Basal Ganglia Volumes: MR-Derived Reference Ranges and Lateralization Indices for Children and Young Adults

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Key words: basal ganglia, brain volumetry, lateralization, reference range

SUMMARY – Previous studies indicate rightward asymmetry of the caudate nucleus (CN) volume and leftward asymmetry of the putamen (PN) and globus pallidus (GP). This study aimed to estimate reference ranges for basal ganglia asymmetry in a large cohort of healthy individuals ($n=949$), aged seven to 21 years. MRI images of 949 (320 female, mean age 12.6 ± 3.3 , range 7–21) healthy individuals were reviewed. Volumetric measurements of the basal ganglia were obtained using automated segmentation (FreeSurfer). We computed two lateralization indices: $(L-R)/(L+R)$ (LI) and right/left ratio (RLR). Tolerance interval estimates were used to calculate reference ranges. Rightward asymmetry of the CN and leftward asymmetry of the PN and GP were confirmed. PN and GP volume decreased with age, but CN volume did not. The lateralization index decreased with age for PN, but not for CN and GP. RLR increased with age for PN and not for CN or GP. Females were associated with smaller volume, but not with either LI or RLR difference. Reference ranges obtained in this study provide useful resources for power analysis and a reference group for future studies using basal ganglia asymmetry indices.

Introduction

It is well known that left and right hemispheres are anatomically and functionally asymmetric^{1–5}. Precise measurements of basal ganglia volume: caudate nucleus (CN), putamen (PN) and globus pallidus (GP), can provide diagnostic information because in certain brain disorders such as autism, depression, schizophrenia and attention deficit hyperactivity disorder (ADHD) interhemispheric asymmetry in size of the basal ganglia has been reported^{6–10}. For instance, in comparison to healthy controls ADHD patients, especially males, have on average smaller left GP^{6,7}, patients with autism display both enlarged CN⁸, patients suffering from depression have significantly smaller PN [9], whereas schizophrenic patients have a smaller total basal ganglia volume¹⁰.

The clinical significance of raw morphometric measurements of the basal ganglia, however, is not yet established. One reason might

be the lack of reliable reference limits of basal ganglia volume established on a large group of healthy subjects of a wide range of age and both genders. Clinicians typically can detect more easily subtle differences in the volume of the basal ganglia between sides based on an assumption they should be symmetric. Precise volume measurements in an individual, however, seldom provide identical values between sides for any brain structure because of anatomical and measurements variability. Furthermore, reported small but substantial interhemispheric differences in average brain volume (less than 1%) indicate that extrapolation of average group symmetry in volume of any brain structure to individual patients may not be correct. Precise volumetric studies of major basal ganglia therefore have a potential to provide important information in detecting structural abnormalities by referring volume measurements to reference tolerance limits of interhemispheric differences. These tolerance

s-Table 1 Consort plot of data recruitment.

limits can inform a diagnostician what side-to-side differences in basal ganglia volume should still be considered still normal in patients with brain disorders.

Thus, the goal of our study was to estimate such reference tolerance limits of volume and lateralization indices based on automatic segmentation of basal ganglia of the brain from a large group of healthy subjects (n=949).

Materials and Methods

Ethical approval

The study data were acquired from two datasets: ADHD-200 Consortium and ABIDE (Autism Brain Imaging Data Exchange). Both projects are distributed by the open science International Neuroimaging Data-sharing Initiative [http://fcon_1000.projects.nitrc.org/]. The ADHD-200 initiative involved eight and ABIDE 17 international sites. Informed consent was collected at each individual site. Anonymised neuroimaging and behavioural data

are HIPPA (Health Insurance Portability and Accountability Act) compliant.

Patient population and cognitive evaluation

The initial dataset includes structural MRI scans from 1087 healthy subjects including 514 (273 males, 238 females) from the ADHD-200 dataset and 573 (474 males, 99 females) from the ABIDE dataset. Because of the large number of demographic variables included in both datasets we decided to analyse four variables as predictors (age, gender, handedness and IQ). Available intelligence measurements (including full scale IQ) depending on the data contributing site were evaluated using the following tests: Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV), Wechsler Abbreviated Scale of Intelligence (WASI), Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R), Differential Ability Scales II (DAS II), Wechsler Intelligence Scale for Children (WISC), Wechsler Adult Intelligence Scales (WAIS), Hamburg-Wechsler Intelligence Test for Children (HAWIK-IV), Groninger Intel-

s-Figure 1 Histogram of age distribution by gender.

ligence Test (GIT). Handedness was assessed using the Reitan-Klove Lateral Dominance Examination, the Edinburgh Handedness Inventory, the Chapman handedness score and the Annett Hand Preference Questionnaire. We selected age range for which each a consecutive year-interval had at least 30 subjects. Moreover we excluded nine subjects with technical segmentation problems. Finally, our study group consisted of 949 participants (629 males, 320 females) [s-Table 1] [s-Figure 1].

Magnetic resonance imaging

Magnetic resonance imaging scans were collected in resting conditions using Siemens Magnetom Trio Tim, Allegra and Avanto (Siemens Medical Solutions, Erlangen, Germany) and Philips Gyroscan (Philips Medical Systems, Amsterdam, Netherlands) 3 Tesla MRI scanners (eight scanner models across 17 imaging sites in two separate projects: ADHD-200 and ABIDE). There was an overlap between some institutions (The Kennedy Krieger Institute, New York University Child Study Center,

Oregon Health and Science University, Portland, University of Pittsburgh), nevertheless there was no overlap between subjects. High-resolution T1-weighted volumetric gradient echo images were obtained for each subject. The parameters for each dataset and research institution are summarized in s-Table 2.

Neuroimaging analysis

The basal ganglia measurements were derived from volumetric analysis of the 792 MPAGE datasets using automated segmentation (FreeSurfer version 5.1.0 software package) [s-Figures 2 and 3]. The methodology of the FreeSurfer pipeline has been already documented in the literature^{11,12}. Briefly, this method consists of five stages: an affine registration with Talairach space, an initial volumetric labelling, bias field correction, non-linear alignment to the Talairach space, and a final labelling of the volume and classifying each native brain voxel into one of multiple brain structures, including left and right cerebellar grey and white matter. The FreeSurfer suite

s-Table 2 Characteristics of MRI scanners depending on the research institutes. *N* indicates the general number of subjects from each imaging site.

<i>Research institution</i>	<i>MRI scanner</i>	<i>Basic sequence parameters</i>	<i>N</i>	<i>Number of subjects used from each site in this project</i>
ADHD-200 DATABASE				
New York University Child Study Center	Siemens Magnetom Allegra syngo MR 2004, 3 T	T1-weighted MPRAGE sequence (TR = 2530 ms; TE = 3.25 ms, flip angle = 7°, voxel size = 1.31×1.3×1.31 mm, slice thickness = 1.33 mm)	105	105
The Kennedy Krieger Institute	Achieva Quasar 3 T Philips scanner	T1-weighted MPRAGE sequence (TR = 2500 ms; TE = 3.76 ms, flip angle = 8°, voxel size = 1.0×1.0×1.0 mm, slice thickness = 1 mm)	67	67
Peking University	Siemens Magnetom TrioTim syngo MR B17, 3 T	T1-weighted MPRAGE sequence (TR = 2530 ms; TE = 3.39 ms, flip angle = 7°, voxel size = 1.3×1.0×1.3 mm, slice thickness = 1.33 mm) T1-weighted MPRAGE sequence (TR = 2530 ms; TE = 3.45 ms, flip angle = 7°, voxel size = 1.0×1.0×1.0 mm, slice thickness = 1.00 mm) T1-weighted MPRAGE sequence (TR = 2000 ms; TE = 3.57 ms, flip angle = 12°, voxel size = 1.0×1.0×1.0 mm, slice thickness = 1.00 mm)	138	137
Washington University in St.Louis	Siemens Magnetom TrioTim syngo MR B13, 3 T	T1-weighted MPRAGE sequence (TE = 3.06 ms, TR = 2400 ms, flip angle = 8°, voxel size = 1.0×1.0×1.0 mm, slice thickness = 1 mm)	57	55
Oregon Health and Science University, Portland	Siemens Magnetom TrioTim syngo MR B17, 3 T	T1-weighted MPRAGE sequence (TR = 2300 ms; TE = 3.58 ms, flip angle = 10°, voxel size = 1.0×1.0×1.0 mm, slice thickness = 1.10 mm)	66	66
University of Pittsburgh	Siemens Magnetom TrioTim syngo MR B15, 3 T	T1-weighted MPRAGE sequence (TR= 2100 ms; TE=3.43 ms, flip angle = 8°, voxel size = 1.0×1.0×1.0 mm, slice thickness = 1.00 mm)	81	81
TOTAL			514	511
ABIDE DATABASE				
California Institute of Technology	Siemens Magnetom TrioTim syngo MR B17, 3T	T1-weighted MPRAGE sequence (TR= 1590 ms; TE=2.73 ms, flip angle =7°, voxel size=1.0×1.0×1.0 mm, slice thickness =1.00 mm)	19	7
Carnegie Mellon University	Siemens Magnetom TrioTim syngo MR B17, 3T	T1-weighted MPRAGE sequence (TR= 1870 ms; TE=2.48 ms, flip angle =8°, voxel size=1.0×1.0×1.0 mm, slice thickness =1.00 mm)	13	4
Kennedy Krieger Institute	Achieva Quasar 3 T Philips scanner	T1-weighted MPRAGE sequence (TR=1870 ms; TE=2.48 ms, flip angle =8°, voxel size=1.0×1.0×1.0 mm, slice thickness=1.00 mm)	33	33
Ludwig Maximilians University Munich	Siemens Magnetom Verio syngo MR B17, 3T	T1-weighted MPRAGE sequence (TR=1800 ms; TE=3.06 ms, flip angle= 9°, voxel size=1.0×1.0×1.0 mm, slice thickness=1.00 mm)	33	7
NYU Langone Medical Center	Siemens Magnetom Allegra syngo MR 2004A, 3T	T1-weighted MPRAGE sequence (TR =2530 ms; TE=3.25 ms, flip= angle 7°, voxel size=1.3×1.0×1.3 mm, slice thickness=1.33 mm)	105	82
Olin, Institute of Living at Hartford Hospital	Siemens Magnetom Allegra syngo MR 2004A, 3T	T1-weighted MPRAGE sequence (TR=2500 ms; TE=2.74 ms, flip angle=8°, voxel size=1.0×1.0×1.0 mm, slice thickness=1.00 mm)	16	15

to be continued.

<i>Research institution</i>	<i>MRI scanner</i>	<i>Basic sequence parameters</i>	<i>N</i>	<i>Number of subjects used from each site in this project</i>
<i>ABIDE DATABASE</i>				
Oregon Health and Science University	Siemens Magnetom TrioTim syngo MR B17, 3T	T1-weighted MPRAGE sequence (TR =2300 ms; TE=3.58 ms, flip angle=10°, voxel size=1.0×1.0×1.1 mm, slice thickness= 1.11 mm)	15	15
San Diego State University	GE 3T MR750, 3T	T1-weighted FSPGR sequence (TR=11.08 ms; TE =4.3 ms, flip angle 8°, voxel size: 1.0×1.0×1.0 mm, slice thickness =1.00 mm)	22	21
Social Brain Lab BCN NIC UMC Groningen and Netherlands Institute for Neurosciences	Philips Intera, 3T	T1-weighted MPRAGE sequence (TR =9.00 ms; TE =3.5 ms, flip angle= 8°, voxel size=1.0×1.0×1.0 mm, slice thickness=1.00 mm)	15	1
Stanford University	GE SIGNA, 3T	T1-weighted MPRAGE sequence (TR= 8.4 ms; TE =1.8ms, flip angle =15°, voxel size= 0.859×1.0×0.859 mm, slice thickness= 0.859 mm)	20	20
Trinity Centre for Health Sciences	Achieva Quasar 3T Philips scanner	T1-weighted MPRAGE sequence (TR= 8.5 ms; TE 3.9=ms, flip angle =8°, voxel size=1.0×1.0×1.0 mm, slice thickness =1.00 mm)	25	23
University of California, Los Angeles: Sample 1	Siemens Magnetom TrioTim syngo MR B15, 3T	T1-weighted MPRAGE sequence (TR =2300 ms; TE=2.84 ms, flip angle =8°, voxel size=1.0×1.0×1.2 mm, slice thickness=1.2 mm)	33	32
University of California, Los Angeles: Sample 2	Siemens Magnetom TrioTim syngo MR B15, 3T	T1-weighted MPRAGE sequence (TR =2300 ms; TE=2.84 ms, flip angle= 8°, voxel size=1.0×1.0×1.2 mm, slice thickness=1.2mm)	14	13
University of Leuven: Sample 1	Philips INTERA, 3T	T1-weighted MPRAGE sequence (TR =9.6 ms; TE =4.6ms, flip angle =8°, voxel size=1.0×1.0×1.2 mm, slice thickness =1.2mm)	15	3
University of Leuven: Sample 2	Philips INTERA, 3T	T1-weighted MPRAGE sequence (TR =9.6 ms, TE =4.6ms, flip angle= 8°, voxel size=1.0×1.0×1.2 mm, slice thickness =1.2mm)	20	20
University of Michigan: Sample 1	GE Signa, 3T	T1-weighted MPRAGE sequence (TR =500 ms, TE =1.8 ms, flip angle=15°, voxel size=1.0×1.0×1.2 mm, slice thickness= 1.2mm)	55	53
University of Michigan: Sample 2	GE Signa, 3T	T1-weighted MPRAGE sequence (TR =500 ms; TE =1.8ms, flip angle =15°, voxel size=1.0×1.0×1.2 mm, slice thickness= 1.2mm)	22	18
University of Pittsburgh School of Medicine	Siemens Magnetom Allegra syngo MR A30, 3T	T1-weighted MPRAGE sequence (TR =2100 ms; TE= 3.93 ms, flip angle =7°, voxel size=1.1×1.1×1.1 mm, slice thickness =1.1mm)	27	20
University of Utah School of Medicine	Siemens Magnetom TrioTim syngo MR B17, 3T	T1-weighted MPRAGE sequence (TR =2300 ms; TE=2.91 ms, flip angle= 9°, voxel size=1.0×1.0×1.2 mm, slice thickness= 1.2mm)	43	23
Yale Child Study Center	Siemens Magnetom TrioTim syngo MR B17, 3T	T1-weighted MPRAGE sequence (TR =1230 ms; TE=1.73 ms, flip angle =9°, voxel size=1.0×1.0×1.0 mm, slice thickness =1.00 mm)	28	28
<i>TOTAL</i>			573	438

produces a table of statistical measures, which include the volume of the caudate nucleus, putamen and globus pallidus. The computation

time for the FreeSurfer pipeline for each subject was 15-20 hours. Two other studies analysing lateralization indices (LI) and volumes

s-Figure 2 An axial T1-weighted MRI scan with the segmented CN (green), PN (red), GP (blue).

s-Figure 3 Basal ganglia structures after segmentation.

of the basal ganglia used manual segmentation by Schabo et al.¹³ and automated segmentation IBASPM (Brain Atlases Statistical Parametric Mapping)¹⁴. The advantage of FreeSurfer's pipeline is that it is fully automated eliminating the need for manual landmarking or intervention. Manual correction was necessary only for poor-quality MRIs due to high noise or movement where the initial Talairach normalization may fail.

Statistical analysis

All analyses were conducted using the R-CRAN statistical package (www.r-project.org). We used two lateralization indices (LI and RLR) to calculate structure asymmetry.

$$LI = (L-R)/(L+R) \quad (1)$$

This lateralization index provides value between -1 and +1. Negative values reflect a rightward laterality and positive values reflect a leftward laterality¹⁵.

$$RLR = R/L \text{ ratio} \quad (2)$$

Positive values indicate larger volume on the right. These two lateralization indices are highly related: $(LI \sim 0.5 \cdot (1 - RLR))$.

Lilliefors test was used to evaluate the distribution of variables. All volumetric measurements were normally distributed. After Grubbs test¹⁶ we computed the LI and RLR (R-right

structure volume, L-left volume). Two-way analysis of variance (ANOVA) was used to examine the effects of gender, handedness and site of lateralization indices and volumetric data. Sex differences for volume and lateralization indices of the basal ganglia were tested with an independent sample t-test (two-tailed).

Correlation analyses were performed using the two-tailed Pearson correlation. Linear regression models were used to identify the relationship between age, gender and each lateralization index and volumetry data. The lowest method was used to visualize deflection points in the volumetric data. The significance level is $p=0.05$.

To calculate the normal reference range of basal ganglia volumes and asymmetries, we used estimates of the Gaussian tolerance interval, which have 0.90 probability of containing 95% of the population¹⁷. If $L1$ and $L2$ are the lower and upper limits of interval then $L1 = \mu - ks$ and $L2 = \mu + ks$ (value of k is 1.96)¹⁸, μ is the mean and s is the standard deviation.

Results

Characteristics of the analyzed group

Analysis included 949 healthy subjects with a mean age of 12.6 ± 3.3 years (range from 7 to 21) [s-Figure 1]. Table 1 shows basic demo-

graphic information for the sample including both datasets [Table 1].

Testing for Gaussian distribution and outlier detection

Grubbs T-Statistic test identified 25 outliers of right GP, four outliers of the left GP, six outliers of the right CN and 35 outliers of the left CN. Therefore, 866 MRI scans were included in the volumetric analysis. All volumetric measurements were normally distributed based on Lilliefors test: on the right GP $p=0.15$, CN $p=0.09$, PN $p=0.09$; on the left GP $p=0.051$, CN $p=0.053$, PN $p=0.34$.

Volume of basal ganglia

Tolerance limits

The normal reference range of basal ganglia volume with descriptive statistics (mean, SD) is summarized in Table 2. Rightward asymmetry of the CN and leftward asymmetry of the PN and GP was observed. All volumes are in cm^3 [Table 2].

Association with age and gender

Volume of the PN (right and left) and GP (right and left) was significantly negatively correlated with age, whereas volume of the CN was not. These age-related changes were also observed in both genders (except right GP in females). In addition, a stronger negative correlation of the PN (right and left) with age was observed more in females than in males. All volumetry values are summarized in Table 3. To identify the trends in volume distribution across age for the

entire group and males and females separately, we plotted lowess regression lines, visualized on supplementary Figures 4 and 5 [s-Figures 4 and 5]. ANOVA analysis showed a significant gender effect on volume of the left CN ($p<0.05$, $F=37.62$), right CN ($p<0.05$, $F=45.95$), of left PN ($p<0.05$, $F=78.89$), right PN ($p<0.05$, $F=96.82$), left GP ($p<0.05$, $F=41.87$) and right GP ($p<0.05$, $F=41.87$). In all structures males had larger volumes than females. Paired t-test analysis also revealed significant differences between males and females in the volume of each structure. Males revealed larger right CN volumes (4.346 ± 0.57 vs. $4.087 \pm 0.51 \text{ cm}^3$, $p<0.05$) and left CN volumes (4.125 ± 0.48 vs. $3.921 \pm 0.47 \text{ cm}^3$, $p<0.05$) than females. Also males had larger right PN volumes (6.641 ± 0.77 vs. $6.137 \pm 0.69 \text{ cm}^3$, $p<0.05$) and left PN putamen volumes (6.869 ± 0.80 vs. $6.392 \pm 0.73 \text{ cm}^3$, $p<0.05$) than females. Additionally, males revealed larger right GP volumes (1.841 ± 0.24 vs. $1.738 \pm 0.20 \text{ cm}^3$, $p<0.05$) and left GP volumes (2.009 ± 0.29 vs. $1.884 \pm 0.24 \text{ cm}^3$, $p<0.05$) than females. The values of the volume are given in Table 2 [Figure 1].

A major factor exerting the greatest influence on the volumetric measurements was gender. Results obtained in ANOVA and t-test analyses confirmed a linear regression model, that is males had a larger volume of all structures than females. Age was negatively associated with the volumes of PN and GP (except CN). Increasing age induces a decrease in the volume [s-Table 3]. ANOVA analysis showed no significant effect of handedness on basal ganglia volumes.

Table 1 Demographic characteristics of the sample.

Variable	ADHD-200 (n=511)	ABIDE (n=438)	Total (n=949)
Gender [M/F]	276/235	353/85	629/320
Age [mean $\pm$ SD]	11.6 $\pm$ 2.9	13.7 $\pm$ 3.5	12.6 $\pm$ 3.3
Handedness			
Right-handed	490	294	784
Left-handed	15	27	42
Ambidextrous	1	8	9
Not declared	5	109	114
Full IQ scale [mean $\pm$ SD]	114 $\pm$ 13	110 $\pm$ 12	112 $\pm$ 13
Not available	57	24	81

*Lateralization indices of volume of basal ganglia**Tolerance limits*

Analyses using both lateralization indices confirmed the rightward asymmetry for the CN, leftward asymmetry for the PN and leftward asymmetry for the GP. All these asymmetries were observed in both genders.

The tolerance intervals with lower and upper limits are summarized in Table 2 [Figures 2 and 3].

Association with age and gender

Because of the wide age range (7-21 years), we divided the study group into five age ranges. Age ranges with a two-year interval can show where are the large differences in basal ganglia volume and lateralization indices. The age distribution of the participants was as follows: 7-9 years =187, 10-12 years = 337, 13-15 years =237, 16-18 years =128 and 19-21 years=61. Neither CN lateralization index correlated with either age or gender. The LI of the PN and GP

(except females) was negatively correlated with age, whereas the RLR was correlated positively. All LI values are summarized in Table 4.

Using analysis of variance (ANOVA) we found no significant gender effect on LI for the CN ($p=0.5$ $F=0.43$), PN ($p=0.16$ $F=1.95$) or GP ($p=0.98$ $F<0.001$). Additionally, these Results were confirmed by the paired t-test analysis. There were no significant differences between males and females. The Results of t-test for LI were as follows: for CN $p=0.48$, $t=0.69$, for PN $p=0.11$, $t=-1.56$, for GP $p=0.98$, $t=-0.02$. ANOVA analysis for RLR also detected no significant gender effect: CN $p=0.42$, $F=0.62$, PN $p=0.08$, $F=2.90$, GP $p=0.73$, $F=0.11$. T-test analyses for CN: $p=0.40$ $t=0.83$, PN $p=0.06$ $t=1.85$, GP $p=0.71$ $t=0.36$. In the linear regression model gender was not significantly associated with either lateralization index. Age was negatively associated with LI of basal ganglia (except CN), while with RLR positively (except CN) [s-Table 4, s-Table 5]. Results of ANOVA analysis revealed no significant effect of handedness on either lateralization index.

Table 2 Lateralization indices and volumetry data.

		Lateralization indices				Volumes					
		LI		R/L ratio		Right		Left		T-test for volume*	
		Mean+/-SD	Tolerance Interval	Mean+/-SD	Tolerance Interval	Mean +/-SD	Tolerance Interval	Mean +/-SD	Tolerance Interval		
Caudate nucleus	All	-0.019+/-0.03	-0.077-0.038	1.042+/-0.06	0.921-1.162	4.259+/-0.56	3.146-5.371	4.055+/-0.48	3.100-5.010	$p<0.05$	$t=-8.30$
	M	-0.020+/-0.03	-0.081-0.040	1.043+/-0.06	0.916-1.169	4.346+/-0.57	3.226-5.466	4.126+/-0.48	3.184-5.067	$p<0.05$	$t=-7.32$
	F	-0.018+/-0.02	-0.070-0.032	1.040+/-0.05	0.931-1.148	4.088+/-0.52	3.069-5.106	3.922+/-0.47	2.994-4.848	$p<0.05$	$t=-4.20$
Putamen	All	0.018 +/-0.03	-0.045-0.082	0.966+/-0.06	0.845-1.086	6.471+/-0.78	4.939-8.003	6.708+/-0.81	5.114-8.302	$p<0.05$	$t=6.47$
	M	0.017+/-0.03	-0.053-0.087	0.968+/-0.06	0.837-1.099	6.641+/-0.77	5.129-8.152	6.869+/-0.80	5.288-8.450	$p<0.05$	$t=5.12$
	F	0.020+/-0.02	-0.028-0.069	0.961+/-0.05	0.866-1.057	6.138+/-0.68	4.786-7.489	6.393+/-0.73	4.960-7.825	$p<0.05$	$t=4.54$
Globus pallidus	All	0.039+/-0.05	-0.065-0.145	0.928+/-0.10	0.721-1.135	1.806+/-0.23	1.347-2.265	1.967+/-0.28	1.413-2.520	$p<0.058$	$t=13.38$
	M	0.039+/-0.05	-0.073-0.153	0.929+/-0.11	0.707-1.151	1.842+/-0.24	1.369-2.313	2.009+/-0.29	1.438-2.579	$p<0.052$	$t=11.02$
	F	0.040+/-0.04	-0.049-0.129	0.926+/-0.08	0.751-1.102	1.739+/-0.20	1.335-2.141	1.885+/-0.24	1.404-2.365	$p<0.05$	$t=8.15$

SD=Standard Deviation; M=Male; F=Female.* t-value and p-value are for differences between right and left basal ganglia volumes.

		Age ranges					Pearson Correlation		
		7-9 (mean +/- SD)	10-12 (mean +/- SD)	13-15 (mean +/- SD)	16-18 (mean +/- SD)	19-21 (mean +/- SD)			
RIGHT Caudate nucleus	All	4.25 +/- 0.58	4.25 +/- 0.53	4.26 +/- 0.58	4.24 +/- 0.61	4.24 +/- 0.51	r=-0.01	p=0.72	
	Male	4.36 +/- 0.58	4.32 +/- 0.53	4.39 +/- 0.58	4.32 +/- 0.63	4.28 +/- 0.51	r=-0.02	p=0.59	
	Female	4.14 +/- 0.57	4.11 +/- 0.51	4.00 +/- 0.48	4.01 +/- 0.46	4.12 +/- 0.50	r=-0.07	p=0.15	
	All	4.09 +/- 0.49	4.03 +/- 0.46	4.03 +/- 0.51	4.04 +/- 0.49	4.14 +/- 0.47	r=0.01	p=0.74	
	Male	4.18 +/- 0.48	4.09 +/- 0.45	4.13 +/- 0.50	4.09 +/- 0.50	4.15 +/- 0.48	r=-0.003	p=0.93	
	Female	3.98 +/- 0.49	3.91 +/- 0.46	3.83 +/- 0.46	3.89 +/- 0.45	4.11 +/- 0.46	r=-0.03	p=0.56	
RIGHT Putamen	All	6.48 +/- 0.84	6.52 +/- 0.77	6.53 +/- 0.73	6.27 +/- 0.78	6.32 +/- 0.71	r=-0.08	p<0.05	
	Male	6.76 +/- 0.84	6.62 +/- 0.82	6.71 +/- 0.70	6.50 +/- 0.69	6.48 +/- 0.66	r=-0.08	p<0.05	
	Female	6.17 +/- 0.73	6.30 +/- 0.60	6.14 +/- 0.66	5.61 +/- 0.64	5.82 +/- 0.65	r=-0.22	p<0.05	
	All	6.76 +/- 0.82	6.77 +/- 0.79	6.75 +/- 0.80	6.47 +/- 0.85	6.52 +/- 0.66	r=-0.12	p<0.05	
	Male	7.03 +/- 0.81	6.87 +/- 0.83	6.93 +/- 0.77	6.69 +/- 0.80	6.63 +/- 0.65	r=-0.13	p<0.05	
	Female	6.46 +/- 0.74	6.56 +/- 0.66	6.36 +/- 0.73	6.83 +/- 0.66	6.17 +/- 0.59	r=-0.23	p<0.05	
RIGHT Globus pallidus	All	1.81 +/- 0.24	1.81 +/- 0.22	1.79 +/- 0.22	1.79 +/- 0.25	1.76 +/- 0.24	r=0.06	p<0.05	
	Male	1.87 +/- 0.25	1.84 +/- 0.23	1.84 +/- 0.23	1.81 +/- 0.25	1.80 +/- 0.22	r=0.09	p<0.05	
	Female	1.75 +/- 0.21	1.76 +/- 0.18	1.70 +/- 0.18	1.74 +/- 0.25	1.63 +/- 0.25	r=0.08	p=0.15	
	All	1.98 +/- 0.24	1.99 +/- 0.27	1.97 +/- 0.30	1.90 +/- 0.31	1.88 +/- 0.25	r=0.11	p<0.05	
	Male	2.05 +/- 0.24	2.02 +/- 0.28	2.03 +/- 0.30	1.93 +/- 0.32	1.90 +/- 0.25	r=0.14	p<0.05	
	Female	1.89 +/- 0.23	1.93 +/- 0.22	1.83 +/- 0.25	1.83 +/- 0.28	1.81 +/- 0.24	r=0.13	p<0.05	
LI	Caudate nucleus	All	-0.015 +/- 0.03	-0.022 +/- 0.03	-0.022 +/- 0.02	-0.020 +/- 0.02	-0.010 +/- 0.03	r=0.02	p=0.45
		Male	-0.014 +/- 0.03	-0.022 +/- 0.03	-0.023 +/- 0.03	-0.020 +/- 0.03	-0.013 +/- 0.03	r=0.01	p=0.70
		Female	-0.016 +/- 0.02	-0.022 +/- 0.03	-0.020 +/- 0.02	-0.019 +/- 0.02	-0.0007 +/- 0.03	r=0.05	p=0.32
	Putamen	All	0.021 +/- 0.03	0.019 +/- 0.03	0.016 +/- 0.03	0.015 +/- 0.03	0.016 +/- 0.03	r=-0.07	p<0.05
		Male	0.020 +/- 0.03	0.019 +/- 0.03	0.015 +/- 0.03	0.014 +/- 0.04	0.011 +/- 0.03	r=-0.08	p<0.05
		Female	0.023 +/- 0.02	0.019 +/- 0.02	0.016 +/- 0.03	0.018 +/- 0.02	0.030 +/- 0.02	r=-0.02	p=0.62
	Globus pallidus	All	0.042 +/- 0.05	0.044 +/- 0.05	0.040 +/- 0.05	0.026 +/- 0.05	0.030 +/- 0.07	r=-0.01	p<0.05
		Male	0.050 +/- 0.05	0.043 +/- 0.05	0.042 +/- 0.05	0.025 +/- 0.06	0.022 +/- 0.08	r=-0.12	p<0.05
		Female	0.040 +/- 0.04	0.044 +/- 0.04	0.035 +/- 0.05	0.028 +/- 0.04	0.054 +/- 0.05	r=-0.06	p=0.24
R/L ratio	Caudate nucleus	All	1.033 +/- 0.06	1.047 +/- 0.06	1.047 +/- 0.05	1.042 +/- 0.05	1.024 +/- 0.07	r=-0.02	p=0.44
		Male	1.032 +/- 0.07	1.048 +/- 0.06	1.049 +/- 0.06	1.043 +/- 0.06	1.030 +/- 0.07	r=-0.01	p=0.68
		Female	1.034 +/- 0.05	1.047 +/- 0.05	1.043 +/- 0.04	1.040 +/- 0.05	1.004 +/- 0.07	r=0.05	p=0.32
	Putamen	All	0.958 +/- 0.05	0.964 +/- 0.06	0.970 +/- 0.06	0.972 +/- 0.07	0.970 +/- 0.06	r= 0.08	p<0.05
		Male	0.961 +/- 0.06	0.965 +/- 0.07	0.971 +/- 0.06	0.975 +/- 0.07	0.979 +/- 0.07	r= 0.09	p<0.05
		Female	0.955 +/- 0.04	0.962 +/- 0.04	0.968 +/- 0.06	0.965 +/- 0.04	0.941 +/- 0.04	r= 0.02	p=0.60
	Globus pallidus	All	0.919 +/- 0.09	0.919 +/- 0.09	0.928 +/- 0.11	0.955 +/- 0.11	0.952 +/- 0.16	r= 0.11	p<0.05
		Male	0.913 +/- 0.10	0.920 +/- 0.09	0.924 +/- 0.11	0.957 +/- 0.12	0.969 +/- 0.17	r= 0.13	p<0.05
		Female	0.926 +/- 0.08	0.916 +/- 0.07					

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s-Figure 4 Scatter plot of age and volume for male subjects including lowess line - a polynomial surface determined by age and volume predictors, using local fitting.

s-Figure 5 Scatter plot of age and volume for female subjects including lowess line - a polynomial surface determined by age and volume predictors, using local fitting.

Figure 1 Boxplots of volumetric data by gender.

s-Table 3 Summary of linear regression volumetric data and two variables (age and gender).

	<i>Estimate</i>	<i>Std. Error</i>	<i>t-value</i>	<i>p-value</i>	<i>Pr (> t)</i>	<i>r²-value for all model</i>
<i>Right Caudate Nucleus (cm³)</i>						0.048
Age	-0.006	0.0053	-1.210	0.22		
Gender (Male)	0.2644	0.0384	6.878	<0.05		
<i>Left Caudate Nucleus (cm³)</i>						0.039
Age	-0.0017	0.0047	-0.374	0.70		
Gender (Male)	0.2042	0.0335	6.089	<0.05		
<i>Right Putamen (cm³)</i>						0.107
Age	-0.0286	0.0071	-4.009	<0.05		
Gender (Male)	0.5283	0.0511	10.336	<0.05		
<i>Left Putamen (cm³)</i>						0.101
Age	-0.0379	0.0074	-5.071	<0.05		
Gender (Male)	0.5097	0.0534	9.540	<0.05		
<i>Right Globus Pallidus (cm³)</i>						0.051
Age	-0.0063	0.0022	-2.853	<0.05		
Gender (Male)	0.1084	0.0159	6.794	<0.05		
<i>Left Globus Pallidus (cm³)</i>						0.061
Age	-0.0115	0.0026	-4.33	<0.05		
Gender (Male)	0.1332	0.0189	7.03	<0.05

Figure 2 Scatter plots by age of both lateralization indices $(L-R)/(L+R)$, R/L ratio for male subjects. Upper solid thin line indicates 3rd quartile; lower solid thin line indicates 1st quartile; middle solid line presents the median. Note that the right caudate nucleus is larger than left ($R>L$); the left putamen is larger than the right ($L>R$); the left globus pallidus is larger than the right ($L>R$).

Imaging site effect

In our dataset there were significant differences in age and gender distribution between the study centres. Consequently, it is not surprising that there are differences in basal ganglia volume, but three-factor MANOVA taking into account both age, gender and volume revealed no differences between the study centres (except right GP, $p<0.05$ and $F=1.40$). Significant volume differences were between the sites in all structures. ANOVA analysis identified a significant site effect on the volume of each structure. The Results were as follows: right CN $p<0.05$ $F=3.82$; left CN $p<0.05$ $F=3.72$; right PN $p<0.05$ $F=8.35$; left PN $p<0.05$ $F=7.31$; right GP $p<0.05$ $F=12.51$; left GP $p<0.05$ $F=12.67$.

Discussion

Our study provides reference ranges for basal ganglia volume and lateralization indices $(L-R)/(L+R)$ and R/L ratio obtained from large

cohort of healthy individuals. Our study sample reflects the population better than previously studied samples.

Volume of basal ganglia

Differences between the left and right hemispheres have been reported in previous brain MRI studies in normal individuals¹⁻⁵. Most of the previous analyses focusing on basal ganglia laterality revealed rightward asymmetry of the caudate nucleus (CN)^{14,19-22}, leftward asymmetry of the putamen (PN)^{2,19,21-22} and globus pallidus (GP)^{2,19,23}, identifying differences in volume without a precise evaluation of the normal reference interval of basal ganglia asymmetry. Our study confirmed basal ganglia asymmetries, but the analysis was based on a larger cohort of healthy individuals ($n=949$). Although our study group included both right-handed, left-handed and ambidextrous subjects, we did not observe any significant association between basal ganglia volumes and handedness.

Figure 3 Scatter plots by age of both lateralization indices $(L-R)/(L+R)$, R/L ratio for female subjects. Upper solid thin line indicates 3rd quartile; lower solid thin line indicates 1st quartile; middle solid line presents the median. Note that the right caudate nucleus is larger than left ($R>L$); the left putamen is larger than the right ($L>R$); the left globus pallidus is larger than the left ($L>R$).

Based on previous studies, we expected that age would contribute to decrease the raw volume of the basal ganglia. Regression analysis was applied to define models including age and basal ganglia volume together with gender. Our data confirmed the age-related bilateral atrophy of the PN and GP volumes in males described by Gunning-Dixon et al., yet we also confirmed this relationship in females²⁴. Caudate nucleus volume is not associated with age, which confirms previous findings from Vernaleken et al.²², but contradicts the Results from Abedelahi et al.²¹, Gunning-Dixon et al.²⁴ and Raz et al.²⁵.

The mechanisms of age-related shrinkage of the basal ganglia are still unknown. One of the possible explanations may be synaptic pruning and neuronal selection. Neuronal network optimization is associated with cognitive development². Such conclusion is limited by the cross-sectional design of this study. Negative associations of age and volume of GP and PN confirm this thesis, yet true verification can be provided only by measurement of dynamic

volume reduction over time in the course of a longitudinal study. This design was applied by Raz et al.²⁵ and reported evidence consistent with our findings for a different age range (20–77). In contrast to their population, our study focuses on childhood and adolescence.

Influence of age on basal ganglia growth and degeneration should be considered in the context of already known neurodegenerative disorders affecting the CN and GP. Huntington disease (HD)²⁶ and dentatorubral-pallidoluysian atrophy (DRPLA)²⁷ are both late clinical onset, polyglutamine repeat disorders inherited in an autosomal dominant way and selectively causing atrophy of the CN in HD and the GP in DRPLA. In both disorders an anticipation phenomenon occurs meaning that the next generation of gene carriers will have a longer polyglutamine repeat region and will present clinical symptoms earlier in life. Such mechanism might be present in relation to basal ganglia volume in healthy individuals not affected by genetic risk of the disorders mentioned above.

Table 4 Age-related differences in lateralization indices.

		Age ranges					Pearson Correlation		
		7-9 (mean+/-SD)	10-12 (mean+/-SD)	13-15 (mean+/-SD)	16-18 (mean+/-SD)	19-21 (mean+/-SD)			
LI	Caudate nucleus	All	-0.015+/-0.03	-0.022+/-0.03	-0.022+/-0.02	-0.020+/-0.02	-0.010+/-0.03	r=0.02	p=0.45
		Male	-0.014+/-0.03	-0.022+/-0.03	-0.023+/-0.03	-0.020+/-0.03	-0.013+/-0.03	r=0.01	p=0.70
		Female	-0.016+/-0.02	-0.022+/-0.03	-0.020+/-0.02	-0.019+/-0.02	-0.0007+/-0.03	r=0.05	p=0.32
	Putamen	All	0.021+/-0.03	0.019+/-0.03	0.016+/-0.03	0.015+/-0.03	0.016+/-0.03	r=-0.07	p<0.05
		Male	0.020+/-0.03	0.019+/-0.03	0.015+/-0.03	0.014+/-0.04	0.011+/-0.03	r=-0.08	p<0.05
		Female	0.023+/-0.02	0.019+/-0.02	0.016+/-0.03	0.018+/-0.02	0.030+/-0.02	r=-0.02	p=0.62
	Globus pallidus	All	0.042+/-0.05	0.044+/-0.05	0.040+/-0.05	0.026+/-0.05	0.030+/-0.07	r=-0.01	p<0.05
		Male	0.050+/-0.05	0.043+/-0.05	0.042+/-0.05	0.025+/-0.06	0.022+/-0.08	r=-0.12	p<0.05
		Female	0.040+/-0.04	0.044+/-0.04	0.035+/-0.05	0.028+/-0.04	0.054+/-0.05	r=-0.06	p=0.24
R/L ratio	Caudate nucleus	All	1.033+/-0.06	1.047+/-0.06	1.047+/-0.05	1.042+/-0.05	1.024+/-0.07	r=-0.02	p=0.44
		Male	1.032+/-0.07	1.048+/-0.06	1.049+/-0.06	1.043+/-0.06	1.030+/-0.07	r=-0.01	p=0.68
		Female	1.034+/-0.05	1.047+/-0.05	1.043+/-0.04	1.040+/-0.05	1.004+/-0.07	r=-0.05	p=0.32
	Putamen	All	0.958+/-0.05	0.964+/-0.06	0.970+/-0.06	0.972+/-0.07	0.970+/-0.06	r=0.08	p<0.05
		Male	0.961+/-0.06	0.965+/-0.07	0.971+/-0.06	0.975+/-0.07	0.979+/-0.07	r=0.09	p<0.05
		Female	0.955+/-0.04	0.962+/-0.04	0.968+/-0.06	0.965+/-0.04	0.941+/-0.04	r=0.02	p=0.60
	Globus pallidus	All	0.919+/-0.09	0.919+/-0.09	0.928+/-0.11	0.955+/-0.11	0.952+/-0.16	r=0.11	p<0.05
		Male	0.913+/-0.10	0.920+/-0.09	0.924+/-0.11	0.957+/-0.12	0.969+/-0.17	r=0.13	p<0.05
		Female	0.926+/-0.08	0.916+/-0.07	0.938+/-0.11	0.948+/-0.07	0.901+/-0.10	r=0.07	p=0.21

In other words, normal variation of polyglutamine region length might directly influence caudate and globus pallidus volume and indirectly impact the behavioural phenotype.

The genetic background related to the polyglutamine repeat within normal range might also explain the heritability of basal ganglia volume which has not been extensively studied so far. From a practical perspective, observing volume decline in basal ganglia and departure from expected reference ranges for age and gender may support quantitative prediction of disease progression.

We hypothesized that female gender is associated with lower volumes of all basal ganglia across the studied age range. We performed two-sided t-test analysis to identify the differences in basal ganglia volume across genders.

Our data confirmed our hypotheses and indicate that differences are present in all structures studied. These findings confirm prior Results from Giedd et al.², Abedelahi et al.²¹ and Rijpkema et al.²⁸.

This sex difference might be related to total cerebral volume, sex chromosomes, hormonal and environmental effects or to their combination. Previous research shows that males have a larger total cerebral volume than females. Some researchers have indicated specific cortical regions where this difference is particularly pronounced^{2,29-30}. According to a study by Munro et al.³¹ the sexual dimorphism of the basal ganglia can be explained by the dopamine release system. Sex hormone concentration may also substantially influence basal ganglia volume because of the high density of estrogen and an-

s-Table 4 Summary of linear regression for lateralization index (L-R)/(L+R) and two variables (age and gender).

	<i>Estimate</i>	<i>Std. Error</i>	<i>t-value</i>	<i>p-value Pr (> t)</i>	<i>r²-value for all model</i>
<i>Lateralization index of caudate nucleus</i>					0.001
Age	0.0002	0.0002	0.838	0.40	
Gender (Male)	-0.0015	0.0020	-0.758	0.44	
<i>Lateralization index of putamen</i>					0.007
Age	-0.0007	0.0003	-2.244	<0.05	
Gender (Male)	-0.0025	0.0022	-1.116	0.26	
<i>Lateralization index of globus pallidus</i>					0.012
Age	-0.0017	0.0005	-3.344	<0.05	
Gender (Male)	0.0014	0.0037	0.385	0.70	

s-Table 5 Summary of linear regression for lateralization index R/L ratio and two variables (age and gender).

	<i>Estimate</i>	<i>Std. Error</i>	<i>t-value</i>	<i>p-value Pr (> t)</i>	<i>r²-value for all model</i>
<i>Lateralization index of caudate nucleus</i>					0.001
Age	-0.0005	0.0006	-0.86	0.39	
Gender (Male)	0.0038	0.0043	0.89	0.37	
<i>Lateralization index of putamen</i>					0.008
Age	0.0014	0.0005	2.381	<0.05	
Gender (Male)	0.0059	0.0042	1.402	0.16	
<i>Lateralization index of globus pallidus</i>					0.013
Age	0.0036	0.0010	3.558	<0.05	
Gender (Male)	-0.0006	0.0073	-0.093	0.92	

drogen receptors³². This relationship is driven by estrogen that regulates the activity of dopamine-containing fibres originating in the mid-brain and terminating in the basal ganglia³³. The combination of sex hormones, dopamine release and basal ganglia volume contribute to higher prevalence of ADHD in male children having small basal ganglia volume³⁴.

Laterality indices of basal ganglia volume

We hypothesized that measures of asymmetry will have mean values different from zero in case of LI and one in case of RLR. We performed t-test analysis of asymmetry indices against the distribution of the same standard deviation and zero mean value. Generally all studied structures showed evidence consistent with our hypothesis.

We found two studies which identified lateralization indices of the basal ganglia. Analysis by Yamashita et al. (2011) in a group of 50 healthy right-handed subjects showed a rightward asymmetry only in the CN¹⁴ and a study by Vernaleken et al. (2007) in a group of 21 healthy males revealed other asym-

metries, namely the leftward asymmetry of the caudate and rightward asymmetry of the PN²². Our study applied two different lateralization indices [(L-R)/(L+R) index and R/L ratio] to provide a better description of the observed asymmetries. Analysis of structural lateralization indices in previous studies used either one or the other lateralization index formula^{14,22}. The Results of our study are consistent with Yamashita et al.'s Results indicating rightward asymmetry of the CN¹⁴, however they did not analyze other basal ganglia structures. The study by Vernaleken et al. focused on metabolic and structural features of basal ganglia shows just the opposite Results of leftward asymmetry of the CN and rightward asymmetry of the PN²², which contradict our findings. In both cases, only small samples of male subjects were analysed. The larger sample size used in our study enabled a more precise computation of basal ganglia volume reference ranges than prior attempts. Taking into account age effect our findings are consistent with the study by Vernaleken et al.²² where LI was not correlated with age in the CN. However, their study group consisted of 21 male volunteers and the age

ranges differed from our ranges (24-60 years). Moreover, the authors also revealed no correlation in the PN, which also differs from our Results. We observed no significant age-related changes of RLR in the CN, which is opposite to the Results of Yamashita et al.¹⁴. None of the previously discussed papers analysed the lateralization indices of the GP, while our analysis found significant age-related changes only in males. According to volumetric data, the volume of the GP (right and left) and PN (right and left) bilaterally decreased with age, the consequence of which the same asymmetries were still observed, confirming measurements of both lateralization indices. Considering that the previously discussed studies analysed only male groups, we identified no significant impact of gender on either lateralization index of the basal ganglia; nor did males differ from females in LI nor RLR values.

Imaging site effect

Previous multicentre neuroimaging studies found that despite similar imaging protocols there are differences in structural segmentation data obtained at different sites. We anticipated that the same effect would be present in our data. We used analysis of variance to identify the between-site effect. Indeed there were differences between the sites, yet they were non-significant when taking into account the age and gender of participants.

Study limitations

Acquisition of brain imaging data from diverse populations most often requires collaboration between multiple sites equipped with different imaging hardware and using variable sequence parameters. This variability produces datasets characterized by different signal-to-noise ratios, which in turn might alter the automatic segmentation Results. The data presented in this paper consist of neuroimaging data acquired on eight scanner models across 17 imaging sites in two separate projects (ADHD-200 and ABIDE). Despite this, ANOVA analysis did not reveal any significant age-gender-site interaction, with a single significant site effect detected.

Multicentre consortia are rapidly gaining popularity in clinical research to date. Recruiting patients from a broad range of settings yields a representative sample and enhances the generalizability of Results. On the other

hand, the trade-off between sample size and the number of participatory institutions becomes more difficult to solve when faced with the multitude of diverse hardware implementations. Data clustering can be considered one of the additional complications arising from multicentre data collection. These problems can be resolved by applying some (not very precise) changes in the process of acquiring data, such as in other projects, e.g. the ADNI (Alzheimer's Disease Neuroimaging Initiative).

We have the largest group across all the studies looking into basal ganglia volume and asymmetry. There is a difference in proportion of females and males driven in comparison to the general population. Our study group contained fewer females because of overrepresentation of males in the patient population in the ABIDE cohort. Male-to-female proportion was 1.96 whereas in the normal population this ratio is 1.06³⁵. An increased frequency of males (Male=629, Female=320, s-Figure 1, Table 1) will contribute to higher mean and median volume of the whole group in comparison to an equal gender proportion population. To adjust for that limitation we provide reference ranges for volume and lateralization indices for males and females separately in Table 2.

Conclusion

In conclusion, our study provides reference ranges of basal ganglia volume and lateralization indices for a large cohort of healthy children and adults (n=949). Moreover, our Results confirmed age-related decline of the basal ganglia volume and gender differences. This study is based on so far the largest dataset of a publicly available neuroimaging cohort of healthy children and young adults.

Our data can serve as a reference and case control dataset for future studies focused on evaluation of subcortical structure volume and lateralization. The next step in explaining phenotypic variability of basal ganglia volume and lateralization might be based on an imaging-genetic approach.

Acknowledgments

The authors gratefully acknowledge Prof G. Króliczak from the Action and Cognition Laboratory for the possibility to use the data processing equipment.

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