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The function of the left anterior temporal pole: evidence from acute stroke and infarct volume

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The role of the anterior temporal lobes in cognition and language has been much debated in the literature over the last few years. Most prevailing theories argue for an important role of the anterior temporal lobe as a semantic hub or a place for the representation of unique entities such as proper names of peoples and places. Lately, a few studies have investigated the role of the most anterior part of the left anterior temporal lobe, the left temporal pole in particular, and argued that the left anterior temporal pole is the area responsible for mapping meaning on to sound through evidence from tasks such as object naming. However, another recent study indicates that bilateral anterior temporal damage is required to cause a clinically significant semantic impairment. In the present study, we tested these hypotheses by evaluating patients with acute stroke before reorganization of structure–function relationships. We compared a group of 20 patients with acute stroke with anterior temporal pole damage to a group of 28 without anterior temporal pole damage matched for infarct volume. We calculated the average percent error in auditory comprehension and naming tasks as a function of infarct volume using a non-parametric regression method. We found that infarct volume was the only predictive variable in the production of semantic errors in both auditory comprehension and object naming tasks. This finding favours the hypothesis that left unilateral anterior temporal pole lesions, even acutely, are unlikely to cause significant deficits in mapping meaning to sound by themselves, although they contribute to networks underlying both naming and comprehension of objects. Therefore, the anterior temporal lobe may be a semantic hub for object meaning, but its role must be represented bilaterally and perhaps redundantly.

Keywords: anterior temporal lobe; aphasia; acute ischaemic stroke; word naming; comprehension; semantic impairment; infarct volume

Abbreviation: BA = Brodmann area

Introduction

The role of the anterior temporal lobes in semantic memory is a controversial topic in the neuropsychological and neuroimaging literature. According to one theory (Patterson *et al.*, 2007; Simmons and Martin, 2009) the anterior temporal lobes form the 'semantic hub' of the brain, or the neural substrates that subserve the processing of 'unique entities' (Tranel *et al.*, 1997,

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2006), or even the areas that subserve 'social conceptual processing' (Olson *et al*., 2007; Simmons and Martin, 2009). More recently, the contribution of each hemisphere, particularly the left, has been brought into investigation. In the experimental section, we concentrate on specific evidence for the role of the left anterior temporal pole, the most anterior portion. First, we present the current neuropsychological and neuroimaging evidence for the role of the anterior temporal lobes defined broadly, and then the temporal pole more specifically, in semantics. Then we address whether the left anterior temporal pole is an area critical for mapping of meaning onto sound as claimed recently by other investigators. Finally, we discuss the role of the bilateral anterior temporal lobes more generally and the specific role of the left temporal pole.

The most prevalent theory on the role of the anterior temporal lobe is that this area acts as a semantic hub (for a review see Patterson *et al*., 2007), i.e. a region that links other modality-specific brain regions, mostly posterior to the anterior temporal lobes, that in turn represent semantic content (object features, object names, etc.), and provides a semantic similarity structure in an amodal format. Evidence for this hypothesis comes from semantic dementia, more recently known as semantic variant primary progressive aphasia (Gorno-Tempini *et al*., 2011; a neurodegenerative disease that results in pronounced deficits in mapping meaning to sound) and herpes encephalitis; both of these diseases result in damage to bilateral anterior temporal lobes. Patients with either semantic dementia (Warrington, 1975; Schwartz *et al*., 1979; Snowden *et al*., 1989) or herpes encephalitis (Warrington and Shallice, 1984; Lambon Ralph *et al*., 2007; Noppeney *et al*., 2007) have been described who have semantic impairments that are apparent in tasks such as categorical discrimination [e.g. inability to distinguish between a robin and a jay, see Rogers *et al*. (2006) for functional imaging results], word comprehension (e.g. pointing to an incorrect picture named) and naming (e.g. naming a pictured eagle as 'robin').

Despite the plethora of neuropsychological studies arguing for the semantic hub hypothesis of the anterior temporal lobe, the functional neuroimaging evidence supporting this hypothesis is scarce. As explained by Devlin and colleagues (2000), it is difficult to see activation in anterior temporal lobes using functional MRI due to field inhomogeneities and magnetic susceptibility artefacts in those areas. More evidence has been accumulated from PET, magnetoencephalography and repetitive transcranial magnetic stimulation. A meta-analysis of 164 functional neuroimaging studies to examine the role of semantic processing in the anterior temporal lobes revealed four factors that helped the detection of this area in semantic processing tasks: (i) use of PET versus functional MRI; (ii) field of view of <15 cm; (iii) use of a high baseline task; and (iv) use of anterior temporal lobe as a region of interest (Visser *et al*., 2009). Moreover, the type of stimuli or task did not influence the likelihood of anterior temporal lobe activation, so this region seems to underpin an amodal semantic system: spoken words, written words and picture stimuli produced overlapping anterior temporal lobe peaks. In contrast to functional MRI, there are numerous PET studies showing anterior temporal lobe activation in semantic tasks such as semantic categorization, category fluency, object naming, category verification and word recognition (Mummery *et al*., 1996; Devlin *et al*., 2000; Bright *et al*., 2004; Price *et al*., 2005; Rogers *et al*., 2006). Magnetoencephalography studies have also shown activation in anterior temporal lobes for supramodal word processing. For example, Marinkovic and colleagues (2003) investigated the stages of word comprehension in real time in the auditory and visual modalities as subjects participated in semantic judgements for written and spoken words. Activity spread from the primary sensory areas along the respective ventral processing streams and converged in anterior temporal lobe and inferior prefrontal regions primarily on the left at $\sim$400 ms. When response patterns across modalities were compared, it was shown that they are initiated by modality-specific memory systems, but that they are eventually integrated mainly in supramodal, anterior temporal lobe areas.

It should be noted that in the functional MRI literature, it is not the whole of the anterior temporal lobe that is affected by inhomogeneities and magnetic susceptibility artefacts; the major problematic regions are the basal anterior temporal lobe (fusiform, inferior temporal gyrus and some of the middle temporal gyrus), just behind the level of Brodmann area (BA) 38 and also along the medial bank of the anterior temporal lobe. This is shown not only by Visser *et al*. (2009), but also by Binder *et al*. (2009). With altered forms of acquisition and post-processing correction (Embleton *et al*., 2010; Visser *et al*., 2009) it is now possible to observe multimodal activations in these problematic areas—and these are typically bilateral in form. This same basal region, posterior to BA 38 and including the fusiform gyrus anterior to BA 37, is implicated in both functional MRI and the atrophy distribution of semantic dementia (Binney *et al*., 2010) and correlations between fluorodeoxyglucose-PET and semantic performance in semantic dementia (Mion *et al*., 2010).

Recently, investigators have questioned whether unilateral damage in the anterior temporal lobe results in the same impairments as bilateral damage and whether or not each hemisphere has an essential contribution to the conceptual representation as manifested in comprehension and naming tasks. Neuropsychological evidence for the unique role of the left anterior temporal lobe comes mainly from studies of left anterior temporal lobe resection and stroke. Whereas there seems to be little doubt that damage to both sides produces an unequivocal deficit of central semantic memory, it is not clear what consequences result from damage to unilateral anterior temporal lobe.

A recent functional connectivity study between the left and right anterior temporal lobe emphasized the role of interconnectedness between the two hemispheres (Warren *et al*., 2009). The study compared the organization of left anterolateral superior temporal cortex functional connections during narrative speech comprehension in normal subjects to a group of patients with chronic aphasic stroke. In normal controls, during narrative speech comprehension, the left anterior temporal lobe had positive connections with the left anterior basal temporal cortex, the left anterior inferior frontal gyrus and the homotopic cortex in the right anterior temporal lobe. Aphasic individuals, as a group, demonstrated a selective disruption of the normal functional connections between the left and right anterior temporal lobe. Deficits in auditory single word and sentence comprehension correlated with the degree of disruption of left–right anterior temporal lobe

connectivity and with local activation in the left anterior temporal lobe. These results are consistent with the hypothesis that conceptual representations are supported via an interconnected bilateral anterior temporal lobe network.

Semantic functions have been studied after left anterior temporal lobe surgical resection, and occasionally deficits in naming have been found. In a case of surgical resection of anterior temporal lobe due to a low-grade glioma, the patient showed intact conceptual knowledge for all categories of items both in accuracy and response latency measures, but was impaired in word retrieval for people, places and artefacts, but not for animate objects (Bi *et al*., 2010). Moreover, a recent study did not confirm clinically significant deficits in receptive or expressive semantic tasks after unilateral left or right anterior temporal lobe lesion at least 1 year after the stroke or resection (Lambon-Ralph *et al*., 2010).

Additional evidence for the role of the left anterior temporal lobe comes from repetitive transcranial magnetic stimulation studies. This method creates a temporary virtual lesion in the targeted area. Studies show that repetitive transcranial magnetic stimulation either at the left or right anterior temporal lobe caused slowing in both picture naming and comprehension (synonym judgement) or semantic association (Pobric *et al*., 2007, 2009, 2010). Finally, Pobric *et al.* (2009) demonstrated support for the hub-and-spoke framework (Rogers *et al.*, 2004) by showing that there was a category-general slowing of naming after anterior temporal lobe stimulation, but a category-specific slowing after inferior parietal lobe stimulation. The authors argue that this is evidence for a single amodal semantic hub represented bilaterally in the left and right anterior temporal lobe. Furthermore, repetitive transcranial magnetic stimulation in the left anterior temporal lobe resulted in selective disruption of irregular past tense verbs, but not regular verbs (Holland & Lambon Ralph, 2010). This last study provides further support for the possibility that the left anterior temporal lobe may play a role in lexical retrieval, irrespective of its potential role as a semantic hub.

There is confusion in the literature when the term 'anterior temporal lobe' is used. The term has been used to describe both areas of atrophy in the semantic dementia literature as well as areas of lesion in the stroke literature (see Damasio *et al*., 2004 for a review of temporal areas implicated in naming of the lesion and functional neuroimaging studies). Whereas atrophy in anterior temporal lobe regions in the early semantic dementia literature implicated mainly the perirhinal cortex and the temporal pole (see Gorno-Tempini *et al*., 2004 for a discussion), in the stroke literature the term 'anterior temporal lobe' also included the basal temporal lobe, i.e. anterior fusiform and inferior temporal gyri, as well as the anterior superior temporal gyrus due to reasons pertaining to the vascular supply. That is, 'watershed' or middle/posterior cerebral artery borderzone strokes and posterior cerebral artery strokes cause lesions in the basal temporal lobe, whereas only large internal carotid artery strokes and occasional middle cerebral artery strokes include the temporal pole. More recent literature on semantic dementia and functional imaging of normal participants engaged in semantic processing has defined the anterior temporal lobe as the temporal pole including BA 38, anterior superior temporal gyrus, anterior middle temporal gyrus/superior temporal sulcus, anterior inferior temporal gyrus and fusiform gyrus anterior to BA 37 (Binney *et al*., 2010).

Part of the left anterior temporal lobe—the part herein referred to as the temporal pole—BA 38 and the tip of superior temporal gyrus anterior to BA 21, along with the middle part of the middle temporal gyrus (in BA 21), was attributed a specific and necessary role in mapping concepts to words in production, in a study by Schwartz and colleagues (2009). The 'temporal pole' generally refers only to BA 38, but for the purposes of this paper we are including the tip of BA 22 because this area was included in the critical area in both the stroke lesions and atrophy in semantic dementia, as being associated with deficits in semantics in previous papers. Schwartz and colleagues (2009) proposed that the left temporal pole and anterior BA 21 within the anterior temporal lobe convey fine-grained semantic distinctions to the lexical system. The temporal pole as we define it here is a part of the anterior temporal lobe that is of particular interest because it is the area of greatest atrophy in a voxel-based morphometry study of semantic dementia (Gorno-Tempini *et al*., 2004). Schwartz and colleagues (2009) argued that left temporal pole damage has, as a consequence, not simply word-retrieval deficits, but more specifically the mechanism of mapping meaning to words by transmitting fine-grained semantic distinctions from the concept to the lexical system for naming, such that a disruption at this level results in semantic errors in naming (e.g. 'horse' for 'cow'). The authors used voxel-based lesion-symptom mapping analysis to test 64 patients with chronic stroke who made semantic errors in picture naming and found that left temporal pole damage, and damage to anterior BA 21, was associated with production of these error types, even after controlling for lesion volume. They argued that these areas are critical for mapping meaning onto sound. This view superficially seems to be in opposition with the view that unilateral left anterior temporal lobe damage does not cause semantic deficits (as argued by Lambon-Ralph *et al*., 2010), but both right and left anterior temporal lobes need to be damaged for a semantic deficit to arise.

As Schwartz and colleagues (2009) discuss, the discrepancy between their study and other studies in the literature may be due to the fact that they studied patients with chronic aphasic stroke with large lesions that included temporal pole, but also other areas of the temporal and frontal lobe that may have contributed to the semantic errors in naming. Thus, there may have been inadequate power in other areas of cortex where lesions contributed to the semantic deficit to detect the association in voxel-based lesion-symptom mapping. On the other hand, several other possible accounts of the discrepancy are possible. Studies in which unilateral temporal pole lesions failed to produce clinically significant semantic deficits included only patients with chronic lesions (some with small lesions) in whom reorganization may have already displaced the critical nodes of the semantic network to other areas such as the right hemisphere homologue or perilesional areas of the left hemisphere as found in functional neuroimaging studies (Musso *et al*., 1999; Crinion and Price, 2005; Crinion *et al*., 2006). Furthermore, production of semantic errors in naming (the one task studied by Schwartz and colleagues, 2009) does not necessarily imply an underlying semantic deficit; in fact, Schwartz *et al*. (2009) argue against the possibility that the

semantic errors produced by the patients they studied were caused by a conceptual deficit or blurred semantic distinctions between concepts themselves. However, semantic errors in oral naming cannot always be attributed to impairment in conveying fined-grained semantic distinctions between concepts to the lexical system; some chronic stroke patients make semantic errors in oral naming even when they are able to write the correct name consistently, indicating that fined-grained distinctions are mapped correctly to lexical representations in one modality (Caramazza and Hillis, 1990). Another possible explanation is that the differential left > right connectivity from a bilateral anterior temporal lobe semantic system to left prefrontal speech production systems might explain why the left anterior temporal pole damage correlates with semantic naming errors (Lambon Ralph *et al*., 2001; Walker *et al*, 2010).

Therefore, unilateral lesions might be associated with production of semantic errors (even after controlling for lesion volume) even if they do not result in a clinically significant semantic or conceptual deficit. Therefore, the hypothesis that left temporal pole damage causes an impairment in mapping semantics to sound (a unilateral mapping deficit, i.e. impaired naming) is not inconsistent with the hypothesis that damage to bilateral anterior temporal lobes is necessary to cause a clinically significant semantic impairment (affecting both naming and comprehension).

In a previous study, we evaluated the role of the left temporal pole as part of a network underlying naming and word comprehension in 156 patients with acute ischaemic left hemisphere stroke, tested within 24 h of onset of symptoms, before the opportunity for substantial reorganization of structure/function relationships or rehabilitation (Newhart *et al*., 2007). Studying patients with acute stroke is actually the closest approximation to repetitive transcranial magnetic stimulation in normal subjects, in order to determine the function of a particular brain area without the confounds of distal effects from the stimulation site. One drawback to studying patients with acute stroke is that to identify the entire area of dysfunctional brain tissue it is essential to obtain imaging of hypoperfused tissue that may be contributing to their deficits. To address this issue, patients had both diffusion-weighted imaging and perfusion-weighted imaging to identify the entire region of dysfunctional brain tissue associated with deficits in naming and comprehension (Newhart *et al*., 2007). Multivariate linear regression analysis was used to identify independent contributions of site ischaemia (diffusion and/or perfusion abnormality in seven Brodmann areas in language cortex), age, total volume of infarct (on diffusion-weighted imaging), and total volume of hypoperfusion (on perfusion-weighted imaging). We found that left BA 38 contributed to predicting error rate in both naming and comprehension, along with BA 22, superior temporal gyrus; BA 39, angular gyrus; and BA 37, fusiform gyrus, independently of volume of hypoperfusion. These variables accounted for 73% of the variance in naming and 79% of the variance in word comprehension. Volume of infarct did not contribute to predicting error rate in either naming or comprehension, independently of volume of hypoperfusion, because in acute stroke the volume of hypoperfusion (when available) is a better marker of dysfunctional tissue than volume of infarct. However, in that study, only a small number of patients had hypoperfusion or infarct in the left temporal pole (BA 38), and none with damage to BA 38 without dysfunction in other areas. Therefore, whether this area alone causes semantic deficits remains unclear. In other studies using the same methodology (multivariate linear regression), we have been able to identify a single area responsible for a single deficit, and the volume of infarct and volume of hypoperfusion have not contributed to predicting the deficit (Shirani *et al*. 2009). However, it seems plausible that most complex language tasks are likely to depend on distributed networks of brain regions. In another study, we found that specific impaired components of naming could be explained by distinct patterns of hypoperfusion identified across BA 22, 37, 38, 39, 44 and 45 (posterior inferior frontal gyrus) using discriminate function analysis (DeLeon *et al*., 2007), again indicating that the temporal pole is likely to be one node in a left hemisphere network underlying naming, whether or not it is essential for semantics.

The main question that still needs to be answered is whether unilateral left temporal pole damage alone causes impairment in semantics, as manifested by deficits in both auditory word comprehension and object naming, before reorganization of structure–function relationships, independent of lesion volume. To answer this question, we studied 20 patients with acute ischaemic stroke within 24 h of onset of symptoms, specifically selected because they had infarcts (on diffusion-weighted imaging) within the temporal pole (because ischaemia in this area is relatively rare except in large strokes), and 28 patients without infarcts in the temporal pole selected to have infarcts of matched volume in three terciles. We compared performance of the two groups in two semantic tasks. Naming tasks have been used extensively in the literature in order to identify semantic deficits (see Damasio *et al*., 2004; Patterson *et al*., 2007; Schwartz *et al*., 2009). Errors in such tasks, i.e. wrong names within subordinate or superordinate category, in either semantic dementia or stroke patients, have been interpreted as evidence that the semantic system is compromised. In the present study, we evaluated 'don't know' responses separately, because they can be due to semantic deficits or word retrieval deficits. We collected diffusion-weighted imaging data from all patients but did not collect perfusion-weighted imaging data from all patients, and therefore did not attempt to evaluate all areas responsible for naming and comprehension deficits for these patients; we simply asked whether infarct (for which diffusion-weighted imaging is sensitive) in anterior temporal pole (left BA 38 and anterior tip of the superior temporal gyrus) caused deficits in naming or comprehension. This area, identified by Schwartz *et al*. (2009) as the area most critical for mapping meaning to sound in chronic stroke, was the area most atrophied in semantic dementia (at least in the study by Gorno-Tempini, *et al*., 2004; but see Binney *et al*. 2010). The present study aimed to determine whether acute infarct in the temporal pole causes semantic naming errors and word comprehension errors, independently of infarct volume, before the opportunity for reorganization of structure–function relationships after stroke. That is, does the temporal pole have some special role in these functions, beyond its participation in a broader bilateral temporal network underlying semantic representations (that includes basal temporal cortex, including BA 21 and fusiform cortex anterior to BA 37) and a left temporal network underlying naming that probably includes

more posterior regions including BA 37? The study by Schwartz and colleagues (2009) suggests that it does have a special role – that it is a critical area for recovery of naming (such that if it is infarcted, the individual continues to make semantic errors in the chronic stage). On the other hand, the study by Lambon-Ralph and colleagues (2010) sheds some doubt on this evidence, indicating that bilateral damage somewhere in the anterior temporal lobe (temporal pole or beyond) would be required to cause a semantic deficit (in naming or comprehension). Here, we tested the hypothesis that infarct volume could explain error rates in word comprehension and naming tasks, irrespective of damage in left temporal pole.

Materials and methods

Participants

Twenty-eight patients with acute stroke not affecting the left temporal pole (14 males and 14 females) were compared to 20 patients (9 male and 11 female) with acute stroke that affected the left temporal pole. Patients were recruited from the Johns Hopkins Hospital on the first day of their stroke and all had MRIs with diffusion-weighted imaging. All patients were right-handed with no evidence of a contralateral organization of language, i.e. they all experienced language problems after their left hemisphere stroke. Their education varied between 8–18 years (mean = 11.2, SD = 3.1). The two groups were also matched for education. They all underwent a full language battery and cognitive testing with particular emphasis on lexical tasks. The patient or their closest relative (for those with comprehension deficits) gave informed consent according to the Declaration of Helsinki. Patients who could not give informed consent themselves gave assent to the best the examiner could ascertain.

Procedure and stimuli

Testing took place in the patients' rooms. We examined the auditory comprehension scores in which the patients had to listen to a word spoken by the examiner and point to a picture or choose from an array of real objects that were placed in front of them. There were four alternatives each time (including the correct choice) that were comprised of different foils within the same category. This task is part of the Western Aphasia Battery, named auditory word recognition (Kertesz, 1982). There are 60 items (tools, forms, colours, furniture and body parts etc.) that the patient must identify. The patients' scores (number of errors out of 60) were converted to percentages for easy comparisons across tasks. The second task was an oral naming task in which the patients were presented with 20 objects (not included in the auditory comprehension task) and were asked to provide their names (the Western Aphasia Battery object naming subtest). The task was scored according to standard Western Aphasia Battery instructions. Patients' performance in this task was also converted to percentages for comparisons.

Imaging

All imaging was performed on a 1.5 Tesla scanner using a standard quadrature transmit–receive head coil. In addition to time-of-flight magnetic resonance angiography, conventional T_1- and T_2-weighted images, and fluid attenuation inversion recovery MRI, isotropic diffusion-weighted imaging images were obtained (b_{max} = 1000 s/mm^2; repetition time = 10 000 ms; echo time = 120 ms). The reported analyses used diffusion-weighted imaging (after confirming the acuity of the lesion as dark on absolute diffusion coefficient maps. Areas were considered dysfunctional if they were bright on diffusion-weighted imaging and dark on absolute diffusion coefficient maps. Volumetric analysis was performed by an investigator with the assistance of ImageJ software, using diffusion-weighted imaging images (Rasband, 2005). Lesions were traced on individual slices and volumes of infarct were calculated based on the slice thickness and were recorded in cm^3. Patients with any infratentorial infarct were excluded. The investigator also compared the diffusion-weighted imaging trace images to BA maps from Damasio and Damasio (1989) at each slice to identify whether or not there was evidence of infarct in left BA 38 or the left superior temporal gyrus anterior to BA 21 (an area we refer to as the temporal pole in this article).

Statistical analysis

For descriptive purposes, we first estimated the average percent error as a function of infarct volume using the non-parametric regression method of Racine and Li (2004) with a uniform kernel type and a uniform bandwidth selected by cross-validation. This was carried out separately for the temporal pole and the no-temporal pole patients, for comparison. More specifically, for each particular value of infarct volume, this method estimates the average percent error as a weighted average of the errors of patients with infarct volumes close to that particular value. The closeness is chosen in a way that minimizes the prediction mean-squared-error as estimated by cross-validation, thus avoiding over- or under-fitting. This non-parametric regression allows for non-normality and for heteroscedasticity of the errors.

To obtain even more robust inferences in assessing the role of the temporal pole and infarct volume in error, we divided patients into three equally populated subclasses according to infarct volume: the 'low' volume subclass comprised patients with infarct volumes >0.230 cc (smallest lesion) and <6.918 cc (33% quantile); the 'medium' volume subclass comprised patients with infarct volumes >6.918 and <32.359 (67% quantile); and the 'high' volume subclass comprised patients with infarct volumes >32.359 cc and <166.227 cc (largest infarct volume). We used the Wilcoxon test to compare error rates across volume subclasses, and to compare error rates between temporal pole and no-temporal pole within a volume infarct subclass. All reported significance levels are two sided. For the implementation of the methods we used the R statistical package [the 'npregbw' function for the Racine and Li (2004) method].

Results

The average error as a function of continuous infarct volume is shown in Fig. 1 for naming and in Fig. 2 for comprehension. The average error in the subclasses of infarct volume is given in Tables 1 and 2. Examples of infarcts from patients with high error rates in both naming and comprehension with spared and not spared left temporal pole are shown in Figs 3 and 4, respectively.

Overall, in both naming and comprehension, the patients in the highest one-third of infarct volumes had significantly more errors than the patients in lowest one-third of infarct volumes (P = 0.001

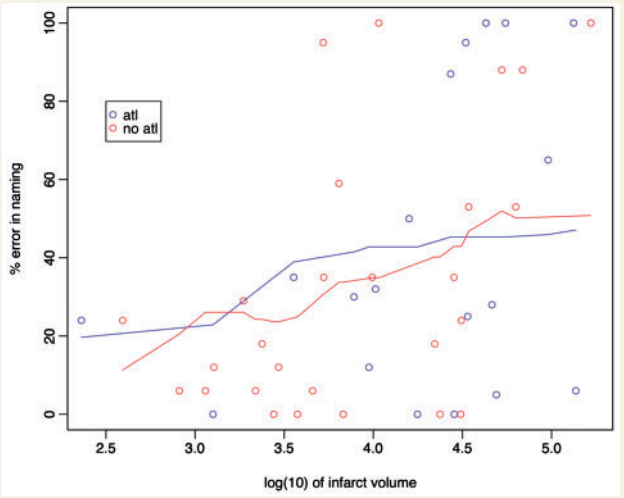

Figure 1 Errors (dots) for each patient and average errors (regression lines) as a function of log(10) infarct volume in ATL (blue) and no ATL (red) groups for naming.

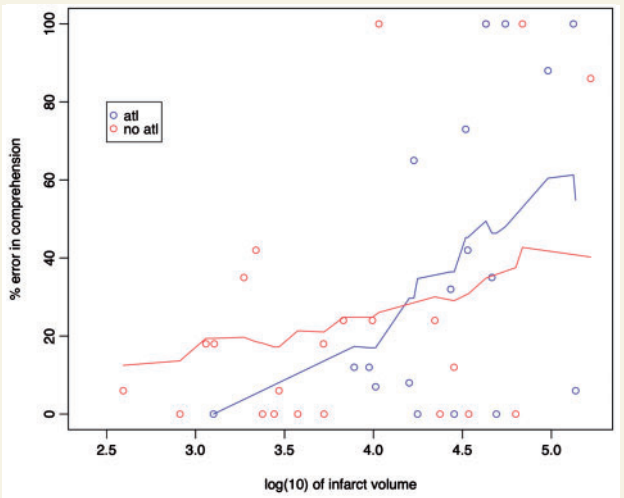

Figure 2 Errors (dots) for each patient and average errors (regression lines) as a function of log(10) infarct volume in ATL (blue) and no ATL (red) groups for auditory comprehension.

for naming; $P = 0.005$ for comprehension). The errors were not statistically significantly different between low and medium infarct volume classes for either naming ($P = 0.398$) or comprehension ($P = 0.30$). The cross-validated R^2 explained by the infarct volume subclasses with a non-parametric regression was 30.4% for naming and 30.0% for comprehension (data not shown).

Errors were not significantly different between temporal pole and no-temporal pole patients either for those in the lowest one-third of infarct volume ($P = 0.86$ for naming; $P = 0.26$ for comprehension), or for those in the medium one-third of infarct volume ($P = 1.00$ for naming; $P = 0.48$ for comprehension), or for those in the highest one-third of infarct volume ($P = 0.51$ for naming; $P = 1.00$ for comprehension). Overall, the only factor for which there is evidence of predictability of patients' performance in both naming and comprehension was the infarct volume.

Table 1 Overall naming scores (percent error rates) for each division of infarct volume (low, medium, high) in the two patient groups with and without temporal pole damage

Infarct volume (cc)	No-temporal pole damage	Temporal pole damage
Low (<6.8)	21 (26)	20 (18)
Medium (6.8–31.2)	30 (34)	30 (31)
High (>31.2)	80 (22)	58 (42)

The numbers in parenthesis are the standard deviations in each category. The results are based on the following number of patients: 18 with low infarct volume (three with temporal pole, 15 without temporal pole infarcts); 16 with medium infarct volume (nine with temporal pole, seven without temporal pole infarcts) and 14 with high infarct volume (eight with temporal pole, six without temporal pole infarcts).

Table 2 Comprehension scores (percent error rates) for each division of infarct volume (low, medium, high) in the two patient groups i.e. with and without temporal pole damage

Infarct volume (cc)	No-temporal pole damage	Temporal pole damage
Low (<6.8)	12 (13)	2 (3)
Medium (6.8–31.2)	19 (15)	14 (21)
High (>31.2)	50 (45)	48 (36)

The numbers in parenthesis are the standard deviations in each category.

Any comprehension error is a semantic error. To focus on the naming errors that can be considered semantic, we further analysed the data according to three different error types in naming: (i) semantic errors (within-category, superordinate or subordinate errors); (ii) 'don't know' responses, which can possibly be semantic as they result from comprehension or word retrieval deficits; and (iii) semantic errors and 'do not know' responses combined, i.e. excluding all other possible error types such as phonological errors. The results are shown in Tables 3, 4 and 5, respectively.

None of the analyses of error types showed statistically significant differences between the error rates of patients with and without left temporal pole damage, in either the lowest one-third infarct volume ($P = 1$ for semantic errors; $P = 0.89$ for 'don't know' responses; $P = 0.95$ for combined errors), or for those in the medium one-third of infarct volume ($P = 0.59$ for semantic errors; $P = 0.59$ for 'don't know' responses; $P = 0.49$ for combined), or for those in the highest one-third of infarct volume ($P = 0.69$ for semantic errors; $P = 0.65$ for 'don't know' responses; $P = 0.9$ for combined; Tables 3–5). As for the effect of infarct volume, the patients in the highest one-third of infarct volumes again had significantly more errors than the patients in lowest one-third of infarct volumes for both the 'don't know' responses' ($P = 0.001$) and for the combined analysis ($P = 0.042$), but not for

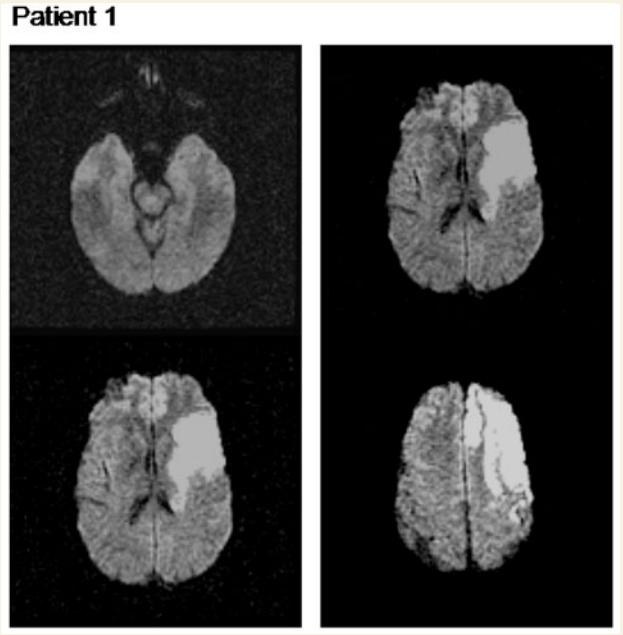

Figure 3 MRI of a patient with very impaired comprehension and naming performance whose lesion spared the left temporal pole.

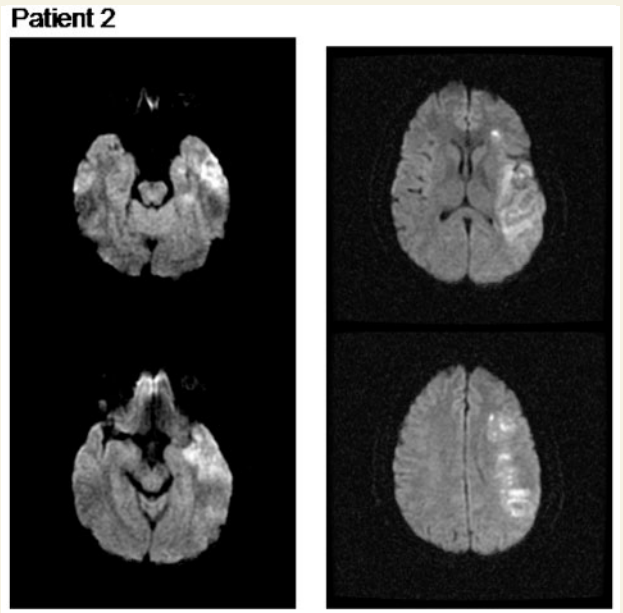

Figure 4 MRI of a patient with very impaired comprehension and naming. performance whose lesion included the left temporal pole as we defined it (including the anterior tip of Brodmann area 22).

the semantic errors only ($P = 0.34$). The errors between low and medium infarct volume classes were not statistically significantly different for any of these analyses ($P = 0.17$ for semantic errors; $P = 0.38$ for 'don't know' responses; $P = 0.92$ for combined), as was the case for the overall naming error in Table 1.

Table 3 Semantic errors in naming scores (percent error rates) for each division of infarct volume (low, medium, high) in the two patient groups i.e. with and without temporal pole damage

Infarct volume	No-temporal pole damage	Temporal pole damage
Low (<6.8 cc)	13 (12)	13 (4)
Medium (6.8–31.2 cc)	9 (8)	7 (5)
High (>31.2 cc)	13 (21)	10 (11)

The numbers in parenthesis are the standard deviations in each category.

Table 4 'Don't know' response errors in naming scores (percent error rates) for each division of infarct volume (low, medium, high) in the two patient groups, i.e. with and without temporal pole damage

Infarct volume (cc)	No-temporal pole damage	Temporal pole damage
Low (<6.8)	10 (24)	4 (7)
Medium (6.8–31.2)	6 (11)	20 (32)
High (>31.2)	34 (29)	38 (39)

The numbers in parenthesis are the standard deviations in each category.

Table 5 Semantic error and 'don't know' response errors combined in naming scores (percent error rates) for each division of infarct volume (low, medium, high) in the two patient groups i.e. with and without temporal pole damage

Infarct volume (cc)	No-temporal pole damage	Temporal pole damage
Low (<6.8)	23 (25)	17 (7)
Medium (6.8–31.2)	15 (14)	27 (30)
High (>31.2)	47 (27)	48 (40)

The numbers in parenthesis are the standard deviations in each category.

Discussion

The present study addressed the question of whether acute infarcts in left temporal pole (defined here as BA 38 and the tip of superior temporal gyrus anterior to BA 21) alone causes semantic deficits in word comprehension and naming. In particular, we examined a relatively large number of patients with acute stroke with acute left hemisphere damage, some including the left temporal pole ($n = 20$) and some others with similar infarct volumes. When we compared the groups with the same infarct volumes we found that there was no difference between patients with and without left temporal pole infarcts in semantic tasks such as auditory word comprehension and object naming (in all types of error analyses), i.e. mapping a concept onto its lexical representation. Although other tasks, such as picture association, have been used to assess semantic dementia, object naming and word

comprehension tasks are also very sensitive to semantic dementia and semantic deficits in stroke. Nevertheless, there are fundamental distinctions between the semantic deficits in semantic dementia and the semantic deficits in left hemisphere stroke, possibly because of the location of the pathology (the former being predominantly in the bilateral anterior temporal lobes) and the latter restricted to the left hemisphere. One way this distinction has been characterized is that the semantic deficit in stroke patients is predominantly revealed in tasks that require access to the meaning of words (lexical-semantics), so that they make semantic errors (e.g. knife confused with spoon) on oral and written naming, spoken and written word comprehension tasks, and sometimes even oral reading and spelling to dictation (e.g. Hillis *et al*., 1990). In contrast, the semantic deficit in semantic dementia is revealed in all tasks that require access to less familiar object concepts. For example, patients with semantic dementia, but not patients with stroke, might try to eat soup with a knife. The semantic errors in naming by patients with semantic dementia and post-stroke aphasia have been attributed to distinct mechanisms as well. Jefferies and Lambon-Ralph (2006) have hypothesized that the semantic errors in patients with semantic dementia arise from a semantic deficit, while those of post-stroke aphasic patients arise from impairment in executive control caused by lesions in frontoparietal areas. Nevertheless, it is a weakness of our study that we did not use the most sensitive tests of object naming and word comprehension, and may have failed to identify some patients with subtle deficits in either, due to acute lesion in the left temporal pole.

The relatively insensitive tests of naming and object comprehension used in our study might account for the conflicting results between this study and previous studies of chronic stroke (Schwartz *et al*., 2009; Walker *et al*., 2010) or acute stroke (Newhart *et al*., 2007), which identified an important role of left temporal pole in object naming and/or word comprehension, in some studies even after controlling for volume tissue dysfunction or infarct (Newhart *et al*., 2007; Walker *et al*., 2010). An alternative explanation of the conflicting results is that many patients in the current study had lesions restricted to the temporal pole, whereas in previous studies, the lesions may have extended beyond the left temporal pole. It may be that a lesion to the left temporal pole alone does not cause a significant deficit, but when present in addition to another part of the network, contributes to the impairment. That is, the network underlying naming or comprehension may be able to tolerate a single 'hit' (damage to the temporal pole alone), but not damage to two or more critical nodes that include the temporal pole.

Our results lead to the conclusion that unilateral temporal pole damage by itself is not a sufficient condition to produce significant word comprehension or naming deficits for objects. To produce a semantic deficit for objects there probably needs to be bilateral damage to anterior temporal lobes, as is the case in semantic dementia, or dysfunction of a more widespread unilateral left temporal network including BA 22 (Hillis *et al*., 2001*a*, *b*; DeLeon *et al*., 2007; Newhart *et al*., 2007) or BA 21 (Walker *et al*., 2010). As voxels in both temporal pole and anterior BA 21 were found to be associated with production of semantic errors in naming in the paper by Schwartz *et al*. (2009), patients who made semantic errors in their study may also have had damage to both areas. Finally, additional damage to a frontoparietal network may be needed to cause impairments in selection from semantic memory (Jefferies and Lambon-Ralph, 2006). Even when we looked at each error type in naming (semantic only, 'don't know' responses and the two collapsed excluding phonological errors) we did not find any difference between the groups with and without anterior temporal lobe damage. This finding does not mean that comprehension and object naming deficits do not appear after left temporal pole infarct (we know that they do), but it means that it is not damage to temporal pole alone, but rather the overall infarct volume or damage to the network in which it takes part, that predicts the deficit. A weakness of voxel-based analyses and most lesion-deficit association studies in the current literature is that they do not identify the entire network underlying the function, but only the clusters of voxels or regions of interest most strongly associated with the impairment (which in part depend on where there is greatest power to detect the associations).

The present study does not begin to address the potential roles of each sub-area of the anterior temporal lobe in semantic processing (see Binney *et al*. 2010, for recent functional MRI and lesion-based evidence on such segregated systems), or even the precise roles of left temporal pole in naming or word comprehension. Some clues regarding its role in these tasks come from the connections this area has with frontal areas as found in both anatomical studies in the macaque monkey and tractography in the human brain. Studies by Petrides and Pandya (1988, 2002, 2006, 2009) indicate that there are association fibres via the uncinate fasciculus that start from the anterior-most part of the superior temporal gyrus, i.e. the anterior temporal lobes and the dorsal part of the temporal polar proisocortex, that terminate in BA 47/12 (as well as in BA 13, the pro-isocortex of the orbital frontal cortex and the medial prefrontal BA 25, 14 and 32). Petrides (2002, 2006) has argued that the mid-portion of the ventrolateral prefrontal cortex (BA 45 and 47/12), where the association fibres from anterior temporal lobes terminate, is critical for 'the active (i.e. controlled strategic) regulation of information in the posterior cortical association areas where information is perceived and coded in short-term and long-term form'. These contributions were found the same for the non-human (primate) as well as for the human brain (Petrides, 2006). The suggestions from monkey experimental anatomical studies are consistent with findings from functional neuroimaging as well as tractography studies (Frey *et al*., 2008; Petrides and Pandya, 2009). It is likely that, with the evolution of language in the human brain, the more general prelinguistic role of the mid-ventrolateral prefrontal region (BA 45 and 47/12) in the active controlled retrieval of information from posterior cortical areas was adapted for the active retrieval of linguistic information, that becomes more pronounced in the left hemisphere (Petrides, 2006). The above neuroanatomical findings are also consistent with the overall picture emerging from functional neuroimaging studies where the ventrolateral prefrontal cortex and its connections with anterior temporal lobe seem to be crucial for tasks such as naming and comprehension that require retrieval of the lexical representation (word form) from

memory (Thompson-Schill *et al*., 2005; Klein *et al*., 2006; Kostopoulos and Petrides, 2008).

Although some role of the left ventrolateral prefrontal cortex in lexical retrieval is relatively well accepted, it is not clear how the right and left anterior temporal lobes contribute to this function. Specifically, a functional connectivity study compared the functional connections of left anterolateral superior temporal cortex during narrative speech comprehension in normal subjects and in a group of patients with chronic aphasic stroke (Warren *et al*., 2009). It was found that in normal subjects, the left anterior temporal lobe had positive connections with the basal temporal cortex, the left anterior inferior frontal gyrus and the homotopic cortex in right anterior temporal lobe. Aphasic patients, however, demonstrated a selective disruption of the normal functional connection between the left and right anterior temporal lobe, indicating that the deficits in auditory single word and sentence comprehension were related to the degree of this left-to-right anterior temporal lobe disruption. Furthermore, evidence from repetitive transcranial magnetic stimulation in normal controls shows that when a temporary virtual lesion in anterior temporal lobe is created using this technique, there is slowing in object naming as well as other verbal and picture based semantic tasks irrespective of the hemisphere targeted (Pobric *et al*, 2007, 2009). The above findings have been taken as evidence for a single amodal semantic hub represented bilaterally in the left and right anterior temporal lobe.

The discussion of a semantic network comprising ventrolateral prefrontal and bilateral anterior temporal lobe also finds support in other comparative patient studies [e.g. Jefferies and Lambon-Ralph (2006)] and repetitive transcranial magnetic stimulation/patient studies [e.g. Hoffman *et al*. (2010)]. In line with the previous suggestions from the functional MRI literature (Thompson-Schill *et al*., 2005), these studies have interpreted this network as one that reflects two components—an anterior temporal lobe semantic representational hub and executive control mechanisms (in left inferior frontal cortex and posterior temporoparietal areas) that work together to give flexible, task- and time-appropriate behaviours (Corbett *et al*., 2010; Noonan *et al*., 2010). As noted above, the uncinate fasciculus connectivity between the temporal pole and ventrolateral prefrontal regions (particularly pars orbitalis) might be especially relevant for the interaction between these two cognitive components.

Previous literature from acute and chronic lesion data indicate that other areas at the left temporal lobe may also be important for word comprehension and naming. There is substantial evidence from the neuropsychological and neuroimaging literature that identifies sites in the posterior superior temporal cortex including Wernicke's area (Hart and Gordon, 1990; Hillis *et al*., 2001*a*; Booth *et al*., 2002; Duffau *et al*., 2005) as critical for word comprehension and naming. Additionally, left posterior inferior and middle-temporal cortex (BA 37) appears to be critical for aspects of naming as well (Raymer *et al*., 1997; Foundas *et al*., 1998; Hillis *et al*., 2001*b*, 2006*a*; DeLeon *et al*., 2007; Cloutman *et al*., 2009; Walker *et al*, 2010). In voxel-based analysis with acute stroke patients, semantic error production in naming without word comprehension deficits was mainly associated with tissue dysfunction in left BA 44, 46 and BA 37 (Cloutman *et al*., 2009), and reperfusion of left BA 37 resulted in recovery of naming in acute stroke (Hillis *et al*, 2006*a*). Furthermore, in electro-stimulation studies that investigated semantic naming errors in patients undergoing surgical resection for low-grade dominant hemisphere glioma, semantic sites within the left temporal lobe were found in the posterior part of the temporal cortex surrounding the superior temporal sulcus, and within the frontal lobe in the lateral orbitofrontal region and in the art of the medial frontal gyrus anterior to the dorsal premotor language area (Duffau *et al*., 2003, 2005).

On the other hand, naming and comprehension of actions seems to depend on networks that are only partially overlapping with those required for naming and comprehension of objects. In a recent comprehensive study of 226 patients with chronic focal lesions in the left or right hemisphere (of which 147 had adequate MRI scan for lesion-symptom mapping), neither anterior temporal lobe was identified as one of the sites associated with any of the six tasks used to evaluate action semantics (Kemmerer *et al*., 2010). Tasks included picture naming, word-picture matching, picture association (odd one out), word association, picture attribute (which could be the most tiring) and word attribute tasks. The areas identified as associated with deficits on most of the tasks were BA 44, BA 45 (posterior inferior frontal cortex), supramarginal gyrus and posterior middle temporal gyrus. The prominent role of BA 44 and 45 in naming actions is consistent with previous focal lesion studies (Tranel *et al*., 2001; Hillis *et al*., 2002*a*) as well as focal dementia studies (Bak *et al*., 2001). In fact, several studies have reported that patients with non-fluent/agrammatic variant primary progressive aphasia, who show atrophy in posterior inferior frontal cortex (Gorno-Tempini *et al*., 2004) have greater difficulty naming actions than objects, while patients with semantic dementia show the opposite pattern, with substantially greater difficulty naming objects than actions (Cappa *et al*., 1998; Hillis *et al*., 2002*b*, 2004, 2006*b*; Cotelli *et al*., 2006). Most studies of semantic dementia have tested conceptualization primarily with objects; the few studies that have tested actions have demonstrated significantly less difficulty in semantic dementia with action concepts (Bak and Hodges, 2003; Hillis *et al*. 2006*b*), indicating that the bilateral anterior temporal lobes may have much less of a critical role in the representation of actions. The posterior frontal cortex, particularly areas engaged in the actions themselves, together with posterior middle temporal gyrus/posterior superior temporal sulcus that receive input from motion-related areas and may represent schematic aspects of event structure, have been proposed as essential for action comprehension (Grossman *et al*., 2002; see Kemmerer *et al*. 2010 for discussion). The inferior parietal lobule also appears to play an important role, at least in spatial aspects of action comprehension (Kalénine *et al*., 2010; Kemmerer *et al*., 2010).

In conclusion, the present study aimed to clarify whether the left temporal pole can be considered the 'specific' neural substrate for mapping meaning onto sound—whether acute left temporal pole lesions alone cause deficits on tasks such as object naming and auditory word comprehension after controlling for lesion volume. Our results showed that, although naming and comprehension deficits for objects can occur after left temporal pole

damage, such deficits are not unique to damage in this area; other areas may also cause such deficits. Moreover, these deficits are proportional to the overall extent of the infarct in the left hemisphere. These results are consistent with the hypothesis that the left temporal pole is one component of both a bilateral semantic system underlying representation of object concepts and a left hemisphere dominant network underlying naming and comprehension of object names. The networks underlying naming and comprehension of objects seem to include a conceptual network that depends on bilateral anterior temporal lobes, including the temporal poles, anterior superior temporal gyri, anterior middle temporal gyri/superior temporal sulci, anterior inferior temporal gyri and fusiform gyri anterior to BA 37 (only one of which must be intact to support object concepts). The anterior temporal lobe including areas described above also seems to be part of a broader left hemisphere dominant network including the remainder of superior temporal gyrus, BA 37 and angular gyrus supporting lexical-semantic processes, as well as ventrolateral prefrontal cortex for lexical selection.

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