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Language function distribution in left-handers: A navigated transcranial magnetic stimulation study

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ABSTRACT

Recent studies suggest that in left-handers, the right hemisphere (RH) is more involved in language function when compared to right-handed subjects. Since data on lesion-based approaches is lacking, we aimed to investigate language distribution of left-handers by repetitive navigated transcranial magnetic stimulation (rTMS). Thus, rTMS was applied to the left hemisphere (LH) and RH in 15 healthy left-handers during an object-naming task, and resulting naming errors were categorized. Then, we calculated error rates (ERs=number of errors per number of stimulations) for both hemispheres separately and defined a laterality score as the quotient of the LH ER – RH ER through the LH ER + RH ER (abbreviated as (L−R)/(L+R)). In this context, $(L-R)/(L+R) > 0$ indicates that the LH is dominant, whereas $(L-R)/(L+R) < 0$ shows that the RH is dominant.

No significant difference in ERs was found between hemispheres (all errors: mean LH 18.0 ± 11.7%, mean RH 18.1 ± 12.2%, $p=0.94$; all errors without hesitation: mean LH 12.4 ± 9.8%, mean RH 12.9 ± 10.0%, $p=0.65$; no responses: mean LH 9.3 ± 9.2%, mean RH 11.5 ± 10.3%, $p=0.84$). However, a significant difference between the results of (L−R)/(L+R) of left-handers and right-handers (source data of another study) for all errors (mean 0.01 ± 0.14 vs. 0.19 ± 0.20, $p=0.0019$) and all errors without hesitation (mean −0.02 ± 0.20 vs. 0.19 ± 0.28, $p=0.0051$) was revealed, whereas the comparison for no responses did not show a significant difference (mean: −0.004 ± 0.27 vs. 0.09 ± 0.44, $p=0.64$). Accordingly, left-handers present a comparatively equal language distribution across both hemispheres with language dominance being nearly equally distributed between hemispheres in contrast to right-handers.

1. Introduction

For a long time, language processing had been exclusively attributed to neural activity in the left hemisphere (LH) (Broca, 1861). As such, the right hemisphere (RH) was thought not to play a crucial role in language function. However, recently, an increasing number of studies have reported a major role of the RH in language processing in epileptic or tumor patients (Chang et al., 2011; Krieg, et al., 2013; Springer et al., 1999; Tivarus et al., 2012) and healthy individuals (Greve et al., 2013; Pujol et al., 1999; Sollmann et al., 2014; Springer et al., 1999). Moreover, the increasing interest in the RH's importance for language processing is reflected in recent reviews (Hartwigsen and Siebner, 2012; Vigneau et al., 2011). Specifically, the degree of activity of the RH in language function has been shown to be particularly pivotal in left-handers (Chang et al., 2011; Duffau et al., 2003; Duffau et al., 2008; Perlaki et al., 2013; Pujol et al., 1999). In Chang et al.'s study, left-handed patients undergoing surgery showed right-hemispheric dominance for language processing (Chang et al., 2011). Similarly, Duffau and colleagues observed the same right-hemispheric activity for language function for left-handed tumor

Abbreviations: APB, Abductor pollicis brevis muscle; CPS, Cortical parcellation system; DCS, Direct cortical stimulation; DT, Display time; EHI, Edinburgh Handedness Inventory; ER, Error rate; fMRI, Functional magnetic resonance imaging; IPI, Inter-picture interval; IPNP, International Picture Naming Project; LH, Left hemisphere; MRI, Magnetic resonance imaging; opIFG, Opercular inferior frontal gyrus; PTI, Picture-to-trigger interval; RH, Right hemisphere; RMT, Resting motor threshold; ROC, Receiver operating characteristics; rTMS, Repetitive navigated transcranial magnetic stimulation; TMS, Transcranial magnetic stimulation; trIFG, Triangular inferior frontal gyrus; VAS, Visual analogue scale

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patients (Duffau et al., 2008). Moreover, functional magnetic resonance imaging (fMRI) studies on healthy left-handed volunteers have also shown right-hemispheric dominance for language function during a word generation task (Pujol et al., 1999) and a verbal fluency paradigm (Perlaki et al., 2013). Interestingly, a study by Knecht and colleagues has shown a linear relationship between handedness and hemispheric language dominance, where a higher degree of left-handedness was associated with a higher activation of the RH in language processing and vice versa (Knecht et al., 2000). However, despite fMRI providing adequate spatial resolution, it does not primarily reveal causality. Correspondingly, the relationship between language processing and the areas activated as observed by fMRI is only correlational, and a lesion-based study in healthy brains would therefore be helpful. On the other hand, repetitive navigated transcranial magnetic stimulation (rTMS), through the causation of temporarily functional lesions, can identify cortical areas that are fundamental for solving a specific function (Krieg et al., 2015; Lioumis et al., 2012; Maurer et al., 2015; Pascual-Leone et al., 1991). In short, a magnetic coil is manually placed on the scalp during transcranial magnetic stimulation (TMS), and this coil is able to induce a temporary magnetic field that triggers the generation of an electrical field (Hallett, 2000; Ruohonen and Ilmoniemi, 1999; Ruohonen and Karhu, 2010). The electrical field modulates cortical neuronal activation and, when applied with a certain frequency in rTMS language mapping, this modulation causes temporary functional impairment that can result in different kinds of language or speech errors which can be detected by post-hoc video analysis (Lioumis et al., 2012).

Through its non-invasive character, rTMS is commonly used for language mapping in patients prior to surgery (Krieg et al., 2014; Picht et al., 2013; Tarapore et al., 2013) and in healthy individuals for neuroscientific purposes (Krieg et al., 2015; Lioumis et al., 2012; Rogic et al., 2014; Sollmann et al., 2014, 2015a, 2015b). However, the exact regions that are involved in language processing in left-handers are still unknown within the scope of a virtual-lesion approach. Therefore, the current study uses rTMS to investigate the cortical distribution of language areas in the LH and RH of left-handers undergoing a single-word production task. This study's aim was to test the following hypothesis: left-handers do not present a strong LH language distribution but rather a more equal cortical distribution of language functions across the LH and RH.

2. Materials and methods

2.1. Ethics

Subjects signed a consent form before undergoing magnetic resonance imaging (MRI). The local ethics committee (registration number: 2793/10) approved the experimental protocol, and the study was conducted in accordance with the Declaration of Helsinki.

2.2. Subjects

Fifteen healthy left-handed native German speaking volunteers (10 males and 5 females, median age: 25 years) participated in the study. Subjects completed the Edinburgh Handedness Inventory (EHI) to test for handedness (Oldfield, 1971). In this context, subjects with an EHI score of < -40 points were regarded as left-handers and included in the present study, whereas volunteers with -40 to $+40$ points were defined as ambidextrous and volunteers with $> +40$ points were regarded as right-handers.

Exclusion criteria were general rTMS exclusion criteria such as pacemaker, cochlear implant, or deep brain stimulation electrodes. In addition to these rTMS-specific criteria, seizure episodes, pathological findings on cranial MRI, bilateral handedness or right-handedness, and other mother tongues were defined as exclusion criteria.

2.3. Magnetic resonance imaging

Volunteers underwent an MRI scan with a 3 Tesla MR scanner (Achieva 3 T, Philips Medical Systems, The Netherlands B.V.) via an 8-channel phased-array head coil prior to the rTMS session. For the scanning protocol 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) was used. No intravenous contrast agent was utilized. Subsequent to MRI, the data were exported to the rTMS system using DICOM standard.

2.4. Repetitive navigated transcranial magnetic stimulation

Language mapping was done using the Nexstim eXimia NBS system (version 4.3) with a NexSpeech® module (Nexstim Oy, Helsinki, Finland). Stimulation was performed with a biphasic figure-of-eight coil, and an infrared tracking camera (Polaris Spectra, Waterloo, Ontario, Canada) was used to be able to precisely navigate the coil across the skull during rTMS. The volunteers sat in a comfortable chair during the mapping procedures, and the head position was tracked by reflectors fastened to the head with an elastic strap. Moreover, the coil position was followed by reflectors situated on the back side of the magnetic coil.

Prior to the examinations, the 3D MRI data of each volunteer was uploaded to the NBS system and used to reconstruct and visualize an individual 3D brain image, which was used as an anatomical reference, co-registered to the subject's skull, to localize the coil with respect to individual anatomical structures (Krieg et al., 2015; Lioumis et al., 2012; Sollmann et al., 2014, 2015a, 2015b). The rTMS coil and its estimated electric field is then displayed onto the adjustable 3D brain image through the infrared camera, which senses the reflectors on the head of the volunteer and on the coil. Thus, the exact coil position and the electric field generated are observable on the 3D reconstruction of the MRI dataset during the stimulation in real time (Ilmoniemi et al., 1999; Ruohonen and Karhu, 2010).

For each volunteer, the resting motor threshold (RMT) was used to determine the stimulation intensity for language mapping. Since both hemispheres were mapped in the present study, we determined the RMT of both hemispheres separately with respect to the same protocol. First, muscle electrodes (Neuroline 720, Ambu, Ballerup, Denmark) were placed over the abductor pollicis brevis muscle (APB), and we identified the most excitable spot in the precentral gyrus that elicited the strongest muscle response in the contralateral APB according to continuous electromyography monitoring (Krieg et al., 2012; Picht et al., 2012). At this spot, we determined the individual RMT with the algorithm provided by the system. The software's algorithm uses the most common determination approach, which defines the RMT as the lowest stimulation intensity that elicits motor evoked potentials over 50 μV in amplitude in 50% of stimulation trials (Krieg et al., 2012; Picht et al., 2012; Rossini et al., 1994; Sollmann et al., 2013a, 2013b). During all stimulations for the RMT measurement, the electric field was oriented perpendicular to the precentral gyrus. The RMT was then used as a basic value for subsequent language mapping.

2.5. Language mapping

The currently used parameters are similar to those repeatedly published for rTMS language mapping (Krieg et al., 2014; Picht et al., 2013; Sollmann et al., 2014, 2015a, 2015b; Tarapore et al., 2013). For the language mapping, participants had to name clearly and as quickly as possible 131 colored photographs of everyday objects that were presented on a screen positioned 60 cm from their eyesight (Krieg et al., 2015; Picht et al., 2013; Sollmann et al., 2014, 2015a, 2015b). The objects had to be named in German, which was the mother tongue of all volunteers. The entire set of objects was provided by the Nexstim NexSpeech® module (Nexstim Oy, Helsinki, Finland), and the photographs showed common living as well as non-living objects (e.g., child, tie, cup, snake, umbrella), similar to the objects of Snodgrass and Vanderwart (Snodgrass and Vanderwart, 1980).

Initially, volunteers had to perform the object-naming task twice without stimulation, where objects that were misnamed or did not elicit clear responses were discarded (e.g., hesitations, no responses, incorrect naming) (Krieg et al., 2015; Picht et al., 2013; Sollmann et al., 2014, 2015a, 2015b). We referred to the German data portion of the International Picture Naming Project (IPNP) database for checking naming agreements (Szekely et al., 2004). The remaining objects constituted the baseline and were used in the mapping session, and these objects were presented in randomized order during stimulation. A video camera recorded both the baseline testing and the language mapping for later offline analysis. The inter-picture-interval (IPI) was 2,500 ms, and each picture was displayed on the screen for 700 ms (display time=DT) with a picture-to-trigger interval (PTI) of 0 ms.

During stimulation, rTMS trains of 5 Hz and 5 pulses were delivered in a time-locked fashion to the objects with 100% RMT (Krieg et al., 2012; Lioumis et al., 2012; Rosler et al., 2014; Sollmann et al., 2014, 2015a, 2015b; Tarapore et al., 2013). The LH was stimulated with the individual LH's RMT, whereas the RH was examined with the RH's RMT. The coil was manually positioned on 46 target points that had been set on the 3D brain image prior to the mapping on each hemisphere by anatomical identification (Fig. 1). Overall, the LH and RH were stimulated twice, and each stimulation target was stimulated three times in a row before moving the coil to