Conceptual knowledge is underpinned by the temporal pole bilaterally: Novel data from rTMS

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Abbreviations: SD – semantic dementia; rTMS – repetitive transcranial magnetic stimulation; fMRI – functional magnetic resonance imaging; PET – positron emission tomography; ATL – anterior temporal lobe; TP – temporal pole

Abstract

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 two novel experiments that used offline, low-frequency, repetitive transcranial magnetic stimulation to disrupt neural processing temporarily in the left or right temporal poles. The time required to make semantic decisions was slowed considerably, yet specifically, by this procedure. The results confirm that both temporal poles form a critical substrate within the neural network that supports conceptual knowledge.

Introduction

In this study, we utilised repetitive transcranial magnetic stimulation (rTMS) for the first time to probe the role of the anterior temporal lobes 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 non-verbal (e.g., drawing and object use). 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 (*1, 2*). The selective nature of their semantic impairment is coupled with a specific pattern of brain damage: SD patients have highly circumscribed bilateral atrophy and hypometabolism of the inferior and lateral aspects of the anterior temporal lobes and the extent of this atrophy correlates with the severity of the semantic impairment (*3, 4*).

Careful and extensive assessment of SD patients indicates that bilateral anterior temporal lobe regions support the formation of amodal semantic representations. Accordingly, SD patients exhibit poor comprehension of items presented in every modality, including spoken and written words, pictures, environmental sounds, smells and touch (*5-7*). The marked semantic deficit is also apparent in production tasks, such as picture naming (*8*), verbal definitions (*9*), object drawing (*10*) and object use (*11*). The singular, amodal nature of the anterior temporal lobe 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 (*12*, *13*).

The anterior temporal lobes 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'(*14*)). Accordingly, Rogers et al. (*13*) implemented a computational model of this anterior temporal lobe system in which semantic representations were formed through the distillation of information required for mappings between different verbal and non-verbal modalities. When damaged, the model reproduced the behavioural performance of SD patients across a wide variety of semantically-demanding receptive and expressive tasks.

While the data arising from semantic dementia clearly implicate the temporal poles, bilaterally, in semantic representation these areas are often overlooked or even disputed in other research on semantic memory (*15*). Several factors probably account for this situation. First, classical aphasiological models have never associated extra-sylvian regions with comprehension disorders – patients with Wernicke's aphasia typically have damage to the left posterior middle temporal and superior temporal gyri, whilst patients with transcortical sensory aphasia have damage to the left temporoparietal or prefrontal cortices (*16*). Second, fMRI studies of semantic memory or comprehension rarely activate anterior temporal lobe regions but, in line with the aphasiological models, find activation in left temporoparietal and prefrontal regions (*17*). Third, following unilateral resection of the temporal pole, epilepsy patients do not have semantic impairment or at least not to the same degree as SD patients (*18*).

Recent studies indicate, however, that these observations are not contradictory with the results from semantic dementia. First, direct comparisons of SD and aphasia-

related comprehension impairments show that whilst both conditions can lead to multimodal impairment of semantic cognition (i.e., impaired semantically-driven behaviour 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 whilst 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 (*19*). 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 (*20, 21*). Second, the failure to find anterior temporal lobe 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 (*15, 22*). Functional neuroimaging that utilises PET (which does not suffer from the same problems) does detect semantically-related activation in the anterior temporal lobes, even when the same experiment conducted in fMRI does not (*22*). Third, results from the outcome of epilepsy-related resections are complicated by two factors: (a) long-standing epilepsy might lead to changes in neural organisation and, indeed, recent imaging studies have shown that white matter connectivity and neurotransmitter function are significantly altered in this condition (*23, 24*); and (b) this procedure is unilateral whilst 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 semantic dementia (*25, 26*).

When combined, these neuropsychological and neuroimaging studies suggest that semantic cognition is supported by a three-part neural network made up of the left prefrontal cortex, the temporoparietal junction and the temporal poles bilaterally(*19*). Although there is convergent evidence for the involvement of the first two regions, the argument for the involvement of the temporal poles rests heavily upon the SD results(*15*). Whilst 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 temporal poles are critical regions for semantic memory.

We achieved this aim by utilising a novel application of repetitive transcranial magnetic stimulation (rTMS) to induce a "virtual lesion" (*27*) in neurological intact participants. Not only did we examine the impact of temporal pole rTMS on semantic performance (Experiment 1) but we also investigated whether this effect held across both left and right temporal poles (Experiment 2) as indicated by the SD patients. Although this is the first time that TMS has been used to probe the function of the temporal poles, TMS has been used to probe other regions and their role in semantic processing. Consistent with the aphasic and fMRI data reviewed above, 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 (*28, 29*).

Results

Figure 1 about here

In Experiment 1 the participants' performance on the semantic task (timed synonym judgement) and the control task (timed number judgement) was compared with and without 10 minutes of offline 1Hz rTMS (at 120% of hand motor threshold) over the left temporal pole for each individual (1cm posterior to the tip of the temporal pole back along the line of the middle temporal gyrus: see online supporting materials for more details on the method and materials). The results are summarised in the left-hand panel of Figure 1. There was a differential effect of temporal pole stimulation on the two tasks [$F(1,9)=19.1$, $p=0.002$]. Despite being the harder and thus slower task, number judgement was completely unaffected by temporal pole stimulation [$t(9)=-1.08$, $p=0.31$] whilst 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 judgement 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 anterior temporal lobes support conceptual knowledge. Accordingly, one might expect semantic decision times to be slowed after rTMS to the right as well as left temporal pole. We tested this hypothesis in Experiment 2. The same experimental procedure and materials were used except that rTMS was applied over the right temporal pole. The results are summarised in the right-hand panel of Figure 1. A very similar pattern of data was produced. Semantic decision times were slowed significantly [on average by 6.2%: $t(8)=2.66$, $p=0.03$] but number judgements 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 × TMS – $F(1,8)=1.10$, $p=0.32$].

Figure 2 about here

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 vs. right temporal pole stimulation was compared within the same individuals. There were no significant differences between the results of the two experiments when directly compared [hemisphere × task × TMS: $F(1,7)=1.04$, $p=0.34$]. The overall pattern was the same as the two individual experiments with an interaction between task and TMS [$(F1,7)=11.2$, $p=0.01$]. None of the other two-way interactions was significant. Semantic decisions were slowed after either left or right temporal pole 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 judgements 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 dataset were carried in speed rather than accuracy. There was an overall effect of task on errors [number – 6.0% vs. synonym judgement – 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 repetitive transcranial magnetic stimulation (rTMS) for the first time to induce a "virtual lesion" (*27*) or temporary slowing of processing in either the left (Experiment 1) or right (Experiment 2) temporal pole. This confirmed the hypotheses arising from neuropsychological studies of patients with semantic dementia. The anterior temporal lobe 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, whilst other aspects of cognition and language are preserved (*1, 5*). 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.

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 (*16, 29, 30*). When data from SD patients are combined with convergent results from this temporal pole rTMS study, then it becomes clear that semantic cognition is actually supported by a three-region neural network: left prefrontal, temporoparietal and bilateral anterior temporal regions. Previous comparative neuropsychological studies suggest that there is a division of labour across these areas such that core semantic representations are reliant upon the anterior temporal lobes while semantic control – like other forms of executive control - is reliant upon prefrontal-temporoparietal circuitry (*20, 21*). In the undamaged system, these regions interact to support flexible, temporally-extended semantic behaviour (semantic cognition). With impairment to the anterior temporal lobe, core semantic representations become degraded and patients are unable to

activate all of the information associated with a concept (*13*, *19*, *26*). Multimodal comprehension deficits can also emerge after damage to the prefrontal-temporoparietal controls 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 (*19*).

The novel application of rTMS over the ATL region, reported in this study, licenses the use of this technique to explore other key research questions about ATL semantic representations. Some obvious research questions for future studies include: (a) which aspects of meaning are supported by the ATL; (b) what are the differential roles of left vs. right ATL in semantic representation; (c) are there specific regions within the ATL that are responsible for semantic representations. 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 (*13, 31*) such that when impaired, the patients demonstrate comprehension deficits across all verbal and nonverbal modalities (*5*) and have significant expressive difficulties in both verbal (e.g., naming and speaking) and nonverbal domains (e.g., picture drawing and object use)(*8, 10*). 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)(*8*). This could indicate that there is a verbal-nonverbal division of labour across left and right ATLs or that the ATL regions function as a single system but modality differences arise through differential patterns of connectivity to verbal and nonverbal inputs (*8*, *32*). 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 judgement). Future studies utilising 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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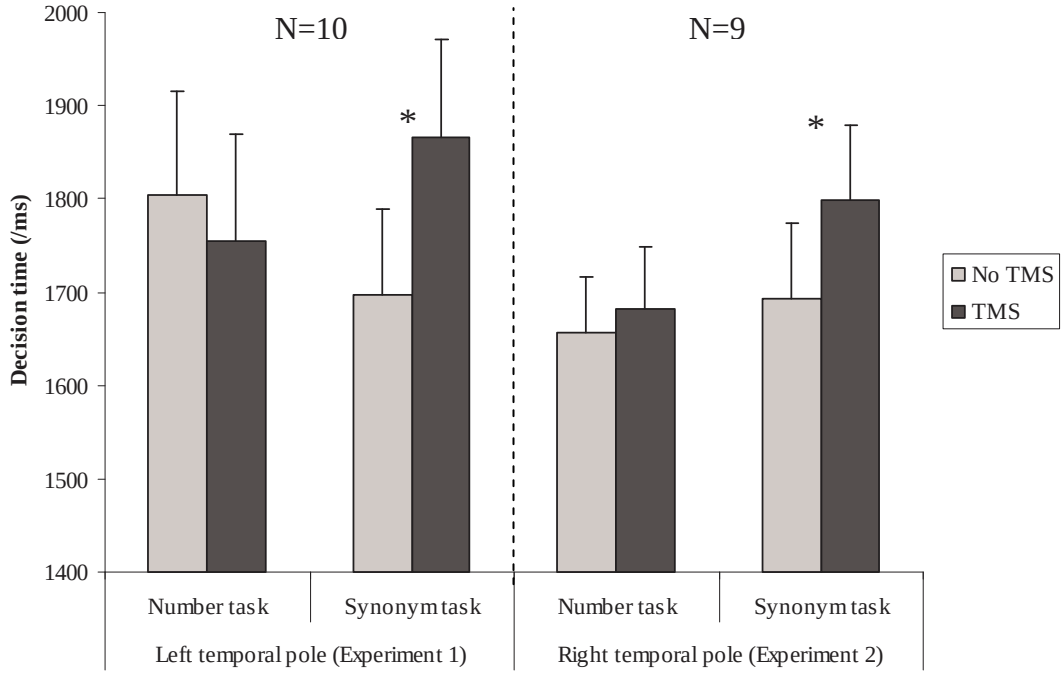
Figure 1: The effect of temporal pole stimulation on semantic and number judgement times in Experiments 1 and 2.



Footnote: Each bar represents the mean decision time alongside the corresponding standard error for each condition. An asterisk notes a significant difference between conditions.

Online supporting material

Methods

Experiment 1:

Design – A 2 × 2 within-participant factorial design was used, with TMS (no stimulation vs. temporal pole stimulation) and task (synonym vs. number judgement) as the two within-participant factors. The study utilised rTMS using the "virtual lesion" method in which the train of rTMS is delivered offline (without a concurrent behavioural task) and then behavioural performance is probed during the temporary refractory period and compared to performance on the same task outside this refractory window. In pilot studies, we found that semantic decision times were suppressed for around 20 minutes after 10 minutes of 1Hz 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 non-specific speeding of reaction times (on all tasks). Accordingly, the study was designed to deconfound order and the specific TMS effect. Half of the participants produced their "baseline", no-TMS data before rTMS was applied. The other half provided their baseline at least 30 minutes or more after the end of rTMS (by which time, our pilot studies indicate that no behavioural 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 (*33*). 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 ethics board (COREC approval).

Stimuli – The synonym judgement task was based on a neuropsychological assessment that we have developed to test verbal comprehension in SD and other aphasic patient groups (*34*). 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 two versions containing 72 trials each (144 in total). Each trial contains four words: a probe word (e.g., ROGUE), the target choice (e.g., SCOUNDREL), and two unrelated choices (e.g., POLKA and GASKET). The number task also contained 144 trials. The format was the same as for the synonym judgement task: a probe number was presented at the top of the screen and underneath three number choices were given. Participants were required to pick which of the three was closest in value. In pilot studies, we found that by using double-digit numbers, the resultant number judgement times were typically slightly slower and less accurate than the synonym judgement tasks (see Results – main text). Accordingly, any specific effects of temporal pole rTMS on synonym judgement could not be due to task difficulty.

Task and procedure - A PC running E-Prime software (Psychology Software Tools Inc., Pittsburgh, USA) allowed the presentation of stimuli and recording of the responses. The participants sat 56 cm in front of a 15" monitor.

Participants performed two synonym and number judgment tasks per experimental session (one within and one 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, numbers) were presented until response followed by a blank screen interval of 500ms. 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 one of three designated keys on a keyboard. The two versions of the tasks were counterbalanced across participants. As noted above, whether the non-TMS session was conducted before or after (at least 30 minutes) 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 approx. 2.2 Tesla). 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 two alternating electrical currents which converge at the point where the two coils meet (at the centre 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, McShane, Fuhr, Hallett, & Cohen, 1992).

Anatomical MRI acquisition - 3D anatomical images for all participants were acquired using a 3T 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 256 _ 256 _ 240 voxels. A conjugate synthesis in combination with an interleaved acquisition resulted in 240 contiguous double-echo

slices whose voxel dimensions were 0.94 × 0.94 × 0.9mm. These high-resolution T1-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 T1-weighted MRI scans were co-registered with the participant's scalp using MRIreg (www.mricro.com/mrireg.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 co-registration within the MRI and Minibird coordinates. Once this calibration was complete, the two frames of reference were co-registered 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 temporal pole we measured 10mm posterior along the middle temporal gyrus. This point was used in each participant as an anatomical landmark for the temporal pole (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 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 75% of maximum stimulator output (mean 77 ± 6.88%).

For the rTMS experiment, participants received 10 min TMS active stimulation (1-Hz for 600 s at the adjusted motor threshold level) applied to the temporal pole. The coil was securely held against the left temple, centred over the site

to be stimulated and oriented such that the maximal induced current flowed approximately in the anterolateral direction, parallel to the middle temporal gyrus. This TMS protocol has been shown to produce behavioural effects that last for several minutes after stimulation (*35, 36*).

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 (*28, 37*). In the present design, behaviour 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. 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. As detailed above, we also used a number judgment task as a control to ensure that neither non-specific effects of the rTMS procedure nor task difficulty could explain the observed results.

Experiment 2

Methods

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 temporal pole. As per Experiment 1 this was implemented by locating 10mm posterior to the tip of the temporal pole 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.