Normal Sexual Dimorphism in the Human Basal Ganglia

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Abstract: Male and female brains differ in both structure and function. Investigating this sexual dimorphism in healthy subjects is an important first step to ultimately gain insight into sex-specific differences in behavior and risk for neuropsychiatric disorders. The basal ganglia are among the main regions containing sex steroid receptors in the brain and play a central role in cognitive (dys)functioning. However, little is known about sexual dimorphism of different basal ganglia nuclei. The aim of the present study was to investigate sex-specific differences in basal ganglia morphology using MRI. We applied automatic volumetry on anatomical MRI data of two large cohorts of healthy young adults ($n = 463$ and $n = 541$) and assessed the volume of four major nuclei of the basal ganglia: caudate nucleus, globus pallidus, nucleus accumbens, and putamen, while controlling for total gray matter volume, total white matter volume, and age of the participant. No significant sex differences were found for caudate nucleus and nucleus accumbens, but males showed significantly larger volumes for globus pallidus and putamen, as confirmed in both cohorts. These results show that sexual dimorphism is neither a general effect in the basal ganglia nor confined to just one specific nucleus, and will aid the interpretation of differences in basal ganglia (dys)function between males and females. *Hum Brain Mapp* 33:1246–1252, 2012. © 2011 Wiley Periodicals, Inc.

Key words: sex differences; brain; magnetic resonance imaging; volumetry; caudate nucleus; globus pallidus; nucleus accumbens; putamen

INTRODUCTION

Using noninvasive imaging methods, sexual dimorphism of human brain anatomy has been intensively studied over the last 30 years [e.g. Cahill, 2006; Cosgrove et al., 2007; DeLacoste-Utamsing and Holloway, 1982; Goldstein et al., 2001]. These studies are important because sex differences in brain morphology may explain observed sex differences in behavior and many neuropsychiatric disorders. It is well established that men have larger overall brains than women, and women have proportionally

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TABLE 1. Description of the study population

	Cohort 1 (1.5T)	Cohort 2 (3T)
Males		
<i>n</i>	202	211
Age (mean ± SD)	23.2 ± 3.8	22.8 ± 3.2
Females		
<i>n</i>	261	330
Age (mean ± SD)	22.7 ± 3.4	22.7 ± 3.2

SD = standard deviation.

greater gray matter volume compared with white matter volume [Goldstein et al., 2001; Gur et al., 1999]. This proportional increase in gray matter in women seems strongest in parietal and temporal lobes [e.g. Im et al., 2006; Luders et al., 2006; Nopoulos et al., 2000; Sowell et al., 2007]. Additionally, also certain specific brain regions show sexual dimorphism relative to total brain size. For example Broca's area [Harasty et al., 1997], hippocampus [Filipek et al., 1994; Murphy et al., 1996], thalamus [Murphy et al., 1996], anterior cingulate gyrus [Paus et al., 1996], and dorsolateral prefrontal cortex [Schlaepfer et al., 1995] appear to be relatively larger in women than in men. On the other hand, the amygdala [Giedd et al., 1997], hypothalamus [Swaab and Fliers, 1985], paracingulate gyrus [Paus et al., 1996], and the genu of the corpus callosum [Witelson, 1989] appear to be larger in men than women relative to total brain size.

Investigations of sexual dimorphism of the basal ganglia however are sparse [Ahsan et al., 2007; Filipek et al., 1994], although basal ganglia nuclei have a high density of sex steroid receptors. Moreover, the pathophysiology of several neuropsychiatric disorders with clear sex-specific prevalence are related to basal ganglia (dys)function. For example, male children with ADHD exhibit smaller caudate, putamen, and globus pallidus volumes compared with controls, which may account for the higher clinical prevalence of this disease in boys [Castellanos et al., 2002; Qiu et al., 2009]. During adulthood, caudate nucleus, putamen, and globus pallidus seem to be impaired in more severe subtypes of depression, a disease more common in females [Lorenzetti et al., 2009; Soares and Mann, 1997]. Later in life, men have a 1.5 times higher risk for Parkinson's disease, a disorder primarily associated with a deficit in the dorsal striatum [e.g. de Lau et al., 2004]. Finally, diseases that have been related to basal ganglia dysfunction, but that do not show sex-specific prevalence may differ in symptomatology and age of onset between men and women, like obsessive-compulsive disorder [Bogetto et al., 1999].

Sex steroid hormones contribute largely to sex-specific brain function and behavior and may affect brain morphology during critical periods of development [Arnold and Gorski, 1984; McEwen, 2001; Pilgrim and Hutchison, 1994] and in young adulthood [Witte et al., 2010]. The basal ganglia have a developmentally high density of estro-

gen and androgen receptors [Pfaff and Keiner, 1973; Sibug et al., 1991] providing a potential mechanism for sex differences. However, brain imaging studies investigating this sexual dimorphism in healthy adult subjects have reported inconsistent findings, possibly due to small sample sizes or heterogeneity between study populations. For example, in a comprehensive study of 48 subjects Goldstein et al. [2001] reported small nonsignificant effect sizes in basal ganglia volumes between males and females. Ahsan et al. [2007] found a larger globus pallidus volume in healthy young males, but not in other basal ganglia nuclei, in a group of 30 subjects. Luders et al. [2009] found larger gray matter volumes for females in caudate nucleus extending into other basal ganglia regions in a sample of 48 adult males and females matched on brain size. In the present study we conduct a large-scale MRI investigation analyzing datasets of 1,004 healthy individuals in two cohorts using automatic volumetry of four of the major nuclei of the basal ganglia: caudate nucleus, globus pallidus, nucleus accumbens, and putamen.

MATERIALS AND METHODS

Subjects

The total study population consisted of 1,004 participants (see Table I) who enrolled in the Brain Imaging Genetics (BIG) project running at the Radboud University Nijmegen (Medical Centre). Subjects of Caucasian origin between 18 and 36 years of age with high education level (bachelor student level or higher) and no self-reported neurological or psychiatric history were included. For all subjects anatomical MRI data were available acquired at either 1.5T or 3T MRI scanners. As the effect of MRI scanner field strength on brain volumetry may be substantial [e.g. Jovicich et al., 2009], we split our study population into two cohorts separating the 1.5T and 3T data. All participants gave written informed consent and the study was approved by the local ethics committee.

MRI Acquisition

Anatomical T1-weighted MRI data were acquired at the Donders Centre for Cognitive Neuroimaging. All scans covered the entire brain and had a voxel size of $1 \times 1 \times 1 \text{ mm}^3$. In the first cohort, images were acquired at 1.5T Siemens Sonata and Avanto scanners (Siemens, Erlangen, Germany) using small variations to a standard T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR 2,300 ms, TI 1,100 ms, TE 3.03 ms, 192 sagittal slices, field of view 256 mm). These variations included a TR/TI/TE/slices of 2,730/1,000/2.95/176, 2,250/850/2.95/176, 2,250/850/3.93/176, 2,250/850/3.68/176, and the use of GRAPPA parallel imaging with an acceleration factor of 2. In the second cohort, images were acquired at 3T Siemens

Figure 1.

FSL FIRST segmentation results for a single subject showing the segmented caudate nucleus (green), globus pallidus (blue), nucleus accumbens (red), and putamen (yellow), projected on the T1-weighted anatomical MRI scan in native space of that subject.

Trio and TrioTim scanners (Siemens, Erlangen, Germany) using small variations to a standard T1-weighted 3D MPRAGE sequence (TR 2,300 ms, TI 1,100 ms, TE 3.93 ms, 192 sagittal slices, field of view 256 mm). These variations included a TR/TI/TE/slices of 2,300/1,100/3.03/192, 2,300/1,100/2.92/192, 2,300/1,100/2.96/192, 2,300/1,100/2.99/192, 1,940/1,100/3.93/176, 1,960/1,100/4.58/176, and the use of GRAPPA parallel imaging with an acceleration factor of 2. Slight variations in these imaging parameters have been shown not to affect the reliability of morphometric results [Jovicich et al., 2009].

Image Data Processing

Whole brain segmentation of gray matter, white matter and cerebrospinal fluid was performed using the VBM 5.1 toolbox version 1.19 (available at: dbm.neuro.uni-jena.de/vbm/) in SPM5 (available at: www.fil.ion.ucl.ac.uk/spm/) using priors (default settings). Total volume of gray matter and white matter was calculated by adding the resulting tissue probabilities. Total brain volume was defined as the sum of white matter and gray matter volume.

For the automatic segmentation of subcortical brain structures we used FIRST v1.2 (available at: www.fmrib.ox.ac.uk/fsl/first/index.html) in FSL 4.1.4 (available at: <http://www.fmrib.ox.ac.uk/fsl/>) [Patenaude 2007; Smith et al., 2004]. This method is based on Bayesian statistical models of shape and appearance for seventeen subcortical structures from 317 manually labelled T1-weighted MR images. To fit the models, the probability of the shape given the observed intensities is used [Patenaude, 2007]. In addition, to model intensity at the structural boundary, automatic boundary correction was applied. After segmentation, the volumes of the caudate nucleus, globus pallidus, nucleus accumbens, and putamen were calculated

by multiplying the number of voxels in a specific structure with the voxel volume (1 mm³). An example of the FSL FIRST segmentation results for a single subject is shown in Figure 1.

To detect obvious segmentation errors (like brain structures located outside the brain) visual inspection of the segmented subcortical structures projected onto the T1-weighted MRI scans was done using the software MRIcroN Version Beta 7 (available at: www.mricron.com/mricron). Datasets in which the segmentation method failed were removed from further analysis (5 out of 1,004 datasets).

Test-Retest Reliability

Although the FSL FIRST method is a validated and generally applied automatic subcortical segmentation method, we assessed the test-retest reliability of this method for our own dataset for all four subcortical structures of interest. For this purpose we used data of 68 subjects where two structural MRI scans were available. A critical parameter in the segmentation, the modes of variation, was varied to achieve optimal reliability. The default values supplied by FSL FIRST are between 30 and 50 modes of variation depending on the subcortical structure. For the nucleus accumbens, globus pallidus, and putamen, the optimal modes of variation were 300, for the caudate nucleus the optimal value was 200. In our dataset, using these optimized values for the modes of variation, the test-retest reliability expressed as Pearson's correlation increased from $r = 0.6-0.9$ to $r > 0.9$ ($P < 0.01$) for all basal ganglia nuclei studied.

TABLE II. Volumes (ml) $\pm$ standard error of the four basal ganglia nuclei studied for males and females in both cohorts, based on the estimated marginal means and controlled for total gray and white matter volume

	Cohort 1 (1.5T)				Cohort 2 (3.0 Tesla)			
	Males	Females	Diff	<i>P</i>	Males	Females	Diff	<i>P</i>
Caudate nucleus	7.48 $\pm$ 0.053	7.49 $\pm$ 0.045	−0.1%	0.92	7.60 $\pm$ 0.054	7.65 $\pm$ 0.040	−0.7%	0.50
Globus pallidus	3.83 $\pm$ 0.016	3.68 $\pm$ 0.014	3.9%	<0.001	3.75 $\pm$ 0.017	3.64 $\pm$ 0.013	2.7%	<0.001
Putamen	11.0 $\pm$ 0.049	10.7 $\pm$ 0.042	2.8%	<0.001	10.8 $\pm$ 0.054	10.5 $\pm$ 0.040	2.6%	<0.001
Nucleus accumbens	1.24 $\pm$ 0.014	1.23 $\pm$ 0.012	0.7%	0.66	1.17 $\pm$ 0.013	1.19 $\pm$ 0.009	−1.7%	0.088

Positive differences indicate that males have larger volumes than females, negative differences indicate that males have smaller volumes than females.

Diff: volume difference between males and females.

Statistical Analysis

Sex differences in basal ganglia were investigated using SPSS 15.0 (SPSS for Windows, Rel. 15.0.0, 2006. Chicago, IL). Outlier analysis was applied to detect subjects with deviating values for gray matter, white matter, or subcortical volumes using *z*-values. Subjects with $z > 3$ or $z < -3$ on any of these volumes were excluded from further analyses ($n = 9$ for cohort 1, $n = 16$ for cohort 2). In both cohorts, sex differences for total gray matter and white matter were tested with independent sample *t*-tests (two-tailed). For the volume of the basal ganglia nuclei, the volumes of both the left and right side were added together. To investigate sex differences in these volumes, univariate analyses of covariance (ANCOVAs) were applied for each structure separately, with sex as the independent variable. Gray matter volume, white matter volume, and age of the participant were added as covariates. All outcome variables were normally distributed. The estimated marginal means are reported here as the number of females is not equal to the number of males. To specifically test the interaction of sex and age on the volumes of the basal ganglia nuclei an additional ANCOVA was performed with both sex and age as factors. Finally, for descriptive purposes, the effect of MRI scanner was tested by adding field strength as an additional factor in an ANCOVA of the total study population.

RESULTS

Independent sample *t*-tests showed that both gray matter volume (males: 879 $\pm$ 66 ml, females: 802 $\pm$ 60 ml) and white matter volume (males: 510 $\pm$ 47 ml, females: 452 $\pm$ 41 ml) were significantly larger in males than females ($P < 0.001$). In the entire study population, the volumes of several subcortical brain structures showed a significant effect of field strength. Subcortical volumes appeared larger in 1.5T data compared with 3T data particularly in the nucleus accumbens ($F_{(1,969)} = 71.9$, $P < 0.001$), putamen ($F_{(1,969)} = 16.4$, $P < 0.001$), and caudate nucleus ($F_{(1,969)} = 4.475$, $P = 0.035$). Therefore, sexual dimorphism was assessed separately in the 1.5T and 3T data. The volumes

of the four basal ganglia nuclei for both cohorts are shown in Table II. Univariate ANCOVA tests for each brain structure when controlled for age and total gray and white matter volume showed that males have significantly larger volumes for globus pallidus and putamen, confirmed in both cohorts (globus pallidus $F_{(1,449)} = 18.8$, $P < 0.001$ and $F_{(1,515)} = 18.4$, $P < 0.001$; putamen $F_{(1,449)} = 40.7$, $P < 0.001$ and $F_{(1,515)} = 14.7$, $P < 0.001$). No significant sex differences were found for caudate nucleus and nucleus accumbens volumes in either cohort when controlling for age and total gray and white matter volume (caudate nucleus $F_{(1,449)} = 2.8$, $P > 0.05$ and $F_{(1,515)} = 0.463$, $P > 0.05$; nucleus accumbens $F_{(1,449)} = 0.197$, $P > 0.05$ and $F_{(1,515)} = 2.916$, $P > 0.05$). No significant interactions of sex and age on volumes of basal ganglia nuclei were found within our study population (all $P > 0.05$).

DISCUSSION

In the present study we used two large cohorts of healthy subjects to investigate sex differences in basal ganglia volumes while controlling for differences in total brain volume. No significant sex differences were found for caudate nucleus and nucleus accumbens, but males showed significantly larger volumes for globus pallidus and putamen. This suggests a complex pattern of sex specificity: sexual dimorphism is neither a general effect in the basal ganglia, nor a specific effect in just one particular nucleus. Within the anatomical connections between basal ganglia and cortex, five parallel information processing circuits can be identified; a motor circuit, an oculomotor circuit, a dorsolateral prefrontal circuit, a lateral orbitofrontal circuit, and an anterior cingulate circuit [Alexander et al., 1986]. However, whether these five circuits are completely segregated or overlapping remains under investigation. This makes the exact role of the separate basal ganglia nuclei still largely unclear. However, the current results will aid the interpretation of sexual dimorphism in basal ganglia function and enable follow-up studies investigating associations of basal ganglia volume with behavioral differences that subsequently may be used for inferences about the

sex-specific pathophysiology of common neuropsychiatric disorders related to basal ganglia (dys)function.

The sexual dimorphism in globus pallidus and putamen found in this study may be related to differences in basal ganglia function between males and females, particularly involving the striatal dopamine system [Munro et al., 2006; Pohjalainen et al., 1998]. Females have greater dopamine release in the right globus pallidus than males [Riccardi et al., 2006] and a higher presynaptic dopaminergic tone in the striatum [Cosgrove et al., 2007]. In response to amphetamines, males have greater dopamine release than females in the ventral striatum, anterior putamen and caudate nucleus, which is most likely related to the influence of sex hormones on the dopaminergic system [Munro et al., 2006]. Also, recent evidence shows that pharmacologically induced changes in dopamine receptor function are associated with striatal volume changes [Tost et al., 2010]. Together, it could be hypothesized that the interplay of dopamine release, dopamine reactivity, sex steroid hormones, and basal ganglia volume may contribute to sex-specific prevalence and course of neuropsychiatric disorders.

In the developing human brain the basal ganglia volumes scale to total brain volume in males and females differently [Caviness et al., 1996; Giedd et al., 1997]. In a study investigating children and adolescents between age 4 and 18 years, Giedd et al. [1997] found larger globus pallidus volume in males that decreased with increasing age, but this was not confirmed in other studies of children [Caviness et al., 1996; Neufang et al., 2009]. More consistently, caudate nucleus volume has been found to be larger in female compared to male children and adolescents [Caviness et al., 1996; Giedd et al., 1997; Neufang et al., 2009]. As in the current study no differences were found in caudate nucleus volume in young adults, it seems that there is a sexual dimorphism in this nucleus in childhood that disappears with puberty. This notion is supported by analysis of longitudinal changes in brain structure showing that caudate nucleus volume peaks earlier in females than males [10.5 and 14 years, respectively, Lenroot et al., 2007]. Despite potential sex differences in brain maturation and age-related brain volume reductions these processes appeared relatively stable within our study population (age range 18–36 years).

Inconsistent results for sexual dimorphism in brain structure reported in the literature may be due to different methods used for segmentation (automatic, semiautomatic, or manual), a small number of subjects studied, or the statistical method used for analyzing the data. Although manual segmentation is considered the “gold standard” for volumetry, automatic segmentation of subcortical structures is gaining more and more popularity, because of advantages including time and labor efficacy, observer-independence, and higher reproducibility [Giesel et al., 2008; Morey et al., 2009]. Several (semi-)automatic segmentation methods are currently available with advantages and disadvantages that seem to be specific for different

brain regions [e.g. Morey et al., 2009]. In the present study, we used the automatic subcortical segmentation method FSL FIRST [Patenaude, 2007; Smith et al., 2004]. De Jong et al. [2008] recently assessed multiple subcortical regions using this method in Alzheimer’s disease patients and found in addition to the expected hippocampal atrophy reduced volumes in the putamen and thalamus, showing the potential of this method to detect volume differences in diverse neurological and psychiatric disorders.

The design of the current study, assessing sexual dimorphism in two large independent cohorts, makes it particularly robust against false positive findings. Whereas small variations in acquisition sequences within one MRI scanner do not affect the reliability of the results, measurements across field strengths may result in volume difference biases [Han et al., 2006; Jovicich et al., 2009]. This effect is largely due to the underlying tissue properties that influence the MRI signal, in particular relaxation times like T1. Relaxation times are different at 1.5T and 3T, which leads to changes in the intensity and contrast of the images. However, the sign and magnitude of the resulting volume bias may not be systematic but dependent on the specific brain structure [Jovicich et al., 2009], as also observed in the current study. In this study, basal ganglia volume differences of around 3% could reliably be detected (Table II). Using automated segmentation routines the volume of specific brain regions can readily be assessed in large cohorts, enabling reliable detection of small differences in regional brain volumes and aiding our understanding of brain differences in cognitive processing and neuropsychiatric disorders.

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