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Gender versus brain size effects on subcortical gray matter volumes in the human brain

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HIGHLIGHTS

- Subjects were regrouped by gender and size to evaluate main effects on both factors.
- Brain size effects were distinguished from apparent gender differences.
- Brain size effects were found in right amygdala and bilateral caudate nucleus.
- Gender effects were found in right globus pallidum and bilateral putamen.
- Results found from two different datasets were consistent.

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ABSTRACT

Previous studies had reported that volume differences of gray matter (GM) in subcortical regions of the human brain were mainly caused by gender. Meanwhile, other studies had found that the distribution of GM in the human brain varied based on individual brain sizes. Main effects of volume differences of GM in subcortical regions remain unclear. Therefore, the goals of this study are twofold, namely, to determine the main effects of volume differences of GM in subcortical regions of the human brain and to investigate the independent or joint contribution of gender and brain size to subcortical volume differences. In this study, 40 male and 40 female subjects with comparable brain sizes were selected from a population of 198 individuals. The sample was divided into the following four groups: male and female groups with comparably large brain sizes and male and female groups with comparably small brain sizes. The main effects of gender and of brain size and interactions between both factors in subcortical GM volumes were examined by analyses of covariance (ANCOVAs) using a 2×2 design matrix. Volumes of GM in subcortical regions were extracted and measured by an automatic segmentation method. Furthermore, we used two datasets to test the reliability of our methods. In both datasets, we found significant brain size effects in the right amygdala and the bilateral caudate nucleus and significant gender effects in the bilateral putamen. No interactions between brain size and gender were found. In conclusion, both gender and brain size independently contributed to volume distribution in different subcortical areas of the human brain.

1. Introduction

Subcortical structures are located between the cerebral cortex and the medulla oblongata in the human brain. These structures include the nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidus, putamen and thalamus that had been reported to be involved in several gender-specific characteristics such as addiction [29], motor control [22], and emotional memory [5]. In addition, several neuropsychiatric disorders that are clearly gender-specific are reported to be related to subcortical areas, such as attention deficit hyperactivity disorder (ADHD) [12], and Parkinson's disease (PD) [4]. Smaller volumes of the amygala [11] and basal ganglia [23] were found in ADHD groups and smaller volumes of the putamen was found in PD [13]. Thus, sexual dimorphism in subcortical regions has gained attention in the neuroscience field.

Structural gender differences in subcortical regions have been recently studied, including the nucleus accumbens in which pre- and post-synaptic gender differences were detected [10]. A larger volume of gray matter (GM) was found in the amygdala among

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males [7] and in the caudate nucleus among females [16,19]. However, no significant gender differences were reported in the caudate in another region of interest (ROI)-based study [24]. In the hippocampus, no volume differences between male and female groups were reported, however, after considering age and brain size, the results showed that females had a larger hippocampus volume than that of males [2]. Studies had observed that males have a significantly larger volume in the pallidum and putamen [24] and in the thalamus among females [19,27]. By contrast, a study stated no gender effects to volume distribution in the thalamus after considering the effects of brain size [26].

The brain sizes of males had been reported to be larger than that of females [18,21]. While the aforementioned studies reported on structural gender differences in subcortical regions, a question emerges regarding the contribution of brain size and of volume distribution to gender differences [14,18]. Independently investigating gender from brain size effects entails an alternative process in comparing male and female groups with comparable brain sizes [16,25,30]. Meanwhile, independently investigating brain size from gender effects requires strict matching of the gender factor.

In this study, we used an automatic segmentation toolkit [20] to extract subcortical structures from the brain. We extracted seven subcortical structures bilaterally that include the left and right nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidus, putamen, and thalamus. After calculating the subcortical GM volumes (SGMVs), we conducted analyses of covariance (ANCOVAs) using a 2×2 design matrix to evaluate the following: (1) gender effects of SGMVs between males and females with comparable brain sizes, (2) brain size effects between large and small brains, and (3) interactions between gender and brain size effects. In addition, we used two large datasets to test the reliability of this study and to assess the consistency of the results.

2. Materials and methods

2.1. Data information

There were two independent datasets involved in this study. All of our data were downloaded from the 1000 functional Connectomes Project [3]. In dataset I, from Beijing_Zang acquired with a SIEMENS 3 T Trio scanner, there were totally 198 subjects (122 males and 76 females) aged from 18 to 26. Parameters for the scans (T1-weighted sagittal three-dimensional magnetization-prepared rapid gradient echo sequence: MP-RAGE) were as follows: 128 slices, TR = 2530 ms, TE = 3.39 ms, slice thickness = 1.33 mm, flip angle = 7°, inversion time = 1100 ms, FOV = 256 mm × 256 mm, and in-plane resolution = 256 mm × 192 mm [15]. In dataset II, from Cambridge_Buckner acquired with a SIEMENS 3 T Trio scanner, there were totally 198 subjects (123 males and 75 females) aged from 18 to 30. Parameters for scans (MP-RAGE) were as follows: TR = 2200 ms, TE = 1.54 ms, flip angle = 7°, inversion time = 1100 ms, FOV = 230 mm × 230 mm, voxel size = 1.2 mm × 1.2 mm × 1.2 mm [32].

2.2. Preprocessing

Using VBM8 (Version 435, http://dbm.neuro.uni-jena.de/vbm/) [1] based on SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), the whole brain was classified into three different types: GM, white matter (WM) and cerebrospinal fluid (CSF). The volumes of each tissue were calculated with VBM8 by summing all the relative tissue probabilities in native space. Total brain volume (TBV) was defined by adding the volumes of GM, WM and CSF [16].

The left and right nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidus, putamen and thalamus were extracted from the whole brain using an automatic segmentation toolkit called FIRST (Version 1.2, FMRIB's Integrated Registration and Segmentation Tool, http://www.fmrib.ox.ac.uk/fsl/first/index.html) [20] based on FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/). All the segmentations were performed on the original structure data. To improve the accuracy of the segmentation, an automatic boundary correction was included [24]. Moreover, for each structure the left and right maps were generated independently. An example of FIRST segmentation results for a single subject is shown in Fig. 1. In this study, all segmented structures were further examined manually by overlaying on the original T1-weighted data. We removed 1 out of 396 (in dataset II) for the failure of segmentation.

After tissue segmentation with VBM, GM images represented GM probabilities voxel-wisely. With the extracted structures from FIRST, SGMVs were calculated by summing all the products of voxel size with GM probabilities voxel-wisely within each structure in native space.

Table 1
Age, gray matter volumes and total brain volumes.

Data set I (Beijing_Zang)			
	Age	GM	TBV
Male (N = 76)	21.145 ± 1.831	718.582 ± 56.082	1503.467 ± 102.829
Female (N = 122)	21.172 ± 1.835	653.903 ± 51.697	1362.347 ± 97.776
MS (N = 20)	21.200 ± 2.285	656.793 ± 39.209	1376.682 ± 48.735
ML (N = 20)	21.300 ± 1.838	710.551 ± 33.350	1488.941 ± 44.448
FS (N = 20)	21.500 ± 2.090	651.378 ± 34.838	1372.751 ± 49.193
FL (N = 20)	20.800 ± 1.908	715.361 ± 27.542	1489.808 ± 46.306
Data set II (Cambridge_Buckner)			
	Age	GM	TBV
Male (N = 74)	21.000 ± 2.158	709.032 ± 49.121	1506.803 ± 109.347
Female (N = 123)	21.057 ± 2.413	640.875 ± 40.527	1354.388 ± 94.739
MS (N = 20)	20.400 ± 1.569	662.361 ± 30.395	1380.453 ± 53.404
ML (N = 20)	20.850 ± 1.599	709.552 ± 26.451	1506.005 ± 39.774
FS (N = 20)	21.250 ± 2.845	648.080 ± 24.596	1372.722 ± 53.289
FL (N = 20)	20.550 ± 2.762	698.505 ± 29.563	1508.090 ± 45.288

Data are presented as mean ± SD or number.
GM, gray matter; TBV, total brain volume; MS: males with smaller brain size; ML, Males with larger brain size; FS, Females with smaller brain size; FL, Females with larger brain size.
Age is shown in years; GM and TBV are shown in milliliters.

2.3. Subject regrouping

Our subject selection strategy was conducted as same as Luders et al. did in [16]. A total of 40 males and 40 females, paired based on comparable TBV, were selected from the original dataset. In our study, the maximum TBV differences between the matched pairs were 5.855 and 11.982 ml for datasets I and II, respectively. We then ranked the subjects in each group in ascending order based on TBVs and identified the first 20 subjects as those with small brains, while the last 20 subjects as those with large brains. More specifically, the first 20 male and female subjects identified with small brains were categorized as MS and FS groups, while the last 20 male and female subjects identified with large brains were categorized as ML and FL groups, respectively. Table 1 shows the demographic information of the subjects from both the original dataset and from the subgroups.

2.4. Statistics analysis

All variables in this study were analyzed using SPSS 19.0. Firstly, we examined age, global GM volume and TBV differences between groups with two sample t-tests. To investigate the main effects of TBV, gender and the interactions between these two, 2×2 ANCOVAs were conducted in SGMVs, with TBV and gender as the