

# How Early Does the Brain Distinguish between Regular Words, Irregular Words, and Pseudowords during the Reading Process? Evidence from Neurochronometric TMS

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## Abstract

■ Cognitive theories on reading propose that the characteristics of written stimuli determine how they are processed in the brain. However, whether the brain distinguishes between regular words, irregular words, and pseudowords already at an early stage of the reading process is still subject to debate. Here we used chronometric TMS to address this issue. During the first 140 msec of regular word, irregular word, and pseudoword reading, TMS was used to disrupt the function of the ventral occipitotemporal, posterior middle temporal, and supramarginal

gyri, which are key areas involved in orthographic, semantic, and phonological processing, respectively. Early TMS stimulation delivered on posterior middle temporal and supramarginal gyri affected regular and irregular word, but not pseudoword, reading. In contrast, ventral occipitotemporal disruption affected both word and pseudoword reading. We thus found evidence for an early distinction between word and pseudoword processing in the semantic and phonological systems, but not in the orthographic system. ■

## INTRODUCTION

Reading aloud consists of mapping an orthographic input to a phonological output. Yet, the underlying cognitive and neural processes of this activity appear to depend on the type of written material. At the theoretical level, a main distinction has been made between dual-route models that claim a dissociation between the lexical and nonlexical reading mechanisms (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001) and connectionist models that postulate a single mechanism that handles the pronunciation of all kinds of written stimuli (Harm & Seidenberg, 2004; Plaut, McClelland, Seidenberg, & Patterson, 1996). According to dual-route models, pseudoword reading relies primarily on the spelling-to-sound conversion system whereas irregular word reading relies on direct access to the memory-based word identification system. Regular word reading could be handled by both systems. This separation between rules and a lexical system is absent in the connectionist models that consider all kinds of stimuli to be processed within a single system involving a parallel contribution of orthographic, phonological, and semantic representations, with activation weights depending on the characteristics of the stimuli.

Brain imaging studies have attempted to identify the neural correlates of the orthography-to-phonology mapping processes. As extensively reviewed by Price (2012), comparisons between different types of stimuli or writing systems show overlapping regions. Yet, both the degree of functional connectivity between different brain areas and the level of activity within specific areas seem sensitive to stimulus familiarity and/or spelling-to-sound regularity. For instance, stronger functional connectivity in the ventral part (visual form-to-meaning pathway) of the reading system was observed during kanji reading whereas stronger functional connectivity in the dorsal part (visual form-to-sound pathway) was observed during kana reading. This finding was explained by the fact that characters in kanji words provide information on meaning but not on pronunciation of the word whereas characters in kana provide information on pronunciation but not on meaning (Kawabata Duncan et al., 2013; Kiyosawa, Itoh, Nakagawa, Kobayashi, & Tamai, 1994). Reading familiar words compared to pseudowords or irregular compared to regular words typically leads to an increased activation in the lexico-semantic system including the left ventral temporal cortex, the posterior part of the middle temporal gyrus (pMTG), the triangular part of inferior frontal gyrus, and the posterior parietal cortex (Graves, Desai, Humphries, Seidenberg, & Binder, 2010; Frost et al., 2005; Binder et al., 2003). Reverse comparisons (reading pseudowords compared to words,

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transparent compared to opaque orthographic system, or kana compared to kanji) led to an increased activation in the areas involved in phonological processing such as the left opercular part of the inferior frontal gyrus, left precentral gyrus, insular cortex, supramarginal gyrus (SMG), and superior temporal areas (Levy et al., 2009; Binder et al., 2003; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Xu et al., 2001). The contribution of the occipitotemporal cortex, considered as one of the key areas involved in orthographic processing, also varies with stimulus type. The posterior area is more activated by pseudowords than real words (Nosarti, Mechelli, Green, & Price, 2010; Levy et al., 2009), the mid area by both words and pseudowords compared to symbols (Herbster, Mintun, Nebes, & Becker, 1997), and the anterior area by irregular more than regular words (Graves, Desai, et al., 2010; Brunswick, McCrory, Price, Frith, & Frith, 1999). This area also showed greater amount and extent of activation for logographic or nontransparent scripts compared to transparent ones such as Chinese versus French (Szwed, Qiao, Jobert, Dehaene, & Cohen, 2014), English versus Italian (Paulesu et al., 2001), or kanji versus kana (Twomey et al., 2013).

Regardless of whether these differences in activation patterns reflect the existence of distinct pathways for different types of stimuli or a difference in the weight of activation within a single neural network, it seems clear that at some point of the process the cognitive system is able to distinguish written stimuli according to their degree of familiarity and spelling-to-sound regularity. However, because of lack of precise temporal information in fMRI studies, it remains unclear how early this distinction takes place.

Techniques with higher temporal resolution like EEG or MEG provide insights into this timing issue. Studies on an early distinction between words and pseudowords (and, to a lesser extent, between regular and irregular words) have particularly focused on the N170, that is, an ERP component that has been associated with individual's perceptual expertise on visual stimuli. In the reading domain, the cortical source of this component is within the ventral part of the occipitotemporal cortex (Schlaggar & McCandliss, 2007; Brem et al., 2006), which suggests that this area might be able to distinguish between different kinds of written stimuli already within the first 200 msec after stimulus presentation. However, probably because of a divergence in task demand, the findings obtained by different research groups remain conflicting. Although some reported a stronger N170 amplitude to words than to pseudowords (Maurer, Brandeis, & McCandliss, 2005), the opposite result or an absence of difference was also obtained (Hauk, Davis, Ford, Pulvermüller, & Marslen-Wilson, 2006; Simon, Bernard, Largy, Lalonde, & Rebai, 2004). In addition to the N170 component, a distinction between words and pseudowords was also found within more anterior sites when later time windows were considered (Hauk, Patterson, et al., 2006; Compton, Grossenbacher, Posner, & Tucker, 1991).

This study aimed to shed further light on this issue by proposing an alternative approach to examine whether regular words, irregular words, and pseudowords were processed in the same way at an early stage of the reading process. To do so, TMS was used to disrupt the function of three brain areas mainly involved in orthographic, phonological, and semantic processing during the first 140 msec of the reading process. Contrary to most ERP studies that require participants to make judgments on specific aspects of the stimuli, here, participants simply had to read them aloud. This minimal task demand puts the participants in a processing context that is closer to normal reading situation.

On the basis of the theoretical framework proposed by the connectionist models that reading involves orthographic, semantic, and phonological systems (Harm & Seidenberg, 2004; Plaut et al., 1996), three specific brain areas that are part of these systems were chosen as targets. We first considered the middle part of the ventral occipitotemporal cortex (vOT), also called the "visual word form area" (Cohen et al., 2002). Although the specialization of vOT for orthographic representations is still under debate (Dehaene & Cohen, 2011; Price & Devlin, 2011; Kronbichler et al., 2004), its involvement in reading has been consistently reported across individuals and writing systems (Dehaene et al., 2010; Bolger, Perfetti, & Schneider, 2005). Training studies also showed that vOT activity increases with reading skill (Brem et al., 2010; Xue, Chen, Jin, & Dong, 2006). The second targeted area was the pMTG. This area is part of the semantic system (Graves, Binder, Desai, Conant, & Seidenberg, 2010; Lau, Phillips, & Poeppel, 2008). In reading, pMTG activation increases when meaningful materials are used or when participants focus on the semantic content of stimuli (Hoffman, Pobric, Drakesmith, & Lambon Ralph, 2012; Jobard et al., 2003; Simos et al., 2002; Pugh et al., 1996; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). The third area was the SMG. Several studies show stronger SMG activation when reading pseudoword than words (Rumsey et al., 1997), transparent to opaque writing systems (Law et al., 1991), and in tasks with a strong phonological component (Price & Mechelli, 2005; Xu et al., 2001). The role of SMG has typically been attributed to phonological analysis and grapheme-to-phoneme conversion (Taylor, Rastle, & Davis, 2013; Pugh et al., 2010; Booth et al., 2003).

On the basis of the above observations, we predicted that, within each brain area, TMS might not affect the different types of material in the same way, as described below.

*Contribution of the orthographic system:* If the middle vOT constitutes a memory-based word identification system (Pugh et al., 2010; Glezer, Jiang, & Riesenhuber, 2009; Kronbichler et al., 2004), interrupting its function would affect word but not pseudoword reading. On the contrary, if this area processes written stimuli at the

prelexical level (Dehaene, Cohen, Sigman, & Vinckier, 2005; Cohen et al., 2002), both word and pseudoword reading might be affected by the stimulation.

*Contribution of the semantic system:* Given the role of pMTG in semantic processing, TMS would be expected to mainly affect word reading, with perhaps stronger disruptive effect for items that include irregular spelling-to-sound correspondences, as the phonological system could more easily handle regular than irregular word reading when the semantic system is disrupted.

*Contribution of the phonological system:* A disruption of SMG, which is involved in phonological analysis and grapheme-to-phoneme conversion, was expected to be particularly deleterious to pseudoword reading.

Note that French materials were used in the current study. Compared with English, French has a higher spelling-to-sound consistency (Ziegler, Stone, & Jacobs, 1997; Ziegler, Jacobs, & Stone, 1996), that is, fewer words with a similar spelling pattern but a different pronunciation. The presence of fewer “enemies” or alternative pronunciations for French irregular words might reduce the difference between regular and irregular words.

In addition to these primary predictions, we also explored the laterality of these three processing systems by applying the TMS stimulation to the homologous areas of the right hemisphere. Although, traditionally, reading has been considered to mainly depend on a distributed network of left-side language areas (Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999), an increasing amount of brain imaging studies showed activation of homologous areas within the right hemisphere (Behrmann & Plaut, 2012, 2013; Hartwigsen et al., 2010; Paulesu et al., 2000; Hagoort et al., 1999; Price, Wise, & Frackowiak, 1996).

Finally, for all the targeted areas mentioned above, we used a chronometric stimulation protocol in which TMS was applied in two separated time windows: 40/80 msec and 100/140 msec poststimulus onset. Although this method did not allow us to precisely specify the time line of word or pseudoword processing, it provided us an alternative approach to investigate whether the areas involved in orthographic, phonological, and semantic processing contribute to reading of different types of material at the same moment. According to serial processing accounts (Liu, Perfetti, & Hart, 2003; Fodor, 1983; Warrington & Shallice, 1980), a written stimulus would be initially analyzed at a low-level perceptual stage to form an orthographic code. This code would then be identified in the orthographic system before reaching the phonological and semantic systems. Accordingly, the TMS effect would occur earlier in vOT than in SMG or pMTG. However, if the output of the initial stage of visual analysis propagates simultaneously to the orthographic, phonological, and semantic systems as claimed by the parallel processing account (Hauk, Coutout, Holden, & Chen, 2012; Price & Devlin, 2011; Cornelissen et al., 2009;

Pulvermüller, Shtyrov, & Hauk, 2009) or slightly earlier in the orthographic system, followed by strong overlaps between the different processes, as claimed by a cascade model (McClelland, 1979), a similar time course of the TMS effect would be observed in the three areas.

## METHODS

### Participants

Ninety-six monolingual French speakers were recruited for the TMS study. All were right-handed and naive to TMS. None had any history of language, neurological disorder, or familial epilepsy according to self-reports. Four participants whose motor thresholds exceeded 65% of the maximum stimulator output were excluded from the study before performing any task. A total of 92 participants (54 women, 18–30 years old, mean = 22 years) were randomly assigned to vOT stimulation (16 participants for the right vOT and 16 participants for the left vOT), pMTG stimulation (16 participants for the right pMTG and 16 participants for the left pMTG), or SMG stimulation experiments (14 participants for the right SMG and 14 participants for the left SMG). An additional 12 participants (8 women, 19–32 years old, mean = 23 years) underwent sham TMS on vertex (a control experiment) where no magnetic stimulation was used (see below). The experiments were approved by the ethics committee of Erasme Hospital, Université Libre de Bruxelles, and were undertaken with the understanding and written consent of each participant.

### Structural MRI and TMS

A frameless stereotaxic system was used to position the TMS coil on the scalp to stimulate a precise anatomical ROI. All volunteers participated in a separate MRI session where a high-resolution anatomical scan was acquired (sense 3D-T1 TFE, repetition time = 8.87 msec, echo time = 4.24 msec,  $0.82 \times 0.82 \times 1.20$  mm<sup>3</sup> resolution; Intera 1.5-T, Philips Healthcare, Best, The Netherlands). During the TMS session, a Polaris Spectra infrared camera (Northern Digital, Inc., Waterloo, Canada) tracked the participant's head, and ASA-Visor software (Advanced Neuro Technology, Enschede, The Netherlands) registered the participant's head to his or her MRI scan. The neuronavigation was used to both target and record stimulation sites. Stimulation was performed using a MagPro X100 MagOption TMS system (MagVenture S/A, Farum, Denmark) and a 70-mm figure-of-eight coil (cool B-65 Butterfly or a MCF-P-B65 Placebo; MagVenture S/A, Denmark). The stimulation intensity was individually determined based on the threshold necessary to observe a visible right-hand twitch when stimulating the hand area of the primary motor cortex in the left hemisphere. This ranged from 34% to 62% of the maximum stimulator output (mean = 47%). During the localizer tasks, short

trains of 10-Hz pulses were delivered starting at the onset of the stimuli and lasted 400 msec. During the main task, paired-pulse stimulations were delivered in different time windows. Because of the summation properties of TMS pulses, paired-pulse TMS gives larger effects than single-pulse TMS but still allows good temporal resolution defined by the temporal distance between the two pulses (Silvanto, Lavie, & Walsh, 2005; Walsh, Pascual-Leone, & Kosslyn, 2003). Several chronometric TMS studies using the same paired-pulse protocol as in this study indeed showed TMS effects in only a single time window, thus suggesting that the TMS effects in two adjacent stimulation time windows could be dissociated (Pitcher, Garrido, Walsh, & Duchaine, 2008; Pitcher, Walsh, Yovel, & Duchaine, 2007; O'Shea, Muggleton, Cowey, & Walsh, 2004). Stimulation parameters were well within international safety guidelines (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998).

### Functional Localization

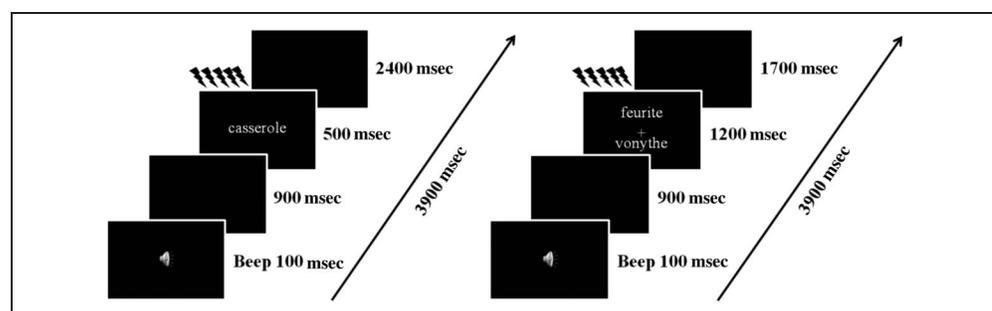
The localization procedure consisted of two stages. In the first stage, before the TMS sessions, three potential target sites within one ROI were identified on each subject's MRI on a neuroanatomical basis (see Figure 3). The Montreal Neurological Institute (MNI) coordinates of these stimulation targets were obtained by normalizing individual MRIs to an MNI template using the spatial normalization implemented in Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, University College London, UK). In the first experiment, in which the left and right vOT were the stimulation sites, the first target was located in the middle left or right fusiform gyrus, medial to the occipitotemporal sulcus on the crest of the gyrus, just superior to the principal sulcus of the cerebellum (coronal plane). The second and the third targets were placed about 5 mm anterior and posterior to this point, respectively. In the second experiment, in which the left and right pMTG were the stimulation sites, the first target was located in the posterior part of the left or right pMTG below the bifurcation point of the STS. The second and third targets were placed along the pMTG about 10 mm anterior and posterior to the first target,

respectively. In the third experiment, in which the left and right SMG were the stimulation sites, the first target was marked just above the termination of the posterior ascending ramus of the Sylvian fissure in the left or right hemisphere. The second was placed at the ventral end of the anterior SMG, superior to the Sylvian fissure, posterior to the postcentral sulcus, and anterior to the posterior ascending ramus of the Sylvian fissure. The third was approximately halfway between these sites and about 10 mm from the other two. In each experiment, these selected targets were tested in a second stage to determine whether stimulation of any of them disrupted orthographic, semantic, and phonological processing, respectively. To do so, three localizer tasks that explicitly required processing of orthographic, semantic, or phonological information were used. If the stimulated area were essential in the processing of a specific type of information, by disrupting its functioning, we should affect the performance that, according to the localizer task, depends on such information. For all the localizer tasks described below, TMS was considered to have a disruptive effect whenever the median RT observed on the trials associated with the stimulation was numerically superior to the median RT obtained on the trials without stimulation. As demonstrated in Terao et al.'s (1997) study, a nonspecific or spurious effect of TMS typically leads to a reduction of the RT because of intersensory facilitation.

### Experiment 1: vOT Stimulation

To identify an area in vOT that plays a critical role in orthographic processing, short bursts of repetitive TMS were used to temporarily interfere with information processing within the anatomically marked areas. The task used to localize the vOT area was visual lexical decision, which has been successfully used to illustrate the critical role of the left vOT in written word processing (Duncan, Pattamadilok, & Devlin, 2010; Pattamadilok, Knierim, Kawabata Duncan, & Devlin, 2010). The stimuli consisted of six blocks of 36 words and 36 pseudowords randomly presented. Each trial consisted of one word or pseudoword appearing at the center of the screen for 500 msec. Trial duration was 3.9 sec, leading to a total duration of 4.8 min per block (Figure 1, left). Half of the word and pseudoword trials

**Figure 1.** Illustration of the timeline of a trial in the visual lexical decision (Experiment 1), semantic judgment (Experiment 2; left), and rhyme judgment localizer tasks (Experiment 3; right). Trials began with a beep, followed by a blank screen, a stimulus, and then a blank screen. The duration (in msec) of each segment is written next to the screen. In trials that included TMS, the 10-Hz stimulation began at the onset of the stimulus and lasted for 400 msec.



had concurrent repetitive TMS (10 Hz, 5 pulses at 100% of the subject's motor threshold) starting at the onset of the stimulus. To ensure that the difference obtained between the trials with and without TMS stimulation was because of the stimulation rather than the material itself, these trials were matched for several psycholinguistic factors (for words: word frequency, number of letters, number of phonemes, orthographic neighbors, orthographic uniqueness point, number of syllables, familiarity rating; for pseudowords: orthographic neighbors, number of letters, number of phonemes, bigram frequency) as well as for the RTs and accuracy scores obtained in an independent behavioral pilot study performed on a different set of 15 participants (all  $p$ s > .72). In addition, during the TMS experiment, the trials with and without stimulation were reversed for half of the participants. The experiment started with a short practice block that allowed the participants to familiarize with the task and the stimulation. They were instructed to respond as quickly and as accurately as possible while ignoring the stimulation. Responses were given by button presses with the right and left index fingers. No feedback was provided. Presentation, timing, and data collection were controlled by E-Prime 1.2 software (Psychology Tools, Inc., Pittsburgh, PA).

During TMS stimulation, the coil was placed on the scalp and oriented so that the line of maximum magnetic flux intersected one of the anatomically marked vOT sites. After each block, RTs on all correct word trials were analyzed (Duncan et al., 2010; Pattamadilok et al., 2010). If TMS led to a numerically smaller median RT (i.e., facilitation), the next site was tested. When there was inhibition, the site was retested to ensure that the interference effect was replicable rather than a spurious one. On average, three localizer blocks were needed to identify the target area within left vOT and three to identify the target area within right vOT. The sites where stimulation consistently interfered with lexical decisions were used as test sites for the main reading task. The same localization procedure and stimulation protocol were used in Experiments 2 and 3, although the localizer tasks differed.

### *Experiment 2: pMTG Stimulation*

To localize the stimulation sites within pMTG, we used a semantic judgment task in which the participants had to decide whether a written word represented a kitchen or garden tool. Three blocks of 40 words (20 kitchen tools and 20 garden tools randomly presented) were constructed. If the "correct" target site could not be identified after three blocks, additional blocks constructed from the same set of stimuli were used. The timeline of each trial, the stimulation protocol, and the material selection procedure were identical to Experiment 1. After each localizer block, RTs on all correct trials were analyzed to determine whether the stimulation impaired performance. On average, it took three localizer blocks to identify the target area within the left pMTG and three to identify the target area within the right pMTG. The sites where stimulation consistently

interfered with semantic judgments were used as test sites for the main reading task.

### *Experiment 3: SMG Stimulation*

To localize the SMG, a rhyme judgment task on written pseudowords was used. The task required phonological analysis and grapheme-to-phoneme decoding ability, which are known to engage SMG. The numbers of shared letters in the rime(s) of the rhyming and nonrhyming pairs were matched (2.1 letters on average), such that it was impossible for the participants to perform the task by relying solely on the pseudowords' spelling. Six blocks of 50 trials (50% rhyming pairs presented in a random order) were constructed. Each trial consisted of two pseudowords presented above and below a fixation cross that appeared at the center of the screen for 1200 msec. The trial duration was 3.9 sec, leading to a total duration of 3.4 min per block (Figure 1, right). Half of the rhyming and nonrhyming trials were presented with repetitive TMS. The stimulation protocol and the material selection procedure were the same as in the previous experiments. On average, it took three and four localizer blocks to identify the target area within the left and right SMG, respectively. The sites where stimulation consistently interfered with rhyme judgments were used as test sites for the main reading task.

### *Control Experiment*

A control experiment was included to ensure that the TMS effects in the main experiments were not because of artifacts, especially as the noise generated by the stimulator might have interfered with reading aloud. The sham coil delivering stimulation was designed to replicate the sound and the vibration of a genuine TMS coil without actually stimulating the brain. This coil was placed over the vertex, the highest point of the skull. Although it was not necessary to functionally localize the vertex, we chose randomly one of the localizer tasks and applied the "localization" procedure. This was done to keep the experimental procedure identical across all participants. Between two and six localizer blocks (three blocks, on average) were used. After the localizer session, all the 12 participants of the vertex condition participated in the main reading task.

### **Main Task: Reading Aloud**

Following the localizer tasks, the participants who showed a consistent inhibitory effect of TMS at either vOT, pMTG, or SMG and all the participants of the control experiment performed the main task, namely, reading aloud written stimuli. The stimuli consisted of 72 regular French words, 72 irregular French words, and 72 pseudowords. Word irregularity was determined by the frequency with which a letter (or a sequence of letters) is pronounced in French. Regular words only contain letters whose

pronunciation is the most frequent or dominant in the language, whereas irregular words are those that contain letters that are pronounced in a less common way. The three kinds of stimuli were matched for relevant sublexical factors, that is, bigram frequency, number of phonemes, number of syllables, and number of letters (all  $ps \geq .70$ ; see Table 1). Regular and irregular words were also matched for frequency, orthographic uniqueness point, orthographic neighbors, and subjective frequency (New, Pallier, Brysbaert, & Ferrand, 2004; all  $ps > .09$ ; see Table 1).<sup>1</sup> During the experiment, the sequence of stimuli of each type was divided into two blocks of 36 trials. Within each block, the stimuli were further divided into three subsets of 12 stimuli, which were matched on the aforementioned psycholinguistic factors as well as on RTs and accuracy scores obtained in an independent behavioral pilot reading task performed on a different set of 23 participants. Each stimulus within a subset was associated with a double pulse of TMS stimulation separated by 40 msec (Juan & Walsh, 2003). The three subsets differed in the onset of the stimulation that was delivered at three time windows: 20 msec before and after the stimulus onset (−20/20 msec), 40 and 80 msec after the stimulus onset (40/80 msec), or 100 and 140 msec after the stimulus onset (100/140 msec). Therefore, there was no “no-TMS” baseline condition in the main reading task. Instead, the −20/20 condition acted as the baseline. Existing EEG/MEG studies suggest that it is unlikely that any phonological, orthographic, or semantic process could already take place in such an early time window. Additionally, a pair-pulse stimulation applied at 0 and 40 msec from the stimulus onset was previously used as baseline in Duncan et al.’s (2010) study. A comparison of the performance obtained in this condition and the one obtained on vertex stimulation were identical, which suggests that the stimulation applied in the 0/40 msec time window (which is even later than our own baseline) provides a valid baseline condition. The association between the stimuli subset and the TMS stimulation timing was counterbalanced across participants. To reduce the possibility that participants feel the

different stimulation timings, within each block, the presentation order of the stimuli associated with the different stimulation timings was pseudorandomized, such that the same stimulation timing (e.g., 40/80 msec) was delivered in three consecutive trials, and, in the next three trials, it either remained constant or was changed up (e.g., 100/140 msec) or down (e.g., −20/20 msec) by one window (Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012). For each participant, the TMS stimulation was applied on the area that had been identified during the localizer session (or sham stimulation on vertex in the control experiment). During the reading task, regular words, irregular words, and pseudowords were presented in separated blocks. Their presentation order was counterbalanced across participants. A trial consisted of the following sequence of events: a 100-msec beep indicating the beginning of the trial was presented. This was followed by 900 msec of blank screen. Then, the stimulus was presented at the center of the screen for 500 msec, followed by a blank screen for 1500 msec, giving a total duration of 3 sec. The participants were instructed to read aloud each written stimulus as quickly and accurately as possible. The vocal response triggered a voice key connected to a button box. Naming latencies were measured from the onset of the stimulus to the onset of the participants’ vocal response. During the session, participants’ pronunciations were monitored and also recorded, which enabled reidentification of mispronunciations (as judged by two of the coauthors). No feedback was provided. Presentation, timing, and data collection were controlled by E-Prime 1.2 software.

## RESULTS

### Localizer Tasks

In each experiment, we successfully localized the ROIs in the left as well as in the right hemisphere. For each ROI, repetitive TMS consistently slowed the RTs in at least 10 participants, as shown in Table 2 and in Figure 2. This

**Table 1.** Characteristics of the Stimuli Used in the Reading Task

	<i>Regular Words</i>	<i>Irregular Words</i>	<i>Pseudowords</i>
Number of letters	6.13	6.13	6.13
Number of phonemes	4.76	4.76	4.68
Number of syllables	1.86	1.86	1.83
Summed bigram frequency	12,742.11	13,207.58	12,998.86
Word frequency (film)	36.84	44.85	
Word frequency (text)	33.85	36.56	
Subjective frequency (max = 6)	4.81	5.05	
Orthographic uniqueness point	5.61	5.78	
Number of orthographic neighbors	2.96	2.11	

Lexical frequency and summed bigram frequency are given in number of occurrences per million.

**Table 2.** Average MNI Coordinates (in mm) of Each ROI, Number of Participants in Each Group, and Mean RT (in msec) Slowdown Obtained in Each Localizer Task (also Presented in Terms of Percentages of the Mean RT Obtained in the Trials without TMS)

	Site	Average MNI Coordinates			No. of Participants	Mean Slowdown RT
		<i>x</i>	<i>y</i>	<i>z</i>		
Exp. 1	Left vOT	-45	-60	-16	12	33 (5.3%)
	Right vOT	45	-60	-18	10	36 (5.6%)
Exp. 2	Left pMTG	-58	-57	9	12	26 (3.9%)
	Right pMTG	57	-49	9	11	35 (5.0%)
Exp. 3	Left SMG	-54	-37	41	10	61 (5.2%)
	Right SMG	55	-34	39	10	56 (4.7%)

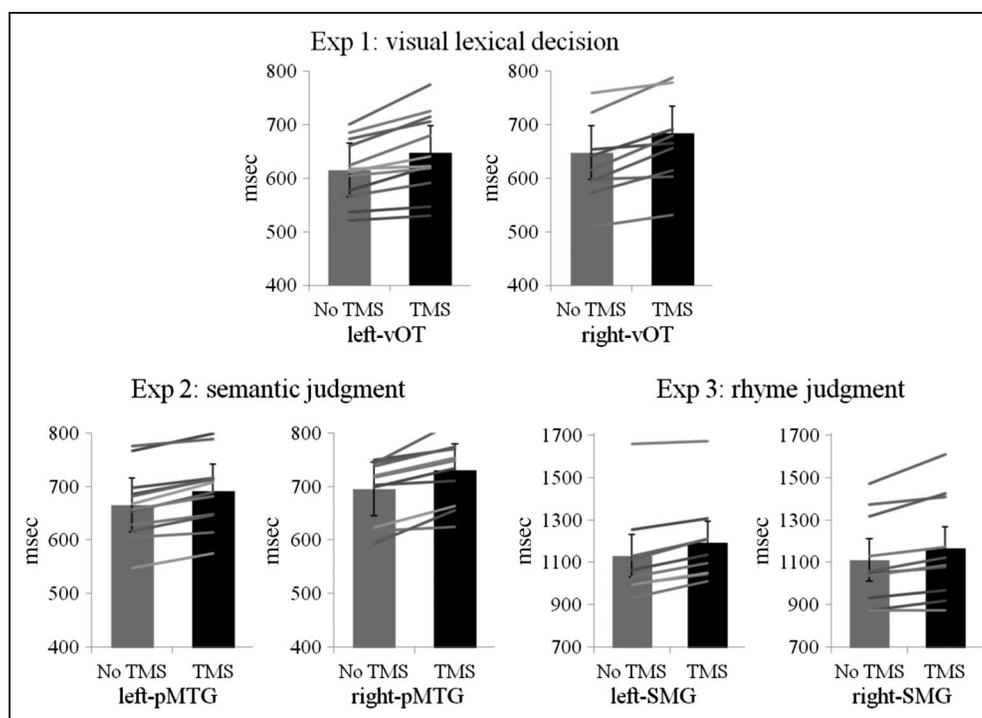
corresponded, on average, to 71% of the participants who were tested. The precise stimulation site of each participant projected on the averaged brain of all participants within each experiment is shown in Figure 3. Generally, within vOT and SMG, the areas localized in the left and right hemisphere were rather symmetrical. A small difference was found in pMTG where the areas localized in the right hemisphere were on average 8 mm more anterior than the areas localized in the left hemisphere.

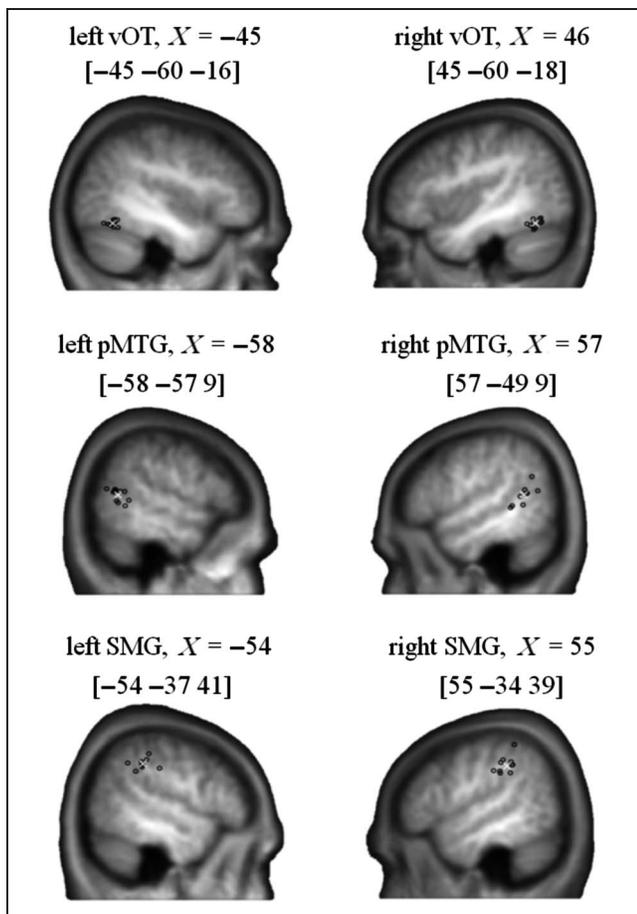
### Reading Task

As stated in the Introduction, within each ROI, TMS effects might vary from one type of stimulus to another: vOT disruption would affect both words and pseudowords according to the prelexical account (Dehaene et al., 2005; Cohen

et al., 2002) but would affect only words according to the lexical account (Pugh et al., 2010; Glezer et al., 2009; Kronbichler et al., 2004). The pMTG disruption was expected to affect only words. Finally, SMG disruption was expected to be particularly deleterious to pseudoword reading. To test our predictions within each ROI, we first ran, for each experiment, three-way repeated-measures ANOVAs on log-transformed RT for trials with correct responses and on accuracy scores, with Material (regular words, irregular words, pseudowords) and TMS (baseline, 40/80 msec, 100/140 msec) as within-subject factors and Hemisphere (right, left) as a between-subject factor. This would provide a general picture of what happened within each ROI. When TMS  $\times$  Material interaction was significant, the TMS effect on each type of material was investigated. Pairwise comparisons using Dunnett's comparison method was used for

**Figure 2.** The RT data (with error bars) obtained in the three localizer tasks and for each ROI are shown as bar plots. The gray bars indicate no TMS trials, and the black bars indicate repetitive TMS trials. Overlaid on this group effect are the lines representing data from individual participants.





**Figure 3.** The final testing sites for all participants (circles) and the mean group location (white cross) on the averaged brain of all participants within each experiment normalized to the standard MNI-152 space with an affine registration (Jenkinson & Smith, 2001) shown on a parasagittal plane. The average MNI coordinates of each site is in brackets.

comparing the results obtained in each of the two stimulation time windows (40/80 msec and 100/140 msec) to the baseline condition (-20/20 msec): If the ROI contributes to reading, one should observe an increase of the RTs compared to baseline. The pairwise comparisons on the effect of Material were performed using Bonferroni correction.

#### Experiment 1: vOT Stimulation

Three-way repeated-measures ANOVAs performed on the RT data showed significant main effects of Material [ $F(2, 40) = 15.6, p < .0001$ ] and TMS [ $F(2, 40) = 10.3, p = .0002$ ] without an interaction between these two factors ( $F < 1$ ; Figure 4). Pairwise comparisons on the effect of Material showed that RTs were significantly longer to pseudowords (606 msec) than to regular (524 msec,  $p < .0001$ ) and irregular words (558 msec,  $p = .02$ ). Irregular words also led to longer RTs compared to regular words ( $p = .03$ ). Pairwise comparisons on the main effect of TMS showed that vOT stimulation delivered in both the

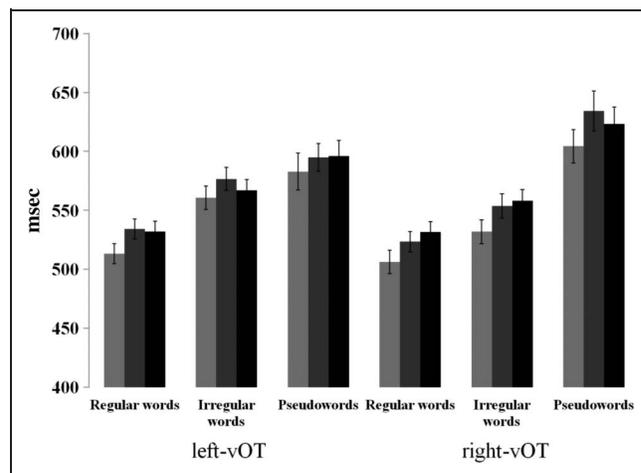
40/80 msec (570 msec) and 100/140 msec (568 msec) time windows slowed reading compared to baseline (550 msec,  $p = .0002$  and  $p = .0006$ , respectively). Neither the main effect of Hemisphere nor its interaction with the other main factors was significant (all  $F$ s  $< 2$ , all  $p$ s  $> .23$ ).

The three-way repeated-measures ANOVA performed on accuracy scores only showed a significant effect of Material [ $F(2, 40) = 22.4, p < .0001$ ]. Pairwise comparisons showed that this reflected higher reading scores for regular words (99.1%) compared to irregular words (96.5%,  $p = .002$ ) and pseudowords (94.8%,  $p < .0001$ ) and for irregular words compared with pseudowords ( $p = .02$ ). With this near-ceiling performance, neither the effect of TMS ( $F < 1$ ) nor its interaction with the other factors was observed ( $p$ s  $> .10$ ).

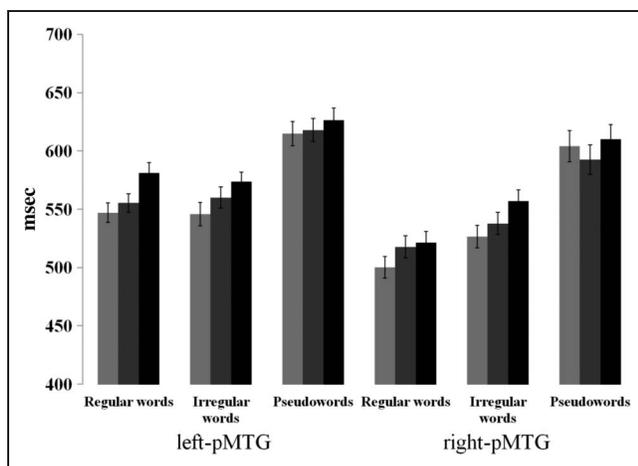
As predicted by the prelexical account (Dehaene et al., 2005; Cohen et al., 2002), the results obtained on vOT showed that TMS equally affected the speed of regular word, irregular word, and pseudoword reading and that the effect was found when the stimulation was applied in both the earliest (40/80 msec) and later (100/140 msec) stimulation time windows.

#### Experiment 2: pMTG Stimulation

The three-way ANOVA performed on the RT data showed that the main effects of Material [ $F(2, 42) = 28.1, p < .0001$ ] and TMS [ $F(2, 42) = 20.6, p < .0001$ ] were significant (Figure 5). The longest RTs occurred for pseudoword reading (611 msec) and were significantly slower than those for reading regular (498 msec,  $p < .0001$ ) and irregular words (523 msec,  $p < .0001$ ). The difference in reading speed between regular and irregular words, however, was not significant ( $p = .45$ ). The main effect of TMS showed that pMTG stimulation delivered in both



**Figure 4.** The RTs obtained for regular word, irregular word, and pseudoword reading in Experiment 1 (vOT stimulation). Light gray, dark gray, and black bars indicate the trials in which the stimulation was applied in the -20/20 msec (baseline), 40/80 msec, and 100/140 msec time window, respectively.



**Figure 5.** The RTs obtained for regular word, irregular word, and pseudoword reading in Experiment 2 (pMTG stimulation). Light gray, dark gray, and black bars indicate the trials in which the stimulation was applied in the  $-20/20$  msec (baseline), 40/80 msec, and 100/140 msec time window, respectively.

40/80 msec (564 msec) and 100/140 msec time windows (578 msec) slowed reading compared to baseline (557 msec,  $p = .015$  and  $p < .0001$ , respectively). Interestingly, the interaction between TMS and Material was also significant [ $F(4, 84) = 2.6, p = .04$ ], indicating that pMTG stimulation did not affect all types of written stimuli equally. Neither the main effect of Hemisphere nor its interaction with the other factors was significant (all  $ps > .18$ ).

The effect of TMS was then considered separately for each type of material. As shown in Figure 5, the TMS effect in both hemispheres seems to be restricted to words. Consistent with our predictions, a two-way ANOVA (TMS  $\times$  Hemisphere) performed on each type of material showed that stimulation to pMTG produced a significant effect for both regular [ $F(2, 42) = 10.7, p = .0002$ ] and irregular words [ $F(2, 42) = 13.6, p < .0001$ ], but not for pseudowords [ $F(2, 42) = 1.8, p = .18$ ]. No interaction between TMS and hemisphere was found [ $F(2, 42) = 1.2, p = .3$  for regular words and  $F_s < 1$  for irregular words and pseudowords]. Planned comparisons showed that, for both word materials, the stimulation delivered in the 40/80 msec and 100/140 msec time windows impaired reading speed compared to baseline (regular words: baseline vs. 40/80 msec,  $p = .01$ ; baseline vs. 100/140 msec,  $p < .0001$ ; irregular words: baseline vs. 40/80 msec,  $p = .02$ ; baseline vs. 100/140 msec,  $p < .0001$ ). This result is illustrated in Figure 7.

The three-way repeated-measures ANOVA performed on accuracy scores showed only a significant effect of Material [ $F(2, 42) = 14.9, p < .0001$ ] reflecting better performance for regular (99.1%) and irregular (97.9%) words compared to pseudowords (95.6%,  $p < .0001$  and  $p = .004$ , respectively), although they were not statistically different from each other ( $p = .17$ ).

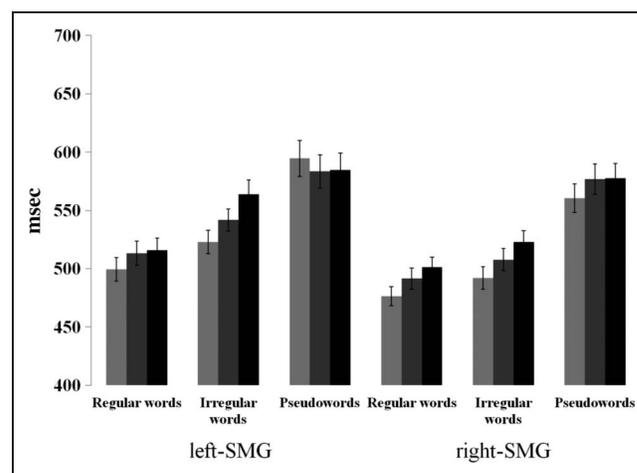
Consistently with our prediction, TMS applied on pMTG affected reading speed for words but not for pseudo-

words. The disruptive effect was found when the stimulation was applied in both the earliest (40/80 msec) and later (100/140 msec) stimulation time windows.

### Experiment 3: SMG Stimulation

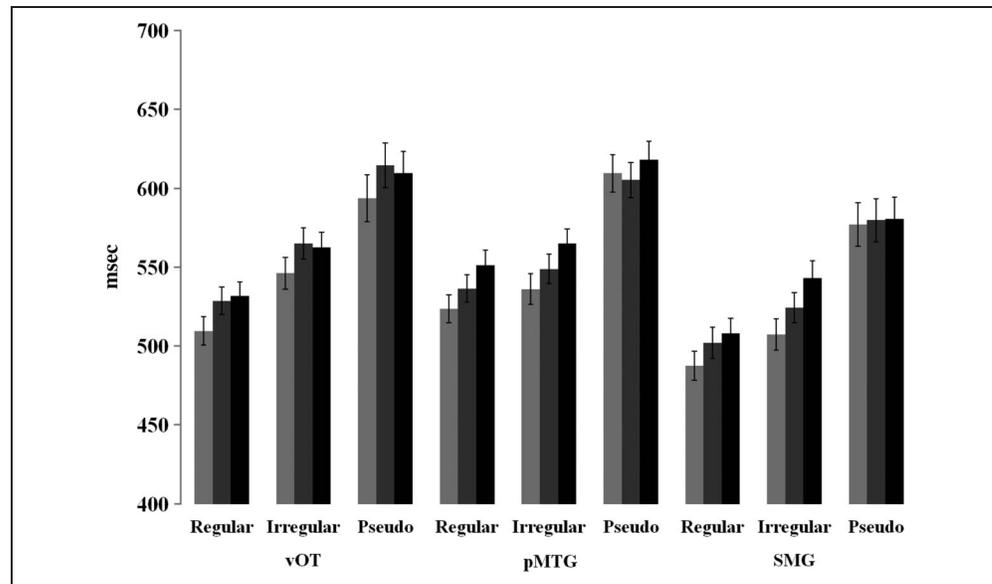
A three-way repeated-measures ANOVA performed on the RT data showed the same result pattern as in Experiment 2, with significant main effects of Material [ $F(2, 36) = 24.4, p < .0001$ ] and TMS [ $F(2, 36) = 7.2, p = .002$ ]. Again, longer RTs were observed for pseudowords (585 msec) compared to regular (503 msec,  $p < .0001$ ) and irregular words (529 msec,  $p = .0002$ ). The difference between the two types of words almost reached significance ( $p = .07$ ). The main effect of TMS showed that SMG stimulation delivered in both the 40/80 msec (540 msec) and 100/140 msec (549 msec) time windows slowed reading compared to baseline (528 msec; baseline vs. 40/80 msec:  $p = .04$ , baseline vs. 100/140 msec:  $p = .0006$ ). The TMS effect also interacted significantly with Material [ $F(4, 72) = 3.3, p = .02$ ], indicating that SMG stimulation did not affect all types of written stimuli equally. As described below, TMS slowed responses to words but not to pseudowords (Figure 7). Although the RTs presented in Figure 6 showed a somewhat stronger effect on pseudowords when the stimulation was applied on the right hemisphere, none of the effects related to Hemisphere was statistically significant (all  $ps > .3$ ).

To examine the TMS effect on each type of material, a two-way ANOVA (TMS  $\times$  Hemisphere) was performed. The stimulation applied during both regular and irregular word reading significantly affect performance [regular words:  $F(2, 36) = 5.3, p = .01$ , irregular words:  $F(2, 36) = 15.9, p < .0001$ ]. Planned comparisons showed that, for both types of words, TMS affected reading speed when it



**Figure 6.** The RTs obtained for regular word, irregular word and pseudoword reading in Experiment 3 (SMG stimulation). Light gray, dark gray, and black bars indicate the trials in which the stimulation was applied in the  $-20/20$  msec (baseline), 40/80 msec, and 100/140 msec time window, respectively.

**Figure 7.** The RTs obtained for regular word, irregular word, and pseudoword reading in Experiments 1, 2, and 3. The data from the left and right hemispheres were pooled. Light gray, dark gray, and black bars indicate the trials in which the stimulation was applied in the -20/20 msec (baseline), 40/80 msec, and 100/140 msec time window, respectively.



was applied in both 40/80 msec and 100–140 msec time windows compared to baseline (regular words: baseline vs. 40/80 msec,  $p = .05$ ; baseline vs. 100/140 msec,  $p = .003$ ; irregular words: baseline vs. 40/80 msec,  $p = .01$ ; baseline vs. 100/140 msec,  $p < .0001$ ). In contrast to word reading, pseudoword reading was surprisingly unaffected by SMG disruption at the early reading stage explored here ( $F < 1$ ).

The same analysis performed on accuracy scores showed only a significant effect of Material [ $F(2, 36) = 24.3, p < .0001$ ], reflecting a similar performance pattern as on the RT data (pseudowords [94.6%] vs. regular words [99.5%],  $p < .0001$ ; pseudowords vs. irregular words [97.7%],  $p = .0003$ ; irregular words vs. regular words,  $p = .05$ ). Neither the effect of TMS ( $p > .30$ ) nor its interaction with the other main factors was significant ( $ps > .09$ ).

Overall, we obtained the same result pattern as in Experiment 2. In contrast to our prediction, TMS applied on SMG affected reading speed for words but not for pseudowords. The disruptive effect was found when the stimulation was applied in both the earliest (40/80 msec) and later (100/140 msec) stimulation time windows (Figure 7).

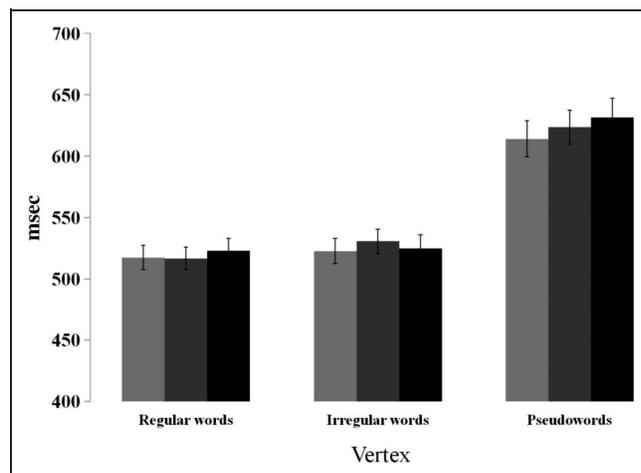
#### Control Experiment: Sham Stimulation on Vertex

The accuracy and RT data were analyzed in two-way ANOVAs with Material and TMS as within-subject factors. For both types of data, the only significant effect was the main effect of Material [RT:  $F(2, 22) = 23.1, p < .0001$ , accuracy:  $F(2, 22) = 13, p < .0001$ ]. For RTs, this was because of longer RTs for pseudowords (623 msec) compared to regular (519 msec,  $p < .0001$ ) and irregular words (526 msec,  $p < .0001$ ), without a significant difference between the two types of words ( $p < 1$ ). As regards the accuracy data, lower reading scores were observed

for pseudowords (92.3%) compared to regular (99.1%,  $p = .0002$ ) and irregular words (97.2%,  $p = .005$ ) without a significant difference between the latter ( $p = .5$ ). Most importantly, neither the TMS effect nor its interaction with Material was significant ( $F_s \leq 1$ , Figure 8). Given that the sham stimulation imitates the noise and vibration produced by the real TMS coil, the absence of a TMS effect in this control experiment helped to rule out non-specific effects of TMS because of these potential artifacts.

## DISCUSSION

Overall, the classic effects of lexicality and regularity were observed, with performance on words being systematically better than on pseudowords and performance on



**Figure 8.** The RTs obtained for regular word, irregular word, and pseudoword reading in the control experiment (vertex sham stimulation). Light gray, dark gray, and black bars indicate the trials in which the stimulation was applied in the -20/20 msec (baseline), 40/80 msec, and 100/140 msec time window, respectively.

regular words being better than on irregular words, either in terms of reading speed or reading accuracy, or both. The TMS effects varied with the type of stimulus. This, together with the absence of the sham TMS effect on vertex, provided control conditions supporting the specificity of the TMS effects reported here. Below, we discuss in detail how TMS stimulation delivered to the three ROIs in both hemispheres affected reading these different types of stimuli.

### **The Contribution of vOT to Reading**

The vOT stimulation applied in the 40/80 msec and 100/140 msec time windows slowed down both word and pseudoword reading, suggesting that this area contributes to the processing of both kinds of written material in the same way. This observation is in line with the assumption that, at least in a very early stage of the reading process, vOT is sensitive to bottom-up information. It is compatible with both the ideas that this region mediates orthographic analysis at the sublexical level, for instance, in terms of bigrams (Dehaene et al., 2005), a variable that had been matched here across stimulus types, and that it processes visual form information that is important for recognizing written words (e.g., Price & Devlin, 2003, 2011).

### **The Contribution of pMTG to Reading**

pMTG stimulation specifically slowed down the RTs for regular and irregular words, that is, stimuli with lexico-semantic information. This finding is coherent with existing brain imaging and TMS studies showing the contribution of this area to semantic processing (Hoffman et al., 2012; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011; Lau et al., 2008). Compared to baseline, the TMS effects were observed in both the 40/80 msec and 100/140 msec time windows. This chronometric information suggests an early contribution of pMTG exclusively to word reading. The fact that, already at an early stage, both regular and irregular words are processed within an area that plays a key role in semantic processing challenges the traditional view of dual-route models claiming for a stronger reliance on the lexical-semantic system during irregular compared to regular word reading (Jobard et al., 2003; Rumsey et al., 1997). At this stage of research, we must nevertheless acknowledge that this result pattern could also depend on the language used in the study. The presence of less "enemies" or alternative pronunciations for French irregular words compared to English irregular words might reduce the difference between regular and irregular words reported here.

### **The Contribution of SMG to Reading**

The activity of SMG has been associated with phonological processing and appears to be stronger in response to

pseudowords than to words (Pugh et al., 2000, 2010; Vigneau et al., 2005; Sandak, Mencl, Frost, & Pugh, 2004; Xu et al., 2001; Price et al., 1996). Therefore, disrupting its function was expected to interfere with pseudoword more than with word reading. Surprisingly, the present finding showed that, although we successfully used repetitive TMS to interfere with rhyme judgments on written pseudowords during the localizer task, only word, but not pseudoword, reading was slowed down by paired-pulse stimulation applied during the reading task.

Here, we consider potential explanations for this unexpected result. First, rhyme judgment may engage cognitive processes beyond those that are required during phonological analysis and grapheme-to-phoneme conversion in reading (Owen, Borowsky, & Sarty, 2004). In other words, TMS applied during the rhyme judgment localizer task might interrupt processes that are not involved in reading. This interpretation, however, is inconsistent with our finding that word reading was affected by the stimulation. One factor that may account for the full range of results is the fact that pseudoword processing is slower than word processing, coupled with the very early TMS timings applied during the reading task. Here, the involvement of two types of phonological processing could be assumed. One, perceptual, would be involved in reading aloud all types of written material, but with a lower threshold activation for lexical entries, whereas the other, post-perceptual and typical of metaphonological tasks, would focus intentionally on a lexicon-independent phonological property. Thus, although an early and extremely transient disruptive effect induced by paired-pulse stimulation was sufficient to interrupt a fast phonological process tuned to lexical entries and appropriate to reading known materials, a higher amount and/or longer lasting disruptive effect (as the one applied during the localizer task) would be necessary to interfere with a more effortful and time-consuming explicit phonological process that takes place during pseudoword reading or metaphonological tasks. An additional factor that could also contribute to or emphasize the difference between word and pseudoword processing observed on SMG (and also on pMTG) was the use of block design. Although this design has been extensively used in studies on reading (Mechelli et al., 2005; Vigneau et al., 2005; Simos et al., 2002; Hagoort et al., 1999), a comparison of the finding obtained when different types of stimuli are presented in separated blocks to the finding obtained when they are presented within the same block could provide insights into the role of reading strategies on both behavioral and brain activation patterns.

Although cross-region comparison was not the aim of the study, our findings might appear to exhibit different patterns across regions. However, when the data from the three experiments were combined into an omnibus ANOVA, the three-way interaction (Material  $\times$  TMS  $\times$  ROIs) did not reach significance [ $F(8, 248) = 1.2, p = .28$ , when the data from the two hemispheres were

considered and  $F(8, 124) = 1.7, p = .11$ , when only the data from the left hemisphere were considered]. It is very likely that our data were underpowered to look for this interaction. Further research is needed to investigate this issue.

### **To What Extent Does the Right Hemisphere Contribute to Reading?**

The TMS stimulation that we applied to vOT, pMTG, and SMG at an early stage of reading process did not affect the left and right hemispheres differently. If anything, the disruptive effects were somewhat numerically larger in the right hemisphere in some experimental conditions (SMG stimulation during pseudoword reading and vOT stimulation during irregular word and pseudoword reading). It would then seem that, at an early stage of written word processing, both hemispheres contribute to reading, consistently with some brain imaging studies that showed an activation of right vOT, pMTG, and SMG during language tasks (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2007; Paulesu et al., 2000; Fiez, Balota, Raichle, & Petersen, 1999; Hagoort et al., 1999; Price et al., 1996).

The fact that the magnetic stimulation applied to the right hemisphere affected reading performance while lesions within the same areas do not always lead to deleterious effects could be explained in terms of the time-scale for functional reorganization after a lesion. Although massive reshaping of the language network may occur during recovery from chronic structural lesions (Saur et al., 2006), the very transient disruptive effect induced by TMS leaves the language system no time to develop adaptive plasticity (Hartwigsen et al., 2010) and is thus able to reveal more subtle contribution of some brain structures.

Nevertheless, some issues related to TMS stimulation must be considered. First, the observation of quantitatively similar TMS effects in both hemispheres does not imply that the two hemispheres contribute equally to the reading process. As shown in previous TMS studies, magnetic stimulation may affect to a greater or to a more crucial extent less active neurons (Pattamadilok et al., 2010; Silvanto, Muggleton, & Walsh, 2008). A dominant left-hemisphere contribution could be hidden by this phenomenon. Second, the effect found following right-hemisphere stimulation could result from cross-callosal spreading of the induced current: The disruption observed when the stimulation was applied on the right hemisphere might not purely reflect a contribution of this hemisphere to reading but also some interfering neural noise triggered by stimulating a site that is homologous to the one dedicated to reading in the left hemisphere. Although this study did not provide direct evidence to discard this possibility, an analysis comparing the size of the TMS effects obtained in the left and right hemisphere argued against it. Indeed, no significant difference

between the two hemispheres was found on any ROIs and in any time window. Logically, TMS effects resulting from ipsilateral stimulation are expected to be stronger than those transcallosally induced by the stimulation applied contralaterally (Kobayashi & Pascual-Leone, 2003).

### **Serial versus Parallel Reading Processes**

The activation time course of the ROIs investigated here begins earlier than what has been observed with EEG or MEG techniques. Indeed, several studies reported a similar activation time course for vOT, pMTG, and SMG around 200 msec from stimulus onset (Pammer et al., 2004; Rossion, Joyce, Cottrell, & Tarr, 2003; Bentin, Mouchetant-Rostaing, Giard, Echallier, & Pernier, 1999; Tarkiainen et al., 1999). The timing difference between EEG/MEG and TMS studies could be explained by the fact that ERP components arise from large-scale neuronal synchrony across activity in multiple structures and, therefore, lag behind the earliest wave of activity that is affected by magnetic stimulation in any given structure (Walsh & Cowey, 2000; Schroeder, Mehta, & Givre, 1998). Interestingly, the effects reported here also begin earlier than the ones reported in previous TMS studies. For instance, in a lexical decision task, Duncan et al. (2010) reported a TMS effect on vOT that became significant when the stimulation was applied in the 80/120 msec time window. The same timing was reported by Sliwiska et al. (2012), who investigated the contribution of SMG during a homophone judgment task. Several factors such as the language used in the studies (French vs. English), psycholinguistic factors related to the material or task demands could potentially explain this timing difference. For instance, in Duncan et al. and Sliwiska et al.'s studies, participants were required to make an explicit judgment on some aspects of the stimuli, which is not the case in this study. This task-specific process might have a top-down influence on the activity of the targeted area and therefore on the effect of TMS (Price & Devlin, 2011; Silvanto et al., 2008; Gilbert & Sigman, 2007). Some fMRI studies indeed showed an effect of task instructions with the brain establishing a task set before the task is actually performed (Sakai & Passingham, 2003, 2006). Further studies should help to clarify this issue.

The main issue here is the fact that the earliest sign of disruption by TMS occurred at the same time for stimulation on vOT, pMTG, and SMG. The serial models posit a temporally linear processing sequence in which the visual information is first analyzed in the primary visual areas before being conveyed to the vOT that processes orthographic representations at an abstract level. The output from this area is then sent to the phonological and lexico-semantic system successively (Liu et al., 2003; Warrington & Shallice, 1980). The fact that the TMS effects already occurred within the 40/80 msec stimulation time window for *all* the ROIs argues against this strictly sequential assumption. Our finding is more compatible with the notion that different types of information can be accessed largely

in parallel and corroborate existing TMS, EEG, MEG, and behavioral evidence that orthographic, phonological, and semantic processes occur within the first 200 msec of the perception and recognition processes (Hauk et al., 2012; Sliwiska et al., 2012; Price & Devlin, 2011; Duncan et al., 2010; Cornelissen et al., 2009; Pulvermüller et al., 2009; Rayner, Sereno, Lesch, & Pollatsek, 1995).

## Conclusion

This study used chronometric TMS to investigate whether the brain distinguishes between regular words, irregular words, and pseudowords already at an early stage of the reading process. We explored this issue in three brain areas that play a central role in orthographic, phonological, and semantic processing. Our findings showed that paired TMS pulses delivered on the brain areas involved in semantic and phonological processing, as early as 40/80 msec after stimulus onset, allowed us to distinguish between word and pseudoword processing. The disruptive effect of TMS in both 40/80 msec and 100/140 msec time windows indicated that only words were processed within these areas at least during the first 140 msec. Within this time window, both words and pseudowords were processed in the key area involved in orthographic processing. Thus, there seems to be an early distinction between word and pseudoword processing in the semantic and phonological systems, but not in the orthographic one. More research on pseudoword reading is needed to better understand whether and how the contributions of the orthographic and phonological systems evolve through different stages of reading process. No distinction was found on regular and irregular words in any brain areas investigated here, even though the behavioral data showed better performance on regular word reading. Taken together, the two types of data suggested that the difference in terms of spelling regularity might occur only at a later processing stage. Nevertheless, this conclusion should be tempered by the fact that, compared to English, French is a language with higher spelling-to-sound consistency. In addition to these main findings, the absence of a differential effect of TMS in the left and the right hemisphere suggests a contribution of the right hemisphere to reading, although further studies are required to clarify the mechanism leading to the TMS effects within and cross-hemisphere. Finally, the similar time course observed across the three ROIs also suggests that the orthographic, phonological, and semantic systems all become active very quickly, probably before 100 msec after exposure to written input.

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## Note

1. A post hoc analysis based on imageability rating scores performed by an independent group of 20 participants (rating scale = 1–5, with 5 corresponding to the *highest degree of imageability*) showed that irregular words had higher degree of imageability (3.67) than regular words (3.14,  $p = .002$ ). To explore whether the effect of TMS on the different materials was modified by the degree of imageability, we performed analyses (a linear mixed model) taking into account material, TMS, hemisphere, and imageability as fixed factors and subject and items as random factors. The results showed that imageability did not significantly affect the main interaction, TMS  $\times$  Material, in any ROI (all  $ps > .09$ ).

## REFERENCES

- Behrmann, M., & Plaut, D. C. (2012). Bilateral hemispheric processing of words and faces: Evidence from word impairments in prosopagnosia and face impairments in pure alexia. *Cerebral Cortex*, *24*, 1102–1118.
- Behrmann, M., & Plaut, D. C. (2013). Distributed circuits, not circumscribed centers, mediate visual recognition. *Trends in Cognitive Sciences*, *17*, 210–219.
- Ben-Shachar, M., Dougherty, R. F., Deutsch, G. K., & Wandell, B. A. (2007). Differential sensitivity to words and shapes in ventral occipito-temporal cortex. *Cerebral Cortex*, *17*, 1604–1611.
- Bentin, S., Mouchetant-Rostaing, Y., Giard, M. H., Echallier, J. F., & Pernier, J. (1999). ERP manifestations of processing printed words at different psycholinguistic levels: Time course and scalp distribution. *Journal of Cognitive Neuroscience*, *11*, 235–260.
- Binder, J. R., McKiernan, K. A., Parsons, M. E., Westbury, C. F., Possing, E. T., & Kaufman, J. N. (2003). Neural correlates of lexical access during visual word recognition. *Journal of Cognitive Neuroscience*, *15*, 372–393.
- Bolger, D. J., Perfetti, C. A., & Schneider, W. (2005). Cross-cultural effect on the brain revisited: Universal structures plus writing system variation. *Human Brain Mapping*, *25*, 92–104.
- Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Choy, J., & Gitelman, D. R. (2003). Modality-specific and -independent developmental differences in the neural substrate for lexical processing. *Journal of Neurolinguistics*, *16*, 383–405.
- Brem, S., Bach, S., Kucian, K., Guttorm, T. K., Martin, E., & Lyytinen, H. (2010). Brain sensitivity to print emerges when children learn letter–speech sound correspondences. *Proceedings of the National Academy of Sciences, U.S.A.*, *107*, 7939–7944.
- Brem, S., Bucher, K., Halder, P., Summers, P., Dietrich, T., & Martin, E. (2006). Evidence for developmental changes in the visual word processing network beyond adolescence. *NeuroImage*, *29*, 822–837.
- Brunswick, N., McCrory, E., Price, C. J., Frith, C. D., & Frith, U. (1999). Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: A search for Wernicke's Wortschatz? *Brain*, *122*, 1901–1917.
- Cohen, L., Lehericy, S., Chochon, F., Lemer, C., Rivaud, S., & Dehaene, S. (2002). Language-specific tuning of visual cortex?

- Functional properties of the visual word form area. *Brain*, *125*, 1054–1069.
- Coltheart, M., Rastle, K., Perry, C., Langdon, R., & Ziegler, J. (2001). DRC: A dual route cascaded model of visual word recognition and reading aloud. *Psychological Review*, *108*, 204–256.
- Compton, P. E., Grossenbacher, P., Posner, M. I., & Tucker, D. M. (1991). A cognitive-anatomical approach to attention in lexical access. *Journal of Cognitive Neuroscience*, *3*, 304–312.
- Cornelissen, P. L., Kringelbach, M. L., Ellis, A. W., Whitney, C., Holliday, I. E., & Hansen, P. C. (2009). Activation of the left inferior frontal gyrus in the first 200 msec of reading: Evidence from magnetoencephalography (MEG). *PLoS One*, *4*, e5359.
- Dehaene, S., & Cohen, L. (2011). The unique role of the visual word form area in reading. *Trends in Cognitive Sciences*, *15*, 254–262.
- Dehaene, S., Cohen, L., Sigman, M., & Vinckier, F. (2005). The neural code for written words: A proposal. *Trends in Cognitive Sciences*, *9*, 335–341.
- Dehaene, S., Pegado, F., Braga, L. W., Ventura, P., Nunes Filho, G., & Jobert, A. (2010). How learning to read changes the cortical networks for vision and language. *Science*, *330*, 1359–1364.
- Duncan, K. J., Pattamadilok, C., & Devlin, J. T. (2010). Investigating occipito-temporal contributions to reading with TMS. *Journal of Cognitive Neuroscience*, *22*, 1–12.
- Fiez, J. A., Balota, D. A., Raichle, M. E., & Petersen, S. E. (1999). Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. *Neuron*, *24*, 205–218.
- Fodor, J. A. (1983). *The modularity of mind*. Cambridge, MA: MIT Press.
- Frost, S. J., Einar Mencl, W., Sandak, R., Moore, D. L., Rueckl, J. G., & Katz, L. (2005). A functional magnetic resonance imaging study of the tradeoff between semantics and phonology in reading aloud. *NeuroReport*, *16*, 621–624.
- Gilbert, C. D., & Sigman, M. (2007). Brain states: Top-down influences in sensory processing. *Neuron*, *54*, 677–696.
- Glezer, L. S., Jiang, X., & Riesenhuber, M. (2009). Evidence for highly selective neuronal tuning to whole words in the “visual word form area.” *Neuron*, *62*, 199–204.
- Graves, W. W., Binder, J. R., Desai, R. H., Conant, L. L., & Seidenberg, M. S. (2010). Neural correlates of implicit and explicit combinatorial semantic processing. *Neuroimage*, *53*, 638–646.
- Graves, W. W., Desai, R., Humphries, C., Seidenberg, M. S., & Binder, J. R. (2010). Neural systems for reading aloud: A multiparametric approach. *Cerebral Cortex*, *20*, 1799–1815.
- Hagoort, P., Indefrey, P., Brown, C., Herzog, H., Steinmetz, H., & Seitz, R. J. (1999). The neural circuitry involved in the reading of German words and pseudowords: A PET study. *Journal of Cognitive Neuroscience*, *11*, 383–398.
- Harm, M. W., & Seidenberg, M. S. (2004). Computing the meanings of words in reading: Cooperative division of labor between visual and phonological processes. *Psychological Review*, *111*, 662–720.
- Hartwigsen, G., Baumgaertner, A., Price, C. J., Koehnke, M., Ulmer, S., & Siebner, H. R. (2010). Phonological decisions require both the left and right supramarginal gyri. *Proceedings of the National Academy of Sciences, U.S.A.*, *16494*–16499.
- Hauk, O., Coutout, C., Holden, A., & Chen, Y. (2012). The time-course of single-word reading: Evidence from fast behavioral and brain responses. *Neuroimage*, *60*, 1462–1477.
- Hauk, O., Davis, M. H., Ford, M., Pulvermüller, F., & Marslen-Wilson, W. D. (2006). The time course of visual word recognition as revealed by linear regression analysis of ERP data. *Neuroimage*, *30*, 1383–1400.
- Hauk, O., Patterson, K., Woollams, A., Watling, L., Pulvermüller, F., & Rogers, T. T. (2006). [Q:] When would you prefer a SOSSAGE to a SAUSAGE? [A:] At about 100 msec. ERP correlates of orthographic typicality and lexicality in written word recognition. *Journal of Cognitive Neuroscience*, *18*, 818–832.
- Herbster, A. N., Mintun, M. A., Nebes, R. D., & Becker, J. T. (1997). Regional cerebral blood flow during word and nonword reading. *Human Brain Mapping*, *5*, 84–92.
- Hoffman, P., Pobric, G., Drakesmith, M., & Lambon Ralph, M. A. (2012). Posterior middle temporal gyrus is involved in verbal and non-verbal semantic cognition: Evidence from rTMS. *Aphasiology*, *26*, 1119–1130.
- Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*, 143–156.
- Jobard, G., Crivello, F., & Tzourio-Mazoyer, N. (2003). Evaluation of the dual route theory of reading: A meta-analysis of 35 neuroimaging studies. *Neuroimage*, *20*, 693–712.
- Juan, C. H., & Walsh, V. (2003). Feedback to v1: A reverse hierarchy in vision. *Experimental Brain Research*, *150*, 259–263.
- Kawabata Duncan, K. J., Twomey, T., Parker Jones, O., Seghier, M. L., Haji, T., & Sakai, K. (2013). Inter- and intrahemispheric connectivity differences when reading Japanese kanji and hiragana. *Cerebral Cortex*, *24*, 1601–1608.
- Kiyosawa, M., Itoh, M., Nakagawa, Y., Kobayashi, N., & Tamai, M. (1994). Effect of kanji and kana reading on cerebral blood flow patterns measured by PET. *Japanese Journal of Ophthalmology*, *39*, 198–205.
- Kobayashi, M., & Pascual-Leone, A. (2003). Transcranial magnetic stimulation in neurology. *Lancet Neurology*, *2*, 145–156.
- Kronbichler, M., Hutzler, F., Wimmer, H., Mair, A., Staffen, W., & Ladurner, G. (2004). The visual word form area and the frequency with which words are encountered: Evidence from a parametric fMRI study. *Neuroimage*, *21*, 946–953.
- Lau, E. F., Phillips, C., & Poeppel, D. (2008). A cortical network for semantics: (De) constructing the n400. *Nature Reviews Neuroscience*, *9*, 920–933.
- Law, I., Kanna, I., Fujita, H., Lassen, N. A., Miura, S., & Uemura, K. (1991). Left supramarginal/angular gyri activation during reading of syllabograms in the Japanese language. *Journal of Neurolinguistics*, *6*, 243–251.
- Levy, J., Pernet, C., Treserras, S., Boulanouar, K., Aubry, F., & Démonet, J.-F. (2009). Testing for the dual-route cascade reading model in the brain: An fMRI effective connectivity account of an efficient reading style. *PLoS One*, *4*, e6675.
- Liu, Y., Perfetti, C. A., & Hart, L. (2003). ERP evidence for the time course of graphic, phonological, and semantic information in chinese meaning and pronunciation decisions. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *29*, 1231–1247.
- Maurer, U., Brandeis, D., & McCandliss, B. D. (2005). Fast, visual specialization for reading in English revealed by the topography of the n170 ERP response. *Behavioral and Brain Functions*, *1*, 1–13.
- McClelland, J. L. (1979). On the time relations of mental processes: An examination of systems of processes in cascade. *Psychological Review*, *86*, 287–330.
- Mechelli, A., Crinion, J. T., Long, S., Friston, K. J., Lambon Ralph, M. A., & Patterson, K. (2005). Dissociating reading processes on the basis of neuronal interactions. *Journal of Cognitive Neuroscience*, *17*, 1753–1765.
- New, B., Pallier, C., Brysbaert, M., & Ferrand, L. (2004). Lexique 2: A new French lexical database. *Behavior Research Methods*, *36*, 516–524.

- Nosarti, C., Mechelli, A., Green, D. W., & Price, C. J. (2010). The impact of second language learning on semantic and nonsemantic first language reading. *Cerebral Cortex*, *20*, 315–327.
- O'Shea, J., Muggleton, N. G., Cowey, A., & Walsh, V. (2004). Timing of target discrimination in human frontal eye fields. *Journal of Cognitive Neuroscience*, *16*, 1060–1067.
- Owen, W. J., Borowsky, R., & Sarty, G. E. (2004). fMRI of two measures of phonological processing in visual word recognition: Ecological validity matters. *Brain and Language*, *90*, 40–46.
- Pammer, K., Hansen, P. C., Kringelbach, M. L., Holliday, I., Barnes, G., & Hillebrand, A. (2004). Visual word recognition: The first half second. *Neuroimage*, *22*, 1819–1825.
- Pattamadilok, C., Knierim, I. N., Kawabata Duncan, K. J., & Devlin, J. T. (2010). How does learning to read affect speech perception? *Journal of Neuroscience*, *30*, 8435–8444.
- Paulesu, E., Démonet, J. F., Fazio, F., McCrory, E., Chanoine, V., & Brunswick, N. (2001). Dyslexia: Cultural diversity and biological unity. *Science*, *291*, 2165–2167.
- Paulesu, E., McCrory, E., Fazio, F., Menoncello, L., Brunswick, N., & Cappa, S. F. (2000). A cultural effect on brain function. *Nature Neuroscience*, *3*, 91–96.
- Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *The Journal of Neuroscience*, *28*, 8929–8933.
- 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.
- Plaut, D. C., McClelland, J. L., Seidenberg, M. S., & Patterson, K. (1996). Understanding normal and impaired word reading: Computational principles in quasi-regular domains. *Psychological Review*, *103*, 56–115.
- Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage*, *62*, 816–847.
- Price, C. J., & Devlin, J. T. (2003). The myth of the visual word form area. *Neuroimage*, *19*, 473–481.
- Price, C. J., & Devlin, J. T. (2011). The interactive account of ventral occipitotemporal contributions to reading. *Trends in Cognitive Sciences*, *15*, 246–253.
- Price, C. J., & Mechelli, A. (2005). Reading and reading disturbance. *Current Opinion in Neurobiology*, *15*, 231–238.
- Price, C. J., Wise, R. J. S., & Frackowiak, R. S. J. (1996). Demonstrating the implicit processing of visually presented words and pseudowords. *Cerebral Cortex*, *6*, 62–70.
- Pugh, K. R., Frost, S. J., Sandak, R., Landi, N., Moore, D., & Della Porta, G. (2010). Mapping the word reading circuitry in skilled and disabled readers. In *The neural basis of reading* (p. 281). New York: Oxford University Press.
- Pugh, K. R., Mencl, W. E., Jenner, A. R., Katz, L., Frost, S. J., & Lee, J. R. (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Mental Retardation and Developmental Disabilities Research Reviews*, *6*, 207–213.
- Pugh, K. R., Shaywitz, B. A., Shaywitz, S. E., Constable, R. T., Skudlarski, P., & Fulbright, R. K. (1996). Cerebral organization of component processes in reading. *Brain*, *119*, 1221.
- Pulvermüller, 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.
- Rayner, K., Sereno, S. C., Lesch, M. F., & Pollatsek, A. (1995). Phonological codes are automatically activated during reading: Evidence from an eye movement priming paradigm. *Psychological Science*, *6*, 26–32.
- Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*, 2008–2039.
- Rossion, B., Joyce, C. A., Cottrell, G. W., & Tarr, M. J. (2003). Early lateralization and orientation tuning for face, word, and object processing in the visual cortex. *Neuroimage*, *20*, 1609–1624.
- Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K., Maisog, J. M., & Andreason, P. (1997). Phonological and orthographic components of word recognition. A PET-RCBF study. *Brain*, *120*, 739.
- Sakai, K., & Passingham, R. E. (2003). Prefrontal interactions reflect future task operations. *Nature Neuroscience*, *6*, 75–81.
- Sakai, K., & Passingham, R. E. (2006). Prefrontal set activity predicts rule-specific neural processing during subsequent cognitive performance. *The Journal of Neuroscience*, *26*, 1211–1218.
- Sandak, R., Mencl, W. E., Frost, S. J., & Pugh, K. R. (2004). The neurobiological basis of skilled and impaired reading: Recent findings and new directions. *Scientific Studies of Reading*, *8*, 273–292.
- Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., & Rijntjes, M. (2006). Dynamics of language reorganization after stroke. *Brain*, *129*, 1371–1384.
- Schlaggar, B. L., & McCandliss, B. D. (2007). Development of neural systems for reading. *Annual Review of Neuroscience*, *30*, 475–503.
- Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cerebral Cortex*, *8*, 575–592.
- Silvanto, J., Lavie, N., & Walsh, V. (2005). Double dissociation of v1 and v5/mt activity in visual awareness. *Cerebral Cortex*, *15*, 1736–1741.
- Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Sciences*, *12*, 447–454.
- Simon, G., Bernard, C., Largy, P., Lalonde, R., & Rebai, M. (2004). Chronometry of visual word recognition during passive and lexical decision tasks: An ERP investigation. *International Journal of Neuroscience*, *114*, 1401–1432.
- Simos, P. G., Breier, J. I., Fletcher, J. M., Foorman, B. R., Castillo, E. M., & Papanicolaou, A. C. (2002). Brain mechanisms for reading words and pseudowords: An integrated approach. *Cerebral Cortex*, *12*, 297–305.
- 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.
- Szwed, M., Qiao, E., Jobert, A., Dehaene, S., & Cohen, L. (2014). Effects of literacy in early visual and occipitotemporal areas of Chinese and French readers. *Journal of Cognitive Neuroscience*, *26*, 459–475.
- Tarkiainen, A., Helenius, P., Hansen, P. C., Cornelissen, P. L., & Salmelin, R. (1999). Dynamics of letter string perception in the human occipitotemporal cortex. *Brain*, *122*, 2119–2131.
- Taylor, J. S. H., Rastle, K., & Davis, M. H. (2013). Can cognitive models explain brain activation during word and pseudoword reading? A meta-analysis of 36 neuroimaging studies. *Psychological Bulletin*, *139*, 766–791.
- Terao, Y., Ugawa, Y., Suzuki, M., Sakai, K., Hanajima, R., & Gemba-Shimizu, K. (1997). Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation. *Experimental Brain Research*, *115*, 541–545.
- Twomey, T., Kawabata Duncan, K. J., Hogan, J. S., Morita, K., Umeda, K., & Sakai, K. (2013). Dissociating visual form from

- lexical frequency using Japanese. *Brain and Language*, *125*, 184–193.
- Vandenberghe, R., Price, C., Wise, R., Josephs, O., & Frackowiak, R. S. (1996). Functional anatomy of a common semantic system for words and pictures. *Nature*, *383*, 254–256.
- Vigneau, M., Jobard, G., Mazoyer, B., & Tzourio-Mazoyer, N. (2005). Word and non-word reading: What role for the visual word form area? *Neuroimage*, *27*, 694–705.
- Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience*, *1*, 73–80.
- Walsh, V., Pascual-Leone, A., & Kosslyn, S. M. (2003). *Transcranial magnetic stimulation: A neurochronometrics of mind*. Cambridge, MA: MIT Press.
- Warrington, E. K., & Shallice, T. (1980). Word-form dyslexia. *Brain*, *103*, 99.
- Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology/ Evoked Potentials Section*, *108*, 1–16.
- 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.
- Xu, B., Grafman, J., Gaillard, W. D., Ishii, K., Vega-Bermudez, F., & Pietrini, P. (2001). Conjoint and extended neural networks for the computation of speech codes: The neural basis of selective impairment in reading words and pseudowords. *Cerebral Cortex*, *11*, 267–277.
- Xue, G., Chen, C., Jin, Z., & Dong, Q. (2006). Language experience shapes fusiform activation when processing a logographic artificial language: An fMRI training study. *Neuroimage*, *31*, 1315–1326.
- Ziegler, J. C., Jacobs, A. M., & Stone, G. O. (1996). Statistical analysis of the bidirectional inconsistency of spelling and sound in French. *Behavior Research Methods, Instruments, and Computers*, *28*, 504–515.
- Ziegler, J. C., Stone, G. O., & Jacobs, A. M. (1997). What is the pronunciation for-ough and the spelling for/u? A database for computing feedforward and feedback consistency in English. *Behavior Research Methods, Instruments, and Computers*, *29*, 600–618.