Functional Representation of Living and Nonliving Domains across the Cerebral Hemispheres: A Combined Event-related Potential/Transcranial Magnetic Stimulation Study

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Abstract

■ Transcranial magnetic stimulation (TMS) over the left hemisphere has been shown to disrupt semantic processing but, to date, there has been no direct demonstration of the electrophysiological correlates of this interference. To gain insight into the neural basis of semantic systems, and in particular, study the temporal and functional organization of object categorization processing, we combined repetitive TMS (rTMS) and ERPs. Healthy volunteers performed a picture–word matching task in which Snodgrass drawings of natural (e.g., animal) and artifactual (e.g., tool) categories were associated with a word. When short trains of high-frequency rTMS were applied over Wernicke's area (in the region of the CP5 electrode) immediately before the stimulus onset, we observed delayed response times to artifactual items, and thus, an increased dissociation between natural and artifactual domains. This behavioral effect had a direct ERP correlate. In the response period, the stimuli from the natural domain elicited a significant larger late positivity complex than those from the artifactual domain. These differences were significant over the centro-parietal region of the right hemisphere. These findings demonstrate that rTMS interferes with postperceptual categorization processing of natural and artifactual stimuli that involve separate subsystems in distinct cortical areas. ■

INTRODUCTION

Category-specific recognition impairments have been widely reported in the neuropsychological literature over the past 30 years. Generally, these impairments have been interpreted as deficits in stored semantic knowledge (Caramazza & Shelton, 1998; Warrington & Shallice, 1984). Although many researchers have agreed that category-specific impairments can inform us about semantic memory, there are competing theoretical models that explain such deficits. Domain-specific theories (Caramazza & Mahon, 2003; Caramazza & Shelton, 1998) favor evolutionary pressure that yields specialized and functionally dissociable neural networks for processing different categories of objects (perceptually and functionally). On the other hand, sensory/functional theories (Humphreys & Forde, 2001; Martin, Wiggs, Ungerleider, & Haxby, 1996; Warrington & Shallice, 1984) argue that semantic knowledge is organized in two separate systems that are modality specific. Natural items depend more on visual information, whereas artifacts rely on

functional/associative information. Hence, it can be argued that semantic knowledge, associated with natural and artifactual (or living and nonliving) domains, is represented in separate subsystems with presumably different anatomical bases (Paz-Caballero, Cuetos, & Dobarro, 2006; Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Martin et al., 1996; Perani et al., 1995). The central idea behind correlated feature theories (Gerlach, Law, Gade, & Paulson, 2002; Moss & Tyler, 2000; Tyler, Moss, Durrant-Peatfield, & Levy, 2000; Moore & Price, 1999) states that conceptual features (object properties) are stored in a single semantic space in which natural objects have more shared features than artifacts. Biological function is correlated with shared properties for natural objects, whereas functional information is correlated with artifacts. Based on this, natural objects are more resistant to damage due to sharing more common features. Further evidence supporting the multiple systems account comes from fMRI, PET (Chao, Haxby, & Martin, 1999; Moore & Price, 1999; Grafton, Fadiga, Arbib, & Rizzolatti, 1997; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Martin et al., 1996; Perani et al., 1995), and ERPs (Paz-Caballero et al., 2006; Kiefer, 2001, 2005; Sim & Kiefer, 2005; Dehaene, 1995). Artifacts, such as tools, frequently activate brain areas involved in action

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representation (e.g., premotor regions, left middle temporal cortex, parietal cortex) more strongly than natural categories. In contrast, natural categories, such as animals, elicit relatively stronger activation in visual association areas of the occipito-temporal cortex. Moreover, it has been demonstrated that the representation of natural objects is more widely distributed in the two cerebral hemispheres, whereas the representation of artifactual items appears to be lateralized to the left hemisphere (Pilgrim, Moss, & Tyler, 2005; Chao, Weisberg, & Martin, 2002; Ilmberger, Rau, Noachtar, Arnold, & Winkler, 2002; Martin & Chao, 2001; Gainotti, 2000; Perani et al., 1999; Grabowski, Damasio, & Damasio, 1998; Grafton et al., 1997; Tranel, Damasio, & Damasio, 1997; Martin et al., 1996; Perani et al., 1995).

Recently, there have been successful efforts to combine TMS with simultaneous ERP recording to study the temporal and functional impact of TMS interference on cognitive processes (Taylor, Nobre, & Rushworth, 2007; Fuggetta, Pavone, Walsh, Kiss, & Eimer, 2006; Thut, Ives, Kampmann, Pastor, & Pascual-Leone, 2005). The value of this combination lies in the fact that the fine temporal resolution of EEG allows one to make an on-line measure of the effects of TMS at different stages of processing (e.g., sensory and postperceptual), within brain regions, which are anatomically remote from the area impaired by the TMS (Fuggetta et al., 2006). We therefore used this combination of methods to investigate the roles of Wernicke's, its homologue in the right hemisphere and a region of the occipital cortex in processing of visual stimuli from natural and artifactual categories in a picture–word matching task. We hypothesized that if the source of category-specific effects originates in postperceptual processing stages, by delivering TMS over centro-parietal areas, we should observe both an impairment of behavioral performance and a modulation of ERP related to semantic memory organization.

Previous TMS studies demonstrated that semantic processing can be temporarily impaired if magnetic pulses are delivered over Wernicke's area during a picture–word verification (Drager, Breitenstein, Helmke, Kamping, & Knecht, 2004; Knecht et al., 2002; Stewart, Meyer, Frith, & Rothwell, 2001; Flitman et al., 1998; Grafman et al., 1994). In line with the current TMS protocol, it was found that high-frequency repetitive TMS (rTMS) over Wernicke's area can induce impairments to semantic processing (Pobric, Mashal, Faust, & Lavidor, 2008; Devlin, Matthews, & Rushworth, 2003). To our knowledge, however, no study has assessed behavioral or electrophysiological effects of TMS on living/nonliving categorization.

In the present ERP/TMS study, we analyzed different stimulus-locked time windows corresponding to the four ERP components P1, N170, N400, and the P600 or late positive complex (LPC), which in previous studies have dissociated between natural and artifactual stimuli presented in the visual modality (Paz-Caballero et al.,

2006; Kiefer, 2001, 2005; Sim & Kiefer, 2005; Vanrullen & Thorpe, 2001). ERP effects related to visual perceptual processing are observed relatively early after stimulus presentation in the P1–N1 time windows (between 80 and 200 msec) at posterior electrode sites. Although not always investigated, the first perceptual activity (P1) seems to reflect more than simply low-level exogenous processing of features of visual stimuli determining the overall stimulus visibility such as luminance and contrast (Mangun & Hillyard, 1991). Rather, it indexes an early stage of nonspatial features of visual processing and appears sensitive to stimuli important to humans such as faces (Itier & Taylor, 2004). It is well established that the N1 component reflects visual perceptual processing and its amplitude is enhanced when attention is directed to visual stimuli (Kiefer, 2001; Mangun & Hillyard, 1991). Due to the greater perceptual similarity in natural items, we predicted a larger N170 to natural categories supporting the assumption of the perceptual account, that perceptual information plays a more important role in processing natural than artifactual categories (Lloyd-Jones & Humphreys, 1997).

Electrophysiological waveforms related to semantic processing are usually obtained in the N400 time window (between 200 and 500 msec) The N400 component was originally observed when subjects read visually presented sentences that ended with semantically incongruent words (Kutas & Hillyard, 1980). Kutas and Hillyard (1984) further showed that unpredictable sentence endings, and not only semantic incongruity, can also increase the N400 amplitude. Given what is known about category-specific semantic memory organization from neuropsychological and neuroimaging studies, artificial and natural categories should differentially modulate the N400 ERP component at different electrode sites. However, our participants were not asked to perform an explicit semantic categorization task, thus we did not expect a difference between the two categories for the N400 component.

The latest stage in the temporal dynamic of semantic processing includes a motor response stage, reflected in the late centro-parietal positivity named LPC occurring between 500 and 1000 msec after target onset, in which different types of information are integrated and reanalyzed (Hahne & Friederici, 2002). In a recent study with a categorization task, the amplitude of the P600 component was significantly larger for stimuli belonging to the natural than the artifactual domain (Paz-Caballero et al., 2006). Because the left hemisphere seems to be more involved in the processing of visually presented artifacts, and reflects processing of action-related knowledge of artifacts (Gerlach et al., 2002; Martin & Chao, 2001), an additional purpose of the present study was to test whether the comprehension of artifactual objects could be impaired by TMS over the left Wernicke's area. Furthermore, we expected selective modulation in the amplitude of the

LPC for natural/artifactual domains along with an increase in the RTs associated with artifactual categorical analyses.

METHODS

Subjects

Nine subjects assessed as right handed by the Edinburgh Handedness Inventory (Oldfield, 1971) with a mean score of 85.36%, monolingual, native English-speaking subjects (mean age [SD] = 26.57 (6.44) years; 6 men and 3 women) were found suitable for reliable ERP analysis. Originally, we recruited 12 subjects, however, the ERP recordings of three of them were discarded either due to excessive number of blinks, eye movements, or muscle activity that decreased the signal-to-noise ratio of the averaged ERP waveforms.

All subjects understood the information given about magnetic stimulation and EEG recording and gave written informed consent according to the Declaration of Helsinki. The experiment was approved by the UCL Research Ethics Committee.

Task

Semantic processing was assessed using a two-alternative forced-choice picture–word verification task (see Figure 1). On each trial, subjects were presented with a picture and a word underneath it. Their task was to look at the picture and judge, as quickly and accurately as possible, whether the word matched (congruent) or did not match (incongruent) the picture. The observers responded by pressing one of two keys on a keyboard corresponding to one of the two possible choices with index and middle fingers of the right hand.

Stimuli

Stimuli were presented at a resolution of 1024 × 768 pixels on a 17-in. monitor with a vertical refresh rate of 100 Hz. Subjects sat 57 cm from the screen and were restricted by a head and chin rest to minimize head movements. Stimuli, responses, and EEG/TMS triggering were generated and measured by E-Prime software running on a Pentium IV computer.

The stimuli consisted of 260 black-and-white line drawings taken from a standardized picture set (Snodgrass &

Figure 1. (A) The electrode montage and placement according to the International 10–20 System. Additional electrodes were placed at halfway between frontal and central sites (FC5, FC6), central and parietal sites (CP5, CP6), parietal and occipital sites (PO3, PO4, PO7, PO8). The gray shadow indexes the groups of bilateral pairs of electrodes selected for statistical analysis. TMS coil positions are also shown. (B) The temporal sequence of events in one trial of the picture–word matching task with an example of the congruent condition.
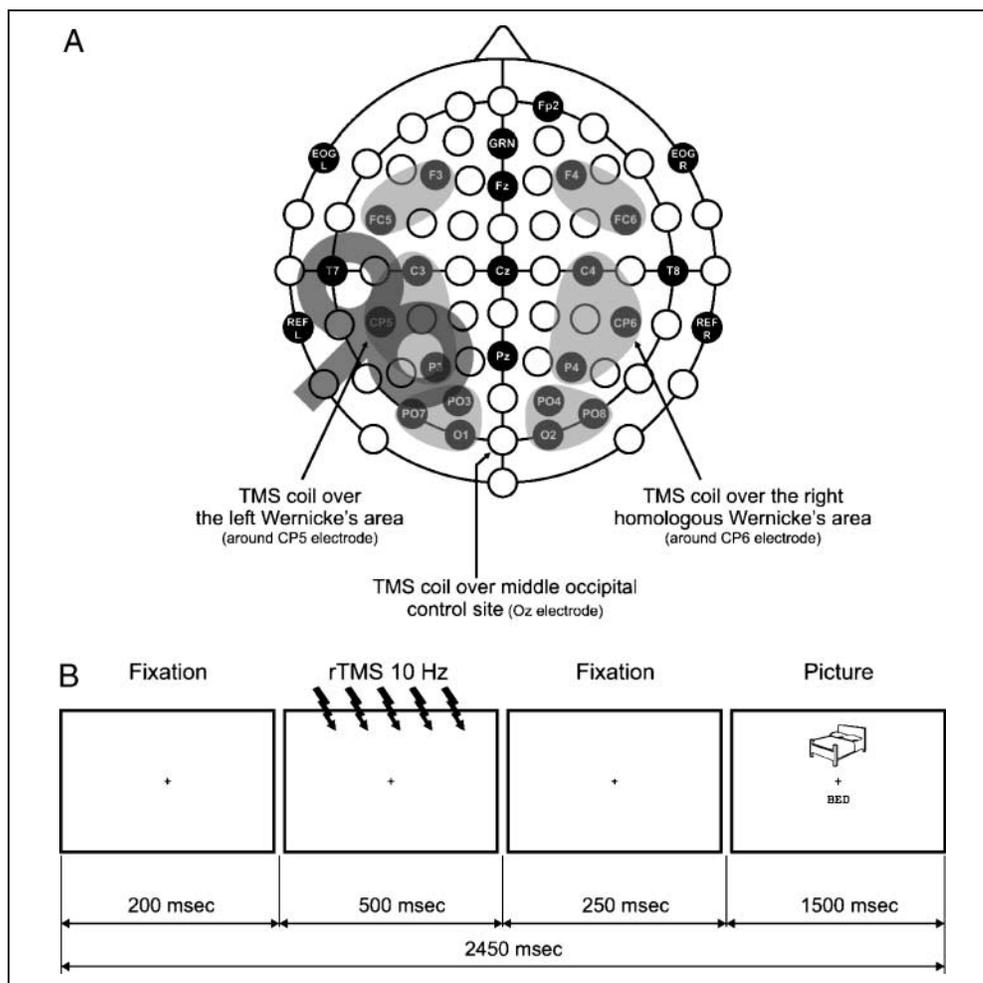
Vanderwart, 1980). Half of the drawings were of natural objects (animals, plants, fruits, and human body parts), and the other half were of artifactual, or man-made, objects (vehicles, tools, furniture, and musical instruments). These categories have been used frequently in previous studies (e.g., Paz-Caballero et al., 2006; Warrington & McCarthy, 1987). To quantify the effect of TMS on neural processing speed, linguistic tasks with homogeneous material and short trial durations are required (Knecht et al., 2002). The pictures were digitized and adjusted in size and presented together with the word in the center of the monitor against a white background. Each picture subtended, on average, 7.0° horizontally and 5.0° vertically.

Procedure

A small fixation mark was presented continuously at the center of the monitor. Each trial started with 200 msec of fixation, which was followed by a 500-msec train of rTMS. There was a short delay of 250 msec before a picture–word stimulus was shown for 1500 msec. The ISI was 2450 msec. Figure 1 illustrates the sequence of events for a single trial.

Each participant performed a single session, which consisted of 5 blocks of 96 trials each. The first block, which contained 96 different drawings from the following 4 testing blocks, was considered a practice exercise and was excluded from further analyses. Trails and testing block orders were randomized across subjects. In order to obtain reliable ERP waveforms, which require multiple trials (Luck, 2005), 33% of the drawings were repeated during the experiment. The repeated pictures were equally distributed across the four testing blocks.

Two independent variables were manipulated within each block (between trials): the category of the drawing of the target object (natural vs. artifactual) and the congruency of trials (matching, nonmatching). Thus, half of the trials belonging either to natural or artifactual picture–word object pairings were presented with congruent (matching) picture–word pairs; that is, the word was the agreed name of the drawing. The rest of the drawings were presented with incongruent (nonmatching) picture–word pairs. Stimuli were selected so that target objects from natural and artifactual categories did not differ between the four experimental blocks in typicality, name agreement, visual complexity, naming latency as well as in word length and in word frequency of the object names (Bates et al., 2003).

TMS Sites and Parameters

Wernicke's area and its homologue in the right hemisphere were localized for TMS using the Brainsight frameless stereotaxy system (Rouge Research, Montreal, Canada; www.rogue-research.com) to guide the coil to its optimal position. These two areas were targeted

because of their established role in receptive language tasks, and thus, their likely involvement in picture–word verification (Knecht et al., 2002). The precise activation pattern of these areas for this task in fMRI or PET studies is yet to be established. The stimulation site was identified on each subject's T1-weighted MRI scan and was then coregistered with scalp coordinates over which TMS was applied (see Figure 2). After normalization of the MRI images into the Montreal Neurological Institute series average (Evans, Collins, & Holmes, 1996), mean Talairach coordinates (Evans et al., 1996; Talairach & Tournoux, 1988) for Wernicke's area were (−55, −38, 12) and for the right hemisphere homologue were (54, −30, 10). These coordinates correspond with Talairach coordinates for the localization of language areas in an fMRI study (Stippich et al., 2003). According to the international 10–20 electrode system, the two TMS scalp locations were within 1–2 cm of the CP5 and CP6 electrodes, respectively (see Figure 1). The CP5 and CP6 sites of stimulation, according to the literature, correlate with the location of Wernicke's area (Jennum, Friberg, & Fuglsang-Frederiksen, & Dam, 1994) and its homologue in the right hemisphere (Knecht et al., 2002). A middle occipital stimulation site (Oz) was also employed as a site to control for possible nonspecific visual effects and also for general arousal effects of TMS induced by somatosensory and acoustic artifacts. The coil current flowed in a mediolateral (CP5, CP6) or anterior–posterior (Oz) orientation with the handle pointing upward. The order of the four stimulation conditions (CP5, CP6, Oz, no TMS) was counterbalanced across subjects.

A Magstim Rapid TMS machine (Magstim, Whitland, UK) was used to apply 5 pulses for 500 msec starting on
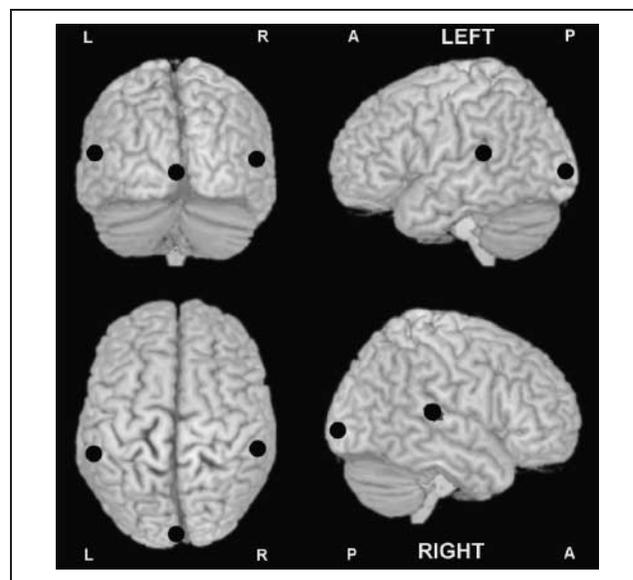

Figure 2. TMS stimulation sites: Wernicke's area in the left hemisphere, the right hemisphere anatomical homologue of Wernicke's, middle occipital area. These were determined by using frameless stereotaxy.

each trial 750 msec before visual stimulus onset (10 Hz) at 60–65% of the stimulator's maximum power. This intensity of stimulation was chosen as it is suprathreshold for the areas of the cortex investigated (Stewart, Walsh, & Rothwell, 2001 for details). The on-line protocol is thought to cause a short-lasting impairment of the function of the targeted brain region that should be captured by both behavioral and electrophysiological measures. The rTMS interference should be short lasting as was demonstrated in a recent EEG/TMS study where short trains of high-frequency rTMS had an effect of less that 2 sec on modulation of cortical oscillatory activities (Fuggetta, Pavone, Fiaschi, & Manganotti, 2008).

A series of four medium-diameter 50-mm figure-of-eight coils were used to apply the stimulation. Each block with TMS administration was split into two halves to allow the experimenter to change the coil to prevent overheating. Each block was followed by a 20-min rest before the next administration to avoid carryover effects from one block to the next. Fitzgerald et al. (2007) demonstrated that multiple short trains of high-frequency rTMS did not modify the cortical excitability 15 min post-stimulation, supporting the view of an absence of a posttrain effect. Subjects wore earplugs to attenuate the sound of the coil discharge.

ERP Recording and Analysis

Continuous EEG and electrooculogram (EOG) signals were recorded by a DC 32-channel amplifier (1-kHz sampling rate; 250 Hz high cutoff frequency; Brain Products, Germany). The EEG activity was recorded via an EasyCap containing 26 Ag–AgCl electrodes Fp2, Fz, Cz, Pz, F3/4, FC5/6, T7/8, C3/4, CP5/6, P3/4, P7/8, PO3/4, O1/2 with linked-earlobes reference. The vertical EOG (VEOG) was recorded from the Fp2 electrode. The horizontal EOG (HEOG) was recorded from electrodes placed at the outer canthi of both eyes. Impedance was kept below 10 kΩ.

Only EEG data for TMS trials with correct responses were analyzed. A notch filter (50 Hz) was used for all recorded channels. EEG was epoched from 100 msec prior to visual stimulus onset to 800 msec following the visual stimulus. Each EEG epoch was visually inspected off-line, and those with movement or ocular artifacts were eliminated. Epochs with eye movements and muscle or movement artifacts (as indicated by HEOG activity exceeding ±40 µV and activity at other electrodes exceeding ±80 µV were excluded from the analysis. ERPs were computed for different combinations of category (artifactual, natural) and TMS coil positions (CP5, CP6, Oz, no TMS), relative to a 100-msec prestimulus baseline. It is important to note that possible existing ERP differences between the two visual categories are independent of task congruity (see ERP Results below). ERPs were filtered using 0.01 Hz high-pass, 30 Hz low-pass filters.

Because the short trains of TMS were delivered before the visual stimulus onset, neither the TMS-induced

electric artifact nor auditory or somatosensory evoked potentials interfered with the subsequent stimulus-locked ERP recording. Thus, it was not necessary to introduce a procedure to remove these sources of artifacts (Litvak et al., 2007; Morbidi et al., 2007; Fuggetta et al., 2006; Thut et al., 2005).

Behavior Statistical Analysis

Mean correct RT and accuracy were submitted to separate repeated measures analyses of variance (ANOVAs). The ANOVAs had three within-subjects factors ''condition'' (CP5, CP6, Oz, No TMS), ''congruency'' (matching, nonmatching), and ''category'' (artifactual and natural) for all subjects. Post hoc paired t tests were Bonferroni corrected for multiple comparisons ($p < .05$).

ERP Statistical Analysis

Scalp voltage was analyzed at bilateral pairs of electrodes selected in several scalp regions of interest according to the theoretical predictions. Differential effects of TMS applied to CP5, CP6, Oz or the absence of magnetic stimulation were quantified on the basis of ERP mean amplitudes in different time windows. Mean amplitudes in different time windows, centered on the maximum of grand-average means, were obtained for each subject and each condition and were measured for selected pairs of bilateral electrodes in three scalp regions (see Figure 1): fronto-central (F3/4, FC5/6 electrodes), centro-parietal (C3/4, CP5/6, P3/4 electrodes), and parieto-occipital (PO7/8, PO3/4, O1/2 electrodes). In the case of the P100–N170 complex prior to 250 msec, we chose the time windows 70–130 and 140–190 msec and analyzed at parieto-occipital areas because early perceptual effects on ERPs were expected in this scalp region. For time windows from 250 msec to the end of the analyzed period, we analyzed the ERP mean amplitudes in the 250–450 and 500–700 msec windows coinciding with the fronto-central and centro-parietal N400 and LPC.

To reduce complexity of statistical analysis, separate repeated measures ANOVAs were conducted for picture–word targets on the mean voltage of each time window for several scalp regions (i.e., fronto-central, centro-parietal, and parieto-occipital electrodes) over the left and right hemispheres. The ANOVAs for ERPs had three within-subjects factors ''condition'' (CP5, CP6, Oz, and No TMS), ''electrode,'' and ''category'' (artifactual and natural). Post hoc paired t tests were Bonferroni corrected for multiple comparisons ($p < .05$).

RESULTS

Behavioral Measures

The mean percentage of correct answers was 93.5 ± 1.3% in the picture–word matching task. ANOVA showed

significant effects of category [$F(1, 8) = 12.631$, $p < .01$, $\varepsilon = .612$]. Natural stimuli were associated with higher accuracy compared with artifactual stimuli (93.8% vs. 91.6%). The main factor of congruency was also significant [$F(1, 8) = 16.586$, $p < .005$, $\varepsilon = .675$]. Matching trials were associated with more errors than noncongruent trials (88.2% vs. 97.3% correct, respectively). The main factor condition was not significant [$F(3, 24) = 1.526$, $p = ns$, $\varepsilon = .160$]. There was a significant Category × Congruency interaction [$F(1, 8) = 8.645$, $p < .05$, $\varepsilon = .519$]. Post hoc comparisons showed a significant difference between natural and artifactual domains for congruent trials with more errors associated with artifactual items (90.5% vs. 85.9% correct, respectively, $p < .005$). The Category × Condition, Condition × Congruency, and Condition × Category × Congruency interactions were not significant [$F(3, 24) = 0.245$, $p = ns$, $\varepsilon = .156$; $F(3, 24) = 0.982$, $p = ns$, $\varepsilon = .007$; and $F(3, 24) = 0.212$, $p = ns$, $\varepsilon = .168$, respectively].

ANOVA on RTs showed significant effects of category [$F(1, 8) = 6.476$, $p < .05$, $\varepsilon = .447$]. Natural stimuli were associated with faster RTs compared with artifactual stimuli (617 vs. 626 msec). The main factor congruency was not significant [$F(1, 8) = 3.941$, $p = ns$, $\varepsilon = .426$]. The main factor condition was not significant [$F(3, 24) = 0.830$, $p = ns$, $\varepsilon = .035$]. There was a significant Condition × Category effect interaction [$F(3, 24) = 3.484$, $p < .05$, $\varepsilon = .303$]. Post hoc comparisons showed a significant difference between natural and artifactual domains for the left Wernicke's area stimulation with longer RTs associated with artifactual items (612 vs. 642 msec, $p < .01$). This dissociation between natural and artifactual stimuli was not observed in the homologue of Wernicke's area in the nondominant hemisphere (610 vs. 618 msec, $p = ns$), the middle occipital control site of stimulation (620 vs. 621 msec, $p = ns$), or the no-TMS condition (626 vs. 625 msec, $p = ns$) (see Figure 3). The Condition × Congruency, Category × Congruency, and

Condition × Category × Congruency effect interactions were not significant [$F(3, 24) = 1.635$, $p = ns$, $\varepsilon = .170$; $F(1, 8) = 0.441$, $p = ns$, $\varepsilon = .052$; and $F(3, 24) = 0.712$, $p = ns$, $\varepsilon = .082$, respectively].

Event-related Potentials

For each subject, we averaged the waveforms of images belonging to the same category independent of their congruent/incongruent target status to maximize number of trials for the ERP analysis. We then compared these two category-specific waveforms to one another. Consequently, the possible difference can only be attributed to intrinsic properties of the natural and artifactual categories in a task-independent manner. The same procedure of ERP analyses employed in this study has been adopted in a previous study, where visual categories (animal and vehicles) were compared across tasks (Vanrullen & Thorpe, 2001). The difference waveforms are presented in Figure 4.

The early ERP components differed significantly in the anterior and posterior locations up to 250 msec after stimulus onset, with the P100–N170 complex largest over the posterior part of the head in the parietal–occipital electrodes. These components reflect perceptual processing of visual stimuli (e.g., Mangun & Hillyard, 1991). From 250 to 450 msec after stimulus onset, the ERPs have very similar morphologies over all the different fronto-central and centro-parietal regions with the deflection of the N400 sensitive to semantic congruity (Kutas & Hillyard, 1980). To compare the category-specific waveforms underlying processing of the different visual categories, we collapsed the data across matching and nonmatching trials belonging to either natural or artifactual domains. Thus, we eliminated the congruency effect with the modulation of the amplitude of N400 for semantically congruent–incongruent pictures–words pairings

Figure 3. Mean response times (RT ± SE) for natural and artifactual domains with TMS applied over the sites shown in Figure 2. The RT for no TMS is also represented. Asterisks denote significant differences between natural and artifactual items (**$p < .01$, pairwise post hoc comparison, Bonferroni corrected).
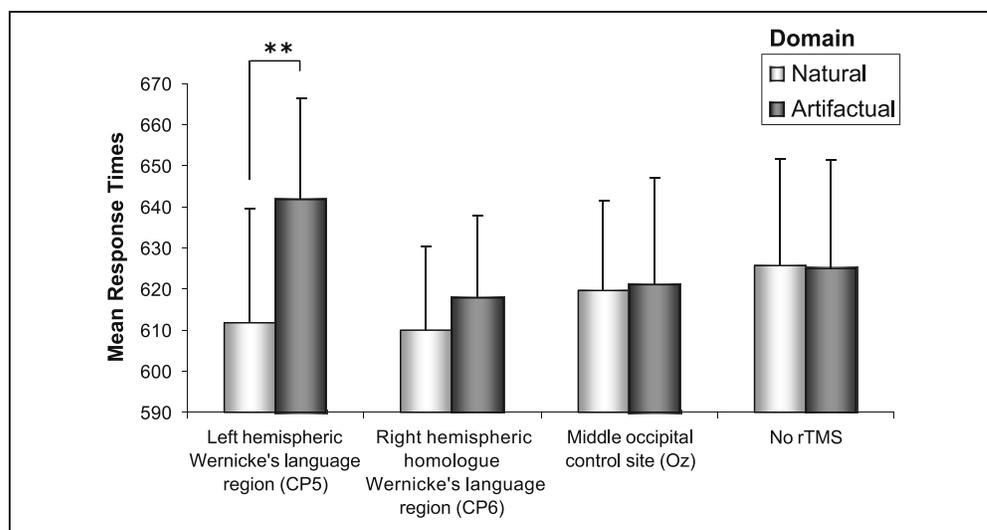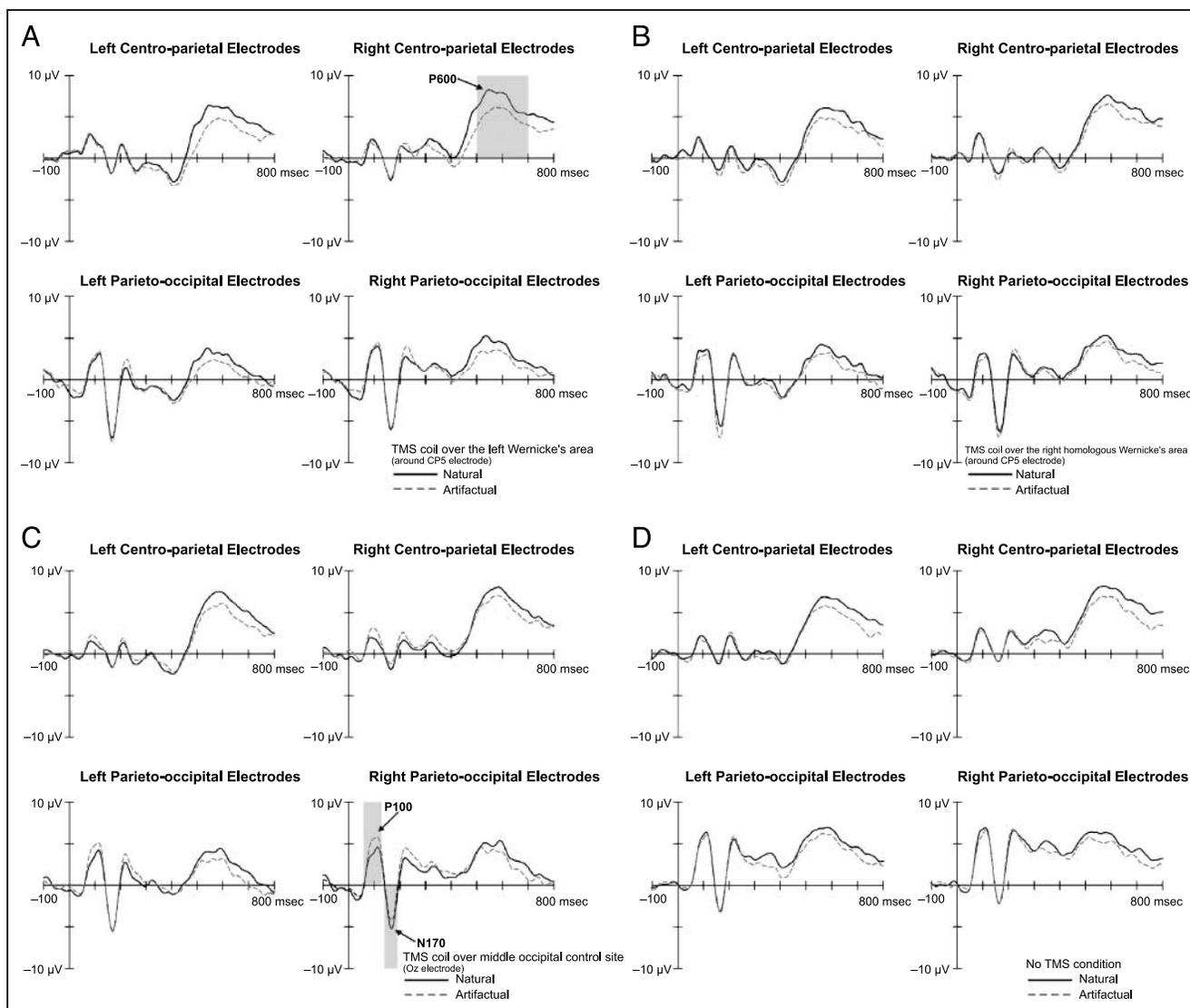
Figure 4. ERPs difference waveforms and the effects of the visual category on left/right hemisphere centro-parietal and parieto-occipital electrodes. Each of the four panels shows the differential activity between two visually defined categories: (A–B) TMS over Wernicke's area and its homologue in the right hemisphere; (C) TMS over the middle occipital cortex; and (D) no rTMS condition. The task-related status (matching, nonmatching) is equally represented in each category. In (A) waveforms representing natural and artifactual items significantly diverge in the time window chosen for the P600 component or LPC and for right centro-parietal electrodes only. In (C) and for right parieto-occipital electrodes only the differential activity between the two categories significantly differs in the two time windows chosen representative of the P100 and N170 components, respectively.

and natural/artifactual domains as already found in others ERP studies (Paz-Caballero et al., 2006; Kiefer, 2001). The end of the analyzed ERP period was characterized by a broad positivity that is known as the LPC, which is frequently centro-parietally distributed and has been claimed to be related to some aspect of syntactic processing where decisions are made rapidly (Friederici, 2002) and with context updating and retrieval of semantic features from working memory (Van Petten & Kutas, 1991) (see Figure 4).

The ANOVAs for the P100 component (time window 70–130 msec poststimulus) represented in the parietal–occipital electrodes showed a significant Site $\times$ Electrode interaction in the left hemisphere [$F(6, 48) = 2.552, p <$

.05]. Post hoc comparisons for the O1 electrode showed a significant difference with decreased ERP amplitudes for the middle occipital site of TMS (Oz electrode) compared with the no-TMS condition ($-1.746\ \mu V, p < .05$). For the right hemisphere parietal–occipital electrodes, there was a significant Site $\times$ Electrode effect [$F(6, 48) = 2.758, p < .05$] and a significant Site $\times$ Electrode $\times$ Category interaction [$F(6, 48) = 2.625, p < .05$]. A significant divergence between the two categories of stimuli for the middle occipital site of stimulation was observed in the greater positivity induced by the artifactual stimuli than the natural stimuli in PO4, PO8, and O2 electrodes, respectively ($-1.335\ \mu V, p < .01; -1.313\ \mu V, p < .05; -1.205\ \mu V, p < .05$).

The ANOVAs for the N170 component (time window 140–190 msec poststimulus) and left parietal–occipital electrodes revealed that there was a significant Condition × Electrode × Category interaction [$F(6, 48) = 3.375, p < .01$]. For the O1 electrode and natural items, there was a significant difference seen in the increased negativity for the middle occipital site of TMS (Oz electrode) compared with the no-TMS condition ($-2.900 \mu V$, $p < .05$). For the PO3 electrode, we obtained a greater negativity in response to artifactual items by comparing TMS over Oz with the no-TMS conditions ($-2.065 \mu V$, $p < .01$). For the right hemisphere parietal–occipital electrodes, there was a significant Site × Electrode effect [$F(6, 48) = 3.793, p < .01$] and a significant Condition × Electrode × Category interaction [$F(6, 48) = 2.727, p < .05$]. A significant divergence between the two categories of stimuli for the middle occipital site of stimulation was observed in a larger N170 amplitude to natural than to the artifactual stimuli at the PO8 electrode ($-1.033 \mu V$, $p < .05$).

For the N400 component (time window 250–450 msec poststimulus) and left and right fronto-central and centroparietal electrodes, analyses did not yield significant main effects or interactions.

Finally, for the LPC (time window 500–700 msec poststimulus), a significant domain effect for the left hemisphere fronto-central electrodes was found [$F(1, 8) = 5.418, p < .05$]. There was a greater positivity component induced by the natural stimuli than by the artifactual stimuli ($0.962 \mu V$). A similar effect for centro-parietal electrodes was found [$F(1, 8) = 12.431, p < .01$] with a greater positivity induced by the natural stimuli than by the artifactual ones ($1.346 \mu V$).

For the centro-parietal electrodes of the right hemisphere, there was a significant domain effect [$F(1, 8) = 17.068, p < .005$] and a significant Condition × Electrode × Category interaction [$F(6, 48) = 2.544, p < .05$]. Post hoc comparisons showed that, for the Wernicke stimulation (CP5), there was a significant difference between the two categories of stimuli with a greater positivity being induced by natural than by artifactual stimuli. This natural/artifactual domains difference was $1.859 \mu V$ ($p < .05$) for the C4 electrode, $1.469 \mu V$ ($p < .05$) for the CP6 electrode, and $1.805 \mu V$ ($p < .05$) for the P4 electrode.

DISCUSSION

In the present study, we used a combined TMS and ERP approach to further investigate the neural basis of the TMS suppression of semantic functions and modulation of the processing of living and nonliving (or natural and artifactual) domains. The main finding of this study is the dissociation between natural/artifactual items with a specific behavioral impairment of category-specific semantic processing and recognition for artifacts. The

dissociation between natural/artifactual items with TMS over Wernicke's area had a direct ERP correlate mainly reflected by systematic effects on the LPC over the central–parietal electrodes of the right hemisphere. These results suggest that different neuroanatomical sources of semantic information contribute to category-specific effects in object categorization.

Behavioral Effects

The main behavioral finding of the present study is that natural items were recognized faster than objects from artifactual categories with TMS over Wernicke's area. The impairment of implicit semantic categorization of artificial items was site specific because there was no behavioral dissociation between the two domains for magnetic pulses applied over the right hemisphere homologue of Wernicke's or the middle occipital site. The effect was independent of motor requirements of the task as subjects always used their right hand. A nonspecific motor effect would not have distinguished between tasks.

A general behavioral inhibition of semantic processing following TMS over the left hemisphere has been shown in several studies (Drager et al., 2004; Knecht et al., 2002; Flitman et al., 1998; Jennum et al., 1994). With a similar picture–word verification task as employed in the present study, a slowing of object matching after suppression of the left Wernicke's area has been found in subjects with left hemisphere language lateralization, as determined by functional transcranial Doppler sonography, and would be compatible with the prominent role of this region in extrapolation of object-related and space-related information (Knecht et al., 2002).

At first sight, it seems that the selective impairment to artifactual but not natural items is related to the evidence that the processing of natural items (e.g., animals) is more widely distributed in the two cerebral hemispheres, whereas the artifactual items (e.g., tools) processing appears to be restricted to the left hemisphere (Pilgrim et al., 2005; Chao et al., 2002; Ilmberger et al., 2002; Martin & Chao, 2001; Gainotti, 2000; Perani et al., 1995, 1999; Grabowski et al., 1998; Grafton et al., 1997; Tranel et al., 1997; Martin et al., 1996). A recent behavioral study aimed to determine whether there were hemispheric asymmetries in the representation and/or processing of concepts from living/nonliving domains of knowledge (Pilgrim et al., 2005) and found a disadvantage for nonliving compared to living concepts in semantic decision tasks when stimuli were presented to the right hemisphere. This was explained in terms of qualitatively different semantic processing in the right and left hemispheres. It has also been demonstrated that the left hemisphere has complementary functions in programming and activating motor schemata (hand and finger movements) related to the use of tools (Beauchamp, Lee, Haxby, & Martin, 2003; Ilmberger et al., 2002; Martin

& Chao, 2001; Chao & Martin, 2000; Gerardin et al., 2000; Hoshi & Tanji, 2000; Chao et al., 1999; Grafton, Arbib, Fadiga, & Rizzolatti, 1996). Thus, Martin and Chao (2001) have suggested that in right-handed subjects different regions of the left hemisphere are involved in processing the information relevant to tools: Areas of the fusiform gyrus, middle temporal gyrus, and left posterior parietal cortex are devoted to the identification of tools, whereas the left ventral premotor cortex is involved in the planning of tools-related actions.

Similar to our results, previous studies which used explicit semantic categorization tasks (Paz-Caballero et al., 2006; Kiefer, 2001; Price & Humphreys, 1989) have found an advantage for natural over artifactual categories in object categorization (living/nonliving decision). To account for this effect, Devlin et al. (1998) suggested that artifactual and natural categories differ in the ''informativeness of distinctiveness of semantic features'' (which is greater in artifactual categories). Accordingly, categories with low informativeness of features (i.e., natural categories that comprise exemplars with many shared features) allow faster and more accurate verification of category membership relative to categories with high informativeness of features (i.e., artifactual categories that include exemplars with few shared features).

Early ERP Effects

The contribution of perceptual and semantic processes in categorization of natural and artifactual items can be analyzed by corresponding ERP events that have been modulated by TMS. As has been shown in ERP (Vanrullen & Thorpe, 2001) and magnetoencephalography (Halgren, Raij, Marinkovic, Jousmaki, & Hari, 2000) studies, P1 activity probably involves mechanisms such as visual features extraction (e.g., shape), that could arise in extrastriate visual areas such as V2 or V4. A previous object categorization study (Vanrullen & Thorpe, 2001) compared the ERPs elicited by photographs of animals and vehicles in a categorization task and observed a difference between the two categories with shorter latencies at 75–80 msec poststimulus onset. In the present study, the mean amplitude of the early perceptual component P1 did not differ between natural and artifactual objects for TMS over Wernicke's area, its homologue in the right hemisphere or the absence of magnetic stimulation (see Figure 4). At first sight, it seems that objects belonging to the two categories do not differ in their early visual features extraction such as shape complexity, local luminance, and local contrast. However, TMS over the middle occipital site (Oz) did interfere with the visual representation of items in the P1 time window. Thus, our method has uncovered the presence of an early category-related mechanism mediated by extrastriate visual areas. This does not imply that identity within visual categories is encoded in these regions. This is consistent with an absence of an RT impairment in the implicit categorization task (see Figure 3).

In the N170 time window, objects from natural categories elicited a greater negative deflection than objects from artifactual categories when TMS was delivered over the occipital site. Thus, it seems that interference with early visual areas by TMS reveals the need for greater recruitment of the underlying generators of the N170 for natural than for artifactual items. This result supports the assumption that perceptual information plays a more important role in processing natural than artifactual categories (Lloyd-Jones & Humphreys, 1997). Kiefer (2001), using a superordinate object categorization task, found that the N1 component related to perceptual processing of items and represented in inferior-temporal and occipital locations had a significantly larger amplitude in response to pictures of natural stimuli. Other studies have also found larger N1 amplitudes for object categories for which subjects already are or are becoming experts compared to objects for which they are novices (Rossion, Gauthier, Goffaux, Tarr, & Crommelinck, 2002; Tanaka & Curran, 2001). Therefore, expertise may explain the larger N1 amplitude for the natural compared with the artifactual category. Our electrophysiological results are in agreement with those from neuroimaging investigations that emphasize the importance of occipital–temporal cortex in the perception of natural objects (Chao et al., 2002; Perani et al., 1999; Martin et al., 1996).

Late ERP Effects

Neural activity correlated with decision processes is, of course, likely to occur at a later stage than the perceptual effects discussed in the previous section. In the N400 time window between 250 and 450 msec after target presentation, a deflection was obtained at fronto-central, centro-parietal, and parieto-occipital recording sites (Paz-Caballero et al., 2006; Kiefer, 2001; Kutas & Hillyard, 1980). As expected, in this study, we did not find evidence of different cortical representations of natural and artifactual domains reflected in the N400. This result may be due to the implicit task we used that consisted in accessing the literal meaning of concrete nouns, and thus, did not require more complex semantic analyses (Knecht et al., 2002).

In the 500–700 msec time window, over all the different sites of TMS, the stimuli from the natural domain elicited a significantly larger amplitude of the LPC at left fronto-central and left/right centro-parietal electrodes compared with those from the artifactual domain. This scalp distribution of the LPC, related to retrieval of semantic features from working memory (Van Petten & Kutas, 1991), is consistent with findings of previous ERP studies and may reflect the lesser difficulty in the categorization of natural stimuli (Paz-Caballero et al., 2006).

Our main finding relevant to altering ERP components is that short trains of TMS over Wernicke's area (around CP5 electrode) induced a specific increase in the dissociation of the two object domains in that the amplitude of the LPC displayed greater positivity to the natural than the artifactual stimuli over right centro-parietal electrodes. The differential modulation of the amplitude of the LPC for natural/artifactual domains (mainly located in the right hemisphere), along with the significant increase in the RTs associated with the artifactual stimuli after rTMS over the left hemisphere, represent two complementary measures confirming the hypothesis that natural and artifactual domains are functionally represented in modality-specific separate subsystems presumably with different neuroanatomical substrates (Paz-Caballero et al., 2006; Devlin et al., 1998; Martin et al., 1996; Perani et al., 1995).

We did not find a behavioral effect of TMS for categorization processing of natural items, probably because the cortical presentation of these objects is strongly associated with sensory and perceptual features in both hemispheres. Thus, the interference induced by TMS over Wernicke's area may have been compensated by the functional involvement of the right hemisphere. Indeed, because language performance is preserved at a normal level in our subjects, we suggest that right hemisphere activity is integrated into the normal language network (Pobric et al., 2008). Clinical studies have frequently shown, in right-handed patients with left-sided focal brain lesions in both the superior temporal gyrus (Weiller et al., 1995) and the inferior frontal gyrus (Thiel et al., 2001, 2006), an activation of the right hemisphere homologue structures of classical language areas. Thus, one interpretation of our study is that we have demonstrated compensatory brain plasticity in reaction to the transient impairment induced by TMS. Moreover, we provide direct neural evidence for such a compensatory transfer of language function from the left to the right because we found an increment of the amplitude of LPC for natural items over the right hemisphere. By contrast, we found a behavioral effect of TMS delivered over Wernicke's area for artifactual items. Given that the representation of artifacts is associated with functional/action-related semantic features more strongly in the left hemisphere, the right hemisphere cannot compensate for the loss of the left hemisphere language function. Correspondingly, participants showed more difficulties in accessing associative information relative to artifactual items. These results support the view that the left hemisphere, and in particular, Wernicke's area is essential for representation and categorization of artifactual objects.

Conclusion

One major advantage of combined TMS neuroimaging studies is that functional neuroimaging picks up physiological signals which are directly generated in the brain, and thus, do not rely on indirect behavioral measures such as motor evoked responses or a disruption in task performance (Siebner & Rothwell, 2003). From a cognitive neuroscience perspective, TMS and ERPs are ideal candidates to be combined to gain new insights into the neural basis of a variety of cognitive processes that could not be obtained on the basis of one of these methods alone.

In the present study, by employing a combined TMS/ERP approach, we demonstrated that disrupting Wernicke's area with TMS created a selective impairment in categorization of artifactual items. This effect was assessed with both an indirect behavioral and a direct electrophysiological measure of category-specific effects. The findings of the present study support the view that the representation of semantic knowledge associated with different conceptual domains is based on a network of partially segregated neural systems of functionally interconnected cortical regions. Further combined TMS/EEG studies aiming to investigate the temporal and functional organization of object categorization processing may be valuable assessing the regional activity and interregional functional connectivity of the two hemispheres (Fuggetta et al., 2008).

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