Transcranial magnetic stimulation-evoked potentials after the stimulation of the right-hemispheric homologue of Broca's area

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The combination of transcranial magnetic stimulation and electroencephalography can be applied to probe effective connectivity. Neurons are excited by magnetic pulses, which produce transcranial magnetic stimulation-evoked potentials that can be monitored with electroencephalography. Effective connectivity refers to causal connections in the brain; it describes how different brain areas communicate with each other. Broca's area is crucial for all phases of speech processing and is located in the frontotemporal region of the cortex. Only a few studies have investigated this region using transcranial magnetic stimulation–electroencephalography because of the large cranial muscles that are located over these areas, resulting in large artifacts covering the transcranial magnetic stimulation-evoked potentials. However, it is shown that this obstacle can be overcome with new artifact-removal tools. We used minimum-norm estimation to locate the sources of the neuronal signals in electroencephalography data after stimulating the right-hemispheric homologue of Broca's area in three right-handed subjects; it was shown that the spreading of brain activity might be different for different individuals and that the brain activity spread fast to the contralateral hemisphere. ***NeuroReport*** **30: 1110–1114**

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Introduction

Transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) can be applied to investigate effective connectivity, that is, causal connections in the brain [1]. The strong magnetic pulse of TMS coil excites neurons noninvasively below the stimulation coil [2], but at the same time, it induces large artifacts in the EEG signal lasting tens of milliseconds [3,4], making it hard to study TMS-evoked potentials (TEPs). However, Mutanen *et al*. [5] showed that signal-space projection (SSP) and source-informed-reconstruction (SIR) [5] (SSP-SIR) are effective together in suppressing muscle artifacts after stimulation of the primary motor cortex (M1) by separating the muscle artifacts from the brain signals.

The SSP-SIR artifact-removal method for EEG data was applied in our previous study, after stimulating M1 and areas with large cranial muscles: the right-hemispheric homologue of Broca's area (right inferior frontal gyrus; rIFG) and right-hemispheric homologue of Wernicke's area (right superior temporal gyrus; rSTG) [6]. After cleaning the data, we were able to locate a dipole explaining the spreading of the first recognized global mean-field amplitude (GMFA) component quite near the stimulation site. The suppression of brain signals was tested with correlation coefficient and relative difference between the cleaned and simulated data showing that the brain signals were most suppressed near the stimulation site. However, the correlation values between the two datasets indicated that the topography of the TEPs remained even after the cleaning; thus, here we observed the individual spreading of brain activity after the stimulation of the right-hemispheric homologue of Broca's area with the latency of the first GMFA component on the cortex using minimum-norm estimation (MNE). The rIFG was chosen as the stimulation site since low-frequency repetitive TMS (rTMS) to rIFG has been applied to restore the function of language network when lesions due to stroke in Broca's area make it inapproachable for direct rTMS interventions [7–9].

TEP-based effective connectivity data can elucidate our understanding of the language network, speech processing, and the interaction of the areas involved in it. It can serve as a guide in neuromodulatory treatment planning for language deficits, such as repetitive TMS (rTMS), for example, in stroke-related aphasia [7–9]. Improved understanding the function of the language network healthy brain could help developing individual therapeutic methods.

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Methods

Subjects

Three healthy right-handed volunteers (S1, female, 25 years old; S2, male, 27; and S3, male, 30) participated in the experiment after the research procedures were explained to them and they had given written informed consent. The study was accepted by the Ethics Committee of Helsinki University Hospital and was compliant with the Declaration of Helsinki.

Electroencephalography and transcranial magnetic stimulation

A 60-channel EEG cap and a TMS-compatible eXimia EEG device (Nexstim Plc, Helsinki, Finland) were combined to record TEPs. EEG was not recorded with sham stimulation. The location of the stimulation coil with respect to the head was tracked with individual MRIs and navigated brain stimulation (NBS 4.3, Nexstim Plc, Helsinki, Finland). Electrooculography electrodes were attached just above the right eyebrow and on the left side of the left eye, the reference electrode to the forehead, and the ground electrode to the right zygomatic bone. All electrode impedances were below 15 kΩ. An electromyography system (NBS 4.3, Nexstim Plc, Helsinki, Finland) was used to record motor evoked potentials (MEPs) of the left abductor pollicis brevis muscle. Biphasic TMS pulse sequences were delivered to the right hemisphere with a TMS system including a figure-of-eight coil (NBS 4.3, Nexstim Plc, Helsinki, Finland). The sensory stimulation of the scalp and auditory evoked potentials were diminished by placing a piece of 1 cm thick foam plastic between the scalp and the coil. Hearing protecting and sound masking with white noise (80–89 dB) via headphones were also applied to reduce auditory evoked potentials due to the coil click [10]. The EEG signals were recorded with a passband of 0.1–350 Hz at a sampling rate of 1450 Hz.

First, the representation area of the left abductor pollicis brevis in the right M1 was mapped by finding the target in the precentral gyrus producing the highest MEPs from the muscle; the applied electric field (E-field) was oriented towards the precentral gyrus. Then, the resting motor threshold was determined as the smallest stimulator intensity producing at least five MEPs with a peak-to-peak amplitude of at least 50 μV in ten trials [11]. The stimulation target for the right-hemispheric homologue of Broca's area was the opercular IFG (opIFG); opIFG is in the inferior part of the frontal lobe consisting of pars opercularis, pars triangularis, and pars orbitalis [12]. The stimulation was targeted to the sulcus between pars opercularis and pars triangularis, and the E-field was oriented anteriorly towards pars triangularis.

The stimulation sequence of 150 pulses was delivered at random intervals from 3.0 to 3.5 s, the stimulation E-field strength being 90% of resting motor threshold. EEG contamination from muscle artifacts and any muscle-activation-related somatosensory responses were minimized with this relatively low stimulation intensity. To prevent TMS-induced artifact saturation of the amplifier, a sample-and-hold circuit was utilized [13].

Lead-field matrix

The digitized locations of the reference and EEG electrodes were applied for the construction of the subject-specific lead-field matrix L (60 × 5124) describing the spreading of TEPs in the brain on an individual level according to the knowledge of the thickness and conductivity of the tissue layers between the brain and scalp and the sensor locations. The row vectors of L describe the cortical sensitivity profiles of EEG sensors while the column vectors present the signal topographies of EEG-generating sources that were assumed to lie in the cortex. A more detailed description of the pipeline for the construction of the anatomical models can be found in Salo *et al.* [14]. In the pipeline, the methods introduced by Fischl *et al.* and Shattuck *et al.* [15] were derived for segmenting the anatomical MR images, and those of Stenroos and Sarvas [16] to build a three-compartment forward model to solve lead fields of the cortically constrained sources.

Data processing

All data processing was done offline with MATLAB R2018b (The Mathworks, Inc., Natick, Massachusetts, USA). At first, the data were segmented into trials from −300 to 500 ms with respect to the TMS stimulus. Bad channels and bad trials with random artifacts, such as ocular artifacts [17], were removed by visually evaluating the data. Average-referencing was applied, and the data were averaged over the accepted trials. Next, muscle artifacts were suppressed with SSP-SIR [5] by focusing the procedure to the time window with the largest artifacts, leaving the late muscle-artifact-free TEP components unaffected. As was described by Mäki and Ilmoniemi [18], only a minor portion of the EEG signals above 100 Hz is due to brain activity; thus, the data were high-pass-filtered with 100 Hz to compute a projection matrix P that projects the data to the subspace that is orthogonal to the space defined by the muscle artifact topographies. By multiplying the original data and the lead-field matrix with P, the effect of muscle artifacts was suppressed resulting in the cleaned, artifact-free data and suppressed lead-field matrix, which was used for the computation of the source estimates. The SSP-SIR method presented in detail can be found in Mutanen *et al.* [5]. Finally, the data were bandpass-filtered with a zero-padded Butterworth filter at 2–80 Hz to further reduce non-neuronal signals.

Analysis

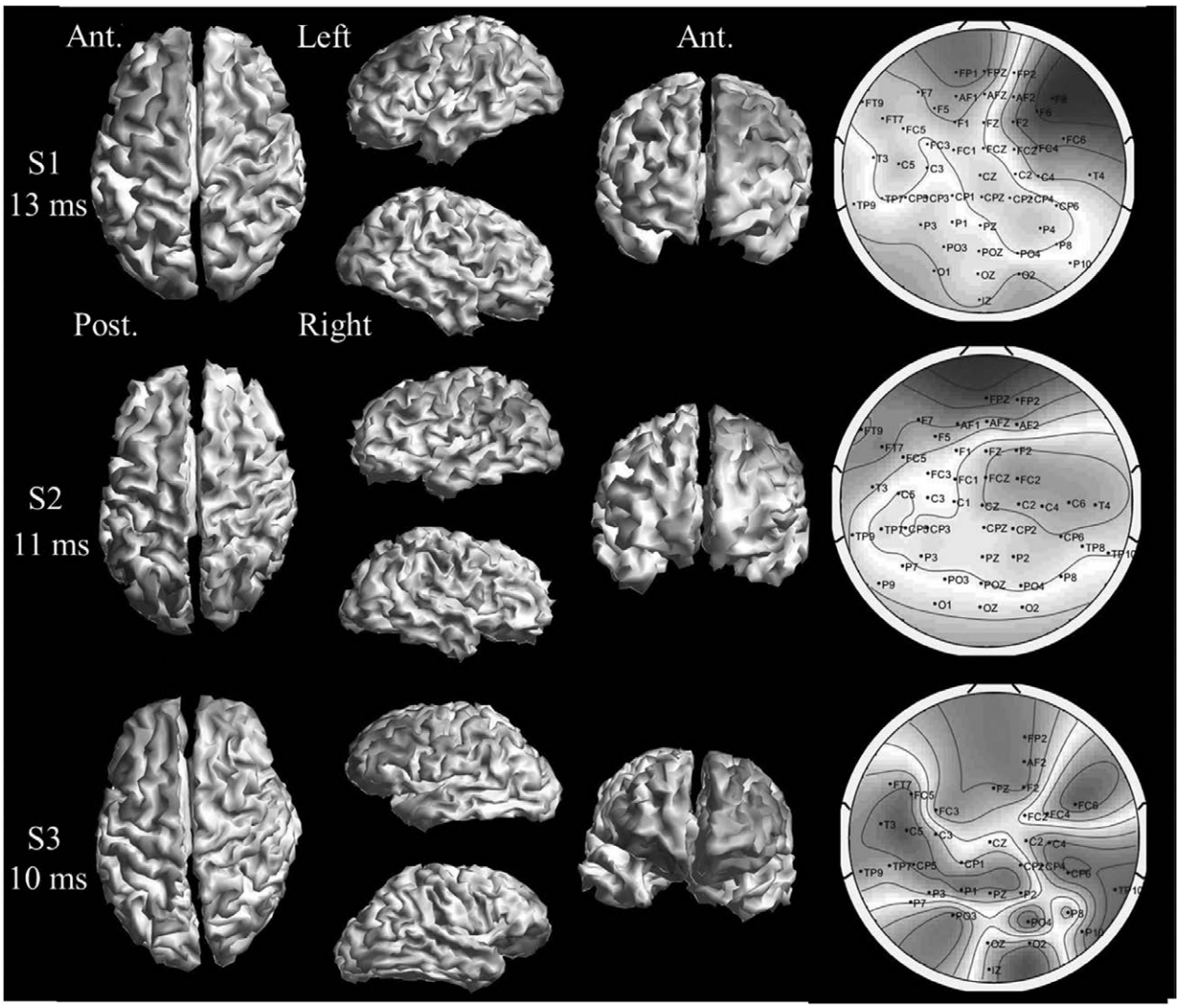
After the preprocessing, GMFA [19] was computed as in our previous study [14] to find the individual latencies of

the typical TEP components (N15, P30, N45, P50, N100, and P180); the signal topography of the first GMFA components was used for source analysis [20,21]. A linear distributed source estimation was performed by assuming that the measured data followed a linear measurement model. Since the inverse problem is ill-posed, a regularized MNE was applied to locate the cortical sources as described earlier [14] using methods introduced in earlier studies [20,22,23]. The regularization parameter was calculated from the whitened lead-field matrix and power signal-to-noise ratio of data, which was defined as the sum of variances over all channels post-stimulus divided by the sum of the pre-stimulus signal (or noise) variances. After deriving the MNEs, they were visualized with in-house plotting tools, and their signal-topography plots were drawn with EEGLAB [24]. The MNE plots are scaled to their maxima, and the color scale is symmetric around zero.

Results

During the data processing, the number of removed channels was 9 for S1, 13 for S2, and 12 for S3, the number of removed artifact components 6 for S1, 3 for S2, and 2 for S3 and the number of removed trials 35 for S1, 56 for S2, and 33 for S3. The latency of the first TEP component found from GMFA was 13 ms for S1, 11 ms for S2, and 10 ms for S3. The spreading of the first GMFA component for all three subjects can be seen in Fig. 1. For S1 and S3, the activity spreads first to the contralateral frontal areas. For S2, the activity also spreads to the contralateral hemisphere but more posteriorly to the centro-parieto-occipital areas.

Fig. 1



The spreading of brain activation after the stimulation of right-hemispheric homologue of Broca's area for all three subjects.

Discussion

We studied individual effective connectivity arising from the right opIFG. To the best of our knowledge, there have not been earlier studies showing the individual spreading of activity from the right opIFG in the ipsi- or to the contralateral hemisphere. We showed that the stimulation of the right opIFG activates homologous nearby areas in the contralateral side. This preliminary proof of concept indicates that the therapeutic TMS used to activate these connections may be effective since the left and right opIFG are strongly connected, and these connections may be modulated by rTMS. The small sample size limits the interpretation of the results since they cannot be generalized.

Although the SSP-SIR method suppresses the brain signals, it has been shown that the suppression is strongest at the stimulation site and the contralateral hemisphere is not as affected. In the same study, it was argued that despite the suppression the topographies of the TEPs are preserved. Here, the first GMFA component was applied for deriving MNEs. MNE was chosen because it does not make strong a priori assumptions regarding the possible sources. The results would vary depending on a priori knowledge that would be the basis for different source localization methods, for simplicity, we avoided any strong assumptions about the sources in the brain. Since the suppression could be assumed to be suppressed most at the stimulation site, the analysis of the contralateral spreading of activity could be done but not the initial ipsilateral spreading of the signal. The used intensities were large enough to overcome the multisensory responses [25] and in a small extend due to the used earplugs, headphones, and foam.

rTMS has been used to treat speech-area impairments, such as stroke-related aphasia [7–9]. However, so far, the stimulation site has been chosen according to the anatomy in the MR images or head. The treatment results might be better if the stimulation site could be made by finding a spot that is connected to the contralateral side to enhance these connections. Our results strengthen the theory that the stimulation of the right opIFG also activates the contralateral opIFG. However, as we showed, the spreading of activity might not reach the contralateral opIFG from the same anatomical target for everyone. Thus, it should be first tested with single-pulse TMS to find the optimal stimulation area to the rTMS therapy for optimizing clinical procedures.

The spreading of activity is individual when the right opIFG is stimulated. However, here, the spreading of the first recognized GMFA component was located in the contralateral hemisphere. For two out of three subjects, it was in the frontolateral areas and, for the third, mainly in parietal areas. These results indicate that the stimulation of the right opIFG might activate the corresponding areas in the contralateral hemisphere.

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Conflicts of interest

R.J.I. is founder, past CEO, advisor, and a minority shareholder of Nexstim Plc. P.L. has been consulting Nexstim Plc for procedures not related to this work. Nexstim Plc has paid S.M.I.V. travel costs to scientific conferences. For K.S.-T.S., there are no conflicts of interests.

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