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An Area Essential for Linking Word Meanings to Word Forms: Evidence from Primary Progressive Aphasia

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Abstract

We investigated the relationship between deficits in naming and areas of focal atrophy in primary progressive aphasia (a neurodegenerative disease that specifically affects language processing). We tested patients, across multiple input modalities, on traditional naming tasks (picture naming) and more complex tasks (sentence completion with a name, naming in response to a question) and obtained high resolution MRI. Across most tasks, error rates were correlated with atrophy in the left middle and posterior inferior temporal gyrus. Overall, this result converges with prior literature suggesting that this region plays a major role in modality independent lexical processing.

1. INTRODUCTION

Everyone has had the frustrating experience of being unable to retrieve a word from memory. In most cases, one is able to retrieve neither the pronunciation nor the spelling of the word. Although occasional instances of difficulty are not generally a cause for concern, brain lesions or neurological disease can cause a pathological level of naming deficits. Interestingly, difficulty with naming can be the residual deficit after incomplete recovery from nearly any vascular aphasia syndrome (e.g. Broca's Aphasia or Wernicke's Aphasia). It can also be one of the earliest manifestations of neurodegenerative syndromes, including all variants of Primary Progressive Aphasia (PPA). In the present study, we investigated the relationship between naming deficits and location of atrophy in individuals with PPA, a neurodegenerative condition in which language is disproportionately impaired for at least two years, without impairment in other cognitive domains other than praxis (Mesulam, 1982).

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Naming is complex in that it involves, at the very least, mapping from various modalities of input (visual, auditory, tactile, etc.) to a semantic representation and then linking that to a word form for output in a particular mode (spoken, written). A deficit in any one of these processes can cause naming errors. In the current study, we evaluate areas of the brain associated with naming across various input modalities, and evaluate the possibility that there is an area critical for accessing spoken word forms (lexical representations) from a modality-independent semantic representation. Damage to this access or “linking” process would result in anomia, or the inability to name an object, although sensory and semantic processing remains intact (Deleon et al., 2007). For example, an individual with anomia would be unable to access the name “shoe” although they could select a shoe (versus glove) if given the name.

In a series of previous studies of acute stroke, we and others have identified areas of hypoperfusion and/or infarct associated with modality-independent naming impairment before the opportunity for reorganization of structure/function relationships. These studies have converged in support of the conclusion that an area in left posterior inferior temporal cortex (within Brodmann Area, BA, 37) when acutely compromised results in anomia (Raymer, et al., 1997; Hillis et al., 2002a; Deleon, et al., 2007). Furthermore, poor perfusion of this area (leading to tissue dysfunction) is associated with anomia, while reperfusion results in recovery from anomia (Hillis et al., 2002a, Hillis et al., 2006b).

Although we have found this area to be critical for accessing modality-independent word forms from meaning, functional imaging studies in healthy participants have indicated that this relatively posterior part of the inferior temporal cortex (including inferior lateral BA 37) may be engaged in a variety of modality-independent lexical tasks in addition to naming (Cohen et al., 2004). Cohen and colleagues dubbed this area, lateral to the midfusiform area critical to reading, the “lateral modality independent area (LIMA). Whether or not this area is “specialized” for naming, the area is not likely to be the only area critical for modality-independent naming, but one important node in a neural network supporting naming.

Most of the evidence that posterior inferior temporal cortex is critical for modality-independent naming comes from stroke. Stroke studies might be biased as a method for identifying lesions associated with particular deficits, because some areas of the brain are particularly vulnerable to ischemia. Areas that are especially vulnerable to ischemia are more likely to be revealed as associated with deficits than areas less vulnerable to ischemia. PPA affects some regions of the brain that are less frequently damaged by stroke such as the anterior temporal pole, in addition to regions that stroke commonly affects (e.g. insula and superior temporal gyrus). Therefore, studying PPA provides another opportunity to test hypotheses about structure/function relationships, about naming in particular. It is especially useful to study all variants of PPA, because they all have naming deficits, but are associated with distinct areas of atrophy. Three variants of PPA (semantic, nonfluent agrammatic, logopenic) have been recognized that are characterized by their behavioral performance on language tasks and their pattern of brain atrophy (Gorno-Tempini, et al., 2004, 2011; Mesulam et al, 2009a; Mesulam et al, 2009b; Wilson, et al., 2009). All three are frequently associated with naming impairment early in the course and throughout the course, and naming impairment is a defining criterion of both svPPA and lvPPA.

Of the three variants, svPPA is associated with the most severe naming deficits. SvPPA is characterized by severe naming and single-word comprehension deficits across input and output modalities (Bozeat, et al. 2000; Hurley, et al., 2012; Coccia, et al., 2004; Luzzi et al. 2007). Naming errors are often empty nouns (“thing”, “stuff”), circumlocutions, or semantic paraphasias, with both coordinate (cat → ‘dog’) and superordinate (cat → ‘animal’) errors observed (Jefferies and Lambon Ralph, 2006). Some patients with svPPA have progressive

impairment in naming objects, with spared naming of actions, and their naming impairment is worse in the written than the spoken modality (Hillis et al., 2004, 2006a), although often severely impaired in the spoken modality as well. In contrast to the other variants, speech in svPPA is fluent, with intact syntax but limited content. This variant is associated with atrophy in the anterior and inferior temporal lobes bilaterally, but generally with greater atrophy on the left (Gorno-Tempini, et al., 2011; Wilson, et al., 2009). Due in large part to the multi-modal nature of the naming and comprehension deficits, there are claims that the anterior temporal lobes involved in amodal semantic processing (Corbett, et al., 2009; Jefferies & Lambon Ralph, 2006; Patterson & Rodgers, 2007).

Nonfluent agrammatic variant PPA (nfvPPA) is characterized by agrammatism and/or apraxia of speech (AOS) (Ash et al., 2009; Gorno-Tempini et al. 2004; Mesulam, Weineke, Thompson, Rogalski, & Weintraub, 2009; Rogalski et al., 2011). Agrammatism is characterized by the production of simple phrases and omissions of grammatical morphemes. Furthermore, syntactic processing becomes more apparent as the difficulty of the structure increases (passives, object relative clauses, etc.). AOS refers to slow, effortful speech articulation with numerous and varied off-target productions of words, especially polysyllabic words, with an awareness of misarticulations, but impaired motor planning. This variant is associated with atrophy in the left posterior frontoinsula region (posterior inferior frontal gyrus, insula, premotor, and supplementary motor areas) (Gorno-Tempini, et al., 2004, 2011; Wilson, et al., 2009).

In a small number of cases, modality-specific impairment in naming, specific to the spoken modality, has been reported in nfvPPA (Hillis et al., 2002b, 2004, 2006a). The naming deficit in these cases has also been specific to impaired naming of actions rather than objects (Hillis et al., 2002b; see also Bak et al., 2001). For example, individuals with nfvPPA have been reported who could name objects both orally and in writing, but could name actions only in writing. Their deficit could not be attributed to a motor speech problem because they are able to say the names of objects without difficulty. Rather, they have difficulty accessing the spoken word form of actions. Because this pattern of performance has only been reported in nfvPPA, we expect that the area of atrophy associated with this component of naming is the posterior frontal cortex, and there is some evidence for this conclusion (Bak, et al., 2001; Hillis et al., 2006a).

Logopenic variant PPA (lvPPA) is characterized by slow, hesitant speech that is often related to word finding pauses and moderately impaired confrontation naming (Gorno-Tempini et al., 2004, 2008). Observed errors include circumlocutions (e.g. “the thing you wear on your feet” for shoe) and phonological errors (“sue” for shoe). In addition, errors processing complex sentence structures seem to be more related to word length than syntactic complexity. These deficits are believed to generally stem from impaired phonological short-term memory, as the main distinguishing feature is disproportionately impaired phrase and sentence repetition. In contrast to svPPA, single word comprehension is relatively preserved. This variant is associated with atrophy in the left temporoparietal junction area (posterior temporal, supramarginal, and angular gyri) (Gorno-Tempini, et al., 2011; Wilson, et al., 2009).

Although there are differences in language deficits, difficulty naming can be one of the first symptoms and can remain a prominent symptom throughout the course in all PPA variants (Budd, et al., 2010; Etcheverry et al. 2012; Grossman et al., 2004; Hurley et al., 2009; Hurley, Paller, Rogalski, & Mesulam, 2012; Kremin et al., 2001; McMillan et al., 2004; Mesulam et al., 2013; Rogalski, Rademaker, Mesulam, & Weintraub, 2008). However, there are fewer studies that have investigated naming across these PPA variants. It is important to investigate all variants, because naming severity is likely to be associated with atrophy in

left temporal pole in svPPA (because that is where they have most atrophy), left superior temporal gyrus and inferior parietal lobule in lvPPA (because that is where they have the most atrophy), and left inferior frontal gyrus in nvPPA (because that is where they have the most atrophy). Those that have studied all variants have reported both spoken naming and comprehension to be related to atrophy in the temporal lobes (anterior temporal and inferior temporal lobe) (Amici et al. 2006; Rogalski et al., 2011). However, these studies have not generally investigated naming across different modes of input (auditory and visual) and across actions and objects. Therefore in the current study, we investigated the relationship between modality-independent naming deficits for actions and objects and atrophy across all variants of PPA. Specifically, we tested naming when the input was visual or visual plus tactile or pure auditory. Finally, we tested participants on two complex naming tasks (Naming to Sentence Completion - (Grass is... → green); Responsive Naming: “Where do nurses work?” → hospital). Although these tasks are more complex than simple naming (and can be failed for other reasons, such as failure to understand the question), they both require producing the correct name for the given input. We hypothesized that there might be one area of the brain (posterior inferior temporal cortex) critical for access to lexical representations from semantic representations (naming), and therefore atrophy in that area would be associated with impairment on all tasks that required naming (although other areas of atrophy might also disrupt performance on the various tasks because of damage to other cognitive components of the task).

2. METHODS

2.1 Participants

We initially enrolled a series of 54 participants with PPA who were seen in one author's (AH) outpatient cognitive neurology clinic and agreed to participate. They were diagnosed with PPA on the basis of having a predominant and progressive deterioration in language in the absence of major change in personality, behavior or cognition other than praxis for at least two years (Mesulam, 1982). Participants were classified, when possible, as one of the variants of PPA according to recent guidelines (Gorno-Tempini et al., 2011). All participants completed a battery of language and other neuropsychological tests that led to their classification. Tests included the Frontotemporal Dementia Module used by the National Alzheimer's Coordinating Center, the Western Aphasia Battery (Kertesz, 1982), the Apraxia Battery for Adults (Dabul, 2000), the Frontal Behavioral Inventory (Kertesz, et al., 1997, 2000), the short form of The Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001), The Hopkins Assessment of Naming Actions (Breining & Hillis, unpublished), a short form of the Pyramids and Palm Trees Test (Howard & Patterson, 1992), and short form of the Kissing and Dancing Test (Bak & Hodges, unpublished), and the Trail Making Test (Tombaugh, 2004). All patients had a brain high resolution T1 weighted image (T1-WI), and many had PET scans (with or without amyloid PET). We excluded patients who did not have a MRI scan within 6 months pre or post testing or who completed fewer than three tests. A final group of 39 participants were included: 22 lvPPA, 14 svPPA, 8 nvPPA, and 1 unclassifiable PPA. Because not all the patients completed all the tests, the sample size in each test varies. The unclassifiable PPA patient had progressive anomia and dysgraphia for at least two years, but did not clearly meet criteria for any one of the three variants. Age ranged from 55 to 84 years (mean=67.7). There were 22 women. Table 1 summarizes the behavioral data.

2.2 Tasks

The picture naming tests included the short form of the Boston Naming Test and the Hopkins Assessment of Naming Actions (HANA; Breining & Hillis, unpublished). The HANA consists of 30 line drawings of actions, matched in frequency to objects in the short

form of the Boston Naming Test, and selected from a larger set for high name agreement by healthy controls. The other naming tests are part of the Western Aphasia Battery (Kertesz, 1982).

2.2.1 Picture Naming

2.2.1.1 Boston Naming Test (BNT, short form): Participants (N = 17) were asked to orally name 30 line drawings of objects that range from easy (e.g. bed) to difficult (e.g. sphinx). If participants had difficulty naming the picture, the experimenter provided a phonemic cue. .

2.2.1.2 Hopkins Assessment of Naming Actions (HANA): Participants (N = 16) were asked to orally name 30 line drawings of actions that range from easy (e.g. kiss) to difficult (e.g. melt). If participants named an object in the picture, they were reminded to name the action, or what the person was doing. If participants had difficulty naming the action, the experimenter provided a phonemic cue.

2.2.3 Object Naming—Participants (N = 28), were given 20 seconds per item to orally name 20 common objects (e.g. ball, knife, toothbrush). If participants could not immediately name the object, they were first allowed to hold the object in order to receive tactile input. If they were still unable to name the item, participants were cued with the first phoneme (e.g. “b” for “ball”) or the first half of a compound word (“tooth” for “toothbrush”). The maximum score an individual could receive for this task was 60 points. For each item, a score of 3 was given when no cue was needed to produce the correct name and if there was no more than a minor articulatory error, such as slurring. Trials were scored as 2 when no cue was needed to produce a recognizable name. Phonemic paraphasic errors (e.g., “fife for “knife”) were allowed as long as the name was recognizable. Trials were scored as 1 when a cue was required to name the item. Finally, trials were scored 0 when there was either an incorrect response (e.g. semantic paraphasias, “fork” for “knife”), or no response.

2.2.4 Naming to Sentence Completion—Participants (N = 28) were asked to complete five simple sentences with the final word (e.g. “The grass is ____”. Answer = “green”). Items were scored with two points if they provided a reasonable answer, one point if there is a phonemic paraphasia, and zero points if the response is unreasonable (“hot”).

2.2.5 Responsive Naming—Participants (N = 28) were asked to answer five simple questions (e.g. “What color is the snow”. Answer = white; “Where do nurses work?” Answer = hospital or clinic). Items were scored with two points if they provided a reasonable answer (hospital/clinic), one point if there was a phonemic paraphasia or alternative, but reasonable response (office), and zero points if the response was unreasonable (grocery store).

2.3 Imaging Analysis

MPRAGE T1-WIs (TR/TE = 8.4/3.9 ms) were acquired using a 3T whole body MRI scanner (Philips Medical Systems, Best, The Netherlands), with axial orientation and a image matrix of 256 × 256 mm. Participants were scanned with two slightly different protocols: one using a field of view (FOV) of 230×230 mm and 120 slices of 1mm thickness; and the other using a FOV of 212×212 mm and 140 slices of 1.1 mm thickness. To measure the volume of 54 anatomical regions, including superficial and deep gray matter, we performed an atlas-based analysis (ABA). In brief, the ABA consists of transforming a brain image (the atlas) and the anatomical parcellation defined in this atlas to each participant's brain. As a result, a specific parcellation is created for each individual and, therefore, each participant's brain can be fully and automatically parceled into multiple regions of interest (ROIs). In this study, the ABA analysis was made possible due the high

accuracy of the mapping algorithm, the large deformation diffeomorphic metric mapping – LDDMM (Ceritoglu et al., 2009; Faria et al., 2010; Faria et al., 2011; Mori et al., 2008; Oishi et al., 2008; Oishi et al., 2009)). As we showed in previous studies (Faria et al., 2010; Faria et al., 2011; Mori et al., 2008; Oishi et al., 2009), the accuracy of this automated parcellation rivals the manual delineation of structures, considered a gold standard.

A schematic diagram of the imaging post-process, performed using DiffeoMap (Li, X., Jiang, H., & Mori, S., Johns Hopkins University, www.MriStudio.org or mri.kennedykrieger.org), is shown in Fig. 1. The images were first normalized to the ICBM-DTI-81 coordinates (Mori et al., 2008) using a 12-parameter affine transformation and further transformed to a single-subject template using LDDMM. The dual-contrast LDDMM (Ceritoglu et al., 2009) was based on T1-WIs and cerebrospinal fluid (CSF) maps. The JHU-MNI “Eve” was chosen as the Atlas. This is a single-subject template in the ICBM-DTI-81 space, extensively parceled and labeled to 181 regions. Because of the reciprocal nature of the LDDMM, the transformation results can be used to warp the parcellation map to the original MRI data, thus automatically parcelling each brain.

This parcellation is based on multiple MRI contrasts and follows classical anatomical boundaries, i.e., sulci and gyri, in the cortical areas (T1 contrast-based) and DTI contrast in the white matter (Oishi et al., 2008). Because in this study the mapping was based on T1-WIs, anatomic-functional correlations were explored just in the cortical parcels ($n=70$). The structural definition of the temporal lobes is shown in Figure 2. The temporal pole was defined as the region lying forward to a vertical plane crossing anterior commissure that consisted of two regions: the anterior parts of both superior and middle temporal gyri (here called superior and inferior temporal pole, respectively), based on the anterior ending of the superior temporal sulcus. The cortex lying between the pole itself and the amygdala, the temporal operculum, was included in the definition of the superior temporal gyrus pole. The remaining three gyri (superior, middle, and inferior) were further divided by a vertical plane crossing postcentral gyrus (Insausti, et al., 1998; Kondo, Saleem, & Price, 2005). We used these gross anatomical boundaries to divide the superior, middle, and temporal gyri, because we wished to achieve high reproducibility across investigators and participants. More subtle anatomical sulci that might demarcate borders of probable Brodmann's areas (BA) 37 vs 20, for example, are difficult to identify in the presence of atrophy. We divided superior temporal gyrus into: posterior and middle temporal gyrus (including BA 41, 42, and 22) and superior temporal pole (superior BA 38). We divided middle temporal gyrus into anterior middle temporal (roughly BA 21) and posterior middle temporal (roughly superior lateral BA 37). We divided inferior temporal gyrus into: posterior inferior temporal (roughly inferior lateral BA 37), middle inferior temporal (roughly BA 20), and inferior temporal pole (roughly inferior BA 38). We avoided the terms “anterior inferior temporal” and “anterior temporal lobe” because these terms have been used synonymously with temporal pole or with all of inferior and middle temporal cortex anterior to BA 37 (see Tsapkini, Frangakis & Hillis, 2011 for discussion).

The volume of each area was transformed in z-score based on a healthy population of 39 individuals at the same age range. The z-scores were calculated from the standard deviations of the predicted values to the linear curve that fitted the model age, in logarithm scale, vs. volume of each region. Therefore, age effects were taken on account. Correlations between z-scores of volumes and BNT and HANA were linearly fitted, with the strength of the correlations represented by the Pearson correlation coefficient, r . For Object Naming, Naming to Sentence Completion, and Responsive Naming, in which participants' performance was binary distributed, the sample was divided into two groups: good performance (participants that scored maximum) and poor performance (the others), and the

differences were accessed by unpaired t-test. The significance level was set at p -value < 0.05 after correction for multiple comparisons using False Discovery Rate (FDR).

3. RESULTS

3.1 Boston Naming Task

Table 2 summarizes the results for the BNT (N =17, 11M 6F, mean age 68.4 ± 7 years; 8 lvPPA, 4 svPPA, 4 nvfPPA, 1 unclassified. Score range: 13-100%, mean: 49.17, median: 33.3). Significant correlations between regional brain volumes and naming accuracy were found in several regions of both the left and right temporal cortex, including left middle and posterior inferior temporal gyrus, but not the left inferior or superior temporal pole (Fig 3). .

3.2 HANA

Table 3 summarizes the results for the BNT (N =16, 11M 5F, mean age 68 ± 6.7 years; 7 lvPPA, 4 svPPA, 4 nvfPPA, 1 unclassified. Score range: 2.85-97.14%, mean: 39.27, median: 38.55). Significant correlations between regional brain volumes and action naming accuracy were found in several regions of both the left and right temporal cortex, including left middle and posterior inferior temporal gyrus, and bilateral inferior temporal pole (Fig. 4). .

3.3 Object Naming

Table 4 summarizes the results for Object Naming. Participants with poor performance (N =15, 8M 7F, mean age: 66.3 years. 8 lvPPA, 6 svPPA, 1 nvfPPA. Score range: 14-56. mean: 40.46, median: 42), differed from those with good performance (i.e. perfect score of 60, N =13, 4M 9F, mean age: 69.5 years; 6 lvPPA, 1 svPPA, 6 nvfPPA) by having greater atrophy in the left middle inferior temporal gyrus (Fig. 5).

3.4 Naming to Sentence Completion

Poor performance (N = 11, 6 lvPPA, 4 svPPA, 1 nvfPPA) and good performance (i.e. perfect score of 10, N = 17, 8 lvPPA, 6 svPPA, 2 nvfPPA, 1 unclassified) were not statistically associated with regional atrophy on this test.

3.5 Responsive Naming

Participants with poor performance (N =9, 3M 6F, mean age: 66.7. 4 lvPPA, 4 svPP, 1 nvfPPA. Score range: 4-9. mean: 6.78, median: 8) differed from those with good performance (i.e. perfect score of 10, N =19, 8M 11F, mean age: 68.2 ; 10 lvPPA, 3 svPPA, 6 nvfPPA) in that they had more atrophy in regions of the left hemisphere (Fig. 6) (prefrontal, dorsal-prefrontal, pars-orbitalis of inferior frontal, anterior insula, rectus gyrus, middle and posterior inferior temporal).

4. Discussion

The goal of the current study was to explore the relationship between naming across modalities and focal atrophy in participants with all variants of PPA. We tested participants on traditional naming tasks (picture naming, object naming) as well as more complex language tasks in which naming is one component (naming to sentence completion, responsive naming). Because this is a ROI-designed study, the results hinge on a pre-defined brain space. We were interested in separating the roles of the temporal pole (which has been proposed to have a critical role as a “semantic hub”; (Binney et al., 2010; Bozeat et al., 2000; Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2010; Patterson et al. 2007; Pobric et al., 2010; Rogers et al., 2006; Schwartz et al. 2009) and is atrophied particularly in

svPPA) from areas of the inferior temporal cortex posterior to the temporal pole, which may have a role in different stages of the naming task.

For each task, performance was associated with atrophy in multiple regions. However, the one area common to all naming tasks, irrespective of input modality, was the left middle inferior temporal gyrus. Middle and posterior inferior temporal gyrus (mITG and pITG) differed only in that pITG was not associated with Object Naming (which was limited in range of performance and number of participants). Overall, left ITG, posterior to the pole, includes BA 20 and the inferior lateral portion of BA 37. Both areas have been found to be associated with modality-independent lexical retrieval in acute stroke studies as shown in Figure 7. This area is similar to the area of activation across auditory and visual word priming tasks, and thus labeled the lateral inferior-temporal multimodality area (LIMA) (Cohen et al., 2004). It is also included in the brain area where we have shown that acute ischemic damage in acute stroke is associated with impaired oral naming, written naming, and oral reading, and furthermore that reperfusion of the same region is associated with improvement in these lexical tasks in acute stroke (Hillis et al., 2006b). For example, the patient whose scans are shown in Figure 7, panel A had no infarct as shown by his diffusion weighted imaging (top) on Day 1 (left), but had poor perfusion in the posterior inferior temporal cortex – the inferior lateral part of BA 37 – on Day 1, as shown by his perfusion weighted image (Panel A, lower image, left). He had poor oral naming, written naming, and oral reading. He received thrombolysis, and reperfused this area. By Day 2, he had normal blood flow in this area (Panel A, lower image, right), and normal oral naming, written naming, and oral reading.

Naming actions (the HANA) was the only task for which error rate was associated with volume of tissue loss in left inferior frontal gyrus, pars triangularis. Responsive naming (naming a word in response to a definition or question) was the only task where error rate was associated with volume loss in left inferior frontal gyrus, pars orbitalis. For both tasks, error rates correlated with atrophy in left lateral fronto-orbital gyrus. These results converge with previous results supporting the claim that these frontal regions are involved in verb and grammatical processing (Bak et al., 2001; Crepaldi, et al., 2006; Hillis et al., 2002b, 2004, 2006a; Luzzatti et al., 2002; Mätzig, Druks, Maesterson, & Vigliocco, 2009; Thompson, Lukic, King, Mesulam, & Weintraub, 2012), the latter of which is required for the responsive naming task.

Finally, we found that error rate in naming actions (on the HANA) but not objects, was associated with atrophy in parietal regions (i.e. bilateral supramarginal gyrus and right angular gyrus). These results also converge with previous studies suggesting that parietal regions are associated with knowledge of actions that is used in naming actions (Canessa et al., 2008; Kemmerer, Rudrauf, Manzel, & Tranel, 2012; Matzig et al., 2009; Vigliocco, Vinson, Druks, Barber & Cappa, 2011).

There are a number of limitations of our study. First, we did not find significant associations with all tasks. There were no significant associations between errors in sentence completion and areas of atrophy, after correction for multiple comparisons. We had too little power to find any association with errors on this test, because nearly all participants were 100% accurate. This task can often be performed “automatically” even without comprehending the sentence (and therefore is often used to “cue” naming). Secondly, on some of the other tasks (responsive naming, object naming with tactile cues) we had to divide performance into two groups (those with accurate performance and those with errors) because of ceiling effects. Furthermore, these tasks were not matched in level of difficulty to the picture naming tasks. However, these tasks were used as supporting evidence for our hypotheses, after we had found robust Pearson correlations between error rate on the BNT and HANA (which have

large range of scores) and atrophy in left middle and posterior inferior temporal gyrus. Finally, not all participants performed all tasks. However, most of the participants performed all of the tasks, and for most tasks, we had sufficient power to identify significant associations between performance and focal atrophy.

In summary, a number of distributed brain areas contribute to impaired naming in PPA patients. However, the left posterior and middle inferior temporal gyrus appears to be especially important for naming, as indicated by the association between atrophy in this region and performance across all naming tasks, across all variants of PPA. Atrophy in this area was more strongly associated with errors in naming than the temporal pole, collapsing across all variants of PPA. There is a great deal of evidence from previous PPA, transcranial magnetic stimulation, and other lesion studies, that bilateral anterior temporal poles are critical to accessing the meaning objects (Bi et al., 2010; Binney, et al., 2010; Lambon Ralph, et al., 2010; Patterson, et al., 2007; Pobric, et al., 2010; Rogers et al., 2006; Tranel et al., 1997), and are likely to be involved in naming as well (Schwartz et al., 2009; Simmons & Martin, 2009; Tranel, 2006; Walker et al., 2010; Newhart et al., 2007). However, our results indicate that the more posterior part of the left inferior temporal cortex (roughly Brodmann's area 20 and inferior lateral 37) is a key component of the network of brain regions supporting oral naming of objects and actions in a variety of everyday tasks, regardless of the modality of input. The importance of the left middle/posterior inferior temporal cortex in modality-independent naming has been demonstrated in acute and chronic stroke and functional imaging. The present results indicate that naming deficits in PPA patients may also be related to atrophy in this area, even though this is not the primary area of atrophy that in any one of the variants.

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We examined the relationship between naming deficits and atrophy in primary progressive aphasia.

Participants were tested over various input (visual, tactile) modalities.

Atrophy in left inferior temporal lobe was related to performance across all tasks.

Results indicate that the left inferior temporal lobe plays a large role in modality independent lexical processing.

Figure 1.

Schematic representation of the normalization procedure. Each subject's brain is accurately normalized to the atlas, which was previously parceled into regions anatomically predefined. Due to the reversible nature of the normalization algorithm, this parcellation can be warped to each subject brain, therefore enabling to automatically measure the volume (and contrast) of hundreds of areas in each individual.

Figure 2. Brodmann's areas (top) and the subdivisions of temporal lobe adapted in this study (bottom). A=superior temporal pole; B=Inferior temporal pole; C=middle superior temporal; D=anterior middle temporal; E=middle inferior temporal; F=posterior superior temporal; G=posterior middle temporal, H=posterior inferior temporal.

Figure 3.

Correlations between regional volumes (in z-scores - y axis) and participants' scores at Picture Naming of Objects (x axis) in the BNT. Regions that showed significant linear correlation with individual performance are colored by the degree of this correlation (r). For visualization purposes, the colors of medial areas were projected in the brain surface. A few representative regional correlation graphics are shown.

Figure 4.

Correlations between regional volumes (in z-scores - y axis) and participants' scores at HANA (x axis). As in Fig. 3, regions with significant correlations are colored by the degree of correlation, r . For visualization purposes, the colors of medial areas, such as Insula, were projected in the brain surface. A few representative regional correlation graphics are shown.

Figure 5. Volumetric differences in patients with good performance vs. poor performance in the Object naming test. Regions with significant differences between groups are colored by the ratio good/bad performance.

Figure 6. Volumetric differences in patients with good performance vs. poor performance in the Responsive naming test. Regions with significant differences between groups are colored by the ratio good/bad performance. For visualization purposes, the colors of medial areas were projected in the brain surface.

Figure 7.

Composite of the current and previous studies showing the common involvement of the left inferior temporal gyrus in naming tasks. Panel A shows a patient whose transient perfusion deficit in left lateral inferior temporal cortex and fusiform gyrus (in BA 37) coincided with a transient deficit in oral and written naming and reading. Panel B shows functional imaging data from Cohen et al., 2004, where they distinguished between modality-specific areas in response to orthographic input in fusiform (blue dots) vs. modality-independent areas in inferior temporal (orange dots). In our current study, atrophy of left inferior temporal gyrus correlated with error rate in BNT (C), HANA (D), and with poor performance in responsive naming (E).

Table 1

Demographic and Behavioral Data.

Task	N	Mean Age	Onset Mean (years)	Score Range (%)	Mean Score	Median Score
Boston Naming Test						
lvPPA	8	69.63	4.37	13-83	42.02	43.3
svPPA	4	68.75	3.93	30	30	30
nfvpPPA	4	63.75	3.33	16-100	70.8	83.3
Unclassified	1	76	2.3	97	96.6	96.6
HANA						
lvPPA	7	70.71	4.4	9 - 66	35.5	31.4
svPPA	4	65.5	5.13	3 - 67	16.42	3.1
nfvpPPA	4	63.75	3.33	9 - 97	61.43	69.99
Unclassified	1	68.57	2.3	69	68.57	68.57
Object Naming						
lvPPA	14	66.97	4.06	23.3-100	83.7	93.3
svPPA	7	65.15	4.27	55-96.7	74.5	70
nfvpPPA	7	72.71	4.51	65-100	93.6	98.3
Naming to Sentence Completion						
lvPPA	14	67.45	3.72	60-100	93.3	100
svPPA	10	65.27	5.56	20-100	80	100
nfvpPPA	4	72.33	4.60	60-100	88.5	100
Responsive Naming						
lvPPA	14	66.57	3.97	40-100	90	100
svPPA	7	65.14	3.07	40-100	84.3	90
nfvpPPA	7	72.71	5.06	60-100	94.2	100
Sentence Repetition						
lvPPA	17	68.88	4.81	0 - 80	40.88	40
svPPA	10	66.5	4.01	10 - 100	65.2	81
nfvpPPA	7	67.71	4.23	0 - 100	62.86	80
Unclassified	1	60	2.3	100	100	100
Pyramids & Palm Trees						
lvPPA	17	68.88	5.11	33 - 100	91.42	100
svPPA	10	66.5	4.01	47 - 77	76.68	81.65
nfvpPPA	11	68.27	4.73	93 - 100	99.21	100
Unclassified	1	60	2.3	100	100	100
Kissing and Dancing						
lvPPA	7	67.85	3.02	46.7-100	77.14	80
svPPA	5	67.8	4.22	53.3-80	71.98	73.3
nfvpPPA	3	62	2.86	93.3-100	97.76	100
Unclassified	1	76	2.3	100	100	100
Word Fluency (F, A, S)						
lvPPA	15	68	3.13	15-90	51.4	50

Task	N	Mean Age	Onset Mean (years)	Score Range (%)	Mean Score	Median Score
svPPA	7	65.14	2.50	25-80	41.2	35
nfvPPA	7	72.71	3.94	25-100	58.5	60

Note. Behavioral data for each variant of PPA across Tasks. Onset reflects approximate time since onset of PPA, as estimated by the family. Score reflects percent correct, except on word fluency, which is given as number of correct words named, for all 3 letters,

Table 2

Regions for which Atrophy is significantly associated with performance on BNT

	<i>r</i>	<i>p-value</i>	<i>q-value</i>
Right posterior middle temporal	0.7343	0.0008	0.0226
Right superior temporal pole	0.6352	0.0061	0.0477
Left posterior superior temporal	0.6308	0.0066	0.0477
Left middle inferior temporal	0.6222	0.0077	0.0477
Right inferior temporal pole	0.6032	0.0104	0.0477
Left fusiform	0.5859	0.0135	0.0477
Left medial fronto-orbital gyrus	0.5847	0.0137	0.0477
Right anterior middle temporal	0.5586	0.0198	0.0477
Left posterior middle temporal	0.5580	0.0199	0.0477
Right posterior insula	0.5569	0.0202	0.0477
Left rectus gyrus	0.5525	0.0214	0.0477
Left posterior inferior temporal	0.5407	0.0250	0.0489

Note. The '*q-value*' is the '*p-value*' after correction for multiple comparisons by FDR; '*r*' is the Pearson correlation coefficient.

Table 3

Regions for which Atrophy is significantly associated with performance on HANA

	<i>r</i>	<i>p-value</i>	<i>q-value</i>
Right posterior middle temporal	0.7480	0.0009	0.0086
Left posterior superior temporal	0.7419	0.0010	0.0086
Right supra marginal	0.6662	0.0048	0.0311
Left rectus gyrus	0.6257	0.0095	0.0389
Left posterior inferior temporal	0.6086	0.0124	0.0389
Right posterior superior temporal	0.6084	0.0124	0.0389
Left posterior middle temporal	0.5915	0.0158	0.0389
Right superior temporal pole	0.5887	0.0164	0.0389
Right angular	0.5872	0.0168	0.0389
Left medial fronto-orbital gyrus	0.5820	0.0180	0.0389
Right inferior temporal pole	0.5785	0.0189	0.0389
Left middle inferior temporal	0.5628	0.0232	0.0389
Left anterior middle temporal	0.5544	0.0258	0.0389
Right fusiform	0.5533	0.0262	0.0389
Right posterior inferior temporal	0.5508	0.0270	0.0389
Left superior temporal pole	0.5507	0.0270	0.0389
Right posterior insula	0.5480	0.0280	0.0389
Left inferior temporal pole	0.5459	0.0287	0.0389
Left inferior frontal, pars triangularis	0.5373	0.0319	0.0410
Left lateral fronto-orbital gyrus	0.5236	0.0374	0.0442
Left supramarginal	0.5227	0.0378	0.0442
Left parahippocampal	0.5107	0.0432	0.0483
Right middle superior temporal	0.5038	0.0466	0.0490
Left anterior insula	0.4923	0.0487	0.0494
Left fusiform	0.4918	0.0487	0.0494
Right anterior middle temporal	0.4855	0.0498	0.0499

Note. The '*q-value*' is the '*p-value*' after correction for multiple comparisons by FDR; '*r*' is the Pearson correlation coefficient.

Table 4

Regions for which Atrophy is significantly associated with Task Performance

	<i>p</i> -value	<i>q</i> -value	fold-change
Object Naming			
Left middle inferior temporal	0.011	0.032	5.1515
Responsive Naming			
Right anterior insula	0.0019	0.0120	3.5549
Left anterior insula	0.0019	0.0120	1.9788
Left superior frontal gyrus (prefrontal)	0.0024	0.0120	10.2802
Left posterior inferior temporal	0.0083	0.0271	5.0951
Left rectus	0.0099	0.0271	3.7963
Left lateral fronto-orbital gyrus	0.0108	0.0271	5.8776
Left inferior frontal (pars orbitalis)	0.0230	0.0465	3.8479
Left middle frontal (dorsal prefrontal)	0.0246	0.0465	4.8769
Left middle inferior temporal	0.0451	0.0494	2.7691

Note. The '*q*-value' is the '*p*-value' after correction for multiple comparisons by FDR. The fold change reflects the ratio 'good performance' / 'poor performance' volumetric z-scores.