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Language and its right-hemispheric distribution in healthy brains: An investigation by repetitive transcranial magnetic stimulation

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ABSTRACT

Object: Repetitive navigated transcranial magnetic stimulation (rTMS) is increasingly used for preoperative cortical language mapping. Unlike direct cortical stimulation (DCS), and due to its non-invasive character, this technique can provide a map of the distribution of human language in the healthy brain as well as a dysfunctional brain. Although functional magnetic resonance imaging (fMRI) studies have reported interhemispheric functional connectivity between language structures, the way in which the right hemisphere helps bring about language function remains only partially investigated. The present study therefore uses rTMS as a virtual lesion model to investigate the right hemisphere's contribution to language processing in the healthy human brain.

Methods: Fifty healthy right-handed volunteers (25 males, 25 females, mean age 25.9 ± 5.4 years) underwent language mapping of the right hemisphere by rTMS combined with an object naming task. All errors induced by rTMS were categorized into six different error groups (no-response error, hesitation, performance error, neologism, semantic error, and phonological error). Afterwards, the error rates for each category were calculated and visualized through the results' being projected into the cortical parcellation system (CPS). To reveal CPS regions having similar functional properties, an additional principal component analysis (PCA) was performed.

Results: rTMS induced 1485 naming errors out of the 9839 stimulation trains (error rate 15.1%). These errors were located mainly in the right hemisphere's homologues of the left hemisphere's visually cued overt speech area (middle superior temporal gyrus: mSTG) and in the sound-to-articulation dorsal pathway consisting of opercular inferior frontal gyrus (opIFG) and anterior and posterior supramarginal gyrus (aSMG, pSMG) in both male and female brains. In addition, rTMS caused many errors in the global language comprehension area in female brains (right posterior superior temporal gyrus: pSTG), in speech motor areas in the middle and ventral precentral and postcentral gyri (mPrG, vPrG, mPoG, vPoG), and in executive-function areas in the middle and posterior middle frontal gyri (mFMG, pMFG).

Conclusions: For the first time, the present study provides data on the right hemisphere's cortical regions causally related to single word production function (right opIFG, aSMG, pSMG, mSTG), and selectively in female brains (right pSTG), from a large sample of 50 healthy adult brains in a virtual-lesion design. Moreover, speech-motor control regions (right mPrG, vPrG, mPoG, vPoG) and cortical regions supporting language task performance (mMFG, pMFG) in the language-non-dominant right hemisphere are described.

Abbreviations: ATL, anterior temporal lobe; CPS, cortical parcellation system; DCS, bipolar direct cortical stimulation; DTI, diffusion tensor imaging; ECoG, electrocorticography; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; IPI, inter-picture interval; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MFG, middle frontal gyrus; MTG, middle temporal gyrus; PC, principal component; PCA, principal component analysis; PoG, postcentral gyrus; PPV, positive predictive value; PrG, precentral gyrus; RMT, resting motor threshold; rTMS, repetitive nTMS; SMG, supramarginal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus; TMS, transcranial magnetic stimulation; TPJ, temporo-parietal junction; VAS, visual analogue scale.

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Introduction

Traditionally, language function was attributed solely to the left hemisphere (Broca, 1861; Wernicke, 1874). Now, however, various studies on language organization using modern examination modalities have made it increasingly obvious that the essential role of the right hemisphere in language function has long been underestimated. Thus, language localization in the right hemisphere has repeatedly been reported in functional magnetic resonance imaging (fMRI) studies (Baum et al., 2012; Baumgaertner et al., 2013; Bonelli et al., 2012; Briganti et al., 2012), in non-navigated transcranial magnetic stimulation (TMS) publications (Schuhmann et al., 2012; Thiel et al., 2005), and in studies based on direct cortical stimulation (DCS) (Chang et al., 2011; Duffau et al., 2008). Furthermore, most recently published studies using repetitive navigated transcranial magnetic stimulation (rTMS) report the non-dominant right hemisphere's language organization of healthy adults as control data in order to gauge clinical populations' language reorganization from a damaged left hemisphere into a healthy right hemisphere (Krieg et al., 2013; Rosler et al., 2014).

One main advantage of rTMS is its non-invasive character. Being non-invasive, it can test cortical areas' functions with confirmed causality, much as DCS does (Devlin and Watkins, 2007; Krieg et al., 2014; Picht et al., 2013). But DCS, though regarded as the gold standard for the mapping of language-eloquent brain areas, cannot examine language distribution in the healthy human brain; and so rTMS is increasingly used for that purpose. It has already been shown that rTMS allows the mapping of language-related cortical brain areas by inducing various kinds of language errors (Epstein, 1998; Epstein et al., 1996; Lioumis et al., 2012; Pascual-Leone et al., 1991; Picht et al., 2013; Sollmann et al., 2013a,b; Sparing et al., 2001; Wassermann et al., 1999). In addition, applying 5 to 7 Hz pulse trains, rTMS language mapping for left-sided perisylvian tumor patients has also shown a good correlation with DCS (Picht et al., 2013) and magnetoencephalography (MEG) (Tarapore et al., 2013) in German and in English respectively.

Based on findings from past rTMS, fMRI, and MEG studies, the present study was designed to test the hypotheses about the causal contribution of the right hemisphere structures that have been shown to be connected in function to the left hemisphere language structures (inferior frontal gyrus: IFG; middle frontal gyrus: MFG; superior temporal sulcus: STS; superior temporal gyrus: STG; middle temporal gyrus: MTG; temporo-parietal junction: TPJ) for language processing by using rTMS as a virtual-lesion method combined with an object naming task.

Material and methods

Ethics

All volunteers provided written informed consent prior to magnetic resonance imaging (MRI), and the experimental protocol was approved by the local ethics committee (registration number: 2793/10) in accordance with the Declaration of Helsinki.

Study design

The study was designed as prospective and non-randomized.

Subjects

The study was conducted on 25 female and 25 male subjects. All subjects were purely right-handed healthy volunteers. Inclusion criteria were right-handedness, German as mother tongue, age >18 years, and a written informed consent. Exclusion criteria were previous seizures, general TMS exclusion criteria (pacemaker, cochlear implant, deep brain stimulation), bilateral handedness or left-handedness, a second mother tongue, or pathological findings on cranial MRI.

MRI

All volunteers underwent MRI prior to rTMS language mapping performed on a clinical 3 Tesla MR scanner (Achieva 3 T, Philips Medical Systems, The Netherlands B.V.) by use of an 8-channel phased-array head coil. The scanning protocol consisted of a 3D gradient echo sequence (TR/TE 9/4 ms, 1 mm^2 isovoxel covering the whole head, 6 min and 58 s acquisition time) without intravenous contrast administration for anatomical coregistration. The three-dimensional dataset was transferred to the rTMS system via DICOM standard.

rTMS language mapping

Experimental setup

3D T1-weighted MRI data of each volunteer were used as an anatomical reference, co-registered to the subject's brain to localize the inhibited brain area during rTMS mapping sessions. Language mapping was performed with the Nexstim eXimia NBS system version 4.3 with a NexSpeech® module (Nexstim Oy, Helsinki, Finland). The rTMS system uses a stereotactic camera to track coil position with respect to the volunteer's head. The head position was tracked by reflectors fastened to the head with an elastic strap.

During rTMS, the stimulating figure-of-eight coil induces an electric field. It is visualized over the brain's 3D reconstruction, and the intracranial points of stimulation are saved for later examination (Ruohonen and Ilmoniemi, 1999; Ruohonen and Karhu, 2010). Before language mapping, the resting motor threshold (RMT) was determined by motor mapping of the cortical representation of the contralateral abductor pollicis brevis muscle, as described previously (Krieg et al., 2012; Picht et al., 2009). As a basic value for rTMS examination, the individual volunteer's RMT, reflecting motor cortex excitability, was used to select the appropriate stimulation intensity.

We used an object naming task (131 colored pictures) to identify language-related cortical regions by causing a transient functional lesion by rTMS, as various studies have described and analyzed (Candidi et al., 2008; Knops et al., 2006; Orosz et al., 2012). As objects were displayed at an inter-picture interval (IPI) of 2.5 s, we applied rTMS pulses 300 ms after the picture presentation onset, according to our current knowledge of the timing of naming-related activity reported in previous studies (Indefrey, 2011; Salmelin et al., 2000; Wheat et al., 2013). Stimulation intensity and frequency were personalized by the following protocol (Krieg et al., 2013; Picht et al., 2013; Sollmann et al., 2013b):

1. RMT on the right hemisphere was determined.
2. A train of 5–7 TMS bursts was administered to the ventral precentral gyrus (vPrG) and the opercular inferior frontal gyrus (opIFG):

a) 5 Hz, 5 pulses, 100% RMT;
b) 7 Hz, 5 pulses, 100% RMT;
c) 7 Hz, 7 pulses, 100% RMT.

3. The setup (a–c) that impaired language most effectively was identified by the volunteer's and examiner's impressions, and in some cases supported by video analysis.
4. If there was no clear difference in the effect on language performance, the most comfortable frequency was chosen.
5. If no evident error responses were obtained, the intensity was increased to 110–120% RMT, and step 1 was repeated.
6. If significant pain was reported, the stimulation intensity was decreased to 80–90% RMT to avoid any discomfort interfering with the consecutive response evaluation (Epstein et al., 1996).

All baseline performances and mapping sessions were digitally video-recorded (Krieg et al., 2013; Lioumis et al., 2012; Picht et al., 2013; Sollmann et al., 2013a).

Language mapping procedure

The procedure was performed as reported earlier (Krieg et al., 2013; Picht et al., 2013; Sollmann et al., 2013a,b). In short, for the object