

Conceptual Knowledge Is Underpinned by the Temporal Pole Bilaterally: Convergent Evidence from rTMS

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Conceptual knowledge provides the basis on which we bring meaning to our world. Studies of semantic dementia patients and some functional neuroimaging studies indicate that the anterior temporal lobes, bilaterally, are the core neural substrate for the formation of semantic representations. This hypothesis remains controversial, however, as traditional neurological models of comprehension do not posit a role for these regions. To adjudicate on this debate, we conducted 2 novel experiments that used off-line, low-frequency, repetitive transcranial magnetic stimulation to disrupt neural processing temporarily in the left or right temporal poles (TPs). The time required to make semantic decisions was slowed considerably, yet specifically, by this procedure. The results confirm that both TPs form a critical substrate within the neural network that supports conceptual knowledge.

Keywords: anterior temporal lobes, rTMS, semantic dementia, semantic memory

Introduction

In this study, we utilized repetitive transcranial magnetic stimulation (rTMS) to probe the role of the anterior temporal lobes (ATLs) in supporting conceptual knowledge. This type of knowledge allows us to comprehend a multitude of different stimuli, such as words, pictures, objects, environmental sounds, and faces. It also allows us to express knowledge in a wide variety of domains, both verbal (e.g., naming and verbal definitions) and nonverbal (e.g., drawing and object use). Perhaps, even more importantly, our semantic representations allow us to generalize knowledge appropriately from one exemplar to another (Lambon Ralph and Patterson 2008). As such, it is integral to our everyday lives, and impairments of semantic memory are extremely debilitating. A key question for neuroscience research, therefore, is which parts of the brain support conceptual knowledge and how do they function?

An apparently clear answer comes from patients with semantic dementia (SD). These patients have a highly specific impairment of semantic memory: They fail diverse semantic tasks even though other aspects of cognition and language, such as phonology, visual processing, and decision making remain intact (Snowden et al. 1989; Hodges et al. 1992). The selective nature of their semantic impairment is coupled with a specific pattern of brain damage: SD patients have bilateral atrophy and hypometabolism, maximal in the inferior and lateral aspects of the ATLs, and the extent of this atrophy correlates with the severity of the semantic impairment (Mummery et al. 2000; Nestor et al. 2006).

Careful and extensive assessment of SD patients is consistent with the notion that bilateral ATL regions support the

formation of amodal semantic representations (Patterson et al. 2007; Lambon Ralph and Patterson 2008). Accordingly, SD patients exhibit poor comprehension of items presented in every modality, including spoken and written words, pictures, environmental sounds, smells, and touch (Bozeat et al. 2000; Coccia et al. 2004; Luzzi et al. 2007). The marked semantic deficit is also apparent in production tasks, such as picture naming (Lambon Ralph et al. 2001), verbal definitions (Lambon Ralph et al. 1999), object drawing (Bozeat et al. 2003), and object use (Bozeat et al. 2002). The singular, amodal nature of the ATL system is underscored by the fact that SD patients show very high correlations between their scores on different semantic tasks and strong item-specific consistency across modalities (Bozeat et al. 2000; Rogers et al. 2004).

The ATLs are ideal for forming amodal semantic representations as they have extensive connections with cortical areas that represent modality-specific information (see also the theory of “convergence zones”: Damasio A and Damasio H 1994; Damasio et al. 1996). Accordingly, Rogers et al. (2004) implemented a computational model of this ATL system in which semantic representations were formed through the distillation of information required for mappings between different verbal and nonverbal modalities. When damaged, the model reproduced the behavioral performance of SD patients across a wide variety of semantically demanding receptive and expressive tasks.

At the present time, there is considerable debate in the literature about the putative role of different brain regions in semantic cognition, with strong advocates for the importance of one brain region over another (Wise 2003; Hickok and Poeppel 2007; Martin 2007; Patterson et al. 2007). Rather than arguing for the preeminence of a single specific region, we suggest a different model: An overview of all these neuropsychological and neuroimaging studies suggest that semantic cognition is supported by a 3-part neural network made up of the left prefrontal cortex, the temporoparietal junction, and the temporal poles (TPs) bilaterally (see General Discussion and Jefferies and Lambon Ralph 2006). Although there is convergent evidence for the involvement of the first 2 regions, the argument for the involvement of the TPs rests heavily upon the SD results (Wise 2003). Although the atrophy and hypometabolism is remarkably circumscribed in this condition, it is always possible that the semantic impairment actually results from damage or infiltration of pathology in regions beyond those maximally damaged in SD. Accordingly, it is imperative to derive convergent evidence from neurologically intact participants that the TPs are critical regions for semantic memory.

We achieved this aim by utilizing rTMS to induce a “virtual lesion” (Walsh and Cowey 1998) in neurologically intact

participants. In a previous study, we found that this form of rTMS (1 Hz for 10 min) applied to the left TP significantly slowed performance on both naming and comprehension tasks, mimicking 2 of the core deficits observed in SD (Pobric et al. 2007). In the present study, we extended these findings by probing the relative roles of left versus right TPs in semantic memory. As noted above, when neurological diseases damage the ATL bilaterally, then considerable semantic impairment can follow. In unilateral resection after epilepsy, however, the semantic impairment is much more subtle (Wilkins and Moscovitch 1978). This suggests that semantic memory may be supported by contributions from both left and right ATL (Lambon Ralph et al. 2001; Lambon Ralph and Patterson 2008). To test this hypothesis, we examined the impact of rTMS on semantic performance after left (Experiment 1) or right TP stimulation (Experiment 2). Although this is the first time that TMS has been used to investigate the semantic function of both TPs, TMS has been used to probe other regions and test their role in semantic processing. Consistent with the aphasic and functional magnetic resonance imaging (fMRI) data reviewed in the Discussion, these studies have shown that semantic decisions are slowed after stimulation of the left inferior prefrontal cortex (and particularly after stimulating the pars orbitalis) and picture–word verification is slowed after stimulation of left Wernicke’s area (Knecht et al. 2002; Devlin et al. 2003).

There are 2 basic, experimental designs for TMS studies: the more common “control site” method and the “control task” method (Jahanshahi and Rothwell 2000). If one is interested in testing the neuroanatomical specificity of a region, then the control site method is most appropriate. Alternatively, if one is interested in the function of a specific region (as we are), then the control task method is more helpful in that one can start to gauge which range of activities/function the target region is involved in. As noted above, we already know that semantic cognition is not uniquely localized to the ATL. Instead, what is controversial is that there is a role of ATL in semantic cognition. Thus in designing our experiment, the focus was to probe the range of functions supported by the ATL by using the control task method in which performance on semantic tasks was compared with equally demanding, nonsemantic processes. If our working hypothesis is correct (semantic memory is supported the ATL bilaterally), then after stimulating either the left TP (Experiment 1) or the right TP (Experiment 2) decision times on a synonym judgment task should be slowed, yet performance on an equally demanding, nonsemantic, cognitive task (number matching) should be unaffected.

Experiment 1

Methods

Design

A 2 × 2 within-participant factorial design was used, with TMS (no stimulation vs. TP stimulation) and task (synonym vs. number judgment) as the 2 within-participant factors. The study utilized rTMS using the virtual lesion method in which the train of rTMS is delivered off-line (without a concurrent behavioral task) and then behavioral performance is probed during the temporary refractory period and compared with performance on the same task outside this refractory window.

In pilot studies, we found that semantic decision times were suppressed for around 20 min after 10 min of 1-Hz rTMS. We also found that rTMS and the associated novel experience, irrespective of site of stimulation, is highly alerting for participants. As a consequence, there is a nonspecific speeding of reaction times (on all tasks). Accordingly, the study was designed to deconfound order and the specific TMS effect. Half the participants produced their “baseline,” no-TMS data before rTMS was applied. The other half provided their baseline at least 30 min or more after the end of rTMS (by which time, our pilot studies indicate that no behavioral effect remains).

Participants

Ten, right-handed volunteers took part in the experiment (6 females; mean age = 21.7 years, SD = 4.05). All were native English speakers and strongly right-handed, yielding a laterality quotient of at least +90 on the Edinburgh Handedness Inventory (Oldfield 1971). They were free from any history of neurological disease or mental illness and not on any medication. All had normal or corrected-to-normal vision. The experiment was reviewed and approved by the local research ethics board.

Stimuli

The synonym judgment task was based on a neuropsychological assessment, which we have developed to test verbal comprehension in SD and other aphasic patient groups (Jefferies et al., in preparation). The 96 trials from the clinical test were augmented with additional trials in order to provide enough trials for the TMS and no-TMS versions. The final experiment includes 2 versions containing 72 trials each (144 in total). Each trial contains 4 words: a probe word (e.g., ROGUE), the target choice (e.g., SCOUNDREL), and 2 unrelated choices (e.g., POLKA and GASKET). The number task also contained 144 trials. The format was the same as for the synonym judgment task: A probe number was presented at the top of the screen and underneath 3 number choices were given. Participants were required to pick which of the 3 was closest in value. In pilot studies, we found that by using double-digit numbers, the resultant number judgment times were typically slightly slower and less accurate than the synonym judgment tasks (see Results—main text). Accordingly, any specific effects of TP rTMS on synonym judgment could not be due to task difficulty.

Task and Procedure

A PC running E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA) allowed the presentation of stimuli and recording of the responses. The participants sat 57 cm in front of a 15" monitor.

Participants performed 2 synonym and number judgment tasks per experimental session (1 within and 1 outside the rTMS induced refractory period—see above). The experiment began with a practice block of 6 trials for each stimulus set. Experimental trials were presented in a random order in 4 blocks of 72 trials (2 blocks of the same task). A fixation point appeared on the screen to signal the start of each trial. The participant then pressed a space bar, which advanced the experiment on to the next stimulus. Stimuli (words and numbers) were presented until response followed by a blank screen interval of 500 ms. Participants were asked to indicate the synonym of the probe word or which number was closest in magnitude to the probe number by pressing with the right hand 1 of 3 designated keys on a keyboard. The 2 versions of

the tasks were counterbalanced across participants. As noted above, whether the non-TMS session was conducted before or after (at least 30 min) the TMS was counterbalanced across participants to deconfound TMS and order effects.

TMS

A MagStim Rapid2 (Magstim Co., Whitland, UK) stimulator with 2 external boosters was used (maximum output ca. 2.2 T). Magnetic stimulation was applied using a 70-mm figure-of-eight coil. The double wire windings, which make up the figure-of-eight coil carry 2 alternating electrical currents which converge at the point where the 2 coils meet (at the center of the figure-of-eight). A focal electrical current can then be induced in the cortex via magnetic conduction from this central point which undergoes minimal attenuation by the intervening soft tissue and bone (Jalinous 1995). Previous studies have demonstrated that magnetic stimulation using this type of coil can produce functionally dissociable effects when moving the coil by 5–10 mm across the scalp (Brasil-Neto et al. 1992).

Anatomical MRI Acquisition

The 3D anatomical images for all participants were acquired using a 3-T Philips MR Achieva scanner (Philips Electronics, The Netherlands). MRI scanning parameters included a slice thickness of 0.9 mm, a field of view of 24 cm, and an acquisition matrix of $96 \times 96 \times 42$. A conjugate synthesis in combination with an interleaved acquisition resulted in 240 contiguous double-echo slices whose voxel dimensions were $0.94 \times 0.94 \times 0.9$ mm. These high-resolution T_1 -weighted images enabled reconstruction of the fine individual cortex folding which was used as anatomical landmarks for the TMS targets.

Selection of TMS Site

The structural T_1 -weighted MRI scans were coregistered with the participant's scalp using MRIreg (www.mricro.com/mrirege.html). Immediately prior to the TMS session, scalp coordinates were measured using an Ascension Minibird (www.ascension-tech.com) magnetic tracking system. A series of scalp landmarks were identified for coregistration within the MRI and Minibird coordinates. Once this calibration was complete, the 2 frames of reference were coregistered using least squares linear estimation. This allowed us to compare the position of the Minibird on the scalp to the underlying cortical surface. From the tip of the TP, we measured 10 mm posterior along the middle temporal gyrus. This point was used in each participant as an anatomical landmark for the TP. The location of the TP was identified on each participant and the scalp location directly above this site was marked with a permanent marker. The left Montreal Neurological Institute (MNI) coordinates for the TP in standard space were $-53, 4, -32$.

Stimulation Parameters

Individual motor threshold was determined for every participant; stimulation was delivered to the optimal scalp position, from which the minimal intensity required to induce contraction of the relaxed contralateral abductor pollicis brevis muscle was established. Motor thresholds ranged between 42% and 62%. The average stimulation (120% of motor threshold) during the experiment was 63% of maximum stimulator output.

For the rTMS experiment, participants received 10-min TMS active stimulation (1 Hz for 600 s at the 120% of motor threshold level) applied to the TP. The coil was securely held

against the left temple, centered over the site to be stimulated. This TMS protocol has been shown to produce behavioral effects that last for several minutes after stimulation (Kosslyn et al. 1999; Hilgetag et al. 2001).

Methodological Considerations

An advantage of low-frequency rTMS is that rTMS modulates the level of excitability of a given cortical area beyond the duration of the rTMS train itself (Pascual-Leone et al. 1998; Knecht et al. 2002). In the present design, behavior was evaluated before and after rTMS. Therefore, a nonspecific disruption of performance due to discomfort, noise, muscle twitches, and intersensory facilitation associated with rTMS during the task was avoided. The rTMS has a considerable alerting effect irrespective of task or location of stimulation and thus has a generic speeding effect on decision times in cognitive tasks. Accordingly, we deconfounded the effects of TMS and order in the experiments. Particular care was taken in the placing of the TP coil because TMS here is more uncomfortable than over occipital or parietal areas. We manipulated coil orientation (a major factor in the nature of the contraction of facial/neck muscles) to find an orientation that minimized the discomfort to a subjective equivalent to that of the stimulation over other sites. Previous rTMS studies, utilizing this figure-of-eight coil, have shown that the behavioral effect is invariant to coil orientation (Niyazov et al. 2005), and we found the same in pilot studies of varying coil orientation over this TP target. As detailed above, we also used a number judgment task as a control to ensure that neither nonspecific effects of the rTMS procedure nor task difficulty could explain the observed results.

Experiment 2

Methods

Design, Stimuli, and Procedure

Design, stimuli, and procedure were identical to the methods of Experiment 1.

Participants

Nine right-handed participants participated in the Experiment 2, of which 8 had taken part in Experiment 1 as well (5 females; mean age = 20.3, SD = 5.12).

TMS Equipment and Protocol

The same TMS protocol was used in Experiment 2. The target location for rTMS was the right TP. As per Experiment 1, this was implemented by locating 10 mm posterior to the tip of the TP along the middle temporal gyrus using each participant's own MR structural scan. This corresponded to average MNI coordinates of $52, 2, -28$ in standard space.

Results

In Experiment 1, the participants' performance on the semantic task (timed synonym judgment) and the control task (timed number judgment) was compared with and without 10 min of off-line 1-Hz rTMS over the left TP. The results are summarized in the left-hand panel of Figure 1. There was a differential effect of TP stimulation on the 2 tasks [$F(1,9) = 19.1, P = 0.002$]. Despite being the harder and thus slower

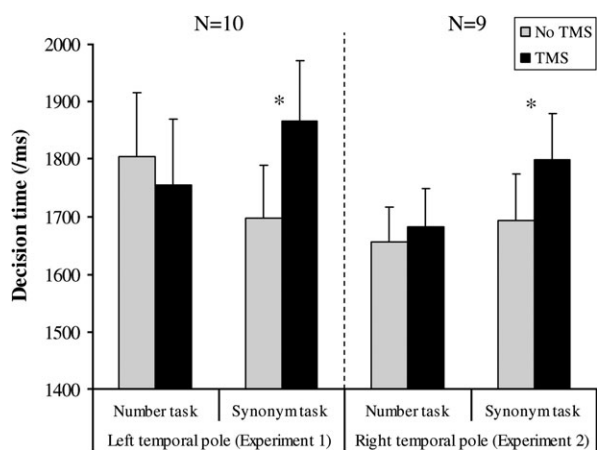


Figure 1. The effect of left or right TP stimulation on semantic and number judgment times.

task, number judgment was completely unaffected by TP stimulation [$t(9) = -1.08$, $P = 0.31$], whereas semantic decision times were slowed, on average, by 9.9% [$t(9) = 7.58$, $P < 0.001$]. The TMS effect was carried entirely in speed rather than accuracy. Errors rates were low. Participants made more errors to the number than synonym judgment task [8.0% and 3.9%, respectively: $F(1,9) = 14.7$, $P = 0.002$], but there was no effect of TMS nor an interaction [both $F < 1$].

As noted in the Introduction, the results from SD suggest that both the left and right ATLS support conceptual knowledge. Accordingly, one might expect semantic decision times to be slowed after rTMS to the right as well as left TP. We tested this hypothesis in Experiment 2. The same experimental procedure and materials were used except that rTMS was applied over the right TP. The results are summarized in the right-hand panel of Figure 1. A very similar pattern of data were produced. Semantic decision times were slowed significantly (on average by 6.2%: $t(8) = 2.66$, $P = 0.03$) but number judgments were not [$t(8) < 1$]. Like Experiment 1, all effects were carried in speed rather than accuracy, and error rates were very low. The number task induced a slightly higher error rate than the synonym task [3.9% vs. 2.0%, respectively: $F(1,8) = 3.83$, $P = 0.09$], but there was no effect of TMS nor interaction [TMS: $F(1,8) < 1.13$, $P = 0.32$; task \times TMS: $F(1,8) = 1.10$, $P = 0.32$].

Because we were able to retest 8 of the same participants in Experiment 2 as Experiment 1, this permitted an additional analysis in which the effect of left versus right TP stimulation was compared within the *same* individuals. There were no significant differences between the results of the 2 experiments when directly compared [hemisphere \times task \times TMS: $F(1,7) = 1.04$, $P = 0.34$]. The overall pattern was the same as the 2 individual experiments with an interaction between task and TMS [$F(1,7) = 11.2$, $P = 0.01$]. None of the other 2-way interactions was significant. Semantic decisions were slowed after either left or right TP stimulation [left pole, mean 10.9% slowing: $t(7) = 7.42$, $P < 0.001$; right pole, mean 11.9% slowing: $t(7) = 5.25$, $P = 0.001$], but number judgments remained unchanged [left pole: $t(7) < 1$; right pole: $t(7) = 1.67$, $P = 0.14$]. As with the individual experiments, the effects for the common data set were carried in speed rather than accuracy. There was

an overall effect of task on errors [number—6.0% vs. synonym judgment—3.0%: $F(1,7) = 12.9$, $P = 0.009$], but there were no interactions with TMS or hemisphere.

General Discussion

In this study, we used rTMS to induce a virtual lesion (Walsh and Cowey 1998) or, perhaps more accurately, a temporary slowing of processing in either the left (Experiment 1) or right (Experiment 2) TPs. This confirmed the hypotheses arising from neuropsychological studies of patients with SD. The ATL regions are critically important in the representation and activation of semantic memory. When these regions are subject to neurological damage, patients demonstrate poor comprehension and expression in both verbal and nonverbal domains, whereas other aspects of cognition and language are preserved (Hodges et al. 1992; Bozeat et al. 2000). When rTMS is applied to these same regions, normal participants exhibit a significant slowing on semantic tasks but not in other more demanding cognitive tasks.

Given that the refractory period produced by the rTMS procedure is limited, it is impossible to run a wide variety of active and control tasks within the same session. In these experiments, we chose to control for general task difficulty and executive/decision processes by comparing the synonym and number judgment tasks directly. This does, however, potentially leave open the possibility that the results reflect other differences between the 2 tasks—and, in particular, the fact that synonym judgment requires linguistic processing that the number task does not. We can reject this possibility, however, by combining the present results with those found in our previous investigation (Pobric et al. 2007). A part of that previous study (stimulating exactly the same TP region) included complex number reading (reading aloud of 6 digit numbers). Despite the fact that this kind of number reading requires phonological and syntactical processes in order to produce the appropriate spoken phrase, the TP rTMS had no effect on the naming times. Taken together, these 2 studies produce results that closely mirror the pattern observed in SD—the patients show poor semantic abilities yet preserved number processing, phonology, and syntax (both receptively and expressively: Hodges et al. 1992; Butterworth et al. 2001).

Although the data arising from SD—and now these rTMS experiments—seem to implicate the TPs, bilaterally, in semantic representation, these areas are often overlooked or even disputed in other research on semantic memory (Wise 2003; Martin 2007). Several factors probably account for this situation. First, there is no doubt that the atrophy and associated hypometabolism of SD is focused upon the anterior, polar aspects of the temporal lobes bilaterally with consistent and substantial gray matter loss in the polar and perirhinal cortices and the anterior fusiform gyri, bilaterally (Patterson et al. 2007). The simplest and most obvious hypothesis, therefore, is that these regions are critical for semantic memory (Rogers et al. 2004; Patterson et al. 2007; Lambon Ralph and Patterson 2008). Given that SD is a neurodegenerative condition, there is no absolute boundary to the damage. There is, therefore, always the possibility that subthreshold 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 (Martin 2007). It is critically important, therefore, to derive convergent evidence from other

techniques about the putative role of ATL regions in semantic cognition—and this was the primary purpose and outcome of this study.

Secondly, classical aphasiological models have never associated extrasylvian regions with comprehension disorders—patients with Wernicke's aphasia typically have damage to the left posterior middle temporal and superior temporal gyri, whereas patients with transcortical sensory aphasia have damage to the left temporoparietal or prefrontal cortices (Berthier 2001). Third, fMRI studies of semantic memory or comprehension rarely activate ATL regions but, in line with the aphasiological models, find activation in left temporoparietal and prefrontal regions (Vandenberghe et al. 1996). Finally, following unilateral resection of the TP, epilepsy patients are not commonly reported to have semantic impairment or at least not to the same degree as SD patients (Hermann et al. 1999).

Recent investigations indicate, however, that these observations are not contradictory with the results from SD. First, direct comparisons of SD and aphasia-related comprehension impairments show that although both conditions can lead to multimodal impairment of semantic cognition (i.e., impaired semantically driven behavior across verbal and nonverbal modalities), there is a qualitative difference between the patient groups; SD results from a gradual dissolution or dimming of the semantic representations themselves, whereas aphasic patients with multimodal comprehension disorders have impairment to the mechanisms that control or shape the activation of task-relevant information rather than damage to semantic knowledge per se (Jefferies and Lambon Ralph 2006). This is consistent with functional neuroimaging which shows that left temporoparietal and inferior prefrontal regions are involved in the control or selection mechanisms that underpin a variety of cognitive processes including semantic cognition (Garavan et al. 2000; Peers et al. 2005). Studies of various patient groups and functional neuroimaging in normal participants have consistently demonstrated a critical role of left prefrontal and temporoparietal regions in semantic cognition (Thompson-Schill et al. 1997; Berthier 2001; Devlin et al. 2003). When all these data are combined, then it becomes clear that semantic cognition is actually supported by a 3-region neural network: left prefrontal, temporoparietal, and bilateral anterior temporal regions. In the undamaged system, these regions interact to support flexible, temporally extended semantic behavior (semantic cognition). With impairment to the ATL, core semantic representations become degraded and patients are unable to activate all of the information associated with a concept (Rogers et al. 2004; Jefferies and Lambon Ralph 2006; Lambon Ralph et al. 2007). Multimodal comprehension deficits can also emerge after damage to the prefrontal-temporoparietal control systems. In these circumstances, the patients are unable to reliably shape or control the aspects of meaning that are relevant for the task in hand or are critical at specific moments during temporally extended tasks (Jefferies and Lambon Ralph 2006).

Second, the failure to find ATL activation in semantic tasks reflects, at least in part, technical limitations of fMRI. Field inhomogeneities around air-filled cavities lead to signal drop out and distortions that are particularly pronounced in orbitofrontal cortex and the inferior and polar aspects of the temporal lobes (Devlin et al. 2000; Wise 2003). Functional neuroimaging that utilizes positron emission tomography (which does not suffer from the same problems) does detect

semantically-related activation in the ATLS, even when the same experiment conducted in fMRI does not (Devlin et al. 2000). Third, results from the outcome of epilepsy-related resections are complicated by 4 factors: 1) although there is an enormous neuropsychological literature on the sequelae of temporal lobe resection, most of it is focused upon episodic memory impairment and anomia (which might itself reflect subtle semantic impairment: Lambon Ralph et al. 2001), and semantic memory is rarely formally tested (Giovagnoli et al. 2005). Where semantic performance has been assessed, studies have found subtle multimodal impairments both in non-resected temporal lobe epilepsy patients (Giovagnoli et al. 2005) and in patients after temporal lobe resection (Wilkins and Moscovitch 1978); 2) long-standing epilepsy might lead to changes in neural organization, and, indeed, recent imaging studies have shown that white matter connectivity and neurotransmitter function are significantly altered in this condition (Hammers et al. 2003; Powell et al. 2007); 3) some reorganization of function might be possible following surgery which is less likely in neurodegenerative conditions when the brain is subjected to constant brain injury (Welbourne and Lambon Ralph 2005)—indeed, consistent with this hypothesis, Wilkins and Moscovitch (1978) found a negative correlation between the severity of semantic impairment and time post surgery; and 4) temporal lobe resection is a unilateral procedure, whereas SD patients have bilateral temporal lobe atrophy. Other neurological disorders, such as herpes simplex virus encephalitis, do produce semantic impairment when damage affects the same bilateral temporal lobe regions as SD (Lambon Ralph et al. 2007; Noppeney et al. 2007).

Given that the TP was identified and targeted specifically for each participant (using careful coregistration with each person's structural scan), we can be confident that the local effect of the figure-of-eight TMS coil was located at the target site. This region of the TP is a relatively easy ATL site to target with the coil given that it sits on the lateral surface. More inferior regions would be hard to target given that they are not optimally oriented for a TMS coil placed on the temple. It would be possible to target superior regions of the TP, although even greater care would be required over the coil positioning in order to avoid the possibility of stimulating inferior aspects of the orbital or prefrontal cortex. This would be important given that these regions have been implicated in controlled semantic processing (see below and Devlin et al. 2003). In addition to local effects of TMS, some recent studies have shown that the stimulation can have some remote effects as well (presumably propagated to regions connected by white matter pathways, e.g., Paus et al. 1997; Lee et al. 2003). Without evidence from post-stimulation functional neuroimaging, this leaves open the possibility that some of the behavioral effects reported here reflect a combination of local and more remote stimulation. It is important to note, however, that we are not claiming that the ATL is the sole basis for conceptual knowledge but, instead, plays a critical role as a part of a wider network for semantic cognition (Rogers et al. 2004). Until recently, there was no suggestion that the ATL was a part of the semantic language network (Wise 2003); yet, the combination of the results from SD and these rTMS studies directly support the hypothesis that this ATL region should be considered as a critical part in this wider network.

The application of rTMS over the ATL region, reported in this and a previous study (Pobric et al. 2007), licenses the use

of this technique to explore other key research questions about ATL semantic representations. Some obvious research questions for future studies include: 1) which aspects of meaning are supported by the ATL, 2) what are the differential roles of left versus right ATL in semantic representation, and 3) are there specific regions within the ATL that are responsible for semantic representations and does their contribution vary quantitatively or qualitatively. Some clues about the answer to these questions are provided by the wealth of SD data, though convergent evidence from rTMS and functional neuroimaging will be necessary because the damage in SD covers the entire ATL bilaterally, making finer neuroanatomical distinctions impossible to draw with absolute certainty.

Studies of SD indicate that the ATL regions support the formation of amodal semantic representations (Rogers and McClelland 2004; Rogers et al. 2004) such that when impaired, the patients demonstrate comprehension deficits across all verbal and nonverbal modalities (Bozeat et al. 2000) and have significant expressive difficulties in both verbal (e.g., naming and speaking) and nonverbal domains (e.g., picture drawing and object use; Lambon Ralph et al. 2001; Bozeat et al. 2003). Although the disease process is bilateral in all patients, the distribution of pathology can be asymmetric at least in the earlier phases of the disease. Previous studies have compared patients with different distributions of damage across left and right ATL. These have shown that patients with more left-sided atrophy have greater word-finding difficulties (anomia) and greater difficulty activating the meaning for verbal than picture stimuli (representing the same concept: Lambon Ralph et al. 2001). This could indicate that there is a verbal-nonverbal division of labor across left and right ATL or that the ATL regions function as a single system, but modality differences arise through differential patterns of connectivity to verbal and nonverbal inputs (Lambon Ralph et al. 2001; Snowden et al. 2004). The results from the present rTMS study confirm that there cannot be an absolute verbal-nonverbal distinction between left and right ATL in that rTMS produces equivalent slowing of semantic decisions on verbal materials (synonym judgment). Future studies utilizing rTMS over the ATL regions will be able to explore whether this also extends to nonverbal comprehension and whether more specific regions within the ATL are responsible for different aspects of meaning as indicated by some functional neuroimaging studies.

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