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Short title: Left-vOT effective connectivity during reading

Effective connectivity of the left-ventral occipito-temporal cortex during visual word processing: Direct causal evidence from TMS-EEG co-registration

Samuel Planton^{a, b}, Shuai Wang^{a, c, *}, Deirdre Bolger^c, Mireille Bonnard^d, Chotiga Pattamadilok^a

^a Aix Marseille Univ, CNRS, LPL, Laboratoire Parole et Langage, Aix-en-Provence, France

^b Cognitive Neuroimaging Unit, INSERM, CEA, CNRS, Université Paris-Saclay, NeuroSpin center, 91191 Gif/Yvette, France

^c Institute of Language, Communication and the Brain (ILCB) / Labex Brain and Language Research Institute (BLRI)

^d Aix Marseille Univ, INSERM, INS, Inst Neurosci Syst, Marseille, France

* Co-first author

Corresponding author

Chotiga Pattamadilok, PhD.

Laboratoire Parole et Langage

Centre National de la Recherche Scientifique (UMR 7309)

5, Av. Pasteur

13100 Aix-en-Provence

France

Email: chotiga.pattamadilok@univ-amu.fr

Tel : +33 601323435

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Abstract

As an interface between the visual and language system, the left ventral occipito-temporal cortex (left-vOT) plays a key role in reading. This functional role is supported by anatomical and functional connections between the area and other brain regions within and outside the language network. Nevertheless, only a few studies have investigated how the functional state of this area, which is dependent upon the nature of the task demand and the stimulus being processed, could influence the activity of the connected brain regions. In the present combined TMS-EEG study, we studied the left-vOT effective connectivity by adopting a direct, causal intervention approach. Using TMS, we probed left-vOT activation in different processing contexts and measured the neural propagation of activity from this area to other brain regions. A comparison of neural propagation measured during low-level visual detection of language versus non-language stimuli showed that processing language stimuli reduced neural propagation from the left-vOT to the right occipital cortex. Additionally, compared to the low-level visual detection of language stimuli, performing semantic judgments on the same stimuli further reduced neural propagation to the bilateral posterior cingulate, right superior parietal lobule and the right anterior temporal lobe. This reduction of cross-hemispheric neural propagation was accompanied by an increase in the collaboration between areas within the left-hemisphere language network. Together, this first evidence from a direct causal intervention approach suggests that processing language stimuli and performing a high-level language task reduce effective connectivity from the left-vOT to the right hemisphere, and may contribute to the left-hemisphere lateralization typically observed during language processing.

Keywords: Visual Word Form Area, visual word recognition, effective connectivity, causal intervention TMS approach, functional state

1. Introduction

The ventral part of the left occipito-temporal cortex (left-vOT) plays a central role in reading (Cohen et al., 2000; Dehaene et al., 2011) and this has been demonstrated across different writing systems (Bolger et al., 2005). The sensitivity of this brain area to written scripts has been illustrated both through developmental studies showing a progressive emergence of left-vOT responses during reading acquisition (Brem et al., 2010; Dehaene-Lambertz et al., 2018) and through comparisons of its responses to known scripts versus other kinds of visual input like false fonts, line drawings (Ben-Shachar et al., 2007) or objects (Szwed et al., 2011). In addition to the nature of visual input, left-vOT activity is also modulated by higher-order information on certain non-visual properties of the input, such as the phonological and semantic content, as well as on task demands (Twomey et al., 2011; Yang et al., 2012; Mano et al., 2013; Pattamadilok et al., 2017).

In terms of informational flow between this area and other parts of the brain, evidence from stimulus- and task-driven modulations of left-vOT activity suggests that this area exchanges information with both the primary visual cortex and areas involved in higher-order cognitive processes, thus, supporting the idea that it may act as an interface or gateway between the processing of visual and linguistic information (Price et al., 2011; Carreiras et al., 2014). So far, these exchanges of information have been investigated through analyses of anatomical and functional connectivity. Anatomically, the left-vOT is connected to the perisylvian language areas (Bouhali et al., 2014) as well as the inferior frontal gyrus, inferior parietal cortex, and anterior temporal lobe via several major fiber tracts whose development covary with children's reading skills (Yeatman et al., 2012, 2013). The existence of these anatomical connections suggests a privileged communication between the left-vOT and the left-hemisphere language network, which has also been confirmed at the functional level. For example, Koyama et al. (2010) conducted a resting-state functional connectivity analysis (RSFC) treating the left-vOT as a seed and showed that this area was connected to the left inferior frontal gyrus and left precentral gyrus, areas typically involved in phono-articulatory processes. Subsequent RSFC studies confirmed this finding and, furthermore, reported its connection with the supramarginal gyrus (Li et al., 2017) and Wernicke's area (Stevens et al., 2017) that are typically involved in phonological processing and speech comprehension, respectively. Interestingly, despite the preferential connections between the left-vOT and the

left-hemisphere language network, some evidence of prefrontal, parietal, and bilateral connections was also reported (Koyama et al., 2010; Vogel et al., 2012; Wang et al., 2015; Chen et al., 2019). This functional connectivity involving brain areas that are, a priori, not part of the language network suggests that even though the left-vOT plays a key role in reading, its activity seems to covary with widely distributed brain regions. In addition to the evidence on non-directional communication between the left-vOT and other brain areas described above, some previous studies used statistical causality such as dynamic causal modelling to estimate the effective connectivity of the left-vOT. However, using this method implies focussing on a pre-specified set of brain regions rather than covering the whole brain (Mechelli et al., 2005; Richardson et al., 2011; Duncan et al., 2014; Schurz et al., 2014). For instance, Mechelli et al., (2005) focused specifically on the connection between different parts of left-vOT and frontal regions. Their results revealed an increase in effective connectivity from the posterior fusiform gyrus to the dorsal premotor cortex during pseudoword reading and from the anterior fusiform gyrus to the pars triangularis during irregular word reading. Studies have also reported an increase in connectivity from the left-vOT to temporal lobe regions during word reading (Richardson et al., 2011).

As Driver et al. (2009) pointed out, most studies that examined the communication between brain regions resort to correlational approaches that consist in observing the changes in neural activity in different brain areas that covary with experimental conditions. The putative directional or causal influences of one specific area upon others have been assessed mainly through analyses of statistical causality (e.g., psychophysiological interaction analyses, coherence analyses, Granger causality or dynamic causal modelling) rather than through direct causal interventions applied at the level of a specific area within a network. The question of whether a specific brain area exerts directional influences upon others remains to be addressed using a direct, causal, intervention approach.

The combined use of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) provides a direct and non-invasive solution that allows researchers to track the directional propagation of brain signals from the cortical area targeted by TMS to other interconnected areas. The TMS-evoked potentials (TEP) reflect a direct, rather than an inferential, index of effective brain connectivity (Rogasch et al., 2013; Bortoletto et al., 2015). TEP is argued to be constrained not only by anatomical and functional connections (O'Shea et al., 2008; Siebner et al., 2009) between different areas but also by the status of the neural network (Morishima et al., 2009; Johnson, et al., 2012). The present study

adopted this intervention approach to examine the causal influence of the left-vOT activity on brain areas within and outside the language network, and more specifically, to test whether such influence depended on the functional status of the neural network defined by the task and the stimulus being processed.

Two aspects of the causal influence of the left-vOT were examined. The first set of analyses examined the *directional propagation* of neural activity from this area to other areas across the whole brain while participants performed low-level visual detection tasks on language and non-language stimuli, and a high-level semantic judgment task on language stimuli. An analysis of the TEP propagation in these different contexts would reveal if the neural impulse from the left-vOT induced by TMS was transmitted to other brain areas depending on the type of visual input and/or task demand. This observation would complement existing evidence on causal and non-causal functional connectivity assessed through the analyses of statistical causality described above. The second set of analyses was conducted based on existing reports of the privileged anatomical and functional connections between the left-vOT and areas within the language network (Koyama et al., 2010; Richardson et al., 2011; Yeatman et al., 2013; Bouhali et al., 2014; Stevens et al., 2017). Based on this information, we restricted the analyses to a set of areas that are commonly associated with language functions (Vigneau et al., 2006; Price, 2012) and examined the time-series correlations of TEP signals in these areas that was induced by left-vOT stimulation. In contrast to the statistical approaches such as DCM that estimate effective connectivity in the inferential manner, the TEP signals reflect direct effective connectivity between the stimulated area and other regions at each time point. This method directly informs us about the dynamic of neural propagation from the left-vOT to other regions. The evidence obtained in the correlation analysis would indicate how the functional state of the left-vOT, as defined by stimulus and task demands, modulates the degree of collaboration between the areas within the language network.

In our application of fMRI-guided combined TMS and EEG, the left-vOT was functionally localized at the individual participant level using an fMRI localizer in which participants processed written inputs. While TMS provided a tool to induce neural impulse within the left-vOT (at an intensity low enough not to interfere with task performance), EEG allowed us to track the propagation of the impulse from the stimulated area to other interconnected areas with a high temporal resolution. The EEG signals were recorded in three processing contexts. Specifically, participants were required to perform two low-level

perceptual tasks in which either non-linguistic (color detection: Do you see a yellow disk?) or linguistic stimuli (symbol detection: Is the symbol % included in the word?) were used, and a linguistic task (semantic judgment: Do you see an animal name?) in which linguistic stimuli were used. The impact of stimulus type on the propagation of TEP from the left-vOT to other brain areas was examined by contrasting TEP signals obtained in the symbol detection and color detection task, while the impact of task demand was examined by contrasting TEP signals obtained in the semantic and symbol detection task. Finally, the degree of collaboration between different language areas was examined through a time-series correlation analyses, considering again the impact of stimulus type and task demand. In these analyses, the activity of the homologous areas in the right hemisphere were used as a reference to validate the specificity of the correlation pattern observed in the left-hemisphere language network.

2. Materials and methods

2.1. Participants

Twelve healthy volunteers participated in the experiment (3 men and 9 women). All were right-handed native French speakers. Ages ranged from 19 to 30 (mean age: 23.0 ± 3.5 years). None of them suffered from a neurological disorder or had any history of language disorders. The experiment was approved by the ethics committee for biomedical research (Sud Méditerranée I). All participants provided written informed consent and were paid for their participation.

2.2. Stimuli

Three behavioural tasks using a go/no-go paradigm were used (Figure 1a). In the symbol detection and semantic judgment tasks, only linguistic stimuli (written words) were used. In the color detection task, only non-linguistic stimuli (colored disks) were used. Each task comprised 140 NoGo trials and 28 Go trials.

A common set of written words was used in NoGo trials presented in the symbol detection and semantic judgment tasks. They consisted of 280 disyllabic nouns, selected from the French database Lexique (New et al., 2004). The stimuli were divided into four lists of 70 words, matched on lexical frequency, number of letters and phonemes, number of orthographic and phonological neighbors, orthographic and phonological uniqueness point,

bigram and trigram frequency (all $ps > 0.40$). Two lists were used during symbol detection, which is a low-level visual, non-linguistic, task in which participants had to detect the “%” character presented in Go trials. The other two lists were used in semantic judgment, a linguistic task in which participants had to detect animal names. The association between the list of stimuli and the task was counterbalanced across participants. In each task, 28 Go trials were added to the material described above. In the symbol detection task, they corresponded to 28 disyllabic words in which one letter was replaced by the “%” character (e.g., ‘la%in’). In the semantic task, the Go trials corresponded to 28 animal names.

In the color detection task, stimuli corresponded to six different colored disks: blue, green, red, orange, pink and yellow. Each color was presented 28 times during the experiment. The yellow disks were used as Go trials.

2.3. Procedure

EEG was recorded continuously while participants performed the tasks. Task order was counterbalanced across participants. In each task, participants were asked to respond as quickly as possible by pressing a button with their right index when the target stimulus (Go trials) appeared and to withhold their response otherwise (NoGo trials). As illustrated in Figure 1a, each trial started with the presentation of a fixation cross for 1000 ms, followed by a visual stimulus (word in black font, or colored disk, on a light grey background) for 500 ms and a blank screen of variable duration (2000 ± 500 ms) as inter-trial interval. Stimuli and trigger codes were delivered by E-prime software (Psychological Software Tools, Inc.). Within each task, the stimuli were separated into 2 blocks of 14 Go and 70 NoGo trials that were presented in a random order.

On half of the trials (70 per condition in total), a single TMS pulse was applied on the left-vOT, 100 ms after stimulus onset (see the bottom of Figure 1a). This timing was chosen based on previous chronometric TMS studies showing that the left-vOT contributes to reading as early as 80-120 ms after word onset (Duncan et al., 2010; Pattamadilok et al., 2015). Each task started with a short training session that allowed the participants to familiarize themselves with the task and the stimulation protocol.

2.4. Localization of the left-vOT

In the case of ten participants, the left-vOT was individually and functionally localized based on the fMRI data obtained in the reading task reported in Pattamadilok et al. (2017).

This fMRI experiment was conducted using a 3-T MEDSPEC 30/80 AVANCE imager (Bruker, Ettlingen, Germany) at the fMRI centre of the Institute of Neuroscience of La Timone, Marseille, France. It included acquisition of a high-resolution structural T1-weighted image (MPRAGE sequence, resolution $1\times 1\times 1$ mm) and of functional images with a T2*-weighted gradient-echo planar sequence (36 interleaved 3 mm-thick/1 mm-gap slices, repetition time = 2.4s, echo time = 30 ms, field of view = 192 mm, 64×64 matrix of $3\times 3\times 3$ mm voxels). The stimulation site for each participant was defined as the highest activation peak at the intersection between an activation map (“visual word vs. fixation” contrast, voxel-wise threshold of $p<0.001$) and a search volume (a 24 mm-diameter sphere centered on the MNI coordinates -44, -58, -15 and transformed into participant’s native space; corresponding to the occipitotemporal cluster reported in a meta-analysis by Jobard et al., 2003). In the case of the two remaining participants for whom only the anatomical MRI was available, the stimulation site was individually localized using the search volume described above and individual anatomical landmarks corresponding to the middle left fusiform gyrus, medial to the occipito-temporal sulcus on the crest of the gyrus, just superior to the principal sulcus of the cerebellum (coronal plane). Figure 1b illustrates the location of the stimulation areas in each participant (circle) and the average coordinates for the group after MNI normalization ($x = -44$, $y = -61$, $z = -14$). Scalp-target distance was 27.7 mm on average ($SD = 3.4$).

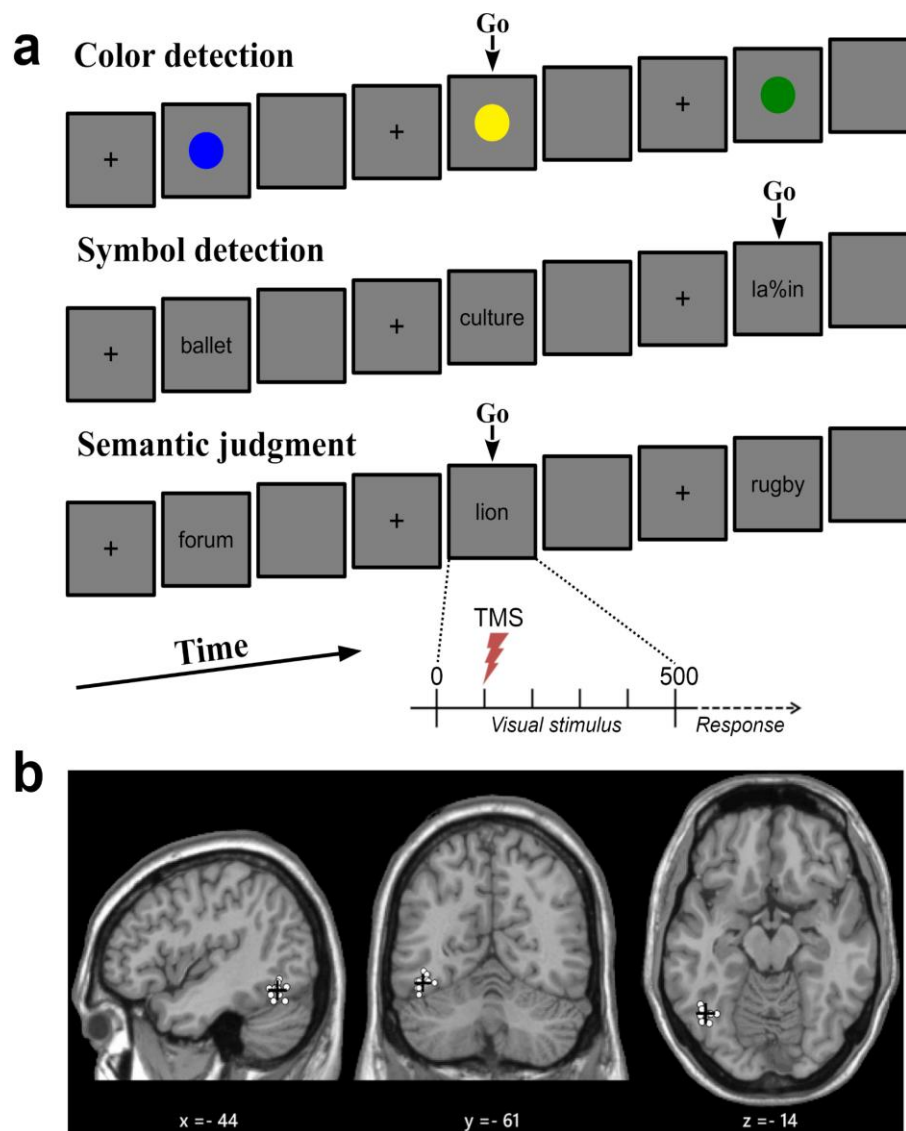


Figure 1: (a) The experiment design. Using a go/no-go paradigm, the color detection, symbol detection and semantic judgment tasks were carried out. The color detection task used non-linguistic stimuli (colored disks). The symbol detection and the semantic judgment tasks used linguistic stimuli (written words). On half of the trials (70 per task in total), a single-pulse TMS was applied on the left-vOT, 100 ms after stimulus onset. (b) Location of the left-vOT projected on a standardized brain template (white circles represent stimulation sites for individual participants, black cross represents group centroid).

2.5. Transcranial Magnetic Stimulation

We used a frameless stereotaxy system to position the TMS coil on the scalp to stimulate the precise anatomical region-of-interest. Neuronavigation (Navigated Brain Stimulation system 2.3, Nexstim, Helsinki, Finland) using anatomical MRI scans of each subject was used to both target and record stimulation sites. On trials with TMS, single-pulse stimulation was delivered using a Magstim figure-of-eight coil and a Magstim 200

monophasic stimulator (Magstim Co., Whitland, UK). Existing TMS-EEG studies already showed that single-pulse stimulation can induce the desired detectable neural signal transmission from the stimulated area to connected brain areas without inducing behavioural effects (Morishima et al., 2009; Mattavelli et al., 2013). However, our previous studies also showed that when longer stimulation protocols (e.g., using double-pulse or repetitive stimulation) were used, TMS applied on left-vOT significantly interfered with visual word recognition performance indicating the causal role of the area (Duncan et al 2010; Pattamadilok et al., 2015). As in these previous studies, stimulation intensity was set to 100% of participant's resting motor threshold. It ranged from 35 to 52% of stimulator output (mean: 43.6%, SD = 5.7%). Participants wore earplugs during the entire experiment to attenuate the TMS click sound.

2.6. EEG recording

The EEG was recorded with TMS-compatible EEG equipment (BrainAMP-DirectCurrent, BrainProducts, Gilching, Germany). We used a 62-electrode cap (Fast&Easy EasyCap) with sintered Ag / AgCl electrodes, mounted on an elastic cap and positioned according to the 10–20 system. The ground electrode was positioned on the forehead and the reference was placed on the right mastoid. All EEG electrode impedances were maintained below 10 k Ω . EEG was sampled continuously at 2500 Hz using BrainVision Recorder software. In order to reduce the TMS-induced artifact in the EEG signal, the cable of each electrode in the vicinity of the coil was tilted so that it was approximately perpendicular to the coil cable.

2.7. Data preprocessing and analyses

Only the data on NoGo trials was considered in the EEG analyses. The false alarms were also discarded. Offline data preprocessing was conducted using EEGLAB (v13.4.4b; Delorme and Makeig, 2004) that runs on MATLAB R2015a (Mathworks Inc., Natick, MA, USA). For most participants, the signals obtained at TP9 and TP10 electrodes showed low S/N ratio, due to their loose contact with the scalp, and were therefore discarded from further analyses. Data from one participant were also excluded after a sanity check due to the absence of stimulus time-locked responses on no-TMS trials.

Prior analysis of event-related potential (ERP): Before performing the analysis of TEP signals, a preliminary ERP analysis was conducted for trials without TMS to ensure the

efficiency of the stimulus-type manipulation and of the task demand. EEG signals were segmented into 800 ms epochs time-locked to stimulus onset (-100 to 700 ms) and the 100 ms period preceding stimulus onset was used for baseline correction. In each subject, electrodes exhibiting a large amount of noise or artifacts were identified using a semi-automatic procedure that combined visual inspection and pre-defined voltage thresholds (electrodes for which peak-to-peak amplitude was higher than 50 μV for more than 10% of all epochs). This procedure led us to discard, on average, 2.5 electrodes per subject ($\text{SD} = 1.4$). The rejected electrodes were interpolated by means of spherical interpolation. Data were re-referenced to the average of all electrodes, down-sampled to 500Hz and band-pass filtered between 1 and 30Hz (default EEGLAB Hamming windowed sinc FIR filter). Finally, individual trials containing ocular or muscular artifacts were removed (3.4 % of trials). Time-windows of interest were selected based on the global field power (GFP; Lehmann et al., 1980) calculated from the grand average across all subjects and all experimental conditions. As illustrated in Figure 2a, two 60 ms time-windows were selected for the analysis: 134-194 ms (peak at 164 ms) and 288-348 ms (peak at 318 ms). In each selected time-window, non-parametric cluster-corrected permutation tests in the FieldTrip software (Maris et al., 2007; Oostenveld et al., 2010) were used to compare the mean amplitudes of the signals obtained in the different tasks (using 1,000 permutations, two-tailed paired T-statistics, correction for multiple comparisons at the level of electrode clusters). The stimulus effect was investigated by comparing the ERPs obtained in the color detection and symbol detection task. The task effect was investigated by comparing the ERPs obtained in the symbol detection and semantic judgment task.

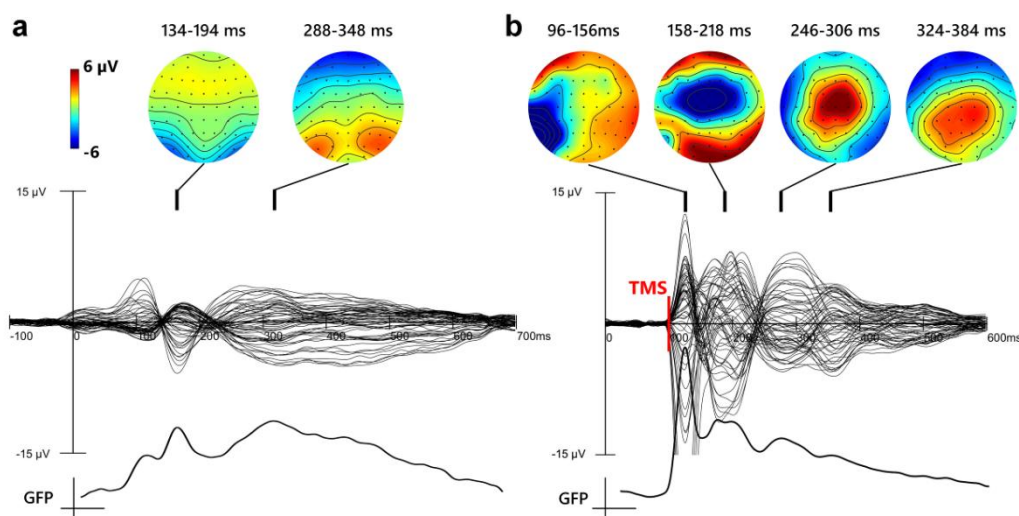


Figure 2: Time-windows (T_0 = stimulus onset) and the associated topographies obtained from Global Field Power analyses performed on (a) ERP signals and (b) TMS-induced ERP signals. The TMS pulse was applied 100 ms after the stimulus onset (indicated by the red vertical bar).

TMS-induced ERP analysis: The main part of the analyses focused on the TMS-evoked potential (TEP) signals, which allowed us to observe the directional propagation of brain signal from the left-vOT to other areas within both hemispheres, and to examine how this signal propagation was modulated by task demand and the type of stimulus being processed. To this end, we followed the method used in previous TMS/EEG studies (e.g., Kičić et al., 2008; Morishima et al., 2009; Mattavelli et al., 2013). Precisely, the neural impulse transmission from the left-vOT was isolated from the overall task and stimulus-induced regional modulations of brain activity by subtracting the signals obtained on no-TMS trials from those obtained on TMS trials. As argued by Morishima et al. (2009), the resulting TEP reflected, for each experimental condition, the degree of effective connectivity from the left-vOT to connected brain areas rather than the intrinsic excitability of those regions. As in the ERP analysis, the effect of stimulus on TEP propagation was examined by contrasting the TEPs obtained in the symbol detection and color detection tasks. The task effect was examined by contrasting the TEPs obtained in the semantic judgment and symbol detection task. Given that the same TMS parameters were applied for all types of stimuli and tasks, any auditory or somatosensory artifacts due to TMS stimulation were cancelled out in these second level contrasts.

At the preprocessing stage of the TEP analysis, the raw signals from both TMS and no-TMS trials were segmented into 600 ms epochs, time-locked to stimulus onset, and baseline-correction was carried out using the mean of the 50 ms period preceding the TMS pulse or the corresponding time points for no-TMS epochs. As in previous studies (Morishima et al., 2009; Akaishi et al., 2013) this short baseline period that preceded the TMS pulse allowed us to avoid the impact of the artefacts inducing noises in the signal and of possible signal differences across conditions. Despite our efforts to reduce TMS artifacts on EEG signals, the signals obtained on TMS trials were contaminated by TMS-induced high-amplitude artifacts of varying duration, from 10 to around 30 ms. As a result, the signals from 0 to 30 ms following the TMS pulse were removed and interpolated using cubic interpolation for all electrode sites (Thut et al., 2011). Following this procedure, electrodes with systematic remaining artifacts (3.8 electrodes per subject on average, $SD = 1.3$) were further rejected and

interpolated. The remaining signals were re-referenced to the average of all electrodes, down-sampled (to 500 Hz) and filtered (1–30Hz). Trials with ocular, muscular or electrical artifacts were further removed (9.6 % of trials per participant on average). Finally, for each participant and each condition, the average evoked response for the no-TMS trials was subtracted from the average evoked response for the TMS trials, thus yielding the final TEP signals.

As in the ERP analysis, time-windows of interest were identified based on local maxima of GFP. Figure 2b indicated four 60 ms time-windows: 96-156 ms (peak at 126 ms, i.e., 26 ms post-TMS), 158-218 ms (peak at 188 ms, i.e., 88 ms post-TMS), 246-306 ms (peak at 276 ms, i.e., 176 ms post-TMS) and 324-384 ms (peak at 354 ms, i.e., 254 ms post-TMS). The earliest time-window, that is adjacent to the TMS pulse, was not included in the analyses since its activity was partly contaminated by the offset of the TMS-induced artifacts. An analysis of the stimulus and task effects was carried out on the TEP waveforms using the above-described nonparametric cluster-corrected permutation tests (Maris and Oostenveld, 2007).

TMS-induced current source density (TMS-induced CSD): To further identify the cortical origin of the TEP effects observed at the surface electrodes, a source estimation analysis was performed using the standard procedure of Brainstorm software (Tadel, et al., 2011). For this purpose, the precise location of each electrode had been collected and recorded for each participant using the neuronavigation system and then coregistered with his/her anatomical MRI. The sLORETA method (Pascual-Marqui, 2002) was used to estimate cortical current source densities over time from the TEP signal obtained in each task and in each participant. After Z-score normalization against the baseline period of the signal amplitude, these time series data were averaged into the aforementioned time-windows of interest (58-118 ms, 146-206 ms and 224-284 ms post-TMS) for statistical tests. The stimulus and task effects were examined across the whole brain using SPM12 software (<https://www.fil.ion.ucl.ac.uk/spm/>). Family-wise error (FWE) correction was applied at the cluster level with initial cluster-forming height threshold $p < 0.01$ (Eklund et al., 2016; Roiser et al., 2016)¹.

¹ Cluster-based correction of multiple comparisons is commonly used in fMRI data analysis at the whole-brain level. Here, we applied the cluster-based FWE correction for the source analysis and set the initial cluster-forming height threshold $p = 0.01$ rather than $p = 0.05$ to prevent the inflated false-positive rates of cluster-based inferences (Eklund et al., 2016; Roiser et al., 2016). However, given that the source analysis of the present study is based on the significant results found at the scalp level, the cluster-forming height threshold would be set to $p < 0.05$ to locate the source if the initial threshold is too stringent to locate the source.

Analysis of correlations of TMS-induced CSDs across language areas: Finally, to examine the correlations of activity between language areas within the left-hemisphere language network, the following analyses specifically focused on a set of brain areas that are commonly involved in phonological, articulatory and comprehension processes (Vigneau et al., 2006; Price et al., 2012). Based on Destrieux atlas (Destrieux et al., 2010), we included in the analyses four ROIs located in the left inferior frontal cortex (or the Broca's area including pars triangularis, pars orbitalis and pars opercularis), precentral gyrus, inferior parietal cortex (angular gyrus and supramarginal gyrus) and superior temporal gyrus. The homologous areas in the right hemisphere were also selected as a reference network in order to validate the specificity of the correlation pattern observed in the left-hemisphere language network.

For each time-window and in each task, we computed time-series correlations between the TMS-induced CSDs measured in the pre-specified left-hemisphere language areas on the one hand, and between the TMS-induced CSDs measured in the homologous areas in the right hemisphere on the other hand. More specifically, in each participant and within each hemisphere, we first computed the Pearson correlation between the time-series of TMS-induced CSDs obtained for each pair of the ROIs. Then all correlation values (Fisher-z transformed values) were averaged. The obtained value reflects the similarity between time-series of TMS-induced CSDs of the selected areas, which was used as an index of the degree of collaboration between the different areas within the same hemisphere. Finally, two sets of repeated-measures ANOVAs taking into account task and hemisphere were conducted to investigate whether the degree of collaboration in the two hemispheres was modulated by stimulus type on the one hand, and by task demand on the other hand.

3. Results

3.1. Behavioral data

Participants achieved a high level of performance on all tasks, as illustrated by high rates of correct detection on the Go trials and low rates of false alarm (100% vs. 0.1%, 99.4% vs. 0.1%, and 95.5% vs. 1.3%, for percentages of correct detection and false alarm obtained in color detection, symbol detection and semantic tasks, respectively). A repeated-measures ANOVA conducted on mean correct reaction times (RTs) with within-subject factors of task (color detection, symbol detection, semantic judgment) and stimulation (no-TMS vs. TMS) revealed a significant effect of task [$F(2, 20) = 45.9, p < 0.0001$; mean RTs of 436 ms, 492 ms

and 610 ms, respectively]. No significant effects of TMS [$F(1, 10) = 2.00, p = 0.19$] or interaction between TMS and task [$F(2, 20) = 0.26, p = 0.77$] were observed (Figure 3). Due to the very low error rates, no further analysis was performed on these scores. The absence of a TMS effect on the behavioural data replicated previous TMS-EEG studies (Morishima et al., 2009; Johnson, et al., 2012) and confirmed that TMS could be used as a probe to examine the effective connectivity of the neuronal network without disrupting the function of the source area.

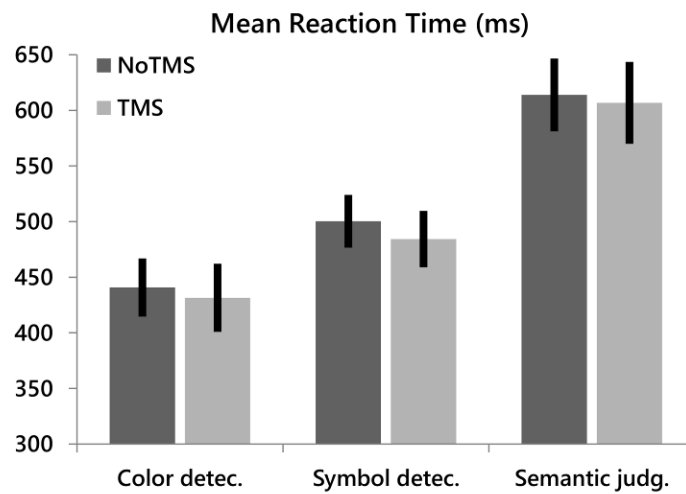


Figure 3: Mean reaction times for the Go trials with and without TMS stimulation obtained in the color detection, symbol detection and semantic judgment tasks.

3.2. Prior analyses of ERP signals on trials without TMS

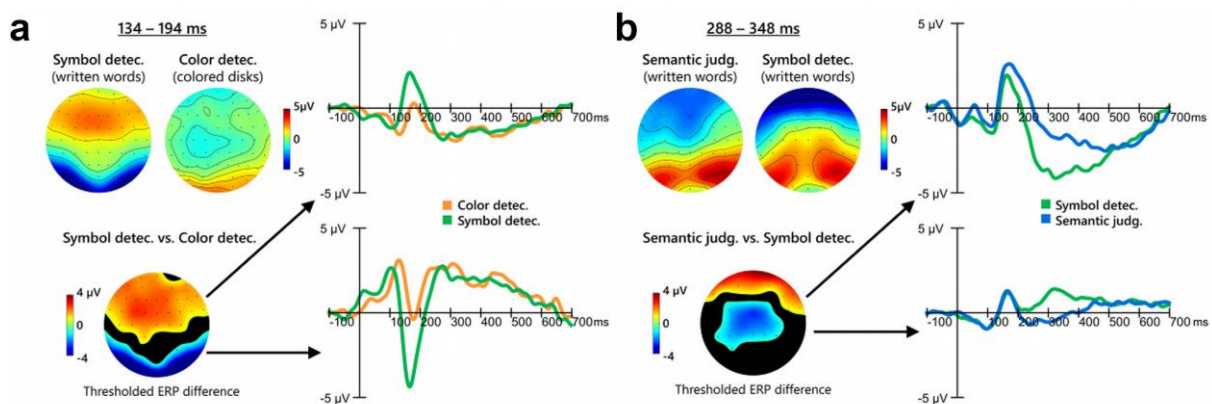


Figure 4: Topographic maps and time-courses of ERPs. (a) Left panel: ERP Topographic maps of the symbol detection and color detection tasks and their contrast map (i.e. stimulus effect) at the 134-194 ms time-window. Amplitude difference is shown in color only for the clusters significant at $p < 0.05$

(cluster-corrected permutation test). Right panel: average ERP waveforms extracted from the fronto-central and occipital electrodes belonging to the significant clusters. **(b)** Left panel: ERP topographic maps of the semantic judgment and symbol detection tasks and their contrast map (i.e. task effect) at the 288-348 ms time-window. Amplitude difference is shown in color only for the clusters significant at $p < 0.05$ (cluster-corrected permutation test). Right panel: average ERP waveforms extracted from the frontal and central electrodes belonging to the significant clusters.

The prior ERP analyses revealed a significant stimulus effect in the first time-window (134-194 ms, Figure 4a) and a significant task effect in the latter time-window (288-348 ms, Figure 4b). As expected, compared to colored disks, written words elicited a stronger negative ERP over occipital electrodes and a reversed polarity over fronto-central electrodes. The topography and time-course of the negative ERP are coherent with previous findings revealing a N170 component in response to written words (Bentin et al., 1999; Rossion et al., 2003; Maurer et al., 2005; Maurer and McCandliss, 2008). The task effect was characterized by two activation patterns. Firstly, a stronger negative ERP was observed in the symbol detection task over anterior frontal electrodes, which might correspond to the N300, a semantic-sensitive component shown to be distinct from the N400 (Franklin et al., 2007). Secondly, a positive peak was observed in the symbol detection task over central electrodes (around 300 ms) but was absent in the semantic task. The amplitude of such a P300 component has previously been reported to depend on task difficulty, with simpler tasks giving rise to higher amplitudes (Bentin et al., 1999; Newman and Connolly, 2004; Maurer et al., 2005). This pattern is coherent with the behavioural data showing higher performance in the symbol detection task. Overall, the prior ERP analyses conducted on the trials without TMS replicated the existing literature and confirmed that the participants were sensitive to the present manipulations of stimulus type and task demand.

3.3. TMS-induced ERP (TEPs)

As illustrated in Figure 5a, applying TMS over the left-vOT induced a fairly similar pattern of topography across tasks, although the strength of the signal seems to vary from one task to another on some electrodes. Soon after the stimulation (30-50 ms post-TMS), we observed a strong negative TEP over the stimulated area. From 50 ms to 130 ms post-TMS, this initial negativity propagated to central sites. The activation pattern suddenly changed around 130-150 ms post-TMS where we observed small positive-going activity at the central

and left parieto-occipital electrodes. After this time-window, a strong positive TEP emerged at the central electrodes and persisted until the end of the epoch. As shown in Figure 5b, the analysis of the stimulus effect revealed a stronger propagation of neural activity from the left-vOT to centro-parietal and right temporal electrodes in the color detection compared to symbol detection task. The effect occurred 58-118 ms after the TMS pulse was applied over the left-vOT. Neither stimulus nor task effect was observed in the intermediate time-window, i.e., 146-206 ms post-TMS. As shown in Figure 5c, we also observed a significant task effect in the latest time-window, i.e., 224 to 284 ms post-TMS: Compared to the semantic task, symbol detection led to a stronger propagation of neural activity from the left-vOT to centro-parietal electrodes.

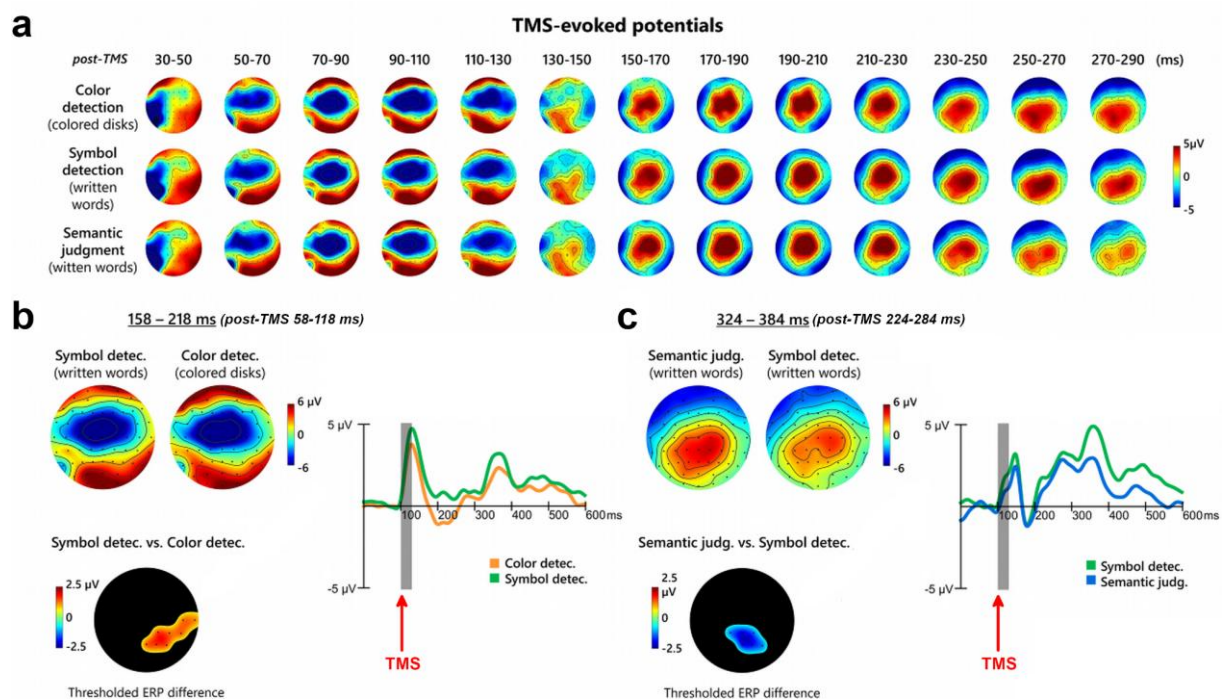


Figure 5: Mean voltage scalp maps, topographic maps and time-courses of TEPs. (a) Time-course of the mean voltage scalp maps of the TEPs obtained in the color detection, symbol detection and semantic judgment tasks. (b) Left panel: TEP topographic maps of the symbol detection and color detection tasks and their contrast map (i.e., stimulus effect) at 58-118 ms post-TMS. Amplitude difference is shown in color only for the cluster significant at $p < 0.05$ (cluster-corrected permutation test). Right panel: average ERP waveforms extracted from the centro-parietal and right temporal electrodes belonging to the significant cluster. (c) Left panel: TEP topographic map of the semantic judgment and symbol detection tasks and their contrast map (i.e. task effect) at 224-284 ms post-TMS. Amplitude difference is shown in color only for the cluster significant at $p < 0.05$ (cluster-corrected permutation test). Right panel: average ERP waveforms extracted from the centro-parietal electrodes

belonging to the significant cluster. The red arrows indicate the onset of the TMS pulse. The grey bar indicates TMS artifact correction period.

3.4. TMS-induced current source density (CSD)

Figure 6a shows the temporal dynamics of the effects of stimulus (left panel) and task (right panel) on the propagation of TEP signals from the left-vOT to other brain areas at the source level. In line with the ERP findings, the impact of task demand emerged later than the impact of stimulus type. Following the significant stimulus effect found at the electrode level in the first time-window (Figure 5b), the source analysis revealed that processing colored disks led to a stronger propagation from the left-vOT to the right inferior and middle occipital cortex than processing written words (58-118 ms post-TMS; see Figure 6a left panel and Figure 6b), although this tendency reached significance only when a lenient threshold was applied (i.e. $p < 0.05$, FWE correction at the cluster level, see also Footnote 1). Regarding the task effect, the low-level symbol detection task led to a significantly stronger propagation of brain signal to interhemispheric regions surrounding the posterior part of the corpus callosum (bilateral posterior cingulate gyrus), and to the right parietal and anterior temporal regions, in the latest time-window (224 -284 ms post-TMS; see Figure 6a right panel and Figure 6c). Overall, these observations suggest that the propagation of brain activity from the left-vOT was more restricted to the left hemisphere during the processing of linguistic material and tasks. More specifically, 1) in comparison to color perception, processing written words reduced the TEP propagation to the right primary visual cortex, and 2) in comparison to low-level written word perception task, extracting semantic information from written words further reduced the neural propagation from the left-vOT to right hemispheric regions, especially in the posterior part of the corpus callosum, right superior parietal lobule and right anterior temporal lobe.

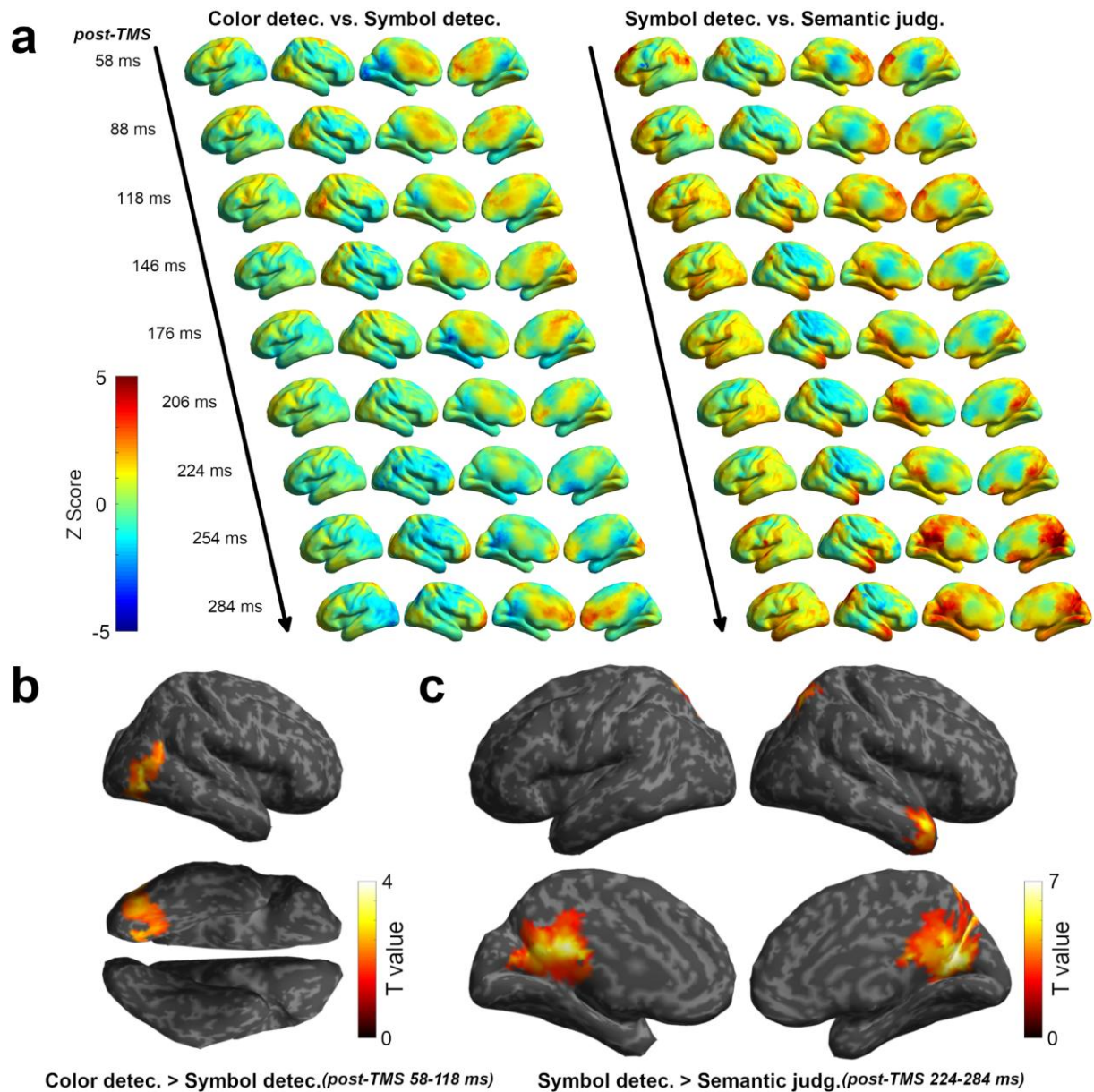


Figure 6: TMS-induced current source density. (a) Z-score maps show the dynamics of the stimulus (color detection vs. symbol detection) and task (symbol detection vs. semantic judgment) effects between 58 ms and 284 ms post-TMS. (b) The comparison between the color and symbol detection tasks (the stimulus effect) showed higher current source density in color detection during the early time-window (post-TMS 58-118 ms) at the right inferior and middle occipital cortex ($p < 0.05$, FWE correction at the cluster level). (c) The comparison between the symbol detection and semantic judgment tasks (the task effect) showed higher current source density in symbol detection in the latest time-window (224-284 ms post-TMS) at the bilateral posterior cingulate gyrus, right superior parietal lobule, and right anterior temporal cortex ($p < 0.01$, FWE correction at the cluster level).

3.5. Analysis of correlations of TMS-induced CSDs across language areas

For each time-window of interest, two repeated-measures ANOVAs were conducted on the correlations of TMS-induced CSDs in the selected areas in both hemispheres to examine the impacts of stimulus and of task demand, respectively. An examination of the stimulus effect considering task (symbol detection vs. color detection) and hemisphere (left vs. right) as within subject factors showed no significant main effect or interaction in any time-window [all $F_s(1, 10) < 3.05$, all $p_s > 0.11$, Figure 7a]. This result suggests that, in the context of low-level perceptual tasks, being exposed to a linguistic or non-linguistic material did not have a significant impact on the degree of collaboration between different areas in either hemisphere. Interestingly, a similar analysis examining the effect of task demand (where the task factor included the semantic judgment and symbol detection tasks) showed a different pattern. Although no main effect was significant [all $F_s(1, 10) < 2.48$, $p_s > 0.14$], we observed a significant interaction between task and hemisphere in the latest time-window, i.e., 224-284 ms post-TMS [$F(1,10) = 8.34$, $p < 0.017$]. As shown in Figure 7b, within the left hemisphere language network, the averaged correlation was significantly higher in the semantic judgment task than in the symbol detection task ($p < 0.013$). This finding indicated that processing the semantic content of written words causes the activity in the left-vOT to increase the degree of collaboration among different areas within the language network. The absence of this task effect in the right hemisphere further confirmed that the pattern was specific to the dominant hemisphere. Note however that a similar pattern was observed in 58-118 ms post-TMS time-window ($p < 0.042$) despite the fact that the interaction between task and hemisphere was not significant [$F(1, 10) = 2.80$, $p > 0.12$]. Finally, we also ascertained that this pattern of functional collaboration was specifically induced by the left-vOT activity. In fact, the same analyses conducted on the ERP data from the trials without TMS did not reveal any task-dependent modulation of the correlations of CSDs in any time window (all $p_s > .22$).

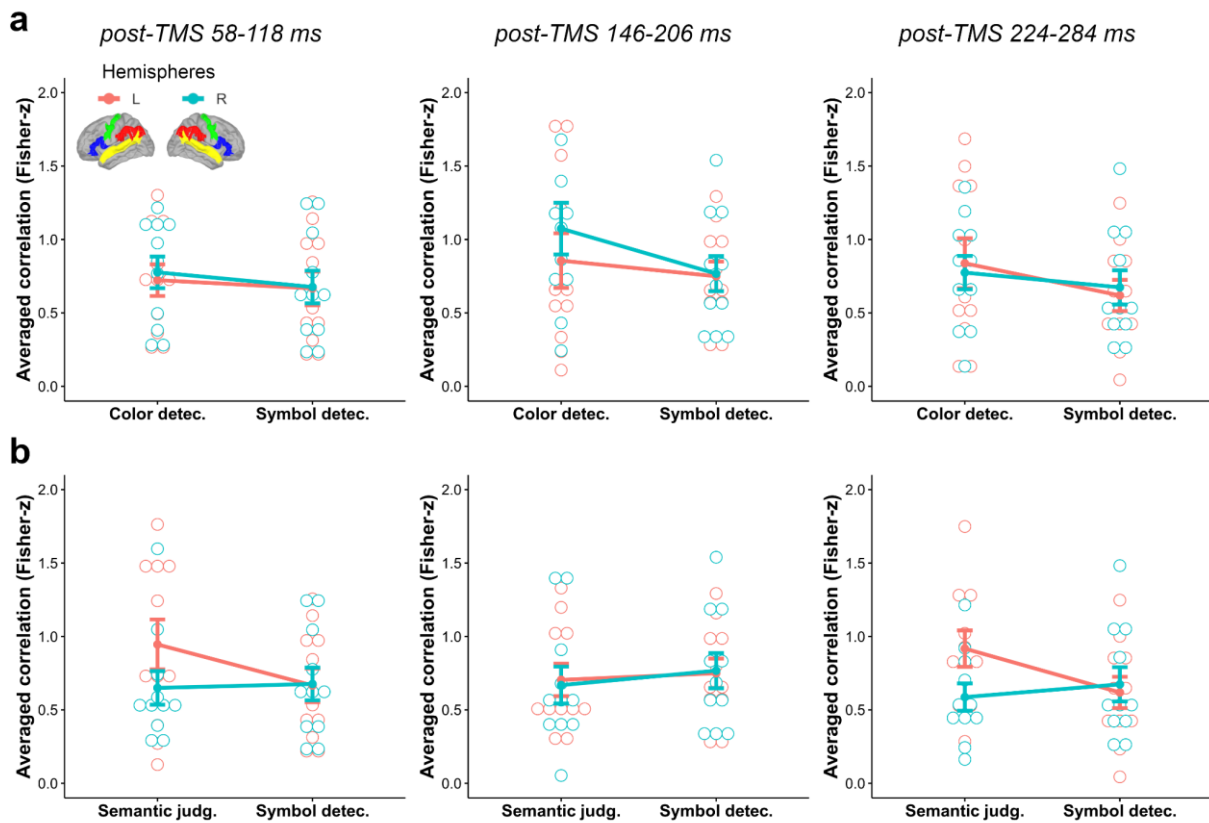


Figure 7: The averaged Fisher-z transformed correlations obtained in the left hemisphere language network (red lines) and in the homologous areas in the right hemisphere (blue lines). (a) The comparisons of the correlations obtained in the color detection and symbol detection task showed no significant effect of stimulus in any time-window. (b) The comparisons of the correlation obtained in the semantic judgment and symbol detection task showed a significant task effect only in the left hemisphere in the 224-284 ms post-TMS time-window, with the semantic task leading to a higher degree of collaboration. The same tendency was also observed in the 58-118 ms post-TMS time-window, although the task x hemisphere interaction was not significant. Error bars represent standard error of the means. Each circle corresponds to a participant.

4. Discussion

In the present study, we used TMS to probe the propagation of neural activity from the left-vOT to the rest of the brain in a stimulus and task-dependent manner. As expected, the current TMS protocol led to a modification of the cortical responsiveness that extended beyond the stimulated area without disrupting the behavioural performance and, therefore,

allowed us to investigate the causal influence of the left-vOT activity across the whole brain while considering non-linguistic vs. linguistic stimuli and low-level vs. high-level tasks.

A prior examination of the ERPs on non-TMS trials, which reflected changes of regional brain activity in response to linguistic vs. non-linguistic stimuli and tasks, replicated existing findings (Dien, 2009). Regardless of task demand, processing written words led to the emergence of an N170 component at occipito-temporal electrodes (Bentin et al., 1999; Rossion et al., 2003; Maurer et al., 2005). This relatively early effect of stimulus was followed by the task effect, which emerged around 300 ms after stimulus onset at central and frontal electrodes. These results confirm that the two manipulations affected brain activity in a different manner.

This initial pattern of brain activity was greatly modified by TMS applied at the left-vOT. Following the TMS pulse, we observed changes in neural propagation, reflecting modulations of effective connectivity from the left-vOT to other brain regions in a stimulus- and task-dependent manner. The comparison of word and color processing in the context of low-level visual tasks revealed reduced neural propagation from the left-vOT to the centro-parietal and right temporal electrodes from 58 to 118 ms after TMS pulse when participants processed words. At the cortical source level, a reduction of neural propagation was found in the right inferior and middle occipital cortex indicating that, compared to colors, written word processing inhibits the propagation of neural activity from the left-vOT to the primary visual cortex in the right hemisphere. This modulation of neural propagation between these two areas is in line with the existence of functional connectivity reported during resting state (Koyama et al., 2010; Vogel et al., 2012; López-Barroso et al., 2020).

In addition to the effect of stimulus, TMS applied on the left-vOT also modified neural propagation in a task-dependent manner. As was the case for the ERP signal, the task effect emerged later than the stimulus effect, i.e., around 200 ms after the TMS pulse. Compared to the low-level symbol detection task, processing the semantic content of written words decreased the neural propagation from the left-vOT to central and parietal electrodes in the right hemisphere. The estimation of current source densities demonstrated a reduced neural propagation from the left-vOT to the areas surrounding the bilateral posterior cingulate gyrus and the posterior corpus callosum, indicating that neural propagation through the splenium of the corpus callosum would be impeded by the semantic processing of written words. Existing literature suggests that the splenium of the corpus callosum connects bilateral dorsal occipital and angular regions and its density is higher in literates than in illiterates (Carreiras et al.,

2009). In addition, it has been reported that lesion of the splenium could lead to severe reading deficit when words presented in the left visual field (Dejerine 1891; Michel et al., 1996), suggesting that the splenial fibres may be responsible for transferring orthographic information between the two hemispheres (Funnell et al., 2000). As argued by Funnell et al. (2000, see also Reuter-Lorenz & Baynes, 1992), the information transfer from the right to left hemisphere posterior regions through the splenium of the corpus callosum allows the transition from letter-by-letter or serial reading processes to whole word recognition. Thus, the stronger neural propagation to the right hemisphere in the task that required participants to serially process the individual written characters in order to detect the “%” symbol among letters (compared to when they were required to extract the meaning of the whole word) fully corroborates this assumption. The observation is also coherent with the stronger neural propagation to the right superior parietal lobule and anterior temporal lobe in the symbol detection task. Specifically, the right superior parietal lobule is involved in spatial attention control (Szczepanski et al., 2010; Wills et al., 2017), which is more demanding in the symbol detection task. The anterior temporal lobe activation tends to be highly left lateralized in the semantic processing of written words (Rice et al., 2015). The weaker neural propagation to the homologous area in the right hemisphere in the semantic task suggests a possible disengagement of this area and could, therefore, contribute to the left lateralized semantic processing typically observed in the literature.

Taken together, these results suggest an overall reduction of neural propagation from the left-vOT to the right hemisphere, that is to say, the left-vOT-induced brain activity is more confined to the left hemisphere during language processing. However, given existing evidence on the anatomical and functional connections between the left-vOT and the language areas (Koyama et al., 2010; Richardson et al., 2011; Yeatman et al., 2013; Bouhali et al., 2014; Stevens et al., 2017), it remains intriguing that processing language stimuli or task did not lead to an increase of neural transmission from the left-vOT to left-hemisphere language areas. A possible explanation for this result is that the TMS-induced neural propagation from the left-vOT is strongly constrained by anatomical connections (O’Shea et al., 2008; Voineskos et al., 2010; Momi et al., 2021). The existence of strong anatomical connections between the left-vOT and the left-hemisphere language areas through major fiber tracts as reported in previous studies (Yeatman et al., 2013; Bouhali et al., 2014) might enable the propagation of brain signal in all processing contexts, which resulted in an indistinguishable amount of propagation from the left-vOT to the rest of the left-hemisphere language network

regardless of stimulus and task. Nevertheless, further research examining the neural propagation in a wider variety of tasks and stimulation areas is necessary to confirm this anatomical hypothesis. Another factor that might contribute to the absence of stimulus and task effects in the left-hemispheric areas is the relatively low spatial resolution of TMS (~ 1 cm; Taylor et al., 2008). Even though single pulse stimulation was applied, the stimulation provided by TMS may not be sufficiently fine-grained to target a specific part of the left-vOT. As suggested by the DCM findings reported by Mechelli et al. (2005), the pattern of connectivity in the anterior vOT should be differentiated from that in the middle or posterior parts (Mechelli et al., 2005). Although TMS allows us to genuinely examine the causal influence of a region on other parts of the brain, the low spatial resolution may remain an obstacle to successfully revealing the existence of different networks in the same or adjacent brain regions.

Interestingly, although the brain areas of the language network showed undifferentiated amounts of the TEP signals (and the underlying TMS-induced CSD) under different functional states of the left-vOT, semantic processing led to a higher correlation of TMS-induced CSD across several left-hemisphere language areas, at least at a late processing stage. This observation suggests that, compared to the symbol detection task, processing the semantic content of written words increased the degree of collaboration between the language areas. This increase in collaboration is restricted to the left-hemisphere, which is in agreement with the reduced neural propagation to the right hemisphere across the semantic judgment, symbol detection, and color detection tasks reported in the TEP analysis. Specifically, the comparison across tasks conducted here led us to assume that 1) the color detection task might exert a minimal constraint on the neural propagation from the left-vOT to other areas in both hemispheres; 2) the symbol detection task that involved low-level visual analysis of written inputs reduced the neural propagation from the left-vOT to the right occipital cortex compared to color detection; 3) the semantic judgment task that required the contribution of brain areas involved in both low and high-level processing of written inputs further restricted the neural propagation from the left-vOT to the left hemisphere, and induced a stronger collaboration between different areas within this dominant hemisphere.

However, as argued by Taylor et al. (2008), effects observed in combined TMS-EEG studies could be due to an immediate feed-forward connection or several loops of interactions between the stimulated site and remote areas. Thus, any results observed at the late stage should be interpreted with caution. In the present case, the early-occurring stimulus effect,

around 60 ms after TMS (or probably earlier, although this could not be revealed due to TMS artifacts), was likely to result from an impulse propagating directly from left-vOT to right occipital regions without rerouting via other areas. This was unlikely to be the case for the task effect which appeared around 200 ms after TMS. At the current stage of research, it seems likely that the late task effect reported here might result from several loops of interactions, possibly mediated by the high-order language areas.

As a final note, the main aim of the present study was to apply a direct, causal intervention approach to examine the influence of the left-vOT activity on other brain areas both within and outside the left-hemisphere language network. In addition to this aim, the obtained findings also provide insightful information on the underlying mechanism of the left-lateralization of language processing itself. While existing correlational evidence from most brain-imaging studies assumes that left-lateralization results from an increased activation within left-hemisphere language regions (Binder et al., 1997), others suggest that it could also result from a decreased activation in the right hemisphere through a modulation of interhemispheric connectivity (Seghier et al., 2011). The reduced neural propagation towards right hemispheric areas observed while participants processed language stimuli or task reported here provides further evidence in favour of the latter assumption and suggests that the causal intervention approach could be considered as an alternative method to investigate brain-lateralization in different cognitive processes.

In conclusion, the present study is the first to examine the stimulus- and task-dependent effective connectivity from the left-vOT to wide-spread brain areas, using a direct causal intervention approach. Thanks to the combination of TMS and EEG, we were able to show that processing written language led to a reduction of neural propagation from the left-vOT to several areas in the right hemisphere, and an increase of collaboration between areas within the left-hemisphere language network. At least in the present context of reading tasks, this modulation of brain activity is driven by the functional state of the left-vOT. It also gives an insight into the underlying mechanism of the left-lateralization during language processing.

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