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Research article

Voxel-wise grey matter asymmetry analysis in left- and right-handers

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HIGHLIGHTS

- We investigated grey matter asymmetries in left- and right-handers.
- We used a new voxel based morphometry toolbox optimized for asymmetry detection.
- We detected typical grey matter asymmetries in the overall sample.
- No significant differences between left- and right-handers were observed.
- Grey matter asymmetries are not a major structural correlate of handedness.

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ABSTRACT

Handedness is thought to originate in the brain, but identifying its structural correlates in the cortex has yielded surprisingly incoherent results. One idea proclaimed by several authors is that structural grey matter asymmetries might underlie handedness. While some authors have found significant associations with handedness in different brain areas (e.g. in the central sulcus and precentral sulcus), others have failed to identify such associations. One method used by many researchers to determine structural grey matter asymmetries is voxel based morphometry (VBM). However, it has recently been suggested that the standard VBM protocol might not be ideal to assess structural grey matter asymmetries, as it establishes accurate voxel-wise correspondence across individuals but not across both hemispheres. This could potentially lead to biased and incoherent results. Recently, a new toolbox specifically geared at assessing structural asymmetries and involving accurate voxel-wise correspondence across hemispheres has been published [F. Kurth, C. Gaser, E. Luders. A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM), Nat Protoc 10 (2015), 293–304]. Here, we used this new toolbox to re-assess grey matter asymmetry differences in left- vs. right-handers and linked them to quantitative measures of hand preference and hand skill. While we identified several significant left-right asymmetries in the overall sample, no difference between left- and right-handers reached significance after correction for multiple comparisons. These findings indicate that the structural brain correlates of handedness are unlikely to be rooted in macroscopic grey matter area differences that can be assessed with VBM. Future studies should focus on other potential structural correlates of handedness, e.g. structural white matter asymmetries.

1. Introduction

When conducting fine motor activities such as writing, a large majority of humans consistently prefer one hand over the other [1]. On average, roughly 10% of the population prefers to use the left hand, while the remaining 90% prefers to use the right hand [2]. Since there are no obvious muscular, osseous or peripheral nervous system differences between the left and right hands of left- and right-handers, it has been suggested that handedness originates in the central nervous system [3,4]. One idea put forward by several authors is that structural asymmetries in grey matter areas might underlie handedness, but empirical results have been surprisingly incoherent. Areas for which associations with handedness have been reported include the left precentral sulcus [5], left central sulcus [6], planum temporale [7] and Boca's area [8]. However, other studies have failed to find any associations between structural asymmetries in these areas and handedness [9]. The largest study so far has been conducted by Guadalupe et al. [10].

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They analyzed cortical surface area differences between 106 left-handed and 1960 right-handed subjects, reporting that no cortical region showed any association with left-handedness that survived statistical correction for multiple testing.

A common technique to assess grey matter asymmetries is voxel based morphometry (VBM). VBM allows for a voxel-wise comparison of local grey matter concentration between two groups of subjects, e.g. left- and right-handers or patients and controls. It involves spatial normalization of structural MRI scans from all participants into the same stereotactic space, followed by segmentation into grey and white matter, and smoothing of grey matter segments. Using these smoothed grey-matter images, voxel-wise statistical tests are then used to compare the two groups [11,12].

VBM is a workhorse tool in neuroimaging that has been used in hundreds of published studies. However, it has recently been pointed out that the standard VBM protocol might not be ideally suited to specifically assess group differences in structural grey matter asymmetries, as it involves accurate voxel-wise correspondence across individuals but not necessarily across both hemispheres [13]. This methodological issue might have lead to biased results in previous asymmetry studies, potentially omitting existing asymmetries or causing false positive results. Recently, Kurth et al. [13] published a novel 12-step protocol for specifically analyzing voxel-wise grey matter asymmetries. This protocol solves the problems standard VBM encounters in asymmetry analyses by ensuring accurate voxel-wise correspondence across individuals and hemispheres by means of spatial normalization into a symmetric space using DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) [14]. Additionally, the protocol avoids blurring of information across hemispheres and controls the possible impact of noise in the data by applying an explicit brain mask and a spatial smoothing procedure. The protocol has recently been successfully used in a study investigating differences in gray matter asymmetry between long-term meditators and non-meditating controls [15], but has not yet been used in the context of handedness.

Here, we used the protocol by Kurth et al. [13,15] to re-investigate structural grey matter asymmetries in left-and right-handers. Using the advanced statistical analysis features of the toolbox, we not only compared left- and right-handers on the group level, but also linked grey matter asymmetries to inter-individual quantitative measures of hand preference and hand skill, an aspect not investigated in previous studies.

2. Material and methods

2.1. Participants and handedness assessment

Overall, 60 volunteers participated in the present study (30 males; 30 females). Mean age was 23.33 years, with a range of 18 to 33 years. None of the participants had any history of psychiatric or neurological disorders.

Participants' hand preference was assessed with the Edinburgh Handedness Inventory [16]. This ten-item questionnaire yields a so-called lateralization quotient (LQ) ranging from −100 (consistent left-handedness) to +100 (consistent right-handedness). There were two groups of participants: right-handers ($n = 30$) with positive LQs (LQ range: 50–100), and left-handers ($n = 30$) with negative LQs (LQ range: −100 to −15.79). To also gain a quantitative measure of hand skill, the classic pegboard task was used [17]. In this simple motor task, participants have to move ten pegs from holes on the upper side of a so-called pegboard to its lower side. This is done three times with the left and three times with right hand, and the time needed to perform this task with each hand is recorded. In order to gain a quantitative measure of hand skill asymmetries, we calculated the so-called PegQ measure using the formula $\text{PegQ} = (2 \times (\text{L-R})/(\text{L} + \text{R}))$, with L being the average time in seconds needed to perform the task with the left hand and R being the average time in seconds needed to perform the task with the right hand.

The study was approved by the local ethics committee of the Faculty of Psychology at Ruhr-University Bochum. Participants were treated in accordance with the declaration of Helsinki. Written informed consent was obtained from each subject. Participation was either paid or compensated with course credit.

2.2. MRI acquisition and processing

MRI data were acquired using a Philips Achiva 3-Tesla MRI scanner equipped with a 32-channel head coil located at the University Clinic Bergmannsheil in Bochum, Germany. The maximum gradient strength of the scanner was 40 mT/m. A T1-weighted high-resolution anatomical scan (MP-RAGE, TR = 8179 ms, TE = 3.7 ms, flip angle = 8°, 220 slices, matrix size = 240×240, resolution = $1 \times 1 \times 1$ mm, acquisition time = 6 min) was obtained from each subject.

Using the T1-scans, we then performed voxel-wise grey matter asymmetry analysis following the recently published protocol for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM) by Kurth et al. [13]. This protocol represents an adapted workflow for classic voxel based morphometry [11,12] that includes modifications to the standard VBM workflow to optimize the accurate detection of grey matter asymmetries. Data were analyzed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/) for SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab. First, images were segmented into separate grey and white matter images and were then flipped using, ImCalc'. From the flipped and unflipped versions we then created a symmetric DARTEL template. Subsequently, the unflipped and flipped grey and white segment images were warped to the DARTEL template. After that, we created a right-hemispheric mask in symmetric template space in MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html). This was done in order to limit the following analysis to the right hemisphere. We then calculated an asymmetry index (AI) for grey matter asymmetries using the formula $\text{AI} = ((\text{i1} - \text{i2})/((\text{i1} + \text{i2})^*0.5))^*\text{i3}$, with i1 being the warped non-flipped images, i2 being the warped flipped images, and i3 being the right-hemispheric mask. Negative AIs indicated larger left-hemispheric grey matter volume in a cluster, while positive AIs indicated larger right-hemispheric grey matter volume in a cluster. The resulting AI images were then smoothed using an 8 mm smoothing kernel. For statistical comparisons, we used voxel-wise FWE (family-wise error) correction and an alpha level of 0.05. In order to avoid spurious findings driven by noise, we applied a cluster extent threshold of 20 [13,18–20]. Anatomical locations of significant clusters were determined using their MNI coordinates in MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html) using the AAL template.

3. Results

3.1. Structural grey matter asymmetries in the overall sample

First we set up two statistical models to check for clusters with AIs significantly different from zero using a one-sample *t*-test (cluster extent threshold = 20, FWE-corrected, $p < 0.05$). One was for positive AIs and the other for negative AIs. Overall, 11 clusters reached significance for positive AIs, indicating larger right-hemispheric volume (see Table 1 and Fig. 1). The three largest clusters were located in middle temporal gyrus, precuneus, and