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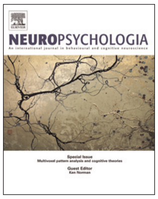

Cortical regions involved in semantic processing investigated by repetitive navigated transcranial magnetic stimulation and object naming

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ABSTRACT

Background: Knowledge about the cortical representation of semantic processing is mainly derived from functional magnetic resonance imaging (fMRI) or direct cortical stimulation (DCS) studies. Because DCS is regarded as the gold standard in terms of language mapping but can only be used during awake surgery due to its invasive character, repetitive navigated transcranial magnetic stimulation (rTMS)—a non-invasive modality that uses a similar technique as DCS—seems highly feasible for use in the investigation of semantic processing in the healthy human brain.

Methods: A total number of 100 (50 left-hemispheric and 50 right-hemispheric) rTMS-based language mappings were performed in 50 purely right-handed, healthy volunteers during an object-naming task. All rTMS-induced semantic naming errors were then counted and evaluated systematically. Furthermore, since the distribution of stimulations within both hemispheres varied between individuals and cortical regions stimulated, all elicited errors were standardized and subsequently related to their cortical sites by projecting the mapping results into the cortical parcellation system (CPS).

Results: Overall, the most left-hemispheric semantic errors were observed after targeting the rTMS to the posterior middle frontal gyrus (pMFG; standardized error rate: 7.3‰), anterior supramarginal gyrus (aSMG; 5.6‰), and ventral postcentral gyrus (vPoG; 5.0‰). In contrast to that, the highest right-hemispheric error rates occurred after stimulation of the posterior superior temporal gyrus (pSTG; 12.4‰), middle superior temporal gyrus (mSTG; 6.2‰), and anterior supramarginal gyrus (aSMG; 6.2‰).

Conclusions: Although error rates were low, the rTMS-based approach of investigating semantic processing during object naming shows convincing results compared to the current literature. Therefore, rTMS seems a valuable, safe, and reliable tool for the investigation of semantic processing within the healthy human brain.

Abbreviations: CPS, Cortical parcellation system; DCS, Direct cortical stimulation; DT, Display time; EHI, Edinburgh Handedness Inventory; FDR, False discovery rate; IFG, Inferior frontal gyrus; ITG, Inferior temporal gyrus; IPI, Inter-picture-interval; IPNP, International Picture Naming Project; fMRI, Functional magnetic resonance imaging; MEG, Magnetoencephalography; MRI, Magnetic resonance imaging; MTG, Middle temporal gyrus; opIFG, Opercular inferior frontal gyrus; PrG, Precentral gyrus; PTI, Picture-to-trigger-interval; RMT, Resting motor threshold; rTMS, Repetitive navigated transcranial magnetic stimulation; SD, Standard deviation; SMG, Supramarginal gyrus; STG, Superior temporal gyrus; TMS, Transcranial magnetic stimulation; VAS, Visual analog scale; vPrG, Ventral precentral gyrus

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1. Introduction

The current knowledge about the cortical representation of semantic processing in both hemispheres of the human brain is predominantly based on findings using functional magnetic resonance imaging (fMRI) (Pulvermuller et al., 2009; Vigneau et al., 2006, 2011) but also on results derived from intraoperative language mapping by direct cortical stimulation (DCS) during awake surgery (Corina et al., 2010; Duffau et al., 2013; Moritz-Gasser et al., 2013; Ojemann, 2003). However, DCS, which is regarded as the current gold standard in terms of functional testing of cortical function, cannot be used for the examination of language subfunctions in the healthy brain due to its highly invasive character, and fMRI is likely to be too inaccurate for language mapping, at least when applied in patients with intracerebral lesions (FitzGerald et al., 1997; Giussani et al., 2010; Sollmann et al., 2013b).

Repetitive navigated transcranial magnetic stimulation (rTMS) combines the advantages of both the DCS and fMRI methods, because comparable to DCS, it elicits an electric field within the cortex and therefore induces a temporary functional lesion, and it is non-invasive, as fMRI is. Moreover, rTMS has been repeatedly used to identify cortical areas causally related with different language subfunctions by influencing language performance within the frame of causing different types of naming errors (Lioumis et al., 2012; Pascual-Leone et al., 1991; Rosler et al., 2014; Sollmann et al., 2014; Tarapore et al., 2013; Wassermann et al., 1999). However, semantic paraphasias as a reflection of rTMS-induced impairment of semantic processing was only observed infrequently in recent mapping studies and has therefore not been in the main focus of rTMS research (Lioumis et al., 2012; Sollmann et al., 2014). Consequently, we investigated 50 left-hemispheric and 50 right-hemispheric rTMS language mappings for semantic paraphasias, which were performed in healthy volunteers during an object-naming task. The results will then be compared and discussed in relation to the current literature on fMRI, DCS, and rTMS studies dealing with the cortical representation of semantic processing.

2. Materials and methods

2.1. Mappings

For the present study, we reevaluated 100 rTMS language mapping sessions, which were performed in our department with the same protocol for investigating various questions of rTMS language mapping. Yet, semantic processing was not investigated in these preceding and partially published trials (Picht et al., 2013; Sollmann et al., 2014). In 50 out of these 100 mappings, the left hemisphere was investigated, while the right hemisphere was stimulated in the remaining 50 sessions. All mappings were performed in the same 50 healthy, monolingual, and purely right-handed volunteers.

Inclusion criteria were right handedness (assessed by the Edinburgh Handedness Inventory=EHI), German as mother tongue and only primary language, age above 18 years, and written informed consent. The exclusion criteria were previous seizures, general rTMS exclusion criteria (pacemaker, cochlear implant), ambidexterity, simultaneous bilingual subjects, and pathological findings on cranial magnetic resonance imaging (MRI).

2.2. Ethics

The experimental protocol was approved by the ethical committee of our university (registration number: 2793/10) in accordance with the declaration of Helsinki. All volunteers provided written informed consent prior to MRI.

2.3. Navigational MRI

After obtaining written informed consent, all volunteers underwent a navigational MRI on the same clinical 3 Tesla MR scanner (Achieva 3T, 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 58 s acquisition time), which was performed without intravenous contrast administration. Subsequently to scanning, the individual 3D MRI dataset was transferred to the rTMS system using the DICOM standard.

2.4. Language mapping by rTMS

2.4.1 rTMS procedure and stimulation parameter selection

All cortical language mappings were performed with the Nexstim eXimia NBS system version 4.3 with a NexSpeech® > module (Nexstim Oy, Helsinki, Finland) as repeatedly published by our and other groups (Krieg et al., 2014a, 2014b; Picht et al., 2013; Rosler et al., 2014; Sollmann et al., 2013a; Sollmann et al., 2014; Tarapore et al., 2013). In short, individual T1-weighted MRI data were used to reconstruct each participant's 3D brain image, which was used as an anatomical reference, co-registered to the subject's brain to localize the stimulated brain area during the individual mapping session. The subject's head position was tracked by reflectors fastened to the head with an elastic strap; thus, head movements did not cause data acquisition problems unlike with MRI or magnetoencephalography (MEG) imaging. For precisely tracking the position of the magnetic coil with respect to the volunteer's head, the rTMS system used a stereotactic camera. Taking all information of the neuronavigation together, the rTMS system was then able to visualize the targeted stimulation points and the electric field induced by the magnetic coil over the above-mentioned brain's 3D reconstruction image, while the examiner moved the coil across the volunteer's head (Ruohonen and Karhu, 2010). All intracranial points of stimulation were automatically saved for later examination (Ruohonen and Karhu, 2010).

To prepare for rTMS mapping sessions, stimulation parameters, like the stimulation intensity and frequency, had to be determined. Both parameters were personalized based on the following protocol, and the individual RMT, stimulation intensity, and frequency were documented:

1. The resting motor threshold (RMT) of the left hemisphere was determined by motor mapping of M1 for the abductor pollicis brevis muscle;
2. A train of 5–7 rTMS bursts was administered to ventral precentral gyrus (vPrG) and 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), which caused the highest error rate (=number of errors/number of stimulations), was identified by the volunteer's and examiner's impressions;
4. If there was no clear difference in the effect on language, the most comfortable frequency was chosen;
5. If naming was not interrupted by rTMS, the intensity was increased to 110–120% RMT, and step 1 was repeated; and
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). This adjustment was also applied if 100% RMT was severely painful.