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NEUROANATOMICAL CORRELATES OF LANGUAGE LATERALIZATION IN THE BRAIN

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Publications

Three publications have been selected for defense. In the first paper T.A. Bolgina is the first / main author and corresponding author, in other papers the author of the dissertation is the second author.

1. **Bolgina T**., Somashekarappa M., Cappa S. F., Cherkasova Z., Feurra M., Malyutina S., Sapuntsova A., Shtyrov Y., Dragoy O. Repetitive transcranial magnetic stimulation modulates action naming over the left but not right inferior frontal gyrus // Brain Structure and Function. 2022. Vol. 227. No. 8. P. 2797–2808.
2. Karpychev V., **Bolgina T**., Malytina S., Zinchenko V., Ushakov V., Ignatyev G., Dragoy O. Greater volumes of a callosal sub-region terminating in posterior language-related areas predict a stronger degree of language lateralization: A tractography study // Plos One. 2022. Vol. 17. No. 12. Article e0276721.
3. Karpychev V., **Bolgina T**., Malyutina S., Zinchenko V., Ushakov V., Ignatyev G., Dragoy O. No Association Between Structural Properties of Corpus Callosum and Handedness: Evidence from the Constrained Spherical Deconvolution Approach // The Russian Journal of Cognitive Science. 2020. Vol. 7. No. 3. P. 68–77.

Conference presentations and public demonstrations of the results

The main results and conclusions of the dissertation research on the neuroanatomical correlates of language lateralization in the brain were presented at six international conferences:

1. European Workshop on Cognitive Neuropsychology (22-27 January 2023, Bressanone, Italy). Poster presentation: Lateralization of action naming in the IFG: a TMS study.
2. VIII SKIL Student conference (22-23 October 2022, Moscow, Russia). Oral presentation: And yet on the left: the effect of transcranial magnetic stimulation over the left inferior frontal gyrus during action naming.
3. International Congress on Cognitive Linguistics (7-9 November 2022, Moscow, Russia). Oral presentation: Transcranial magnetic stimulation over the left but not the right inferior frontal gyrus modulates action naming despite individual language lateralization.
4. 46th Annual conference of Psychology and Brain (2-4 June 2021, online). Oral presentation: The association of handedness with language lateralization measured by a sentence completion fMRI paradigm in healthy participants.

5. Society for the Neurobiology of Language Annual Meeting (5-8 October 2021, online). Oral presentation: Transcranial magnetic stimulation over the IFG facilitates action naming but is modulated by language lateralization and handedness.
6. The Fourth Conference "Cognitive Science in Moscow: New Research” (15 June 2017, Moscow, Russia). Poster presentation: Relation of the corpus callosum volume and language lateralization in the brain.

Introduction

The dissertation includes the papers devoted to language lateralization and evaluation of some neuroanatomical correlates contributing to the representation of language in the brain. Several factors such as manual asymmetry, genetic predisposition to left-handedness, anatomy of the white and gray matter of the brain, rate of hemispheric maturation in healthy development, and altered brain processes due to pathology are currently discussed in relation to language lateralization in the brain. The first paper focuses on clarifying the role of the right hemisphere in language production at the word level in a representative and balanced group of participants with varying degrees of manual asymmetry. The second paper describes the relationship between functional language lateralization and structural characteristics of subregions of the corpus callosum in the same cohort of participants. The third paper separately assesses the association of structural characteristics of the corpus callosum fibers and manual asymmetry. The combination of several neuroimaging and neurostimulation methods allows us to comprehensively study the phenomenon of language lateralization and advance our understanding of the fundamental principles of the neurobiology of language.

The study of language lateralization is important and relevant for the development of scientific knowledge about the structure and functioning of language, consciousness, communication processes, perception and thinking processes. In addition, lateralization studies allow us to understand more about the structure and functioning of the healthy and pathological brain. It is known that in case of developmental disorders and language impairment atypical right hemispheric language lateralization is observed (Fakhri et al, 2013): stuttering (Fox et al., 2000), dyslexia (Xu et al., 2015), autism spectrum disorder (Lindell & Hudry, 2013). Language lateralization studies also shed light on the processes of language recovery after aphasia (Ansaldo et al., 2004; Olulade et al., 2020; Ries et al., 2016). At the moment, many questions remain regarding atypical language organization in the brain often found in patients with brain pathology, brain plasticity and possible functional reorganization caused by pathology or individual developmental features. Finally, an understanding of language lateralization in each individual case is urgently needed in clinical practice during neurosurgical operations, where the preservation of brain regions involved in the processes of language production and comprehension is at issue.

According to functional magnetic resonance imaging (fMRI) studies, language is realized predominantly in the left hemisphere in 90-95% of right-handed individuals and approximately 70-85% of left-handed individuals (Bradshaw et al. 2017; Price, 2012). It has also been shown that in some individuals, more likely in non-right-handers, language is organized in the brain bilaterally or predominantly in the right hemisphere (Bradshaw et al. 2017; Carey & Johnstone 2014;

Packheiser et al., 2020). Moreover, the contribution of the right hemisphere to language in healthy individuals regardless of handedness is evidenced by fMRI data of language mapping in the brain (Szafarski et al., 2001). It remains unclear whether patterns of right hemisphere activity are critical for language, which is highly relevant for clinical preoperative language mapping. The available current data are contradictory. Thus, with individual variability in language lateralization, there is an urgent need to reliably identify the neural substrate critical for language in preoperative mapping. However, fMRI, as one of the most widely used non-invasive neuroimaging techniques for language mapping and language lateralization measurement, does not causally assess the criticality of activation during a language task (Lehtinen et al., 2018). Such an assessment requires a method of transcranial magnetic stimulation (TMS) of the brain. Section 1 describes the results of fMRI and subsequent TMS studies on the same cohort of participants to clarify the role of the right hemisphere in language processing.

Language lateralization has traditionally been associated with individual handedness: a higher degree of left-handedness increases the likelihood of bilateral or right-hemispheric language organization (Knecht et al., 2000; Szaflarski et al., 2001). However, cases of crossed aphasia, neuroimaging data, neurostimulation and behavioral studies in neurologically healthy adults have shown that the relationship between the functional representation of language in the brain and handedness is ambiguous (Bruckert et al., 2021; Mazoyer et al., 2014). Furthermore, recent genetic studies suggest that handedness and language lateralization are partly controlled by the same set of genes and partly by a unique set of genes (Packheiser et al., 2020). Thus, the available evidence suggests the multifactorial nature of language lateralization.

Among the neuroanatomical correlates of language lateralization, the role of the commissural pathway connecting the left and right hemispheres, the corpus callosum (CC), has been extensively discussed (Gazzaniga, 2000; Josse et al., 2008; Hinkley et al., 2016). Previous attempts to investigate the relationship between the CC metrics and language lateralization have used structural MRI and measured the midsaggital area of the CC. Today, more relevant tractography methods are diffusion tensor imaging (DTI) and constrained spherical deconvolution (CSD), which, in contrast to structural MRI, allow more accurate reconstruction and quantification of volumes and microstructural properties of white matter tracts. Section 2 describes a study focusing on the relationship of language lateralization to the CC metrics reconstructed by modern tractography methods.

On the other hand, the neuroanatomical correlates of manual asymmetry (Ocklenburg et al., 2020), a factor often discussed in relation to language lateralization, are still unclear. It has been proposed that manual asymmetry may also be related to the CC metrics (Budisavljevic, Castiello & Begliomini, 2020). Chapter 3 describes the results of a study aimed at investigating this relationship in the same cohort of individuals as in Sections 1, 2.

Thus, the **aim of the dissertation** was to identify the individual lateralization of language in the brain of healthy adults with different degree and direction of manual asymmetry (left-handed, right-handed, ambidextrous) and its neuroanatomical correlates. To this end, the **objectives of the research** were:

1) To test whether the left and right hemisphere regions showing fMRI activation associated with language processing respond equally to TMS to these areas;

2) To measure the volumes and microstructural metrics of the CC subregions using modern tractography techniques (DTI and CSD) and test their relationship to the degree of language lateralization;

3) To verify the relationship of the CC metrics with the degree and direction of manual asymmetry which is related to language lateralization.

The **object of the research** is individual language lateralization in the brain of healthy adults. The **subject of the research** is the identification of neuroanatomical correlates associated with language lateralization and manual asymmetry. The **relevance of the research** is determined by the fact that currently the role of the right hemisphere in language processing is not sufficiently clear, and research data in this area are contradictory. In addition, reconstruction of the CC as a candidate for the role of a neural correlate of language lateralization has been reduced to the analysis of structural MRI images or the use of one of the tractography methods. The **research novelty** is that to clarify the role of the right hemisphere in language processing, we used fMRI and TMS methods on the same cohort of individuals and in contrast to previous studies included not only right-handed, but also left-handed and ambidextrous participants. In addition, the picture naming task for the TMS experiment included not only object naming but also action naming, thus offering a more reliable task for intraoperative language mapping. To reconstruct white matter pathways, we used and compared two modern tractography methods, DTI and CSD, testing for the first time their relationship to the degree of language lateralization and the degree and direction of manual asymmetry of the participants.

Theoretical significance of the dissertation:

1) according to the results of the TMS study, the right hemisphere, namely the inferior frontal gyrus, showed no critical involvement in language processing at the level of word generation independent of the handedness of the participants;

2) a larger volume of one of the CSD-reconstructed CC subregions connecting posterior temporo-parieto-occipital language areas was associated with a greater degree of functional language lateralization in these areas;

3) the CC microstructural metrics are not related to language lateralization;

4) the CC volume and microstructural metrics are not related to individual manual asymmetry;

5) CSD is a more reliable method of white matter pathways reconstruction.

Practical significance of the dissertation:

1) The action naming task was shown to be more reliable compared to object naming and is proposed for use in interoperative language mapping;

2) Based on the results of the dissertation research, a lecture "Neural Basis of Language Processing" was developed and implemented in the curriculum of the course "Psychology and Neurophysiology of Speech" (Bachelor program "Psychology", 4th year, Faculty of Social Sciences, HSE) and "Psycho- and Neurolinguistics" (Bachelor program "Fundamental and Computational Linguistics", 4th year, School of Linguistics, HSE).

The main results of the study and provisions for the defense:

1) TMS modulation of the left but not right inferior frontal gyrus resulted in more correct but slower action naming in a picture naming task. Thus, action naming despite individual variability and manual asymmetry critically engages only the left hemisphere of the brain.

2) It is necessary to include action naming tasks rather than object naming for intraoperative language mapping in the frontal lobe of the brain.

3) Larger volumes of the corpus callosum reconstructed by the constrained spherical deconvolution approach predict a stronger degree of functional language lateralization in posterior language areas.

4) The restricted spherical deconvolution approach is a more appropriate tractography method when lateral crossing projections are under the focus in studies of neural representation of language.

5) Micro- and macrostructural metrics of the corpus callosum subregions are not related to the degree and direction of manual asymmetry of participants.

1. **Repetitive transcranial magnetic stimulation modulates action naming over the left but not right inferior frontal gyrus.**

Paper selected for the defense: *Bolgina T.*, Somashekarappa M., Cappa S. F., Cherkasova Z., Feurra M., Malyutina S., Sapuntsova A., Shtyrov Y., Dragoy O. Repetitive transcranial magnetic stimulation modulates action naming over the left but not right inferior frontal gyrus // Brain Structure and Function. 2022. Vol. 227. No. 8. P. 2797-2808.

Unlike fMRI, the TMS method has an advantage of establishing causal functional relationships rather than a simple correlation between brain regions and language skills and allows for a more reliable measure of language lateralization in the brain (Lehtinen et al., 2018). However, evidence from the TMS studies investigating involvement of the right hemisphere in language is contradictory. On the one hand, TMS language mapping has confirmed right hemisphere involvement in language lateralization in an object naming task in healthy right-handed (Tussis et al., 2016) and left-handed individuals (Sollmann et al., 2015). These data are consistent with the results of some fMRI studies showing cases of atypical language lateralization (Szaflarski et al., 2001).

On the other hand, in a study with a combined use of fMRI and TMS methods, no systematic language impairment was found after stimulation of the right hemisphere, but only after stimulation of the posterior frontal regions of the left cerebral hemisphere despite the fMRI activation in areas of both hemispheres (Könönen et al., 2015). Such result means that fMRI activation in the right hemisphere regions reflected only co-activation and was not critical for language. In another recent study (Sakreida et al., 2020), fMRI inhibition of the left and right inferior frontal brain regions resulted in errors in an object naming task, which were observed more frequently with left than right hemisphere inhibition. The data from the mentioned studies indicate a traditional left-hemispheric organization of language in the brain. However, both studies included only right-handed individuals, excluding left-handed and ambidextrous participants, who are more likely to have atypical language organization (Josse & Tzourio-Mazoyer, 2004).

Controversial findings from the TMS studies and the unspecified role of the right hemisphere in language served as a prerequisite for the present study. The aim of the current study was to compare the result of TMS stimulation over the left and right brain hemispheres showing fMRI activation during a language mapping task. The main region of investigation and stimulation was chosen to be the left and right inferior frontal gyri, where activation is regularly detected as a result of different language fMRI paradigms (Becker et al., 2020). To test a more representative cohort of participants with various language lateralization profiles, including atypical cases, participants with varying degrees of manual asymmetry – right-handers, left-handers, and ambidexters – were invited into the study. In the first part of the study, for each subject, we obtained functional maps of language activation using a sentence completion fMRI paradigm. In the second part of the study, in the same group of participants, we applied TMS inhibition to the areas of peak activation in the left and right inferior frontal gyri during a picture naming task. We hypothesized that TMS inhibition of the right inferior frontal gyrus would lead to errors in the naming task if this area was indeed critically involved in language.

Moreover, in contrast to previous studies (Könönen et al., 2015; Sakreida et al., 2020; Tussis et al., 2016), we included not only objects but also actions in a picture naming task to compare the effect of TMC modulation of the left and right inferior frontal gyrus on object and action naming. Object (noun) processing has been shown to involve left temporal regions, whereas action (verb) processing involves left posterior inferior frontal regions (Daniele et al., 1994). Also, action naming tasks are preferred over object naming tasks because they allow for a more thorough assessment of language abilities during awake neurosurgery in the left frontal lobe (Rofes et al., 2017). Although some studies report a higher sensitivity of the object naming task during TMS mapping of the left inferior frontal gyrus (Hernandez-Pavon et al., 2014; Lubrano et al., 2014), we followed the majority of the evidence and hypothesized that the action naming task is more sensitive to TMS modulation over the inferior frontal gyrus.

Thirty-one neurologically healthy native Russian speakers (12 males, mean age 25.6 ± 5 years, 8 ambidextrous; 12 left-handers) participated in the study. All participants had normal or corrected-to-normal vision and hearing. The degree of handedness of the participants was assessed using the Edinburgh questionnaire (Oldfield, 1971) and ranged from +100 (absolute right-handed) to -100 (absolute left-handed).

High-resolution structural and functional MRI scans in the first part of the study resulted in individual functional activation maps for each participant. Language lateralization indices were calculated from the fMRI results and ranged from -0.44 to 0.62, where -1 indicates strong right-hemispheric language lateralization and +1 indicates strong left-hemispheric language lateralization. During the fMRI sentence completion paradigm, participants read aloud Russian sentences and completed them with a word that matched their meaning and grammar (e.g., "Now the minister signs an important ..."). In the control condition, participants were asked to read aloud strings with syllables and complete them with the same syllable at the end (e.g., "Peeeee peeeeee peeeeeeee peeeeeeee peeeeeeee peeeeeeee peeeeeeeeee peeeeeeeeeee..."). The length of sentences and lines was similar by number of syllables and letters. Based on individual functional maps, activation peaks were identified for each subject in the region of the left and right inferior frontal gyri for subsequent TMS modulation.

The second part of the study involved navigational TMS modulation of language to individual coordinates within the left inferior frontal gyrus, right inferior frontal gyrus, and vertex real and sham modulation as control conditions. During the TMS experiment, participants performed a picture naming task with objects (N = 100) and actions (N = 100). The task was to name an object or to say in one word what the character was doing in the picture as quickly and accurately as possible.

The TMS picture naming experiment showed that participants made more errors when naming actions than when naming objects (16% vs 8% errors). The effect of a stimulation site was also shown: with TMS modulation over only the left inferior frontal gyrus, the accuracy of action naming was significantly higher compared to the control condition of sham vertex modulation. At the same time, the accuracy and reaction time of object naming did not change significantly as a result of TMS modulation. It was also found that participants named actions slower than objects. However, no significant differences were found between the stimulation site in action and object naming.

Contrary to our expectation that both left and right inferior frontal gyri would show a significant effect as a result of TMS modulation, as most participants showed robust bilateral fMRI activation, our study showed that TMS over only the left but not right inferior frontal gyrus modulated participants' verbal behavior – they were better at action naming. This result is consistent with recent studies (Könönen et al., 2015; Sakreida et al., 2020) and suggests that fMRI activation in the right inferior frontal gyrus is not critical for language. The present study confirmed the critical involvement of only the left hemisphere but not the right hemisphere in action naming despite the variability of language brain representation. The study also showed that action naming required more time than object naming. This result indicates that verb production is generally slower than noun production because it requires more cognitive load and more processing time. Action naming in our study proved to be a more sensitive task for TMS language mapping compared to the object naming task, and this result is consistent with an earlier study (Ohlerth et al., 2021). Thus, the present study has practical implications: action naming should be included in preoperative mapping protocols in addition to a more traditional object naming task.

It is important to note that the localization of speech areas by fMRI and the stimulation of the localized areas by TMC used different tasks that address different linguistic levels. It is possible that in the fMRI study, areas critically involved in the task of sentence completion are not critically involved in the more localized tasks associated with lexical retrieval during TMC mapping. On the one hand, the two methods map differently due to physiological features; on the other hand, differences caused specifically by speech tasks may be caught. Nevertheless, the paper showed how fMRI mapping and TMC mapping are associated with each other, since both used typical language tasks.

2. Greater volumes of a callosal sub-region terminating in posterior language-related areas predict a stronger degree of language lateralization: A tractography study

Paper selected for the defense: Karpychev V., *Bolgina T.*, Malytina S., Zinchenko V., Ushakov V., Ignatyev G., Dragoy O. Greater volumes of a callosal sub-region terminating in posterior language-related areas predict a stronger degree of language lateralization: A tractography study // Plos One. 2022. Vol. 17. No. 12. Article e0276721.

Although the causation of language lateralization remains largely unknown (Güntürkün & Ocklenburg, 2017), attempts have been made to find its anatomical correlates in gray and white matter brain structures (Vingerhoets, 2019; Ocklenburg et al., 2016). Among gray matter structures, it has been suggested that insular asymmetry predicts language lateralization (Keller et al., 2011). However, although the insula is actively involved in various aspects of language processing, its role is not restricted to them (Nieuwenhuys, 2012), and the specific contribution of the insula to language lateralization is still unclear. In turn, asymmetry in explicitly language-related areas, namely the planum temporale and Broca's area, does not correlate with language lateralization (Tzourio-Mazoyer et al., 2018). In contrast, interhemispheric white matter structures, primarily the CC, which controls functional interaction between hemispheres, have been empirically shown to be associated with language lateralization (Gazzaniga, 2000). Since there is less language lateralization in adults with the CC agenesis (Hinkley et al., 2016), Adibpour and colleagues (2018) attributed this to the crucial role of callosal fibers in infants with this disease. Thus, the CC contributes to the development of language lateralization early in life.

Two different models explain how the CC may contribute to language lateralization (Bloom & Hynd, 2005). The excitatory model assumes functional activation of both hemispheres through the CC because most of its fibers rely on excitatory glutamate neurotransmitters. According to the inhibitory model, the subdominant hemisphere is suppressed by the dominant one during language tasks via inhibitory CC interneurons (van der Knaap & van der Ham, 2011). Depending on the different functions of the cortical areas involved in language processing, both excitation and inhibition may occur via callosal subregions. In addition, the functional diversity of CC contributions may be further enhanced by the microstructural heterogeneity of the callosal subregions (Aboitiz et al., 1992). An important question, therefore, is whether specific CC subregions, rather than CC as a whole, make distinct contributions to language lateralization, and whether these contributions are excitatory or inhibitory.

Previous attempts to investigate the relationship between the CC and language lateralization have used structural MRI and measured the midsagittal region of the CC (Ocklenburg et al., 2016). However, first, structural MRI does not provide insight into microstructural properties such as myelination, axon diameter, and white matter fiber density. Second, it does not adequately assess individual variability in the overall shape of the tract and, consequently, its volume, which is the closest indicator of fibers' number. This has led to mixed results in previous structural MRI studies (Westerhausen et al., 2009). While some studies (Labache et at., 2020; Bartha-Doering et al., 2021) have shown that a larger midsagittal area of the whole CC predicts reduced language lateralization, which has been interpreted in favor of the excitatory model, Josse and colleagues (Josse et al., 2008) showed the opposite effect and thus supported the inhibitory model.

In contrast to structural MRI, tractography allows researchers to reconstruct and quantify the volumes and microstructural properties of white matter tracts. Early tractography studies of language lateralization examined microstructural properties derived from diffusion-tensor imaging (DTI). Using the fractional anisotropy (FA) metric, different contributions of the anterior and posterior CC subregions to interhemispheric inhibition and excitation were shown (Putnam et al., 2008). However, both findings are inconsistent: Häberling and collegues (2011) identified excitation via the anterior CC subregion, while Westerhausen et al. (2006) identified inhibition through the posterior subregion of the CC using another DTI metric, relative anisotropy. It should be noted that none of these studies analysed the CC subregion volumes. Thus, the application of DTI has not resulted in consistent findings on the contribution of cerebral subregions to interhemispheric regulation in language processing. This may be due to the fact that DTI cannot reliably quantify structural properties due to its poor ability to resolve multiple fiber crossings in the CC (Tournier et al., 2011). Thus, DTI does not fully reconstruct all fibers of the CC and underestimates the volumes of the CC subregions.

To overcome the DTI limitations, a more advanced tractography approach, constrained spherical deconvolution, is more suitable for modelling crossing fibers and allows for more accurate estimation of the CC subregions' volumes (Steventon et al., 2016). However, as with DTI, CSD has not been used to investigate the relationship between the CC subregion volumes and language lateralization. To fill this gap, in the present study, we applied both tractography methods and tested the limitations of DTI compared to CSD. In addition to volume extraction using the two approaches, following previous DTI studies, we investigated the microstructural properties of the CC fibers in subregions and their relation to language lateralization. To do so, we used FA in DTI and Hindrance Modulated Oriental Anisotropy (HMOA) in CSD, which reflects axon diameter, fiber density and dispersion, representing fiber microstructural properties more accurately than FA (Dell'Acqua et al., 2013). HMOA has previously been used to study lateralization of spatial attention (Chechlacz et al., 2015), but has not yet been used to study language lateralization.

Finally, in previous DTI studies aimed at identifying the contribution of the CC to language lateralization, the latter has been measured with fMRI paradigms using word generation (Häberling et al., 2011) or word listening tasks (Steinmann et al, 2018). These two tasks mainly activate anterior or posterior language-related areas, respectively. Thus, each of the previous DTI studies have reported results based on language lateralization of either anterior or posterior language areas, but, importantly, not both at the same time. Thus, the differences in associations between structural properties of the CC subregions and language lateralization in anterior or posterior language areas were based on studies with different groups of participants, but not within the same group using the same language task. In the present study, we measured language lateralization using a more comprehensive sentence completion task using fMRI that reliably activates anterior and posterior language areas in the same individual. To allow for variability in the degree of language lateralization, we balanced participants by handedness and included right-handed, left-handed, and ambidextrous individuals in the sample. The aim of the study was to measure the volumes and microstructural indices of the CC subregions using both DTI and CSD tractography approaches and to test their relationship to the degree of language lateralization obtained with a comprehensive fMRI sentence completion task.

Fifty neurologically healthy native Russian speakers (18 males, mean age = 24.38 years, SD = 4.8 years), the same adults as in Sections 1, 3, participated in the study. Accordingly, the handedness questionnaire and the calculation of lateralization indices obtained by the fMRI sentence completion paradigm correspond to Study 1. Structural and diffusion-weighted images were acquired using a Siemens 3T Magnetom Verio MRI scanner. After preprocessing the tractography data for each participant in FSL, ExploreDTI and StarTrack programs, five CC subregions were manually reconstructed in the TrackVis program using DTI and CSD approaches: CC-I with fibers projected into the prefrontal cortex; CC-II (premotor cortex and supplementary motor area); CC-III (primary motor cortex); CC-IV, primary somatosensory cortex; and CC-V (parietal, temporal, occipital lobes according to the Hofer's scheme) (Hofer & Frahm, 2006). FA and HMOA values were then extracted for each subregion.

For all CC subregions, volumes were significantly larger reconstructed by the CSD than DTI method, and this result is consistent with a previous study (Steventon et al., 2016). The results showed that all CC subregions differed significantly in FA, except for comparisons between subregions CC-II and CC-IV and between CC-III and CC-V. Analysis of the DTI-based metrics showed no significant association with language lateralization. In contrast, analysis based on the CSD reconstruction method showed that the volume of the CC-V subregion linking posterior language areas predicted a stronger degree of language lateralization. This result supports the inhibitory model implemented through the CC fibers connecting posterior parietal, temporal, and occipital regions associated with language processing and is consistent with an earlier study (Josse et al., 2008).

In conclusion, we conducted the first tractography study to investigate the relationship between volumes and microstructural properties of the CC subregions and the degree of language lateralization using two tractography approaches DTI and CSD. We found that, consistent with the inhibitory model, larger volumes of the CC reconstructed by the CSD method predicted a stronger degree of language lateralization in the posterior language areas – posterior temporal/parietal/ occipital lobes. Thus, the effect of the CC fibers on the degree of language lateralization is not uniform, but rather anatomically specific. Furthermore, the CSD approach has been confirmed to be more appropriate when lateral crossing projections are under the focus of attention, as in studies of neural language representation.

3. No Association Between Structural Properties of Corpus Callosum and Handedness: Evidence from the Constrained Spherical Deconvolution Approach

Paper selected for the defense: Karpychev V., *Bolgina T.*, Malyutina S., Zinchenko V., Ushakov V., Ignatyev G., Dragoy O. No Association Between Structural Properties of Corpus Callosum and Handedness: Evidence from the Constrained Spherical Deconvolution Approach // The Russian Journal of Cognitive Science. 2020. Vol. 7. No. 3. P. 68-77.

Handedness is the most studied example of human functional asymmetry (Marcori & Okazaki, 2019) related to a lateralized cognitive function – language (Somers et al., 2015). More than 90% of the world's population is right-handed and 10% are left-handed (Papadatou-Pastou et al., 2020). It is known that manual asymmetries are largely determined by genetic and epigenetic factors (Ocklenburg et al., 2017), while their manifestation at the neuronal level is still unclear (Ocklenburg et al., 2020).

The corpus callosum (Budisavljevic, Castiello & Begliomini, 2020) has been proposed as one of the candidates for the neuroanatomical correlate of handedness, and its functional action has been explained by the excitatory and inhibitory models. According to the excitatory model, the two brain hemispheres activate each other through exposure to the excitatory neurotransmitter glutamate via the CC fibers (Bloom & Hynd, 2005). On the other hand, according to the inhibitory model, the handedness-dominant hemisphere suppresses the activity of the other hemisphere through inhibitory interneurons connected by the CC fibers (van de Knaap & van der Ham, 2011). These studies support the presence of multiple CC subregions composed of fibers of different properties (Ocklenburg et al., 2016).

Previous studies have assessed the CC metrics based on the midsagittal surface in structural images, which is not a reliable method for reconstructing white matter fibers (Ocklenburg et al., 2016). There have also been studies using DTI to examine the micro-characteristics of the CC fibers, showing that the FA of the CC fibers is greater in left-handed individuals (McKay et al., 2017;). However, this method has a limitation – DTI fails in reconstructing crossing white matter fibers. An alternative tractography approach that addresses this shortcoming is the CSD method (Steventon et al., 2016). Until now, the relationship between the degree and direction of handedness and volume of the CC subregions reconstructed by the CSD method has not been investigated. Thus, the aim of the present study was to evaluate, for the first time, the relationship between structural characteristics of the CC fibers reconstructed by the CSD method and measures of manual asymmetry in neurologically healthy right-handed, left-handed, and ambidextrous individuals.

Fifty neurologically healthy native Russian speakers (16 males, mean age = 24.9 years, SD = 5.1 years) participated in the study. To assess handedness, each participant completed the Edinburgh questionnaire (Oldfield, 1971). Based on the questionnaires, participants were categorized into three groups: 20 right-handed (handedness index from +45 to +100), 10 ambidextrous (handedness index from -45 to +45), and 20 left-handed (handedness index from -100 to -45). Similar to the Study 2, structural and diffusion images were acquired for each participant, followed by preprocessing and manual fiber reconstruction for five CC subregions using the Hofer's scheme (Hofer & Frahm, 2006). Volume and HMOA metrics were extracted for each CC subregion. One-way ANOVA analysis of variance within the framework of Frequentist and Bayesian statistical approaches was performed to compare the CC subregions metrics between groups of participants, and generalized linear models with Bonferroni correction for multiple comparisons were performed to determine the relationship between the degree of handedness and the CC subregions metrics. Statistical analysis was performed in the MATLAB program.

The results of the one-way analysis of variance within the frequentist approach revealed no significant differences between volume and microstructural characteristics of the CC subregions in groups of participants with different handedness. Bayesian one-way analysis of variance confirmed no significant differences in volume and HMOA of the CC fibers for the subregions CC-I, CC-II, CC-III, and CC-V, and no clear evidence of differences was found for the CC-IV region, indicating that this subregion could be studied in more detail in future. Also, linear models did not confirm a significant linear relationship between absolute measures of handedness, volume and HMOA of the CC subregions.

This study was the first to test the relationship between the structural characteristics (volume and HMOA) of five CC subregions reconstructed by the CSD approach using the Hofer scheme and the direction and degree of handedness of the participants. The division of the CC into subregions was motivated by differences in their microstructural properties, which may be related to an inhibitory or excitatory role with respect to handedness. In contrast to previous studies (Josse et al., 2008; Cowell & Gurd, 2018), we found no significant differences in the CC regions volume between right-handed, left-handed and ambidextrous participants. Future studies are needed to identify metrics that characterize fiber microstructural properties and clarify their relationship to handedness.

Conclusion

The papers included in this dissertation addressed language lateralization in the brain and described some of its neural correlates. Section 1 presented the study aimed at clarifying the role of the right hemisphere in language processing in a balanced cohort of neurologically healthy left-handed, right-handed, and ambidextrous participants. The results showed that despite the direction and degree of the participants' handedness, only the inferior frontal gyrus of the left hemisphere was critically involved in language processing at the level of word production.

Section 2 described a tractography study aimed to evaluate the relationship between micro- and macrometrics of the corpus callosum and the degree of language lateralization in a balanced cohort of neurologically healthy left-handed, right-handed, and ambidextrous individuals. The results confirmed that, consistent with the inhibitory model, a larger volume of one of the CC subregions reconstructed by the CSD method predicted a stronger degree of language lateralization in the posterior language areas, the posterior parietal-temporal-occipital lobes. CSD also proved to be a more reliable method for reconstructing white matter fibers.

Section 3 presented a description of a study designed to assess the relationship between micro- and macrometrics of the corpus callosum and participants' degree of handedness as one of the frequently discussed correlates of language lateralization. The study found no significant association between the two measures, but one of the CC subregions needs further testing for association with handedness.

Regarding the statistical power of the identified effects, the sample of participants in the above studies included from 30 to 50 people. For neuroimaging studies, such a sample size is quite large, and it is difficult to justify a specific sample size because it is necessary to predict the approximate effect size for each of the indicators, and there are many indicators in the study. This raises questions about how to optimize the sample size. On the other hand, a sample size of 30-50 people is small for a language lateralization study. The heterogeneous results of the research may be due to an insufficient sample size due to technical reasons. Therefore, future studies are needed to continue investigation on the language lateralization larger samples of participants.

Thus, the results obtained in the present dissertation study contribute to the understanding of the language lateralization phenomenon and its neural correlates in a group of neurologically healthy participants. Work is currently underway to investigate the contribution of other correlates, such as characteristics of the associative white matter language pathways and the factor of familial sinistrality. The work conducted by the author of this dissertation is interdisciplinary in nature and combines approaches and methods of experimental linguistics and modern neurolinguistics.

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