The Timing of Anterior Temporal Lobe Involvement in Semantic Processing

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Abstract

■ Despite indications that regions within the anterior temporal lobe (ATL) might make a crucial contribution to pan-modal semantic representation, to date there have been no investigations of when during semantic processing the ATL plays a critical role. To test the timing of the ATL involvement in semantic processing, we studied the effect of double-pulse TMS on behavioral responses in semantic and difficulty-matched control tasks. Chronometric TMS was delivered over the left ATL (10 mm from the tip of the temporal pole along the middle temporal gyrus). During each trial, two pulses of TMS (40 msec apart) were delivered either at baseline (before stimulus presentation) or at one of the experimental time points 100, 250, 400, and 800 msec poststimulus onset. A significant disruption to performance was identified from 400 msec on the semantic task but not on the control assessment. Our results not only reinforce the key role of the left ATL in semantic representation but also indicate that its contribution is especially important around 400 msec poststimulus onset. Together, these facts suggest that the ATL may be one of the neural sources of the N400 ERP component. ■

INTRODUCTION

The anterior temporal lobe (ATL) appears to make a critical contribution to pan-modal semantic representation (Lambon Ralph, 2014; Lambon Ralph, Sage, Jones, & Mayberry, 2010; Patterson, Nestor, & Rogers, 2007), but little is known about the timing within this area. Neuropsychology, functional neuroimaging, and repetitive TMS experiments have identified a three-part network responsible for multimodal semantic representation and control, including the pFC, temporoparietal region, and bilateral ATL (Noonan, Jefferies, Visser, & Lambon Ralph, 2013; Visser, Jefferies, Embleton, & Lambon Ralph, 2012; Visser & Lambon Ralph, 2011; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011; Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Hoffman, Jefferies, & Lambon Ralph, 2010; Binder, Desai, Graves, & Conant, 2009; Pobric, Jefferies, & Lambon Ralph, 2007; Jefferies & Lambon Ralph, 2006; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). In contrast, the temporal dynamics of processing within the ATL have not been studied comprehensively. The temporal resolution of fMRI studies is poor, and although electrophysiological techniques have good temporal resolution, spatial resolution is sacrificed (Walsh & Cowey, 2000). A long history of EEG and MEG studies have related semantic processing across a variety of modalities to a negative ERP, the N400, found 250 to 550 msec after stimulus onset (Kutas & Federmeier, 2011b). Although somewhat inconsistent, attempts to localize the N400 have identified a number of sources within the semantic network, including areas in the temporal lobe (Kutas & Federmeier, 2011b; Helenius, Salmelin, Service, & Connolly, 1998; McCarthy, Nobre, Bentin, & Spencer, 1995). Beyond N400-focused studies, one MEG investigation showed converging auditory-related and visually related activity for a semantic judgment task within the ATL around 400 msec (Marinkovic et al., 2003). However, other studies have suggested much earlier semantic influences in reading and visual object recognition (Liu, Agam, Madsen, & Kreiman, 2009; Pulvermuller, Shtyrov, & Hauk, 2009; Bar et al., 2006; Halgren et al., 2002). Finally, a recent MEG investigation found that these differential timing effects may be related to the precision of semantic activation required, with earlier (120 msec) synchronization between anterior and posterior temporal regions for domain-level picture–name verification and later (260 msec) for basic level decisions (Clarke, Taylor, & Tyler, 2011).

In contrast to electrophysiological approaches (where data are correlational and therefore could be epiphenomenal), TMS assesses the necessity of a specific brain area for a task (Silvanto & Pascual-Leone, 2012; Sandrini, Umilta, & Rusconi, 2011b). This may be performed offline (in a rest period before the task) or online (during processing within a trial; Sandrini, Umilta, & Rusconi, 2011a; Pascual-Leone, Walsh, & Rothwell, 2000). Although the effects of online TMS are more subtle, they allow increased temporal specificity (Walsh & Cowey, 2000). One form of online TMS involves varying the time at which the pulse is delivered during the trial. As such, chronometric TMS (cTMS) assesses when neural activity within a specific brain area is critical for a task (Silvanto & Pascual-Leone, 2012; Sandrini

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et al., 2011b). Thus, the time at which there is a direct relationship between the activity of a specific region and a particular behavior may be identified (Silvanto & Pascual-Leone, 2012; Duncan, Pattamadilok, & Devlin, 2010). Concurrent imaging suggests that the disruption caused by a TMS pulse has an effect on activity lasting around 10–30 msec (Walsh & Cowey, 2000; Ilmoniemi et al., 1997). Similarly, the temporal specificity of cTMS is considered to be around 10–20 msec (Walsh & Cowey, 2000). This specificity has allowed detection of behavioral effects in time windows separated on the order of 10 msec. This feature of cTMS allows processing to be tracked in detail over time, either within one area or in different regions (Schuhmann, Schiller, Goebel, & Sack, 2012; Pitcher, Walsh, Yovel, & Duchaine, 2007; Jahanshahi & Dirnberger, 1999; Schulter, Rushworth, Mills, & Passingham, 1999; Terao et al., 1998).

This study investigated the timing of ATL involvement in semantic processing by applying TMS in a chronometric fashion. Double-pulse TMS was applied to the left ATL during a synonym judgment task and a nonsemantic control task (to assess for any nonspecific effects of ATL cTMS and to test if the cTMS effect is specific to semantic processing). This allowed identification of the time at which the ATL is crucial for semantic processing, hypothesized to be around 400 msec from stimulus onset. The ATL may also be active at other time points, for instance, by contributing to early top–down processing, but it is unclear whether this activation is vital for semantic processing.

METHODS

Participants

Fifteen healthy, native, English-speaking volunteers with normal or corrected-to-normal vision (seven women; mean age = 24.39 years, SD = 5.98 years) completed the experiment, which was approved by the local ethics board.

Materials

The synonym judgment task was adapted from previous ATL offline rTMS, neuropsychological, and fMRI studies (Lambon Ralph, Ehsan, Baker, & Rogers, 2012; Binney et al., 2010; Jefferies, Patterson, Jones, & Lambon Ralph, 2009; Pobric et al., 2007). This paradigm has proved to be a sensitive probe of semantic processing and has generated convergent cross-methodology evidence for the selective role of the ATL in semantic processing. These studies have not provided information, however, about the time course of this ATL semantic computation (the aim of the current study). As dual-pulse TMS has a small effect size, we picked a task known to be sensitive to semantic impairment and tried to maximize the number of trials per condition. The TMS task was developed in a series of steps to meet these design goals but to maintain

a minimal level of accuracy and thus relatively stable item RTs. In the first step, we selected 300 low-imageability (target words mean imageability = 265.95, SD = 59.30, using Bird, Franklin, & Howard's, 2001, ratings) and low-frequency (target words mean CELEX frequency = 9.85, SD = 5.35) words because past studies have shown them to be more sensitive to ATL rTMS, to the mild semantic impairment in patients with unilateral ATL resection, and to lead to poorer performance in SD patients (Hoffman, Jones, & Ralph, 2013; Lambon Ralph et al., 2012; Hoffman & Lambon Ralph, 2011; Jefferies et al., 2009; Lambon Ralph, Pobric, & Jefferies, 2009; Pobric, Lambon Ralph, & Jefferies, 2009). In the second step, we screened these items in a behavioral pilot of eight postgraduate students and staff (six women; mean age = 27 years). Only items that reached 75% accuracy were selected for further consideration, as is commonly performed in psycholinguistic studies (e.g., Gibson, Piantadosi, & Fedorenko, 2011; Aoshima, Phillips, & Weinberg, 2004; Gibson & Warren, 2004). As a result, each task contained 200 experimental and 55 practice trials. A third and final screening of the items was necessary: The TMS experiment employed predominantly undergraduate students (seven women; mean age = 24.39 years) who displayed a different speed–accuracy trade off on the two tasks (they were around 10% faster on the synonym task yet less accurate than the participants in the second item screening step). Accordingly, the least accurate trials were again screened at the 75% accuracy level to remove the most errorful items and to maintain a low level of noise within the associated RTs. Seventeen items in the synonym judgment task and 23 in the control judgment task had a mean accuracy below 75%. These items were removed from the analyses.

Semantic Task

In each semantic trial, participants were presented with three words: a probe (e.g., rhythm), a target synonym (e.g., cadence), and an unrelated foil (e.g., network). Participants were asked to select which word was most related in meaning to the probe. The two options were matched within trials for frequency (foil mean 10.01, SD = 11.15, $t(199)$ = −0.22, p > .05), imageability (foil mean 268.78, SD = 58.00, $t(199)$ = −1.51, p > .05), and part of speech. The RT and accuracy was examined in a pilot study (mean RT = 1265.4 msec, mean accuracy = 94.4%).

Intertask and Intratask Controls

The number judgment task was designed to match the synonym test in overall difficulty (RTs and accuracy: pilot study, mean RT = 1295.38, mean accuracy = 96.2%). Participants were asked to choose which three-digit number was closest to the probe in terms of numerical value (e.g., probe, 391; target, 379; foil, 377). This intertask

comparison provides, therefore, an important assessment for the selectivity of semantic processing in the ATL and also for any nonspecific effects of ATL cTMS. Following previous rTMS examinations of ATL function (e.g., Chiou, Sowman, Etchell, & Rich, 2013; Pobric et al., 2007), we expected a slowing of semantic decision times but no effect on the control task—which would rule out any alternative explanation of the semantic data in terms of nonspecific effects of ATL cTMS. In addition, a further potential advantage of cTMS over offline rTMS is that cTMS can provide an "intratask control" if decision times are slowed at some but not all of the probed time points (e.g., Duncan et al., 2010). As noted above, we hypothesized that cTMS might have its greatest effect on the semantic task around 400 msec poststimulus presentation, but not at its onset. If this timing pattern was coupled with no effect of TMS on the control task at any time point, then the intertask and intratask data would provide evidence for both task and time selectivity of semantic processing in the ATL.

Procedure

A PC running ePrime (Psychology Software Tools, Inc., Pittsburgh, PA) was used to present the items and record participant's responses. The participants completed two sessions (one for each task) at least 1 week apart. The order of sessions was counterbalanced across participants.

The order of trials was randomized. At the start of every trial, a fixation point was presented in the middle of the screen for 500 msec. Then the target and foil

choices appeared at the top of the screen and remained for 2500 msec. These items were replaced by a fixation cross at the bottom of the screen, which remained for 200 msec before the probe item appeared in its place. The target and foil item returned at the same time. All three items remained on screen for 2500 msec or until the participant's button-press response (see Figure 1). They were instructed to respond as quickly and accurately as possible. Displaying the foil and target before the probe allowed us to measure RT and to compute stimulation times against a single stimulus event (presentation of the probe item) rather than the complexities involved in timing from dual presentation of the target and foil items.

Design

The experiment employed a 2 × 5 repeated-measures design with Task (semantic vs. control) and TMS time (−40 msec vs. 100 msec vs. 250 msec vs. 400 msec vs. 800 msec) as the within-participant factors. The −40 msec time point was employed as a baseline. This is superior to comparison against a no-TMS condition, because TMS can produce generalized alerting effects (Pobric et al., 2007; Dräger, Breitenstein, Helmke, Kamping, & Knecht, 2004). Interleaving trials without TMS stimulation has also been shown to affect the online TMS results and our own pilot study found slowing in the trials immediately after no TMS trials, perhaps reflecting increased attention to the stimulation following its absence (Kapoula, Yang, Coubard, Daunys, & Orssaud, 2005). Accordingly, we

Figure 1. The structure and timing of a trial. In both tasks, a target and a foil item appeared after a fixation cross. Participants had time to read these items before presentation of the probe item in place of a fixation cross. The participants were then required to indicate which item was closer numerically or semantically.
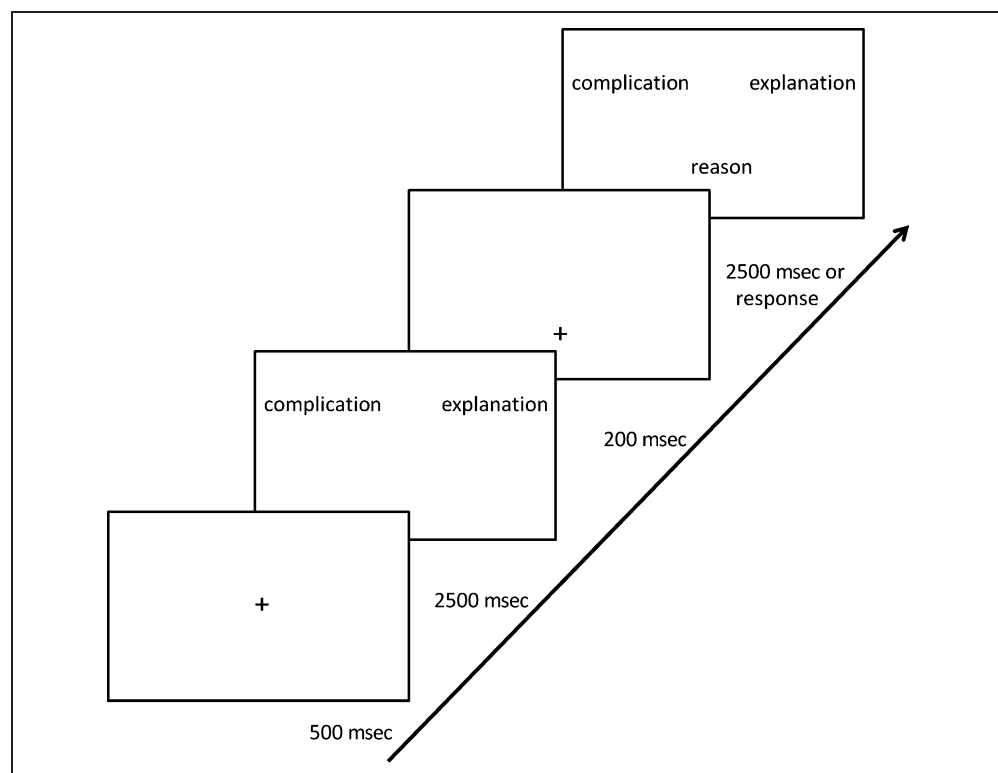
adopted two types of control/baseline: (a) comparison to stimulation at −40 msec when semantic processing of the probe item had not yet started and (b) an RT-matched nonsemantic control task used to detect potential nonsemantic variation of decision times after stimulation at different SOAs. In both sessions, participants completed a practice of 55 trials. They then completed 200 trials with TMS delivered at five different time points. These trials were split into blocks of 40, allowing participants to take a break in between.

Stimulation Parameters

TMS was delivered using a Magstim Rapid2 stimulator (Magstim Co., Whitland, UK) and a figure-of-eight coil with a diameter of 50 mm. Stimulation was performed at 100% of the individual's motor threshold, measured before the start of each session. The resting motor threshold of the relaxed contralateral abductor pollicis brevis muscle was measured as the lowest stimulation intensity able to cause a visible twitch in the muscle 5 out of 10 times (Sandrini et al., 2011b). Motor thresholds ranged from 40% to 66% of stimulator output (mean = 57.2, SD = 7.06).

Double-pulse TMS was used as the effects of two pulses summate while maintaining temporal specificity (Pitcher et al., 2007). This inhibitory effect has been demonstrated in a variety of domains including language processing (Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012; Duncan et al., 2010; O'Shea, Johansen-Berg, Trief, Gobel, & Rushworth, 2007; Pitcher et al., 2007; Juan & Walsh, 2003). Two TMS pulses were delivered 40 msec apart in each trial. This gap is the smallest possible with the TMS equipment used and has been consistently employed in double pulse studies (Sliwinska et al., 2012; O'Shea et al., 2007; Pitcher et al., 2007; Juan & Walsh, 2003). The two pulses were applied at −40 and 0 msec, 100 and 140 msec, 250 and 290 msec, 400 and 440 msec, and 800 and 840 msec following presentation of the probe number or word. Participants received stimulation in every trial, but the stimulation time was randomized. These stimulation times were designed to sample a full range of potentially important times at which crucial semantic processing might occur in the ATL, including the hypothesized time of 400 msec as well as earlier and later time points.

Selection of TMS Site

A Phillips MR Achieva scanner (Phillips Electronics, Amsterdam, The Netherlands) was used to acquire high-resolution T1-weighted anatomical images of each participant. The scan had an in-plane resolution of 1 mm with a slice thickness of 1.8 mm. The acquisition matrix was 256 × 256 voxels. Full head coverage was maintained, causing the number of slices acquired to vary depending on head size.

An Ascension Minibird magnetic tracking system (Ascension Technology Co., Burlington, VT) was used to coregister the participant's scalp and T1-weighted MRI scan on MRIreg (www.MRIcro.com/mrireg.html). The individual's ATL coordinates were determined by measuring 10 mm posterior along the middle temporal gyrus from the tip of the left temporal pole. The average MNI coordinates were [−50, 12, −29].

Every effort was taken to minimize the potential discomfort of stimulating the ATL. Following the procedures developed in our previous studies (Pobric, Jefferies, & Lambon Ralph, 2010a; Pobric et al., 2007), coil orientation was manipulated for maximum comfort and stimulus intensity was reduced if the participant considered the stimulation unpleasant. As noted above, nonspecific effects of online TMS (such as muscle twitches) on RTs were evaluated using the difficulty-matched nonsemantic control task as well as intratask comparisons (different time points during the semantic task).

Analyses

A composite RT–accuracy measure was used as the primary indicator of overall performance, because it allows for speed–accuracy trade-off variation across participants. The measure is commonly used in experimental psychology for this reason and is also useful in TMS studies where, across participants, the effects of TMS can be found in RTs, errors, or both (Cattaneo, Vecchi, Pascual-Leone, & Silvanto, 2009; Chambers, Stokes, & Mattingley, 2004; Townsend & Ashby, 1983). Following the standard method, the composite measure was computed as RT/accuracy (Townsend & Ashby, 1983). For each participant and each time point, trials with RTs more than 2 SDs from the mean were considered outliers and removed, causing a loss of 4.42% of the remaining semantic and 4.4% of the control trials.

The effects of double-pulse TMS at different time points on the composite performance was assessed using a 2 × 5 within-subject ANOVA with the repeated-measures factors Task (synonym judgment, number judgment) and TMS time (−40, 100, 250, 400, 800 msec). To assess the time points at which there was a greater effect of TMS on the semantic task, the ANOVA was repeated for two subsets of time points. The change in performance caused by TMS at time points implicated in these ANOVAs was computed by subtracting the individual's mean composite score at these time points from their mean composite score at the baseline time point on the each task. This allowed comparison of the effect of TMS at each time point on the two different tasks.

RESULTS

The results for the two tasks at each time point are shown in Figure 2, with a clear effect of cTMS arising

Figure 2. Composite score (RT/accuracy) for the semantic and control tasks at each different TMS time point. Error bars denote *SEM*, corrected for a within-participant design (Loftus & Masson, 1994). A significant TMS effect was found for the later time points (denoted by the asterisk). A borderline, weak effect was detected at 250 msec (see main text).
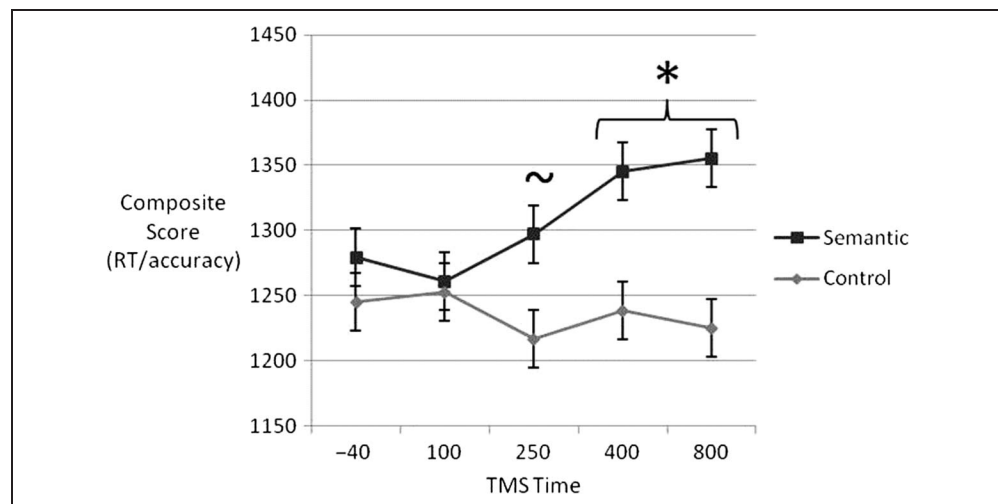
for the semantic task but no effect at any time point for the control task. A 2 (Task; control vs. semantic) × 5 (Stimulation time point; −40 vs. 100 vs. 250 vs. 400 vs. 800 msec) repeated-measures ANOVA found no significant main effects, but, crucially, there was an interaction of Task and TMS time point, $F(4, 56) = 2.6$, $p = .046$, partial $\eta^2 = .156$. The nature of this TMS interaction was confirmed in the following way. As expected, given the pilot data and careful RT matching of the tasks for general difficulty, performance was not significantly different between the two tasks at the −40 msec baseline time point, $t(14) = −.632$, $p = .538$, two-tailed; thus, this time point provided a suitable baseline reference to compare changes in performance across the other time points. Accordingly, the relative effect of cTMS at each time point was extracted by subtracting the baseline (−40 msec) composite score from the composite score at each experimental time point. The two tasks were then compared directly by computing direction-specific, one-tailed t tests as we expected ATL TMS to slow semantic decision times, as found in numerous previous ATL offline rTMS studies (e.g., Chiou et al., 2013; Pobric et al., 2007). As is clear from Figure 2, this analysis confirmed that there was significant slowing of the semantic over control task at 400 msec, $t(14) = −2.101$, $p = .027$, and 800 msec, $t(14) = −2.038$, $p = .030$. The difference at 250 msec was of borderline significance ($p = .15$).

There were no significant effects at any of the other time points ($p > .05$).

A second additional analysis confirmed these same results. We used an interaction contrast to confirm the significant effects of cTMS at 400 and 800 msec on the semantic task alone. Specifically, we averaged the data across these two time points for each task and contrasted them against the combined data for the earlier time points. Again, following the pattern shown in Figure 2, there was no change in performance on the control task between the earlier and later time points, $t(14) = .224$, $p = .826$, whereas there was a significant slowing for the semantic task, $t(14) = 9.536$, $p < .001$. We also formally compared the early-to-late changes in performance across the two tasks and confirmed that the early-to-late slowing on the semantic task was significantly greater than the null effect on the control task, $t(14) = 4.891$, $p < .001$.

Accuracy and RT scores were also analyzed separately (see Table 1). Accuracy was relatively stable across conditions and tasks. The ANOVA on these data demonstrated no significant results, although numerically the greatest TMS effects were apparent at the 400 and 800 msec time points in the semantic task. RT changes mirrored those in the composite score, and the ANOVA on these data confirmed the same interaction between Task and TMS

Table 1. Mean RT (msec) and Accuracy per TMS Time Point

TMS Time (msec)	Semantic Task		Control Task	
	RT (SD)	*Accuracy (SD)*	*RT (SD)*	*Accuracy (SD)*
−40	1177.31 (231.58)	.924 (.06)	1149.58 (297.16)	.922 (.05)
100	1150.57 (261.07)	.919 (.08)	1141.11 (288.99)	.911 (.05)
250	1178.56 (310.07)	.907 (.04)	1108.46 (292.72)	.906 (.06)
400	1206.56 (291.9)	.895 (.08)	1125.34 (327.71)	.912 (.08)
800	1234.15 (310.09)	.917 (.05)	1145.72 (303.90)	.939 (.04)

time, $F(4, 56) = 2.556$, $p = .049$, partial $\eta^2 = .154$. We explored this interaction in the same way as described above for the composite score. The same pattern emerged, with a significant slowing in the semantic compared to control task at 400 msec, $t(14) = -2.694$, $p = .009$, and 800 msec, $t(14) = -2.109$, $p = .026$. As before, the TMS effect at these time points was not significantly different to the -40 msec baseline for the control task, $t(14) = -.127$, $p = .901$, but was for the semantic task, $t(14) = -2.50$, $p = .025$. Again, this difference between the two tasks was significant, $t(14) = 2.528$, $p = .024$.

DISCUSSION

cTMS was used to elucidate the time at which the left ATL is crucial for semantic processing. TMS had a significant effect on semantic performance at 400 and 800 msec poststimulus onset. No significant effects of TMS were observed at any point during the control task. These results add to the convergent evidence for a critical role of the ATL in semantic processing (from neuropsychological, offline TMS, and neuroimaging studies: Visser et al., 2012; Visser & Lambon Ralph, 2011; Binney et al., 2010; Patterson et al., 2007; Pobric et al., 2007) and reveal the temporal dynamics of this processing for the first time.

MEG studies demonstrate two stages of processing in semantic tasks: early processing within sensory areas and then a large degree of interactivity between higher-order pan-modal areas (Marinkovic et al., 2003; Halgren et al., 2002; Dale et al., 2000). A translational phase between modality-specific and pan-modal processing is thought to start around 230 msec poststimulus presentation (Marinkovic et al., 2003). ATL involvement has been identified within the second pan-modal stage, peaking around 400 msec (Shimotake et al., 2014; Marinkovic et al., 2003; Halgren et al., 2002). The current study not only provides convergent evidence for these hypotheses but goes further to demonstrate that ATL activity at this time point is critical for semantic processing, which neuroimaging studies alone cannot establish. Although this has only been demonstrated here in a single modality using visually presented abstract words, the evidence of a more general necessity from rTMS and the demonstration of a multimodal processing stage support the likelihood that the critical role of the ATL occurs at a similar time for different modalities. Theories that limit the role of the ATL to social entities (e.g., Ross & Olson, 2010; Olson, Ploaker, & Ezzyat, 2007; Moll, Zahn, de Oliveira-Souza, Krueger, & Grafman, 2005), unique entities (e.g., Tranel, 2009), or combinatorial processes (Lau, Phillips, & Poeppel, 2008; Hickok & Poeppel, 2007) cannot easily explain the current and prior rTMS studies that used a range of stimuli including single basic-level, nonsocial concepts and found significant effects of TMS in all cases (see Lambon Ralph, 2014, for a more detailed review and discussion).

Our results indicate that there was a contribution from the left ATL to semantic processing (as probed by synonym judgements), which began to emerge at 250 msec and became statistically reliable from 400 msec after stimulus presentation. This fits the timing of the N400 in electrophysiological studies, suggesting the ATL as one potential source. Source localization of the EEG signal in previous studies has generated conflicting results about the N400 source, although a number of studies have implicated a distributed frontotemporal network (Kutas & Federmeier, 2011b; Lau et al., 2008; Van Petten & Luka, 2006). In addition, intracortical recordings have localized an N400-like ERP to areas including anterior fusiform gyrus and the temporal pole (McCarthy et al., 1995; Nobre & McCarthy, 1995; Halgren, Baudena, Heit, Clarke, & Marinkovic, 1994; Nobre, Allison, & McCarthy, 1994), and MEG studies indicate a pan-modal role for the ATL at this time point as well (Maess, Herrmann, Hahne, Nakamura, & Friederici, 2006; Marinkovic et al., 2003; Halgren et al., 2002). Finally, damage to left or right ATL can result in a loss of the N400 (Kotz, Opitz, & Friederici, 2007).

One interpretation of the N400 is that it reflects semantic access regardless of input modality (Kutas & Federmeier, 2011b; Kutas & Federmeier, 2000). This implies that the areas involved are responsible for pan-modal processing (Kutas & Federmeier, 2011b; Holcomb & Anderson, 1993). Within the hub-and-spoke semantic model, the ATL hub is responsible for pan-modal representation, whereas the "spokes" represent modality-specific information (Pobric, Jefferies, & Lambon Ralph, 2010b; Patterson et al., 2007). Thus, the modality-invariant processing within the ATL could be reflected in the N400, a notion consistent with the current cTMS findings.

Instead of viewing the N400 as representing semantic processing per se, some researchers have suggested that it is an index of violations of expectation, reflecting a process whereby words or other constituent parts are integrated into a context (Brown & Hagoort, 1993; Kutas & Hillyard, 1980). This violation requires semantic and lexical access, however, and so it is unclear that these explanations are mutually exclusive. The left ATL may be one of the N400 sources responsible for access and integration of pan-modal semantic representations. To assess whether the ATL is a source of the N400, future studies could assess the effect of ATL TMS in eradicating the N400 component. The left ATL seems to remain involved in the semantic task at 800 msec after stimulus presentation. This extends beyond the time of the N400, although studies of the N400 typically use simpler stimuli and single items (for a review, see Kutas & Federmeier, 2011a). This longer involvement of the left ATL in semantic processing might reflect continued semantic processing of the items and comparison between them.

In keeping with most TMS explorations of higher cognition, we observed an effect on RT and the combined efficiency measure, rather than on accuracy alone (e.g., Sliwinska et al., 2012; Ishibashi, Lambon Ralph, Saito, &

Pobric, 2011; Duncan et al., 2010; Hoffman et al., 2010; Stoeckel, Gough, Watkins, & Devlin, 2009; Gough, Nobre, & Devlin, 2005; Dräger et al., 2004; Devlin, Matthews, & Rushworth, 2003). Two possible interpretations of this outcome are possible. One explanation is that double-pulse TMS does not stop processing in the target region but instead "injects noise" into the local computation undertaken by that area, resulting in inefficient rather than deficient processing. The second is that TMS might halt local computation, but this is transient in nature and limited in coverage (e.g., like a small lesion in some neuro-psychological patients—which can generate changes in RTs rather than accuracy). The second possibility is consistent with the facts that TMS disruption is transient (around 10–20 msec) and relatively focal (around 20 mm). The precise mechanism by which TMS affects behavior is not well understood. Both hypotheses have been proposed, before; that is, TMS might inhibit activity (the traditional "virtual lesion" view) or inject noise into the system (Miniussi, Ruzzoli, & Walsh, n.d.; Sandrini et al., 2011a; Harris, Clifford, & Miniussi, 2008; Walsh & Cowey, 2000). In this context, it is perhaps worth noting that even the effect resulting from partial removal of neural tissue can be considered in both ways: for example, partial removal of units or connections in computational models of semantic memory generates a combination of reduced flow of activation and noisy processing (e.g., Schapiro, McClelland, Welbourne, Rogers, & Lambon Ralph, 2013; Lambon Ralph, Lowe, & Rogers, 2007). Even if one conceives dual-pulse TMS as injecting transient noise into local processing, then the main conclusions from this study hold: namely, the left ATL is directly implicated in semantic cognition and its involvement (at least in verbal tasks such as synonym judgment) is maximally important 400 msec after stimulus onset.

Finally, we note that, although we only obtained a borderline, minimal effect of cTMS at 250 msec, some neuroimaging studies have implicated this and earlier time points. Superordinate semantic differences have been shown in the phase-locking of the ATL from 120 msec and in activity level from 170 msec (Clarke et al., 2011). Similarly, intracortical electrode recordings have shown category-sensitive responses in inferior anterior temporal areas less than 200 msec poststimulus presentation (Liu et al., 2009). There are at least three possible explanations. First, electrophysiological data reflect changes in activity level, whereas TMS might elucidate the time at which an area becomes necessary (Walsh & Cowey, 2000). Thus, it may be that the left ATL starts to become involved before 250 msec, but its contribution does not become crucial until around 400 msec. A second possibility is that the early activity may be critical in certain conditions, such as more general semantic (domain/category) distinctions than those probed in this cTMS study (Clarke et al., 2011) or in tasks using impoverished stimuli that may promote greater top–down processing (e.g., Bar et al., 2006). Finally, an alternative possibility is that there is an earlier critical

phase of ATL involvement but that this is much smaller and transient in nature, making it much harder to detect with cTMS (the borderline effect observed at 250 msec is consistent with this hypothesis).

Acknowledgments

REFERENCES

Aoshima, S., Phillips, C., & Weinberg, A. (2004). Processing filler-gap dependencies in a head-final language. *Journal of Memory and Language, 51,* 23–54.

Bar, M., Kassam, K. S., Ghuman, A. S., Boshyan, J., Schmidt, A. M., Dale, A. M., et al. (2006). Top–down facilitation of visual recognition. *Proceedings of the National Academy of Sciences, U.S.A., 103,* 449–454.

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex, 19,* 2767–2796.

Binney, R. J., Embleton, K. V., Jefferies, E., Parker, G. J. M., & Lambon Ralph, M. A. (2010). The ventral and inferolateral aspects of the anterior temporal lobe are crucial in semantic memory: Evidence from a novel direct comparison of distortion-corrected fMRI, rTMS, and semantic dementia. *Cerebral Cortex, 20,* 2728–2738.

Bird, H., Franklin, S., & Howard, D. (2001). Age of acquisition and imageability ratings for a large set of words, including verbs and function words. *Behavior Research Methods Instruments & Computers, 33,* 73–79.

Brown, C., & Hagoort, P. (1993). The processing nature of the N400—Evidence from masked priming. *Journal of Cognitive Neuroscience, 5,* 34–44.

Cattaneo, Z., Vecchi, T., Pascual-Leone, A., & Silvanto, J. (2009). Contrasting early visual cortical activation states causally involved in visual imagery and short-term memory. *European Journal of Neuroscience, 30,* 1393–1400.

Chambers, C. D., Stokes, M. G., & Mattingley, J. B. (2004). Modality-specific control of strategic spatial attention in parietal cortex. *Neuron, 44,* 925–930.

Chiou, R., Sowman, P. F., Etchell, A. C., & Rich, A. N. (2013). A conceptual lemon: Theta burst stimulation to the left anterior temporal lobe untangles object representation and its canonical color. *Journal of Cognitive Neuroscience, 26,* 1066–1074.

Clarke, A., Taylor, K. I., & Tyler, L. K. (2011). The evolution of meaning: Spatio-temporal dynamics of visual object recognition. *Journal of Cognitive Neuroscience, 23,* 1887–1899.

Dale, A. M., Liu, A. K., Fischl, B. R., Buckner, R. L., Belliveau, J. W., Lewine, J. D., et al. (2000). Dynamic statistical parametric mapping: Combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron, 26,* 55–67.

Devlin, J. T., Matthews, P. M., & Rushworth, M. F. S. (2003). Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and

transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 15,* 71–84.

Dräger, B., Breitenstein, C., Helmke, U., Kamping, S., & Knecht, S. (2004). Specific and nonspecific effects of transcranial magnetic stimulation on picture-word verification. *European Journal of Neuroscience, 20,* 1681–1687.

Duncan, K. J., Pattamadilok, C., & Devlin, J. T. (2010). Investigating occipito-temporal contributions to reading with TMS. *Journal of Cognitive Neuroscience, 22,* 739–750.

Gibson, E., Piantadosi, S., & Fedorenko, K. (2011). Using mechanical turk to obtain and analyze English acceptability judgments. *Language and Linguistics Compass, 5,* 509–524.

Gibson, E., & Warren, T. (2004). Reading-time evidence for intermediate linguistic structure in long-distance dependencies. *Syntax, 7,* 55–78.

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience, 25,* 8010–8016.

Halgren, E., Baudena, P., Heit, G., Clarke, M., & Marinkovic, K. (1994). Spatiotemporal stages in face and word-processing. 1. Depth recorded potentials in the human occipital and parietal lobes. *Journal of Physiology-Paris, 88,* 1–50.

Halgren, E., Dhond, R. P., Christensen, N., Van Petten, C., Marinkovic, K., Lewine, J. D., et al. (2002). N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. *Neuroimage, 17,* 1101–1116.

Harris, J. A., Clifford, C. W., & Miniussi, C. (2008). The functional effect of transcranial magnetic stimulation: Signal suppression or neural noise generation? *Journal of Cognitive Neuroscience, 20,* 734–740.

Helenius, P., Salmelin, R., Service, E., & Connolly, J. F. (1998). Distinct time courses of word and context comprehension in the left temporal cortex. *Brain, 121,* 1133–1142.

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience, 8,* 393–402.

Hoffman, P., Jefferies, E., & Lambon Ralph, M. A. (2010). Ventrolateral prefrontal cortex plays an executive regulation role in comprehension of abstract words: Convergent neuropsychological and repetitive TMS evidence. *Journal of Neuroscience, 30,* 15450–15456.

Hoffman, P., Jones, R. W., & Ralph, M. A. L. (2013). Be concrete to be comprehended: Consistent imageability effects in semantic dementia for nouns, verbs, synonyms and associates. *Cortex, 49,* 1206–1218.

Hoffman, P., & Lambon Ralph, M. A. (2011). Reverse concreteness effects are not a typical feature of semantic dementia: Evidence for the hub-and-spoke model of conceptual representation. *Cerebral Cortex, 21,* 2103–2112.

Holcomb, P. J., & Anderson, J. E. (1993). Cross-modal semantic priming—A time-course analysis using event-related brain potentials. *Language and Cognitive Processes, 8,* 379–411.

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., et al. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *NeuroReport, 8,* 3537–3540.

Ishibashi, R., Lambon Ralph, M. A., Saito, S., & Pobric, G. (2011). Different roles of lateral anterior temporal lobe and inferior parietal lobule in coding function and manipulation tool knowledge: Evidence from an rTMS study. *Neuropsychologia, 49,* 1128–1135.

Jahanshahi, M., & Dirnberger, G. (1999). The left dorsolateral prefrontal cortex and random generation of responses: Studies with transcranial magnetic stimulation. *Neuropsychologia, 37,* 181–190.

Jefferies, E., & Lambon Ralph, M. A. (2006). Semantic impairment in stroke aphasia versus semantic dementia: A case-series comparison. *Brain, 129,* 2132–2147.

Jefferies, E., Patterson, K., Jones, R. W., & Lambon Ralph, M. A. (2009). Comprehension of concrete and abstract words in semantic dementia. *Neuropsychology, 23,* 492–499.

Juan, C. H., & Walsh, V. (2003). Feedback to V1: A reverse hierarchy in vision. *Experimental Brain Research, 150,* 259–263.

Kapoula, Z., Yang, Q., Coubard, O., Daunys, G., & Orssaud, C. (2005). Contextual influence of TMS on the latency of saccades and vergence. *Neuroscience Letters, 376,* 87–92.

Kotz, S. A., Opitz, B., & Friederici, A. D. (2007). ERP effects of meaningful and non-meaningful sound processing in anterior temporal patients. *Restorative Neurology and Neuroscience, 25,* 273–284.

Kutas, M., & Federmeier, K. D. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Sciences, 4,* 463–470.

Kutas, M., & Federmeier, K. D. (2011a). Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). In S. T. Fiske, D. L. Schacter, & S. E. Taylor (Eds.), *Annual review of psychology* (Vol. 62, pp. 621–647). Palo Alto, CA: Annual Review, Inc.

Kutas, M., & Federmeier, K. D. (2011b). Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). *Annual Review of Psychology, 62,* 621–647.

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences—Brain potentials reflect semantic incongruity. *Science, 207,* 203–205.

Lambon Ralph, M. A. (2014). Neurocognitive insights on conceptual knowledge and its breakdown. *Royal Society Proceedings B, 369,* 20120392.

Lambon Ralph, M. A., Ehsan, S., Baker, G. A., & Rogers, T. T. (2012). Semantic memory is impaired in patients with unilateral anterior temporal lobe resection for temporal lobe epilepsy. *Brain, 135,* 242–258.

Lambon Ralph, M. A., Lowe, C., & Rogers, T. T. (2007). Neural basis of category-specific semantic deficits for living things: Evidence from semantic dementia, HSVE and a neural network model. *Brain, 130,* 1127–1137.

Lambon Ralph, M. A., Pobric, G., & Jefferies, E. (2009). Conceptual knowledge is underpinned by the temporal pole bilaterally: Convergent evidence from rTMS. *Cerebral Cortex, 19,* 832–838.

Lambon Ralph, M. A., Sage, K., Jones, R. W., & Mayberry, E. J. (2010). Coherent concepts are computed in the anterior temporal lobes. *Proceedings of the National Academy of Sciences, U.S.A., 107,* 2717–2722.

Lau, E. F., Phillips, C., & Poeppel, D. (2008). A cortical network for semantics: (De)constructing the N400. *Nature Reviews Neuroscience, 9,* 920–933.

Liu, H. S., Agam, Y., Madsen, J. R., & Kreiman, G. (2009). Timing, timing, timing: Fast decoding of object information from intracranial field potentials in human visual cortex. *Neuron, 62,* 281–290.

Loftus, G. R., & Masson, M. E. J. (1994). Using confidence intervals in within-subject designs. *Psychonomic Bulletin & Review, 1,* 476–490.

Maess, B., Herrmann, C. S., Hahne, A., Nakamura, A., & Friederici, A. D. (2006). Localizing the distributed language network responsible for the N400 measured by MEG during auditory sentence processing. *Brain Research, 1096,* 163–172.

Marinkovic, K., Dhond, R. P., Dale, A. M., Glessner, M., Carr, V., & Halgren, E. (2003). Spatiotemporal dynamics of modality-specific and supramodal word processing. *Neuron, 38,* 487–497.

McCarthy, G., Nobre, A. C., Bentin, S., & Spencer, D. D. (1995). Language-related field potentials in the anterior-medial temporal lobe. 1. Intracranial distribution and neural generators. *Journal of Neuroscience, 15,* 1080–1089.

Miniussi, C., Ruzzoli, M., & Walsh, V. (n.d.). The mechanism of transcranial magnetic stimulation in cognition. *Cortex, 46,* 128–130.

Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., & Grafman, J. (2005). The neural basis of human moral cognition. *Nature Reviews Neuroscience, 6,* 799–809.

Nobre, A. C., Allison, T., & McCarthy, G. (1994). Word recognition in the human inferior temporal lobe. *Nature, 372,* 260–263.

Nobre, A. C., & McCarthy, G. (1995). Language-related field potentials in the anterior-medial temporal-lobe. 2. Effects of word type and semantic priming. *Journal of Neuroscience, 15,* 1090–1098.

Noonan, K. A., Jefferies, E., Visser, M., & Lambon Ralph, M. A. (2013). Going beyond inferior prefrontal involvement in semantic control: Evidence for the additional contribution of dorsal angular gyrus and posterior middle temporal cortex. *Journal of Cognitive Neuroscience, 25,* 1824–1850.

Olson, I. R., Ploaker, A., & Ezzyat, Y. (2007). The enigmatic temporal pole: A review of findings on social and emotional processing. *Brain, 130,* 1718–1731.

O'Shea, J., Johansen-Berg, H., Trief, D., Gobel, S., & Rushworth, M. F. S. (2007). Functionally specific reorganisation in human premotor reorganization cortex. *Neuron, 54,* 479–490.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience—Virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology, 10,* 232–237.

Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience, 8,* 976–987.

Pitcher, D., Walsh, V., Yovel, G., & Duchaine, B. (2007). TMS evidence for the involvement of the right occipital face area in early face processing. *Current Biology, 17,* 1568–1573.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2007). Anterior temporal lobes mediate semantic representation: Mimicking semantic dementia by using rTMS in normal participants. *Proceedings of the National Academy of Sciences, U.S.A., 104,* 20137–20141.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2010a). Amodal semantic representations depend on both anterior temporal lobes: Evidence from repetitive transcranial magnetic stimulation. *Neuropsychologia, 48,* 1336–1342.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2010b). Category-specific versus category-general semantic impairment induced by transcranial magnetic stimulation. *Current Biology, 20,* 964–968.

Pobric, G., Lambon Ralph, M. A., & Jefferies, E. (2009). The role of the anterior temporal lobes in the comprehension of concrete and abstract words: rTMS evidence. *Cortex, 45,* 1104–1110.

Pulvermuller, F., Shtyrov, Y., & Hauk, O. (2009). Understanding in an instant: Neurophysiological evidence for mechanistic language circuits in the brain. *Brain and Language, 110,* 81–94.

Ross, L. A., & Olson, I. R. (2010). Social cognition and the anterior temporal lobes. *Neuroimage, 49,* 3452–3462.

Sandrini, M., Umilta, C., & Rusconi, E. (2011a). The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neuroscience and Biobehavioral Reviews, 35,* 516–536.

Sandrini, M., Umilta, C., & Rusconi, E. (2011b). The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neuroscience and Behavioural Reviews, 35,* 516–536.

Schapiro, A. C., McClelland, J. L., Welbourne, S. R., Rogers, T. T., & Lambon Ralph, M. A. (2013). Why bilateral damage is worse than unilateral damage to the brain. *Journal of Cognitive Neuroscience, 25,* 2107–2123.

Schuhmann, T., Schiller, N. O., Goebel, R., & Sack, A. T. (2012). Speaking of which: Dissecting the neurocognitive network of language production in picture naming. *Cerebral Cortex, 22,* 701–709.

Schulter, N. D., Rushworth, M. F., Mills, K. R., & Passingham, R. E. (1999). Signal-, set-, and movement-related activity in the human premotor cortex. *Neuropsychologia, 37,* 233–243.

Shimotake, A., Matsumoto, R., Ueno, T., Kunieda, T., Saito, S., Hoffman, P., et al. (2014) Direct exploration of the ventral anterior temporal lobe in semantic memory: Cortical stimulation and local field potential evidence from subdural grid electrodes. *Cerebral Cortex*. doi: 10.1093/cercor/bhu262.

Silvanto, J., & Pascual-Leone, A. (2012). Why the assessment of causality in brain-behavior relations requires brain stimulation. *Journal of Cognitive Neuroscience, 24,* 775–777.

Sliwinska, M. W., Khadilkar, M., Campbell-Ratcliffe, J., Quevenco, F., & Devlin, J. T. (2012). Early and sustained supramarginal gyrus contributions to phonological processing. *Frontiers in Psychology, 3,* 161.

Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *Cortex, 45,* 1091–1096.

Terao, Y., Fukuda, H., Ugawa, Y., Hikosaka, O., Hanajima, R., Furubayashi, T., et al. (1998). Visualisation of the information flow through human occulomotor cortical regions by transcranial magnetic stimulation. *Journal of Neurophysiology, 80,* 936–946.

Townsend, J. T., & Ashby, F. G. (1983). *Stochastic modelling of elementary psychological processes*. London: Cambridge University Press.

Tranel, D. (2009). The left temporal pole is important for retrieving words for unique concrete entities. *Aphasiology, 23,* 867–884.

Van Petten, C., & Luka, B. J. (2006). Neural localization of semantic context effects in electromagnetic and hemodynamic studies. *Brain and Language, 97,* 279–293.

Visser, M., Jefferies, E., Embleton, K. V., & Lambon Ralph, M. A. (2012). Both the middle temporal gyrus and the ventral anterior temporal area are crucial for multimodal semantic processing: Distortion-corrected fMRI evidence for a double gradient of information convergence in the temporal lobes. *Journal of Cognitive Neuroscience, 24,* 1766–1778.

Visser, M., & Lambon Ralph, M. A. (2011). Differential contributions of bilateral ventral anterior temporal lobe and left anterior superior temporal gyrus to semantic processes. *Journal of Cognitive Neuroscience, 23,* 3121–3131.

Wagner, A. D., Pare-Blagoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. *Neuron, 31,* 329–338.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience, 1,* 73–79.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., & Jefferies, E. (2011). The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. *Cerebral Cortex, 21,* 1066–1075.