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The inferior, anterior temporal lobes and semantic memory clarified: Novel evidence from distortion-corrected fMRI

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ABSTRACT

The neural basis of semantic memory generates considerable debate. Semantic dementia results from bilateral anterior temporal lobe (ATL) atrophy and gives rise to a highly specific impairment of semantic memory, suggesting that this region is a critical neural substrate for semantic processing. Recent rTMS experiments with neurologically-intact participants also indicate that the ATL are a necessary substrate for semantic memory. Exactly which regions within the ATL are important for semantic memory are difficult to detect from these methods (because the damage in SD covers a large part of the ATL). Functional neuroimaging might provide important clues about which specific areas exhibit activation that correlates with normal semantic performance. Neuroimaging studies, however, have not consistently found anterior temporal lobe activation in semantic tasks. A recent meta-analysis indicates that this inconsistency may be due to a collection of technical limitations associated with previous studies, including a reduced field-of-view and magnetic susceptibility artefacts associated with standard gradient echo fMRI. We conducted an fMRI study of semantic memory using a combination of techniques which improve sensitivity to ATL activations whilst preserving whole-brain coverage. As expected from SD patients and ATL rTMS experiments, this method revealed bilateral temporal activation extending from the inferior temporal lobe along the fusiform gyrus to the anterior temporal regions, bilaterally. We suggest that the inferior, anterior temporal lobe region makes a crucial contribution to semantic cognition and utilising this version of fMRI will enable further research on the semantic role of the ATL.

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1. Introduction

The importance of the anterior temporal lobes (ATL) in semantic memory (our font of meaning for verbal and nonverbal stimuli and experiences) has become a major topic of reviews and debates in the recent neuroscience literature (Hickok & Poeppel, 2007; Martin, 2007; Patterson, Nestor, & Rogers, 2007). On the one hand, neuropsychological studies indicate that the ATL makes a critically important contribution in semantic cognition (Damasio & Damasio, 1994; Lambon Ralph, Lowe, & Rogers, 2007; Lambon Ralph & Patterson, 2008; Patterson et al., 2007) and this has been reinforced by recent repetitive transcranial magnetic stimulation (rTMS) investigations of this same region in normal participants (Lambon Ralph, Pobric, & Jefferies, 2009; Pobric, Jefferies, & Lambon Ralph, 2007; Pobric, Jefferies, & Lambon Ralph, in press). On the other hand, the fMRI literature has been relatively quiet on the topic of the ATL and semantic memory. Despite a large number

of fMRI studies of comprehension, semantic memory and other aspects of semantic cognition, very few of them have implicated a relationship between the ATL and semantic memory (Patterson et al., 2007; Visser, Visser, Jefferies, & Lambon Ralph, 2010; Wise, 2003). Instead, fMRI studies of semantic tasks have focussed on activations that arise consistently in prefrontal and posterior temporal regions (Demb et al., 1995; Devlin et al., 2000; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). The limited and inconsistent fMRI evidence for ATL involvement in semantic processing runs counter to the expectations arising from SD and rTMS studies and consequently, the two literatures look incompatible. In the remainder of this Section 1 we briefly review the evidence in favour of ATL involvement in semantic processing, potential limitations of fMRI in revealing ATL activation and the need for a new form of fMRI, in particular, for answering important neuroscience questions with regard to semantic cognition.

Evidence for ATL involvement in semantic cognition comes from four sources: neuropsychology, rTMS and PET- and MEG-based neuroimaging studies. Semantic impairments arise in a number of different acute and neurodegenerative neurological conditions. Of these semantic dementia (SD: Hodges, Patterson, Oxbury, &

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Funnell, 1992; Snowden, Griffiths, Neary, & Mann, 1989) is the best neurological model of semantic impairment because of two characteristics unique to the condition: the semantic deficit is both *selective* and *progressive* (Lambon Ralph & Patterson, 2008; Patterson et al., 2007). The semantic impairment is selective in the sense that other aspects of memory, cognition and perception are relatively well preserved right up to and sometimes including the late stages of the disorder, allowing the inexorable degradation of concepts to be tracked over time (Lambon Ralph & Patterson, 2008). This specificity of semantic deficit means that test performance is not clouded or confounded by other cognitive and language impairments – as they can be in other neurological conditions such as Alzheimer's disease, herpes simplex virus encephalitis, stroke aphasia and head injury. It should be noted, however, that semantic impairment in HSVE, head injury and Alzheimer's disease is also associated with damage to the inferior and lateral anterior temporal region (Hodges & Patterson, 1995; Lambon Ralph et al., 2007; Noppeney et al., 2007) – reinforcing the conclusion from SD itself.

A debate in the literature arises when this specific semantic impairment is related to the pattern of brain damage in semantic dementia. There is no doubt that the atrophy and associated hypometabolism of SD is focused upon the anterior, inferior aspects of the temporal lobes bilaterally with consistent and substantial grey matter loss in the polar and perirhinal cortices, and the anterior fusiform gyri, bilaterally (Davies, Graham, Xuereb, Williams, & Hodges, 2004; Nestor, Fryer, & Hodges, 2006). Thus, the simplest and most obvious hypothesis is that these regions are critical for semantic memory (Lambon Ralph & Patterson, 2008; Patterson et al., 2007). Given that SD is a neurodegenerative condition, there is no absolute boundary to the damage. There is, therefore, always the possibility that sub-threshold damage or dysfunction due to invading pathology occurs elsewhere and it is this more subtle, widespread damage that is the root of the patients' semantic impairment (Brambati et al., 2009; Martin, 2007). At worst, the maximal area of damage in SD is like a magician's pledge or misdirection – as neuropsychologists, our attention and subsequent theorising is erroneously drawn to the anterior temporal lobes when, in reality, semantic memory is realised elsewhere (the magician's prestige).

Convergent evidence for the role of ATL regions in semantic cognition comes from other neuroimaging and rTMS studies of normal participants. When asked to perform receptive or expressive semantic tasks, then ATL activations can be observed with PET (Mummery et al., 2000; Tranel, Grabowski, Lyon, & Damasio, 2005; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996) and MEG (e.g., Marinkovic et al., 2003). Likewise rTMS to the lateral ATL, slows receptive (synonym judgement) and expressive (picture naming) tasks but has no effect on non-semantic (number-based) tests matched for overall difficulty (Pobric et al., 2007). This pattern holds whether left or right temporal poles are stimulated (Lambon Ralph et al., 2009). In contrast, the fMRI results are very inconsistent; although some studies find ATL activation during semantic processing (for review see, Binder, Desai, Graves, & Conant, 2009; Visser et al., 2010), activation is not found in many studies using similar receptive and expressive tasks (Binder et al., 2009; Canessa et al., 2007; Chao & Martin, 2000; Mechelli, Sartori, Orlandi, & Price, 2006; Pilgrim, Fadili, Fletcher, & Tyler, 2002). In the context of this convergent evidence from SD patients, PET, MEG and rTMS, the absence of ATL activation in many fMRI-based studies of semantic processing is a key and prominent divergent element in the neuroscience literature.

As noted above, a brief cursory glance at the semantic neuroimaging literature would not reveal consistent and overwhelming evidence for the involvement of the ATL in semantic memory (unlike prefrontal cortex, posterior MTG, etc.). There are strong indications, however, that this is an absence of evidence

rather than evidence of absence: a recent meta-analysis of the semantic neuroimaging literature demonstrated that the likelihood of reporting ATL activation is subject to three technical issues (Visser et al., 2010). These included the imaging modality (PET is more likely than fMRI to reveal ATL semantic activations – most likely reflecting the inherent distortions found in fMRI), the field of view (many PET and fMRI studies previously used a restricted field of view (<15 cm) and in doing so the inferior and anterior aspects of the temporal lobes are most likely to be sacrificed) and the “control” task (ATL activation is less likely when a “rest” or low-level baseline is used – presumably because in such situations participants are able to engage in self-generated inner speech: Binder et al., 1999; McKiernan, D'Angelo, Kaufman, & Binder, 2006). Given the great influence of fMRI research in neuroscience theorising, the technical limitations of this neuroimaging modality are critically important to understand and overcome. The ability of fMRI to detect activation is not constant across the brain. The ATL and adjacent orbitofrontal cortex reside near air-bone interfaces that cause inhomogeneities in the magnetic field leading to image distortion and signal loss when using conventional gradient-EPI (Schmithorst, Dardzinski, & Holland, 2001; Weiskopf, Hutton, Josephs, & Deichmann, 2006). The impact of the signal distortion on the ability to detect ATL activation was demonstrated by Devlin et al. (2000). Using a semantic categorisation task, Devlin et al. directly compared 3T GE EPI fMRI with H₂O¹⁵ PET. Both techniques detected greater activation in prefrontal regions for the semantic over the control task, however, ATL activation (particularly in the left anterior, inferior temporal lobe) was only identified with H₂O¹⁵ PET (see Fig. 2a, reproduced with permission).

Functional neuroimaging of the ATL will be critical in answering the next cycle of research questions about the neural basis of semantic cognition. These include which specific regions within ATL support semantic memory and whether there are divisions of labour across these regions for different types of semantic information. These questions are hard to answer with studies of SD patients because the atrophy associated with this disease covers the whole region. Repetitive TMS studies can sequentially probe different ATL regions only if they sit on the lateral surface, as the ventral surfaces of the brain are relatively inaccessible with this technique. As noted above, PET functional neuroimaging provides one method for investigating different ATL subregions but it does have a number of drawbacks in comparison to fMRI. These include: the limited number of scanning runs (typically 12, in order to limit radiation exposure) that heavily constrain the behavioural designs that can be adopted and reduce the sensitivity of the technique; only block designs can be used; and participants can only be scanned once.

In this fMRI-based study, our aims were to confirm the hypothesis that the ATL (in addition to other regions) are implicated in semantic cognition and to use the advantages of this neuroimaging technique to begin to answer more specific neuroanatomical questions. These include: (a) is semantic memory supported by regions in the ATL bilaterally (as suggested by the bilateral atrophy of SD); and (b) is the anterior, inferior temporal region especially important (a region that is particularly vulnerable to the magnetic inhomogeneities and has the highest rate of grey matter loss in SD: Davies et al., 2004; Devlin et al., 2000)? The study also represents the first application of a novel distortion-corrected, spin echo (SE) EPI technique (based on dual-direction *k* space transformation: Embleton, Haroon, Lambon Ralph, Morris, & Parker, *in press*) that significantly reduces the problems associated with imaging the anterior and inferior temporal lobes. Although SE EPI is less sensitive to haemodynamic activation, it is not subject to the signal loss due to intravoxel dephasing that occurs with gradient echo (GE) EPI (Jones, Brookes, & Moonen, 2001; Li et al., 2007). Substantial spatial mismatching of the signal in the phase encode direction occurs in areas of altered magnetic susceptibility in GE and SE EPI. However,

as the total signal is preserved in SE EPI, it is possible to apply post-processing, spatial correction that cannot be applied to GE EPI (Embleton et al., *in press*).

To provide an initial formal starting point in the use of an improved fMRI recipe, we deliberately conducted a comparative study by adopting the same behavioural task (rapid semantic categorisation) as used by Devlin et al. (2000). To improve the comparability we also ran a similar number of participants and imaging analysis. Devlin's behavioural task involves rapid semantic categorisation of basic level concepts and so provides an important theoretical test for different theories of ATL semantic function. Work arising from semantic dementia and rTMS suggests that the ATL supports an amodal representational hub that codes all types of concept (Lambon Ralph & Patterson, 2008; Pobric et al., 2007; Pobric et al., *in press*; Rogers et al., 2004). In contrast, other work has indicated that there may be graded representational specificity along the temporal lobe such that the ATL codes for specific entities or subordinate exemplars (Martin, 2007; Martin, Wiggs, Ungerleider, & Haxby, 1996; Tranel, Damasio, & Damasio, 1997; Tyler et al., 2004). If the latter theories are correct then, even with successful distortion correction, no ATL activation should be found if the task requires processing of basic level concepts.

2. Methods

2.1. Experimental procedure

Eleven participants (right-handed, mean age = 32, SD = 6.8, 5 males) completed semantic and letter (control) categorisation tasks as described by Devlin et al. (2000). The experiment comprised eight semantic blocks and eight control blocks, which lasted for 32 s each. The task was an ABCX categorisation task, in which participants saw three words sequentially from a single semantic category and then had to decide if a fourth word was also drawn from that category (e.g., taxi, boat, bicycle followed by AEROPLANE vs. taxi, boat, bicycle followed by SPOON). All concepts and categories were drawn from the manmade domain. Each word was presented in lowercase letters for 200 ms, with an inter-stimulus interval of 400 ms. The fourth word was presented in upper case and underlined to indicate that a decision was required. The trial finished with a blank screen for 2000 ms during which the participants made their decision. Semantic categorisation was contrasted with a control letter categorisation task, in which subjects viewed a series of lower-case, letter strings matched to the length of the words. Participants saw three strings of a specific letter sequentially and then had to decide if a fourth letter string (in capitals) was the same letter (e.g., rrrr, rrr, rrrrr followed by RRR or DDDD). The timings followed those used in the semantic task.

2.2. Image acquisition

All imaging was performed on a 3T Philips Achieva scanner using an eight element SENSE head coil with a sense factor of 2.5. The SE EPI fMRI sequence included 30 slices with TE = 75 ms, TR = 3200 ms, 112×112 acquisition matrix, reconstructed resolution $1.875 \text{ mm} \times 1.875 \text{ mm}$, and slice thickness 4.2 mm. Brief (10 volumes for each k space traversal) dual direction k space traversal SE EPI scans with matching parameters were made before the functional acquisitions in order to achieve sets of images matching the functional time-series but with opposing direction distortions. These pre-scans were made on each participant and were used to compute a spatial remapping matrix that could be applied to the functional time-series. The main fMRI image sequences of 160 time points were acquired with a single direction k space traversal. A high resolution T2 weighted turbo spin echo scan with in-plane resolution of 0.94 mm and slice thickness 2.1 mm was also obtained as a structural reference to provide a qualitative indication of distortion correction accuracy.

2.3. Distortion correction

Single-shot gradient echo EPI (GE EPI) is a fast magnetic resonance imaging (MRI) method with a high signal-to-noise ratio. However, the detected MRI signal is vulnerable to geometric distortion and signal loss, especially in regions subject to large magnetic susceptibility variation (brain areas near bone or air). Moreover, this effect is increased at higher magnetic fields (Deichmann, Josephs, Hutton, Corfield, & Turner, 2002; Jezzard, Matthews, & Smith, 2001; Schmithorst et al., 2001; Weiskopf et al., 2006). In addition, spatial distortion is more pronounced in the phase-encoding direction than in the frequency encoding direction (Morgan, Bowtell, McIntyre, & Worthington, 2004). Spin echo EPI (SE EPI) was used to acquire the data because this imaging technique only suffers from spatial distortion without signal loss and this licenses a post-acquisition correction procedure. Although SE EPI has lower signal-to-noise than GE EPI in unaffected areas (Jezzard et al., 2001), it has signifi-

Fig. 1. Sections slices summarising significantly activated temporal lobe clusters arising from the comparison of semantic over control tasks.

Footnote: Results from a fixed effect analysis in which clusters are determined by $Z > 3$ and corrected at $p = 0.05$ (Worsley et al., 1992). (a) A left hemisphere sagittal section showing greater activation in fusiform and prefrontal regions; (b) An axial slice (in standard AC-PC orientation) showing greater activation in bilateral, anterior fusiform gyri extending to pole; (c) An axial slice (tilted at 25° to AC-PC) showing activation along the length of the fusiform bilaterally but more extensively in the left hemisphere; and (d) An axial slice showing the same activated clusters after random-effects analysis with a cluster threshold of $Z > 2$ and corrected at $p = 0.05$.

cant potential benefits in these problematic regions. In addition, unlike some other corrective measures such as special shimming, this process retains whole-brain coverage.

A gradient reversal technique was used to correct geometrical distortion in the phase-encoding direction (Chang & Fitzpatrick, 1992; Embleton et al., *in press*; Morgan et al., 2004). During a pre-scan volume, two images of each slice were acquired that were identical, except that the phase-encoding gradient was reversed. These images had equal geometrical distortion but in opposing directions along the phase-encoding gradient. Thus by integrating the signal of these images, the correct location can be determined (Chang & Fitzpatrick, 1992; Embleton et al., *in press*; Morgan et al., 2004). This process generates a correction map of pixel displacement. The rest of the volumes were acquired in one phase-encoding direction. Each volume was registered to the original distorted mean pre-scan volume using a six-degrees of freedom translation and rotation algorithm (FLIRT, FSL, Oxford). The map of pixel displacement was then used to correct the distorted data. An in-house algorithm devised by Embleton et al. (*in press*) was used to register image pairs to sub-voxel accuracy in the frequency encoding direction. This resulted in a distortion-corrected dataset of 160 volumes maintaining the original temporal spacing and TR of 3200 ms. In addition, the phase-encoding direction was set from left to right, instead of anterior to posterior for two reasons. First, the number of phase-encoding lines is reduced due to the rectangle shape of the brain. Secondly, eye movement causes distortion and by using this acquisition method only a few slices will include eye movement.

2.4. fMRI data analyses

Analysis was carried out using FEAT version 5.63 (FMRI Expert Analysis Tool), which is part of the FSL analysis package (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Single-subject analyses included the following pre-statistics processing stages: motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of 8 mm FWHM; mean-based intensity normalisation of all volumes by the same factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma = 64.0$ s). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Registration to high resolution and/or standard images was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001).

Following Devlin et al. (2000), multi-subject analysis was carried out using a fixed effects model, by forcing the random-effects variance to zero in FLAME (FMRIB's local analysis of mixed effects: Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 3.0$ and a (corrected) cluster significance threshold of $P < 0.05$ (Worsley, Evans, Marrett, & Neelin, 1992). The same analysis was repeated with clusters determined by $Z > 2.3$. Furthermore, analyses were performed on the uncorrected data with clusters determined by $Z > 1.7$. In addition, we included a random effect analysis to ensure activation was still present after accounting for the variation between subjects. Clusters were determined by $Z > 2.0$. Functional images were overlaid on the MNI brain template using MRICro (www.mricro.com) to investigate anatomical position of the activated clusters.

3. Results

The contrast of the semantic task against the control condition yielded five extensive regions of activation when the cluster was determined by fixed effect analyses and a $Z > 3.0$. These regions are shown in Figs. 1 and 2c. Peak activations are listed in Table 1. The bilateral temporal cluster defined by a cluster threshold of $Z > 3.0$ extends anterior to a y -value of 0. The extent of these clusters can

be described as follows. Anteriorly, the cluster includes the entorhinal cortex, perirhinal cortex and the posterior part of the temporal pole as defined by Insausti et al. (1998). This anterior part spreads more laterally in the right hemisphere (an x -range of 30–58 compared to –27 to –32 in the left hemisphere). When the cluster threshold was lowered to $Z > 2.3$, the activation extended all the way to the anterior parts of the temporal poles (TP) as defined by Insausti et al. (1998); coordinates (–32, 21, –40) and (–23, 12, –40). This is presented in Fig. 2d. In the posterior part of the same cluster ($Z > 3.0$), the left temporal cluster is restricted to the fusiform gyrus until a y -value of –28, but then spreads more laterally to the inferior temporal lobe extending posteriorly until a y -value of –62. The cluster in the right temporal lobe remains relatively anterior extending to a y -value of –28, covering the fusiform gyrus and inferior temporal lobe. Local maxima, peak activations of the left and right temporal clusters are listed in Tables 2 and 3.

In addition, the inferior frontal gyrus including the pars triangularis was activated bilaterally and the clusters extended to the middle frontal gyrus. In the left hemisphere, frontal activation included Broca's area (BA 45). Because we used the same tasks as

Fig. 2. Direct comparison of rendered images (ventral surface) from Devlin et al. (2000), required spatial distortion correction and resultant functional activations from the current study. (a) PET vs. fMRI comparison from Devlin et al. (2000). (b) Map of required spatial distortion correction. (c) Results from distortion-corrected fMRI at $Z > 3$. (d) Results from distortion-corrected fMRI at $Z > 2.3$.

Footnote: (a) Colour code as per original report: red denotes PET-only activation, green = fMRI-only activation, yellow = activation found in both imaging modalities (reproduced with permission from author). (b) Individual example of a corrected SE EPI data set (K_1 phase encode) showing the ventral surface; coloured overlays show the degree of spatial remapping required to correct the original distorted image. Yellow denotes that voxels were shifted right to left (maximum 5.85 voxels) and blue from left to right (maximum 12.23 voxels). As expected, minimal distortion correct is required throughout the brain except for two regions: (i) orbital frontal (middle blue region in the figure), and (ii) inferior and anterior temporal lobes bilaterally. Overlapping regions were activated in the PET study of Devlin et al. (2000) – see Fig. 2a – and is resolved in SE EPI fMRI once the distortion correction is applied (Fig. 1c). (c and d) Results from the current study, based on distortion-corrected SE EPI fMRI at 3T. Clusters are determined by $Z > 3$ (c) and $Z > 2.3$ (d) and corrected at $p = 0.05$ (Worsley et al., 1992). Bilateral fusiform activation was found extending to temporal pole – consistent with semantic dementia. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1

Activated clusters revealed by the contrast of semantic over letter (control) task.

Brain region (COG)	Voxels	Max. Z value	MNI coordinates		
			Mean x	Mean y	Mean z
L. Fusiform gyrus	4306	6.13	−44	−58	−12
R. Inferior frontal gyrus	3435	5.76	36	22	0
L. Inferior frontal gyrus	2721	5.58	−38	4	32
R. Fusiform gyrus	2586	4.58	40	−8	−38
Cerebellum	1146	5.12	6	−82	−20

MNI coordinates of the centre of gravity (COG) of each cluster, determined by $Z > 3$ and a (corrected) cluster significance threshold of $P = 0.05$.**Table 2**

Local maxima in the right temporal lobe cluster revealed by the contrast of semantic over letter (control) task.

Brain region (COG)	BA (COG)	Z value	MNI coordinates		
			Mean x	Mean y	Mean z
Fusiform gyrus	20	4.58	40	−8	−38
Fusiform gyrus	20	4.16	34	−12	−40
Fusiform gyrus	20	4.09	58	−20	−26
Fusiform gyrus	20	4.03	52	−8	−40
Anterior temporal lobe	38	4.01	28	2	−42
Cerebellum		3.75	38	−34	−38

MNI coordinates of the centre of gravity (COG) of each cluster, determined by $Z > 3$ and a (corrected) cluster significance threshold of $P = 0.05$.

Devlin et al. (2000), the current study did not control for executive demands between the semantic and the control task and, therefore, we cannot verify whether this frontal activation can be attributed to general executive processes or to specific semantic control processes. Previous literature has associated frontal areas with both types of processing (Banich et al., 2000; Jefferies & Lambon Ralph, 2006). Finally, a cluster in the cerebellum was activated.

In order to provide directly comparable data to Devlin et al. (2000), both the same task and analysis (fixed-effects) were used. To check for the generalisation of findings across participants, we also conducted a random-effects analysis. This resulted in the same activated clusters (see Fig. 1d). *In contrast to the fMRI results reported by Devlin et al. (2000)*, our fMRI results show good comparisons with the PET images from their study – which, for ease, are reproduced in Fig. 2a [PET (red) and fMRI (green)]. We found the same areas activated but, in addition, the current study highlighted bilateral ATL activation as opposed to the unilateral activation in Devlin's et al. (2000) study. As noted in Section 1, the fact that we identified bilateral activation in this study is consistent with the bilateral ATL atrophy associated with semantic dementia and the effects of left or right temporal pole rTMS in normal participants (Davies et al., 2004; Lambon Ralph et al., 2009; Nestor et al., 2006).

It should be noted that the improved fMRI results obtained in this study, probably reflect a combination of three factors: advances in MR engineering (e.g., SENSE head coils), the use of SE EPI and the distortion correction. This study was not designed to measure the efficacy of each factor, independently, as it was focussed primarily on an applied research question (which regions of the ATL contribute to semantic memory). We can be fairly certain that the distortion correction made a significant, independent contribution for two reasons: first, when we repeated the same analyses but on the uncorrected data (i.e., SE EPI data acquired with SENSE head coils), the ATL activations were *not* present. Secondly, the amount of spatial correction varies systematically across the brain. Fig. 2b shows an individual EPI volume after the spatial correction has been applied. The overlay denotes the amount of spatial correction required to bring each voxel back to its correct position. This shows very clearly that, in addition to adjustment for orbitofrontal regions, considerable correction is required for much of the ventral surface of the temporal lobes (and to a lesser extent the polar and lateral aspects of the ATL too). The differences between GE and SE EPI can be seen in the within-participant comparison (see

Fig. 3). As noted in Section 1, where EPI signal is present (displayed in the greyscale, coronal sections) then the signal-to-noise (coloured coronal sections: calculated as per Murphy, Bodurkab, & Bandettinia, 2007) is generally higher in GE than SE. However, in some regions there is clear absence of signal in the GE EPI scans which is retained in SE EPI. As well as orbitofrontal areas, these problematic regions include the anterior, inferior temporal lobe and inferior polar regions. Given this is exactly the same region that was activated by this study and other PET-based investigations (Crinion, Lambon Ralph, Warburton, Howard, & Wise, 2003; Scott, Blank, Rosen, & Wise, 2000; Wise, 2003), then it is not so surprising that the majority of GE EPI fMRI studies fail to observe inferolateral, ATL activations.

On a purely practical final note, we would suggest that this recipe of imaging factors (SE EPI, SENSE or its equivalents, and spatial correction) is a good one if researchers are keen to probe the functioning of the ATL or other areas affected by susceptibility artefacts, whilst also maintaining whole-brain coverage. In any event, it should be remembered that it is difficult to conclude much about

Fig. 3. Within-participant comparison of gradient-echo vs. spin-echo EPI. Footnote: Comparative spin-echo (panel A) vs. gradient-echo EPI images (panel B) from the same participant. Both raw EPI and SNR maps (Murphy et al., 2007) are displayed. Two key differences can be observed. Where EPI signal is present, then SNR tends to be higher for GE than SE data. In the GE scans, however, there are regions of signal drop out (marked by white arrows) – in orbitofrontal, inferior-anterior and polar temporal lobe regions. Signal is present, however, in the same regions for the SE-EPI.

Table 3

Local maxima in left temporal lobe cluster revealed by the contrast of semantic over letter (control) task.

Brain region (COG)	BA (COG)	Z value	MNI coordinates		
			Mean x	Mean y	Mean z
Inferior temporal gyrus	20	6.13	−44	−58	−12
Inferior temporal gyrus	20	6.09	−42	−50	−14
Fusiform gyrus	20	5.78	−36	−14	−40
Fusiform gyrus	20	5.3	−44	−40	−14
Fusiform gyrus	20	4.95	−36	−28	−22
Fusiform gyrus	20	4.83	−34	−20	−28

MNI coordinates of the centre of gravity (COG) of each cluster, determined by $Z > 3$ and a (corrected) cluster significance threshold of $P = 0.05$.

the inferior ATL if only standard GE EPI is used. On the flip side, given the better sensitivity and temporal resolution of GE over SE EPI, the former is favourable for fMRI studies when the areas of interests are not prone to the susceptibility artefact. These limitations of SE EPI may be more problematic in event-related designs.

4. Discussion

Patients with semantic dementia (SD) have a specific impairment of semantic memory following bilateral atrophy of the anterior temporal lobes (ATL), suggesting that areas within this region form a critical substrate for semantic memory (Lambon Ralph & Patterson, 2008; Patterson et al., 2007). In addition, PET neuroimaging and rTMS studies of healthy subjects show the importance of the ATL in semantic processing (Lambon Ralph et al., 2008; Pobric et al., 2007; Vandenberghe et al., 1996; Wise, 2003). In contrast, previous fMRI studies on semantic memory have largely failed to observe activation within the ATL (Visser et al., 2010) and, perhaps because of the predominance of fMRI in cognitive neuroscience, the role of the ATL in semantic cognition has tended to be overlooked. Indeed, several recent reviews of the neural basis of semantic memory have not pointed to any involvement of this region (Catani & Ffytche, 2005; Mesulam, 1998). We suggest that this disparity across neuroscience methods reflects a series of factors that generate a relative absence of neuroimaging evidence with regard to the ATL. Visser et al. (2010) found that the likelihood of finding evidence of ATL activations in the literature reflected the size of the field-of-view used, the nature of the baseline task and whether the imaging technique suffered from susceptibility artefacts. By adopting a whole-brain, SE EPI fMRI technique with a spatial correction and parallel receiver coils (Embleton et al., *in press*), we were able to demonstrate that the inferior, anterior temporal lobes are bilaterally activated by a rapid semantic categorisation task (previously used by Devlin et al., 2000). As such, these results are in line with the investigations of semantic dementia and recent rTMS studies. It should be noted that we found activation in this inferior ATL region despite the fact that participants were making category-membership decisions to basic level concepts. This would suggest that this region processes all levels of concept and not just subordinate exemplars or specific entities (Martin, 2007; Martin et al., 1996; Tranel et al., 1997; Tyler et al., 2004).

The observation of anterior, inferior ATL activation is important for two reasons: (a) this study provides convergence results across neuropsychology, rTMS and neuroimaging, implicating the importance of the inferior aspects of ATL regions in semantic cognition; and (b) it licenses the use of this form of distortion-corrected fMRI in future studies. These investigations will be able to explore which aspects of the ATL are particularly important in semantic cognition and whether these vary according to important factors such as category/domain, modality of input, specificity of processing and so on. We should note that distortion correction can be achieved using methods other than the reversed gradient approach used in this

study. For example, corrections based on field mapping methods (Andersson, Hutton, Ashburner, Turner, & Friston, 2001; Hutton et al., 2002; Jezzard et al., 2001; Reber, Wong, Buxton, & Frank, 1998; Yeo, Fessler, & Kim, 2008) can successfully be combined with SE-EPI for fMRI. It remains for future work to assess the relative benefits of different distortion correction methods. In any event, the purpose and conclusion of the present study is unchanged: with correction, fMRI studies of semantic behaviour align with the rest of the neuroscience literature and implicate the anterior temporal lobes in semantic cognition.

By adopting the same behavioural paradigm, procedure and analysis, we were able to compare our results directly with those reported previously by Devlin et al. (2000). As expected, our findings from this study are similar to the PET neuroimaging results from Devlin et al. (2000). Both studies revealed a large cluster of activation in the left hemisphere extending from the inferior ATL to the middle temporal cortex, the inferior and middle frontal regions and, in addition, a cluster in the cerebellum. Our study also revealed involvement of right anterior, inferolateral temporal regions. This is of particular interest because semantic dementia always arises in the context of bilateral ATL atrophy/hypometabolism and recent direct comparisons of left vs. right rTMS have found equivalent effects on semantic decision times (Lambon Ralph et al., 2009). Taken together, these results suggest that the contribution made by the ATL – especially its inferior aspects – to semantic memory is reflective of a bilateral, neurally coupled system. In another rTMS study (Pobric et al., *in press*), we have replicated the previous result (slowed semantic decisions after left or right ATL stimulation) and have found that it holds whether semantic decisions are made to either pictured or verbal labelled concepts (timed semantic association decisions to pictures or written names). This result seems to rule out a strong division of labour across the two ATL regions in terms of verbal vs. nonverbal semantic memory. Instead, it seems likely that bilateral representation of amodal semantic concepts has beneficial value in that the representations become more robust to damage or neural disruption.

Nonetheless, the right ATL cluster revealed in this study was somewhat weaker than the cluster in the left ATL, perhaps reflecting the importance of language processing in these particular semantic tasks. This could result from differential connectivity from the bilateral amodal semantic system to left dominant language centres (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001). Consistent with this, a recent combined re-analysis of 18 PET studies involving object naming tasks found bilateral ATL activation, which was stronger on the left (Price, Devlin, Moore, Morton, & Laird, 2005). Therefore, the absence of activation in the right ATL in Devlin et al.'s (2000) study might reflect the fact that their method was not sensitive enough to detect the weaker activation in the right ATL. Generally fMRI is thought to be more sensitive to activation than PET, because more data are acquired over the same time (Mechelli, Friston, & Price, 2000; Owen & Coleman, 2007; Owen, Epstein, & Johnsrude, 2001). Furthermore, differences in spatial resolution, smoothing kernels and signal characteristics might con-

tribute to the discrepancies between fMRI and PET results (Price, Veltman, Ashburner, Josephs, & Friston, 1999).

This study also allows us to begin to examine more specific neuroanatomical questions. Volumetric studies have reported bilateral, anterior temporal atrophy in SD patients (Davies et al., 2004; Galton et al., 2001; Gorno-Tempini et al., 2004; Mummery et al., 2000; Nestor et al., 2006). Although the atrophy in SD extends across the entire anterior temporal lobe region, it tends to be particularly pronounced in the inferolateral aspects (atrophy being the greatest in the perirhinal, fusiform and ITG regions: Davies et al., 2004). This is intriguing because (a) these are the same areas that were maximally activated in this fMRI study (and other PET studies) and (b) are some of the regions that suffer the most from distortion arising from magnetic field inhomogeneities (see Fig. 2b and Fig. 3). The fact that these three findings point to the same regions, not only indicates the importance of these areas in semantic cognition but also might be the root of the previous disparity between fMRI and patient-studies of semantic memory. Future studies will be able to test whether this region is implicated in all semantic tasks (e.g., irrespective of modality of input) and also its relationship to other ATL regions that have been highlighted in other PET studies (e.g., the anterolateral STS: Scott et al., 2000).

Given that many theories of semantic cognition do not include or mention ATL regions at all (see above), it is useful to consider what function the keys areas within this region may bring to semantic cognition. It is clear from this and many other patient and neuroimaging studies that semantic cognition (semantically driven behaviour) is supported by a network of brain regions. Broadly-speaking these can be split into two types: information-bearing regions and control/regulatory areas. Following models of cognitive control (Garavan, Ross, Li, & Stein, 2000; Peers et al., 2005), there is now fMRI, rTMS and patient evidence to suggest that prefrontal and temporoparietal regions help to shape or in some way regulate which aspects of meaning are relevant to the language or nonverbal activity in hand (Devlin, Matthews, & Rushworth, 2003; Jefferies, Baker, Doran, & Lambon Ralph, 2007; Jefferies & Lambon Ralph, 2006; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010; Thompson-Schill et al., 1997). These regions are especially important, therefore, when complex semantic judgements are needed, when there is strong intrinsic competition between alternative meanings and in everyday verbal and non-verbal activities that require some but not all aspects of the meaning.

Many models of semantic memory (that is of semantic information rather than semantic control) emphasise that concepts may be formed by linking together different types of modality-specific information (e.g., what things look, smell, taste like and the words we use to describe them) arising in different association areas (an idea that stems back to Wernicke and Meynert: Eggert, 1977; Martin, 2007). Rogers et al. (2004) have suggested that the ATL works as a representational hub, connecting modality-specific information to form amodal semantic representations. Such a hub is required when performing complex generalisations, based on central semantic relationships rather than superficial similarities found in one particular domain (e.g., being able to recognize a Chihuahua as dog even though it does not look like a dog) (Lambon Ralph & Patterson, 2008; Lambon Ralph, Sage, Jones, & Mayberry, 2010). These computational challenges are hard, if not impossible, to overcome by directly connecting different types of modality-specific information (Rogers et al., 2004). Implemented computational models indicate, however, that successful conceptualisation can follow if modality-specific information is combined and translated via an additional, single set of amodal units (Rogers et al., 2004). Our working hypothesis, therefore, is that ATL regions (via their wide spread neocortical connectivity: Gloor, 1997) provide the neural basis for this central and critical aspect of semantic

memory (Lambon Ralph & Patterson, 2008; Lambon Ralph et al., 2010).

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