Anterior temporal lobes mediate semantic representation: Mimicking semantic dementia by using rTMS in normal participants

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Studies of semantic dementia and PET neuroimaging investigations suggest that the anterior temporal lobes (ATL) are a critical substrate for semantic representation. In stark contrast, classical neurological models of comprehension do not include ATL, and likewise functional MRI studies often fail to show activations in the ATL, reinforcing the classical view. Using a novel application of low-frequency, repetitive transcranial magnetic stimulation (rTMS) over the ATL, we demonstrate that the behavioral pattern of semantic dementia can be mirrored in neurologically intact participants: Specifically, we show that temporary disruption to neural processing in the ATL produces a selective semantic impairment leading to significant slowing in both picture naming and word comprehension but not to other equally demanding, nonsemantic cognitive tasks.

repetitive transcranial magnetic stimulation | semantic cognition | temporal pole

Semantic memory encompasses the meaning of all types of verbal and nonverbal stimuli including words, pictures, objects, and faces. In addition to underpinning comprehension, 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). As such, it is integral to our everyday lives, and impairments of semantic memory are extremely debilitating. Key questions for neuroscience research, therefore, are which parts of the brain support semantic memory, and how do they function?

Various neurological disorders cause impairments of semantic processing; however, the purest syndrome is semantic dementia (SD; the temporal lobe variant of frontotemporal dementia) (1). This neurodegenerative disease results in relatively focal atrophy and hypometabolism of the anterior temporal lobes (ATL) bilaterally (2, 3). SD is characterized by progressive impairment of verbal and nonverbal semantic tasks, with anomia as the first presenting symptom (4–6). Strikingly, other aspects of language and cognition remain largely intact. SD patients have increasing difficulty distinguishing concepts from their semantic neighbors, reflecting an increasing loss of "semantic acuity" (6, 7). As such, the patients have greater difficulty activating specific semantic information (e.g., "zebras have stripes") than more general properties (e.g., "zebras are animals") (6, 8). Likewise, their naming difficulties are graded by specificity (higher naming accuracy for basic-level concepts such as dog than specific ones, e.g., springer spaniel) (9) with errors reflecting more general semantic knowledge (e.g., dog → "animal").

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 (4, 10, 11). The marked semantic deficit is also apparent in production tasks, such as picture naming (5), verbal definitions (12), object drawing (13), and object use (14). 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 (6, 15).

The anterior temporal lobes are ideal for forming amodal semantic representations because they have extensive connections with cortical areas that represent modality-specific information (16) (see also the theory of "convergence zones" in ref. 17). Accordingly, Rogers *et al.* (6) 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 nonverbal modalities. When damaged, the model reproduced the behavioral performance of SD patients across a wide variety of semantically demanding receptive and expressive tasks.

Although 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 (18–20). Several factors probably account for this situation. First, classical aphasiological models have never associated anterior temporal lobe 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 (21). Second, functional MRI (fMRI) studies of semantic tasks rarely activate anterior temporal lobe regions but, in line with the aphasiological models, find activation in left temporoparietal and prefrontal regions (22, 23). Third, after unilateral resection of the temporal pole, epilepsy patients do not have semantic impairment, or at least not to the same degree as SD patients (24).

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, although both conditions can lead to impairment of multimodal 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* (7). This indicates that semantically driven

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behavior (which we have come to refer to as "semantic cognition") comprises two key, interacting components: (*i*) the core amodal semantic representations and (*ii*) "semantic control," executive-control mechanisms that interact with the underlying semantic representations to produce task- and time-appropriate activation of key knowledge for the specific task in hand. 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 (23, 25). 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 dropout and distortions that are particularly pronounced in orbitofrontal cortex and the inferior and polar aspects of the temporal lobes (18, 22). Functional neuroimaging that utilizes 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). Because of the preeminence of fMRI in cognitive neuroscience, however, the potentially central importance of the ATL within a network of regions that support semantic cognition can be overlooked (18, 26). Third, results from the outcome of epilepsy-related resections are complicated by two factors: (*i*) longstanding 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 (27, 28); and (*ii*) this procedure is unilateral, 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 semantic dementia (9, 29).

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 (18–20). Rather than arguing for the preeminence of a single specific region, we suggest a different model: an overview of all of these neuropsychological and neuroimaging studies suggests 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 (7). Although there is convergent evidence for the involvement of the first two regions, the argument for the involvement of the temporal poles rests heavily on the SD results (18). Although the atrophy and hypometabolism are remarkably circumscribed in this condition (2), it is always possible that the semantic impairment actually results from damage or infiltration of pathology in regions beyond those maximally damaged in SD (19, 20). 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 utilizing a novel application of repetitive transcranial magnetic stimulation (rTMS) to induce a "virtual lesion" in neurologically intact participants. TMS is a well established noninvasive technique that generates magnetic pulses over the scalp, inducing electrical activation in a highly specific area of underlying cortex. A long train of low-frequency rTMS temporarily suppresses neural processing and disrupts behavioral tasks that rely on this cortical region. Although the use of rTMS to probe the function of the temporal poles is new, 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 (30, 31).

There are two basic, experimental designs for TMS studies: the more common "control site" method and the "control task" method (32). 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.

The aim of the present study was to test whether rTMS over the ATL in neurologically intact participants led to a behavioral "symptom" pattern like that observed in SD. Specifically, we tested whether this produced a combined impairment to comprehension and picture naming yet left performance on equally demanding nonsemantic cognitive tasks (number matching and naming) unaffected.

Results

Two separate experiments were conducted. In one, participants named pictures of objects at the basic (e.g., boat, bird) and specific (e.g., yacht, robin) levels (see *Materials and Methods*). They also named six-digit numbers (e.g., 524,673) as a control task. In the second investigation, participants completed a timed synonym judgment task and their performance was compared with a number matching task. We picked these tasks for two reasons: in our pilot studies we have found that rTMS effects are much more subtle (showing themselves in reaction time) than the patient data (reduced accuracy). Ultra-mild SD gives us clues as to which types of task are the most sensitive to semantic decline. In addition to an early drop in accuracy on the same synonym judgment used here, the patients also have an early and pronounced semantically driven anomia—especially if required to name at the most specific level (5, 9). Number-related tasks provide an appropriate cognitive control condition in that number quantity knowledge is thought to rely on the left parietal regions and is preserved in SD (34, 35). Furthermore, these tasks can be configured so that they are as cognitively demanding as picture naming or word comprehension and thus ensure that any results on the semantically related tasks cannot be ascribed to task difficulty alone. To target the temporal pole accurately, this region was identified individually for each participant by coregistering scalp coordinates with structural MRI scans. In both experiments we stimulated the same region, 10 mm posterior to the tip of the temporal pole along the middle temporal gyrus in the left hemisphere.

The results from the object and number naming tasks are shown in Fig. 1*A*. Statistical analysis of reaction times yielded a main effect of task [$F(2,10) = 34.39, P < 0.001$], as well as a main effect of TMS condition [$F(1,10) = 5.10, P < 0.05$]. Crucially, there was a significant interaction between TMS and the naming task [$F(2,10) = 4.79, P = 0.03$]. Bonferroni tests revealed that TMS significantly slowed naming responses in the specific-level task [$t(10) = 3.87, P < 0.02$] but not in the other two tasks [$t(10) < 1.5$, not significant]. In addition, specific-level naming was slower than both basic-level naming and number naming [Bonferroni $t(10) > 5.75, P < 0.001$]. A separate analysis of response accuracy yielded a main effect of the naming task [$F(2,10) = 11.97, P < 0.001$]. This reflected poorer accuracy in specific-level naming than basic-level or number naming [13% errors in specific naming vs. 2% in basic-level naming or 4% in number naming: $t(10) > 3.75, P < 0.03$].

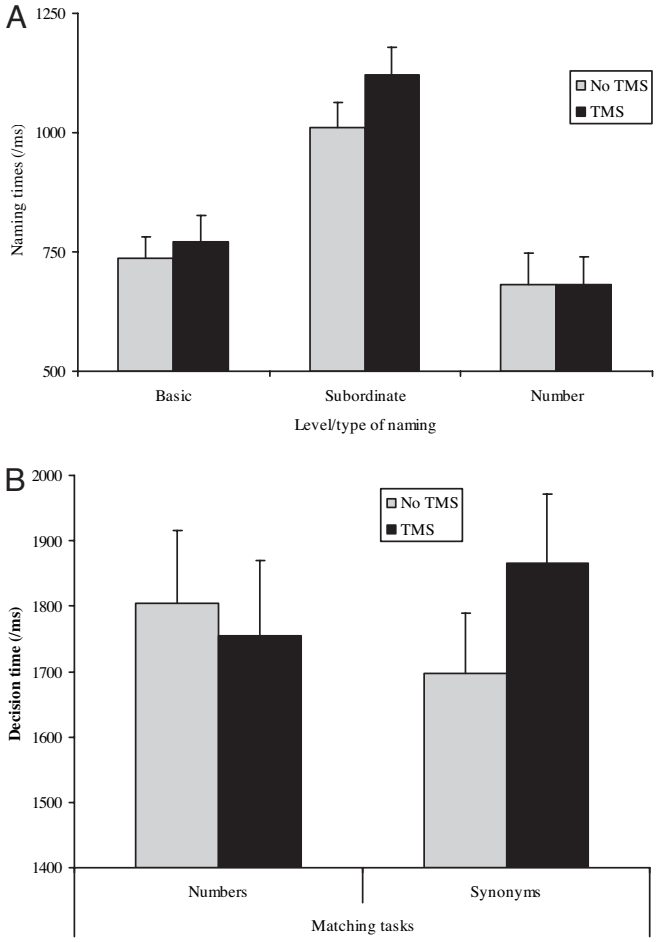

Fig. 1. Effect of rTMS to the left temporal pole on naming (*A*) and synonym judgments (*B*). Each bar represents mean reaction time for that condition. Error bars represent the standard error for each mean. *A* summarizes data from the naming tasks (objects and numbers), and *B* shows the results from the synonym and number judgment tasks.

The results for synonym vs. number judgments are shown in Fig. 1*B*. Statistical analysis confirmed that 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 judgment was completely unaffected by temporal pole stimulation [$t(9) = -1.08$, $P = 0.31$] whereas semantic decision times were slowed, on average, by 9.9% [$t(9) = 7.58$, $P < 0.001$]. Like the naming tasks, 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 and no interaction (both $F < 1$).

Discussion

These findings demonstrate that the ATL plays a necessary role in semantic cognition in healthy participants. A temporary virtual lesion induced by low-frequency rTMS over left ATL significantly increased naming latencies for a specific-level naming task but not for number naming. Additionally, stimulating the same region significantly slows synonym judgment times but not number quantity decisions. The results of this study mirror the core features of semantic dementia (SD) patients, who show a progressive and highly selective deterioration of semantic memory in the context of focal atrophy of the ATL (2, 5). Like the patients, rTMS over the ATL produces a combination of impaired comprehension and a resultant naming impairment but does so in a selective manner. The parallelism between the patient data and these novel rTMS results is consistent with the notion that the anterior temporal lobe region integrates all types of verbal and nonverbal information into an amodal representation that allows all information associated with a concept to be activated from any particular, single input modality and also allows for appropriate generalizations from one concept to another (6).

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 (21, 31, 36). 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 labor across these areas such that core semantic representations are reliant on the anterior temporal lobes whereas semantic control—like other forms of executive control—is reliant on prefrontal–temporoparietal circuitry (23, 25). In the undamaged system these regions interact to support flexible, temporally extended semantic behavior (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 (6, 7, 9). 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 at hand or are critical at specific moments during temporally extended tasks (7).

In this study rTMS significantly slowed specific-level naming, but there was only a weak, nonsignificant trend to slow basic-level naming. The ATL atrophy of semantic dementia also induces a specificity effect in both comprehension and naming (6, 8, 9). Likewise, a recent PET functional imaging study demonstrated greater activity in the ATL when participants were required to verify picture–name pairings at the specific level (37). There are two possible explanations for this effect. The first is that specific-level conceptual differences are simply more demanding for the normal semantic system and thus are the first to exhibit effects of brain disease, show greater neural activation, or, in this study, the effects of rTMS (6, 9). An alternative explanation is that there is a basic-to-specific representational gradient along the temporal lobe such that the anterior regions are specialized for specific concepts (38). Although this alternative hypothesis is consistent with the rTMS results presented here, other neuroimaging and patient data would seem to argue against it. Although SD patients show worse performance for specific-level than basic-level distinctions, their performance on basic-level concepts is also impaired, suggesting a graded difference underpinning the specificity effect (6). In addition, a number of neuroimaging studies have found that anterior temporal lobe regions are activated in normal participants by speech production or comprehension tasks involving basic-level concepts (22, 39). Such findings are consistent with the notion that ATL regions form an amodal semantic representation system and that performance differences reflect systematic variations in the formation and thus representation of these concepts (6, 26).

Materials and Methods

Participants. Twelve participants took part in the naming tasks (seven females; mean age = 21.7, SD = 4.05). Ten participants took part in the synonym and number judgment tasks (six females; mean age = 22.3 years, SD = 4.82). All participants were native English speakers and strongly right-handed, yield-

ing a laterality quotient of at least +90 on the Edinburgh Handedness Inventory (40). They were free from any history of neurological disease or mental illness, and they were not on any medication. All had normal or corrected-to-normal vision. The experiments were reviewed and approved by the local ethics board (Central Office for Research Ethics Committees approval).

Design. A within-participant factorial design was used in both experiments, with TMS (no stimulation vs. temporal pole stimulation) and task (basic vs. specific vs. number naming or synonym vs. number judgment) as the two within-participant factors. The study utilized rTMS using the virtual lesion method in which the train of rTMS is delivered offline (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 ≈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 of 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).

Stimuli and Procedure. ***Naming tasks.*** A total of 128 picture stimuli and 64 number stimuli were used. To allow for direct comparisons with SD data, these stimuli were taken from existing neuropsychological assessments (4, 9). For the basic naming task, 64 line drawings were taken from the Snodgrass and Vanderwart set (41), covering various different categories (animals, birds, fruit, household items, tools, and vehicles) and are the same items as those used to assess basic naming function in some studies of semantic dementia (4). For the specific naming task, there were 64 color photographs drawn from the same semantic categories. Colored pictures were required for this condition, rather than line drawings, to identify the target, specific concept uniquely. There is no evidence to suggest that the type of material affects performance in semantic dementia, and, if anything, one might expect colored pictures to improve performance on the specific level condition, thus working against the specificity effects found here (33). For these specific-level items the participants were asked to provide a specific-level name (i.e., swan, poodle, mini, hovercraft). In pilot tests, these items had >95% name agreement at this specific level. For the number naming task, participants provided English names for six-digit numbers (e.g., 316,565, "three hundred and sixteen thousand five hundred and sixty-five"). In pilot studies we had found that these longer numbers provided longer naming latencies that matched the typical basic-level naming speeds. Each group of items was split into two sets matched for name frequency and age of acquisition, one set being used in the baseline/no-TMS condition and the other immediately after the rTMS (see *Design*). The two sets were counterbalanced across participants. A PC running E-Prime software (Psychology Software Tools) presented the stimuli and recorded the responses. The participants sat in front of a 15-inch monitor and were instructed to name the stimuli as quickly and accurately as possible. Participants performed all three naming tasks in each experimental session. The order of the tasks was counterbalanced across subjects. There were eight practice trials for each stimulus set followed by 32 experimental trials in a random order. A fixation point appeared on the screen to signal the start of each trial. The participant then pressed a space bar to display the stimulus to be named. Stimuli were presented until the response was given and were followed by a blank screen interval of 500 ms. Verbal responses were recorded by using a microphone placed in front of each participant. The latency of each response was recorded by the computer, and the accuracy was checked offline by listening to audio recordings. Response times that did not fall within 2 SD of the mean for each participant in each condition were discarded. This resulted in the removal of ≈3.7% of all responses. One participant made a large number of errors and was excluded from the analysis.

Judgment tasks. The synonym judgment task was based on a neuropsychological assessment that we have developed to test verbal comprehension in SD and other aphasic patient groups. The 96 trials from the clinical test were augmented with additional trials to provide enough trials for the TMS and no-TMS versions. The final experiment includes two versions containing 72 trials each (144 in total), matched for the imageability and frequency of the words. 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 judgment 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 judgment times were typically slightly slower and less accurate than the synonym judgment tasks (see *Results*). Accordingly, any specific effects of temporal pole rTMS on synonym judgment could not be due to task difficulty.

A PC running E-Prime software allowed the presentation of stimuli and recording of the responses. 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 six trials for each stimulus set. Experimental trials were presented in a random order in four blocks of 72 trials (two 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 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 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 min) the TMS was counterbalanced across participants to deconfound TMS and order effects.

rTMS Procedure. Focal magnetic stimulation was delivered by using a 70-mm figure-of-eight coil attached to a MagStim Rapid2 stimulator (Magstim). For every subject and in each session, motor threshold (MT) was determined before the experiment as a visible twitch in the relaxed contralateral abductor pollicis brevis muscle. Stimulation was set at 120% of MT corresponding to an average intensity of 67% ± 6.88 (mean ± SD) of maximum stimulator output for the participants in the naming study and 77 ± 6.88% for those in the matching experiment. Structural T1-weighted MRI scans were obtained for each subject to guide the positioning of the TMS coil. Scalp position was coregistered with the underlying cortical surface for each individual by using an Ascension minibird magnetic tracking system and MRIreg software (www.mricro.com/mrireg.html). Eight fiducial markers (oil capsules attached to nasion, vertex, inion, tip of the nose, left/right mastoids, and left/right tragus during scanning) were used during the coregistration process. The ATL site was defined as the region 10 mm posterior from the tip of the left temporal

pole 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 average MNI coordinates for the ATL in standard space were (−53, 4, −32). At this site the scalp-to-cortex distance can be greater than for other cortical regions (including the hand area), and rTMS effects may be somewhat weaker as a consequence (although we have found that this distance varies considerably from individual to individual). The coil was held securely over the site to be stimulated and oriented such that the maximal induced current flowed approximately in the anterolateral direction along the middle temporal gyrus. Particular care was taken in the placing of the coil because TMS over ATL is more uncomfortable than over occipital or parietal areas. Participants received TMS stimulation for 10 min (1 Hz for 600 s at 120% MT).

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