average irregular word score minus average nonword score*. This derived measure represents an index of lexical-semantic (represented by irregular word performance) versus sub-lexical (represented by nonword performance) contributions to written language processing, with a positive number indicating an over-reliance on lexical-semantic processing

(manifested as better irregular word than nonword scores) and a negative number indicating an over-reliance on sub-lexical processing (manifested as better nonword than irregular word scores).

Voxel-based morphometry (VBM) was used to examine regional gray matter atrophy relative to the control group and also to correlate gray matter volumes with the behavioral composite measures. VBM was implemented using the automated segmentation routines in SPM5 (Ashburner & Friston, 2005). A custom template comprising patient and normal control scans was used in order to achieve an optimal segmentation and gray matter images were modulated by Jacobian determinants derived from the normalization process in order to preserve original gray matter volumes. Segmented, modulated gray matter maps were smoothed with a 12mm full width half maximum Gaussian kernel.

In order to determine areas of regional cortical atrophy in the progressive aphasia group relative to controls, we conducted a two-population group comparison. For this and all subsequent analyses, differences in overall cranial volume were accounted for by entering total intracranial volume (TIV) for each individual into the design matrix as a covariate. Composite scores for each language domain were then correlated with gray matter volume for the patient group only. This analysis was limited to left hemisphere regions implicated in language processing, including the inferior frontal gyrus/rolandic operculum, insula, supramarginal gyrus, angular gyrus, temporal pole, superior/middle/inferior temporal gyri, and visual word form area (Cohen et al., 2000). We predicted that behavioral measures would significantly correlate with gray matter volume in regions (Brodmann areas) implicated in the focal lesion and functional neuroimaging literature (see Table 3: "Predicted Brodmann Areas").

Results

The two-group comparison examining gray matter volume in the patient group relative to the control group revealed areas of significant atrophy in left hemisphere perisylvian and extrasylvian cortical regions as well as in the right temporal lobe (Figure 1).

Analyses examining correlations between gray matter volume and behavioral composites revealed significant correlations in regions identified as critical in the focal lesion and fMRI literature, as predicted (see Table 3: "Observed Brodmann Areas"): the syntactic composite correlated significantly with gray matter volume in left inferior frontal and temporo-parietal cortices (Figure 2a); the semantic composite correlated with volumes in left middle and inferior temporal cortex (Figure 2b); and the phonological composite correlated with gray matter volume in left inferior frontal and temporo-parietal cortices (Figure 2c). Worse irregular word than nonword performance (a sub-lexical bias) in reading/spelling correlated with damage to left temporal cortex, whereas worse nonword than irregular word performance (a lexical-semantic bias) in reading/spelling correlated with damage to frontal and temporo-parietal cortex (Figure 3a).

In order to further explore the relation between damage to these cortical regions and performance on our written language measures, we directly compared gray matter maps for patients demonstrating a sub-lexical bias to those demonstrating a lexical-semantic bias. Results were confirmatory, again indicating that damage to the left temporal lobe results in a sub-lexical bias, while damage to left perisylvian cortex results in a lexical-semantic bias (Figure 3b).

Conclusions

The approach used in this study allowed for examination of the role of specific cortical regions in language processing, not just at the level of individual measures (e.g., naming, sentence comprehension), but at the level of cognitive processing domains. Our results provide evidence for the role of left perisylvian and extrasylvian cortical regions in language. Specifically, left perisylvian cortex is critical for phonological processing in both spoken and written language and also for syntactic processing. In contrast, left temporal cortical regions are critically involved in semantic processing for both spoken and written language. Findings are consistent with studies of focal lesions in stroke patients and provide additional information about cortical regions not typically affected in stroke.

References

Amici, S., Gorno-Tempini, M. L., Ogar, J. M., Dronkers, N. F., & Miller, B. L. (2006). An overview on primary progressive aphasia and its variants. *Behavioural Neurology, 17*(2), 77-87.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage, 26*(3), 839-851.

Cohen, L., Dehaene, S., Naccache, L., Lehericy, S., Dehaene-Lambertz, G., Henaff, M.., et al. (2000). The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain, 123*(2), 291-307.

Gorno-Tempini, M. L., Brambati, S. M., Ginex, V., Ogar, J., Dronkers, N. F., Marcone, A., et al. (2008). The logopenic/phonological variant of primary progressive aphasia. *Neurology, 71*(16), 1227-1234.

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., et al. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology, 55*(3), 335-346.

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain: A Journal of Neurology, 115 (Pt 6)*, 1783-1806.

Howard, D., & Patterson, K. (1992). Pyramids and palm trees: A test of semantic access from pictures and words. Bury St.Edmunds, UK: Thames Valley Test Company.

Kertesz, A., Davidson, W., McCabe, P., Takagi, K., & Munoz, D. (2003). Primary progressive aphasia: Diagnosis, varieties, evolution. *Journal of the International Neuropsychological Society, 9*(05), 710-719.

Kaplan, E., Goodglass, H., & Weintraub, S. (2001). Boston Naming Test, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins.

Kay, J., Lesser, R., & Coltheart, M. (1992). PALPA: Psycholinguistic Assessment of Language Processing in Aphasia. Sussex, UK: Lawrence Erlbaum Associates Ltd.

Mummery, C. J., Patterson, K., Price, C. J., Ashburner, J., Frackowiak, R. S., & Hodges, J. R. (2000). A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology, 47*(1), 36-45.

Nestor, P. J., Graham, N. L., Fryer, T. D., Williams, G. B., Patterson, K., & Hodges, J. R. (2003). Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. *Brain: A Journal of Neurology, 126*(Pt 11), 2406-2418.

Table 1. Demographic characteristics for individuals with progressive aphasia

Subj ID	Age	Time Post Onset (years)	Profile	WAB AQ†	WAB type‡
PPA1	75	5	fluent/SD+	91.4	anomic
PPA2	80	8	fluent/SD	72.6	anomic
PPA3	65	4.5	fluent/SD	70.6	anomic
PPA4	71	5	fluent/SD	98.2	non-aphasic
PPA5	79	9	fluent/SD	86.3	anomic
PPA6	73	6.5	logopenic	76.5	conduction
PPA7	53	2.5	logopenic	90.3	anomic
PPA8	76	2.5	logopenic	90.6	anomic
PPA9	71	6	logopenic	65.6	conduction
PPA10	70	2	logopenic	93.6	anomic
PPA11	80	2	nonfluent	55.6	TcM*
mean (sd)	72.1 (7.9)	4.8 (2.4)		81.03 (13.6)	

†WAB AQ = Western Aphasia Battery aphasia quotient (max. = 100)
‡WAB type = aphasia type as determined by the Western Aphasia Battery
+SD = semantic dementia
*TcM = Transcortical motor aphasia

Table 2. Language measures administered in each of the four language processing domains

Language Domain	Type of assessment	Measure
Syntax	Verb and sentence comprehension and production	Northwestern Assessment of Verbs and Sentences (NAVS; Thompson, unpublished)
Semantics	(1-2) Nonverbal assessment of knowledge of semantic relations	1)Pyramids and Palm Trees Test (Howard & Patterson, 1992) 2) Arizona Semantic Test (Beeson, unpublished)
	(3) Spoken picture naming	3) Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2001)
	(4) Spoken/written single word comprehension	4) Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay, Lesser & Coltheart, 1992) subtest 47: spoken word-picture matching
Phonology	Assessment of phonological processing involving both input and output modalities	Arizona Phonological Battery (APB; Beeson & Rapcsak, unpublished)
Orthography	Spelling and reading of regular words, irregular words, and nonwords	Arizona Battery for Reading and Spelling (ABRS; Beeson, Henry, & Rapcsak; unpublished)

Table 3. Predicted and observed Brodmann areas implicated in each language processing domain

Language domain	Predicted Brodmann Areas (BA)	Observed Brodmann Areas (BA)
SYNTAX:		
Comprehension and production or sentences	BA 44/45, 6/4, 22, 40, insula	BA 44/45, 6, 22, 40, insula
SEMANTICS:		
Retrieval, storage, and manipulation of conceptual information	BA 47, 38, 20/21, 37/39	BA 47, 38, 20/21
PHONOLOGY:		
Speech production and perception; phonological awareness	BA 44/45, 6/4, 22, 40, insula	BA 44/45, 6, 22, 40, insula
ORTHOGRAPHY:		
Sub-lexical/phonological bias	BA 47, 38, 20/21, 37/39	BA 38, 20/21, 37
Lexical-semantic bias	BA 44/45, 6/4, 22, 40, insula	BA 44/45, 6/4, 22, 40, insula

Figure 1. Two-group comparison of 11 progressive aphasia patients to 15 normal controls (p<.001, FDR correction)

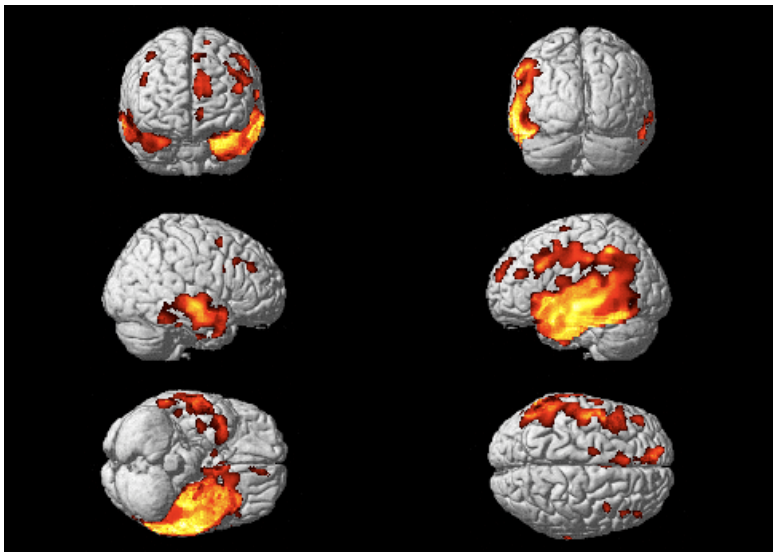
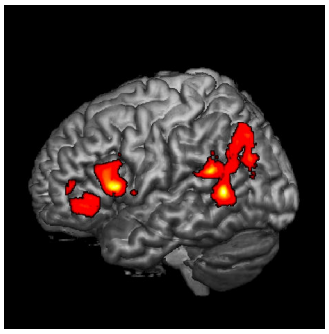
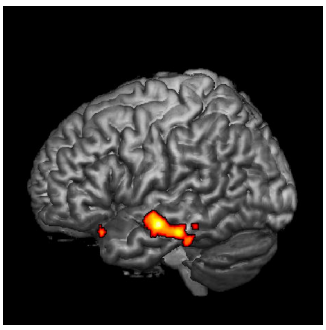


Figure 2a-c. Correlation between gray matter volume and behavioral composites for a) syntax b) semantics c) phonology (p<.001, uncorrected)

a.



b.



c.

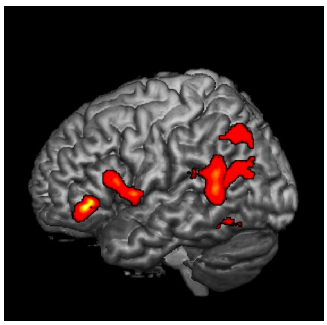


Figure 3a. Correlations between written language bias measures and gray matter volume (**blue**= worse irregular word than nonword performance (sub-lexical bias); **orange**= worse nonword than irregular word performance (lexical-semantic bias); p<.05, uncorrected)

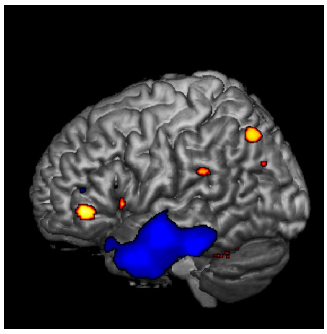


Figure 3b. Two-group comparison examining patients with a sub-lexical bias relative to those with a lexical-semantic bias on written language measures (**blue** = area damaged in patients demonstrating a sub-lexical bias; **red** = area damaged in patients demonstrating a lexical-semantic bias; p<.05, uncorrected)