Brain Struct Funct
DOI 10.1007/s00429-015-1158-9

SHORT COMMUNICATION

Genetic sex and the volumes of the caudate-putamen, nucleus accumbens core and shell: original data and a review

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Received: 2 April 2015 / Accepted: 24 November 2015
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Abstract Sex differences are widespread across vertebrate nervous systems. Such differences are sometimes reflected in the neural substrate via neuroanatomical differences in brain region volume. One brain region that displays sex differences in its associated functions and pathologies is the striatum, including the caudate-putamen (dorsal striatum), nucleus accumbens core and shell (ventral striatum). The extent to which these differences can be attributed to alterations in volume is unclear. We thus tested whether the volumes of the caudate-putamen, nucleus accumbens core, and nucleus accumbens shell differed by region, sex, and hemisphere in adult Sprague–Dawley rats. As a positive control for detecting sex differences in brain region volume, we measured the sexually dimorphic nucleus of the medial preoptic area (SDN-POA). As expected, SDN-POA volume was larger in males than in females. No sex differences were detected in the volumes of the caudate-putamen, nucleus accumbens core or shell. Nucleus accumbens core volume was larger in the right than left hemisphere across males and females. These findings complement previous reports of lateralized nucleus accumbens volume in humans, and suggest that this may possibly be driven via hemispheric differences in nucleus accumbens core volume. In contrast, striatal sex differences seem to be mediated by factors other than striatal region volume. This conclusion is presented within the context of a detailed review of studies addressing sex differences and similarities in striatal neuroanatomy.

Keywords Striatum · Caudate-putamen · Dorsal striatum · Ventral striatum · Volume · Nucleus accumbens · Sex · Hemisphere · Lateralization

Introduction

Sex differences in the nervous system are found in many brain regions and animal taxa. These differences can be reflected by the neural substrate in several forms, including its fundamental neuroanatomy (Cahill 2006; Tommasi 2009). Sometimes these neuroanatomical differences are quite dramatic, with robust variation in the overall volume of the relevant brain region. Examples include the sexually dimorphic nucleus of the preoptic area (SDN-POA) (Gorski et al. 1980), the spinal nucleus of the bulbocavernosus (SNB) (Breedlove and Arnold 1981), the medial amygdala (Hines et al. 1992; Cooke and Woolley 2005), and the telencephalic song control nuclei in sexually dimorphic songbirds (Nottebohm and Arnold 1976; Suthers 1997). Another brain region that displays sex and hemispheric differences in its neural properties and associated functions and pathologies is the mammalian striatum, comprising the caudate-putamen (also called dorsal striatum), nucleus accumbens core, and nucleus accumbens shell (ventral striatum) (Calhoun 1962; Zimmerberg et al. 1974; Glick and Ross 1981; Castellano et al. 1987, 1989; McDermott et al. 1994; Eckel et al. 2000; Scholz et al. 2000; Becker 2002; Davis et al. 2005; Zurkovsky et al.

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Published online: 14 December 2015

2007; Becker and Hu 2008; Capper-Loup and Kaelin-Lang 2008; Capper-Loup et al. 2009; Carroll and Anker 2010; Kloppel et al. 2010; Meitzen et al. 2011; Bobzean et al. 2014; Fattore et al. 2014; Hosseini-Kamkar and Morton 2014; Yoest et al. 2014). Currently, the extent to which striatal sex differences can be attributed to underlying variation in neuroanatomical volume is unclear. In the rat, only the volume of the nucleus accumbens core has been compared between males and females (Wissman et al. 2012). This is a particularly relevant question as it directly contributes to understanding the documented sex differences and steroid sex hormone actions in striatal electrophysiological properties (Dorris et al., 2015), dendritic spine and excitatory synapse properties (Forlano and Woolley 2010; Staffend et al. 2011; Wissman et al. 2011; Peterson et al. 2015), gene expression (Chen et al. 2009; Trabzuni et al. 2013; Ghahramani et al. 2014), and steroid sex hormone and catecholamine action (Becker 1990; Di Paolo 1994; Mermelstein et al. 1996; Xiao and Becker 1998; Walker et al. 2000; Hu et al. 2006; Becker and Hu 2008; Dluzen and McDermott 2008; Schultz et al. 2009; Grove-Strawser et al. 2010).

We tested whether the volumes of the caudate-putamen, nucleus accumbens core, and nucleus accumbens shell differed by region, sex, and hemisphere in adult gonadectomized Sprague–Dawley rats. Gonadectomized rats were used to avoid any potential confounds induced by circulating steroid sex hormones, since striatal regions express membrane-associated estrogen receptors α, β, and GPER-1 (Mermelstein et al. 1996; Kuppers and Beyer 1999; Schultz et al. 2009; Grove-Strawser et al. 2010; Almey et al. 2012; Almey et al. 2015). As a positive control for detecting sex differences in volume, we measured the SDN-POA. As expected, SDN-POA volume was larger in males than in females. No sex differences were detected in the volumes of the whole striatum, caudate-putamen, or nucleus accumbens core or shell. Nucleus accumbens core volume was larger in the right than left hemisphere. These findings extend previous reports of lateralized nucleus accumbens volume in humans (Ahsan et al. 2007; Neto et al. 2008), and suggest that this may be driven via hemispheric differences in nucleus accumbens core volume. In contrast, striatal-associated sex differences appear to be driven by factors other than gross volume. The manuscript concludes with a detailed review of studies of genetic sex and striatal region volume.

Materials and methods

Animals

The Institutional Animal Care and Use Committee at the University of Minnesota approved all procedures in this study. The tissue analyzed in this study was previously acquired for an earlier study (Meitzen et al. 2011). Briefly, four adult male and four adult female Sprague–Dawley rats were purchased from Harlan Laboratories. Rats were gonadectomized on day 60 of life at Harlan Laboratories. The absence of gonads was verified post-mortem. It is unknown whether rats were littermates. Food and water were available ad libitum, and animals were maintained on a 14-h light 10-h dark cycle in a climate controlled colony.

Brain histology and imaging

On day 75 of life, animals were deeply anesthetized using pentobarbital (200 mg/kg, i.p.) and perfused transcardially with saline until liver clearance, and then with 300 ml of 4 % paraformaldehyde over 12 min. The anticoagulant heparin (0.5 ml of 1000 UPS units/ml) was injected into the left ventricle prior to perfusion. Brains were post-fixed overnight in 4 % paraformaldehyde at 4 °C, cryoprotected in 30 % sucrose solution in 0.1 M phosphate-buffered saline (PBS), and the sectioned coronally (50 µm) on a freezing microtome. The right hemisphere of each brain was nicked to distinguish hemispheres. Every section was mounted onto slides and stained with cresyl violet. Sections containing the SDN-POA were imaged using a Leica DM5000B light microscope coupled to a Q-imaging Retiga 2000R digital color camera. Sections containing the caudate-putamen and nucleus accumbens core and shell were imaged using a LabX Northern Light R95 Lightbox coupled to a Q-imaging 12-bit (mono) digital camera. Images were acquired and processed using MCID Core 7.0 and exported as TIFFs.

Stereology

Neuroanatomical boundaries of each brain region of interest were traced from the photomicrographs using ImageJ (NIH, Bethesda, MD). The volume of each region of interest was estimated using Cavalieri's principle (Mayhew et al. 1990; Wissman et al. 2012). Volumes were calculated using the formula for the volume of a cone frustum (Smith et al. 1997). Anterior brain volume (the region between Bregma +3.215 mm to Bregma −1.566 mm) was measured to control for differences in brain size, section compression and/or tissue shrinkage between subjects, following a previous study (Chakos et al. 1998). Anterior brain volume did not differ by sex (male: $363.3 \pm 6.8\ \mathrm{mm}^3$; female: 373.8 ± 3.4; $t_{(6)} = 1.393$; $p > 0.05$). Thus, presented volumes were not adjusted by anterior brain size. The use of adjusted or non-adjusted volumes did not alter overall experimental conclusions. We note that all brains underwent the same histological preparation in parallel, and that the hypotheses in this study compared differences between groups internal to the study, as recommended for non-adjusted volumetric measurements (Mayhew et al. 1990). The SDN-POA was defined as a dense cluster of neurons lateral to the third ventricle in the preoptic area, inferior to the anterior commissure, superior to the suprachiasmatic nucleus, and rostral to the paraventricular nucleus (Gorski et al. 1980; Bleier et al. 1982). SDN-POA measurements were only made from the left hemisphere. Measurements of the caudate-putamen were made from Bregma +2.474 mm to Bregma −1.566 mm and measurements of the nucleus accumbens from Bregma +3.125 mm to Bregma +0.485 mm. For striatal brain regions volume was calculated separately for both the left and right hemispheres. The borders of the dorsal striatum, nucleus accumbens core and shell were defined following the rat brain atlas (Paxinos et al. 2008), following previous studies (Meitzen et al. 2011). Overall volumes were similar to measurements of previous studies, validating this approach (Fig. 1). We note that the use of immunohistochemical staining can aid in the identification of striatal region borders, including tyrosine hydroxylase, calbindin, and calretinin (Seifert et al. 1998; Brauer et al. 2000; Paxinos et al. 2008). All measurements and calculations of brain volumes were conducted blind to sex, and a subset of tissue was measured by two independent observers and the same observer multiple times as internal controls for measurement accuracy.

Statistics

We performed a two-tailed *t* test to assess SDN-POA volume, a one-way repeated measures ANOVA with Bonferroni post-tests to make comparisons between striatal regions regardless of hemisphere and sex, and two-way repeated measures ANOVA with Bonferroni's post-tests to make comparisons between sex and hemisphere within each striatal region. Software used was Prism 5.0 (GraphPad, La Jolla, CA). Probability values less than 0.05 were considered a priori as significant. Data are presented as mean ± SEM.

Literature search

The literature search was conducted in PubMed, and included articles with publications dates between 1992 and 2015. Search terms used were "striatum" AND "sex

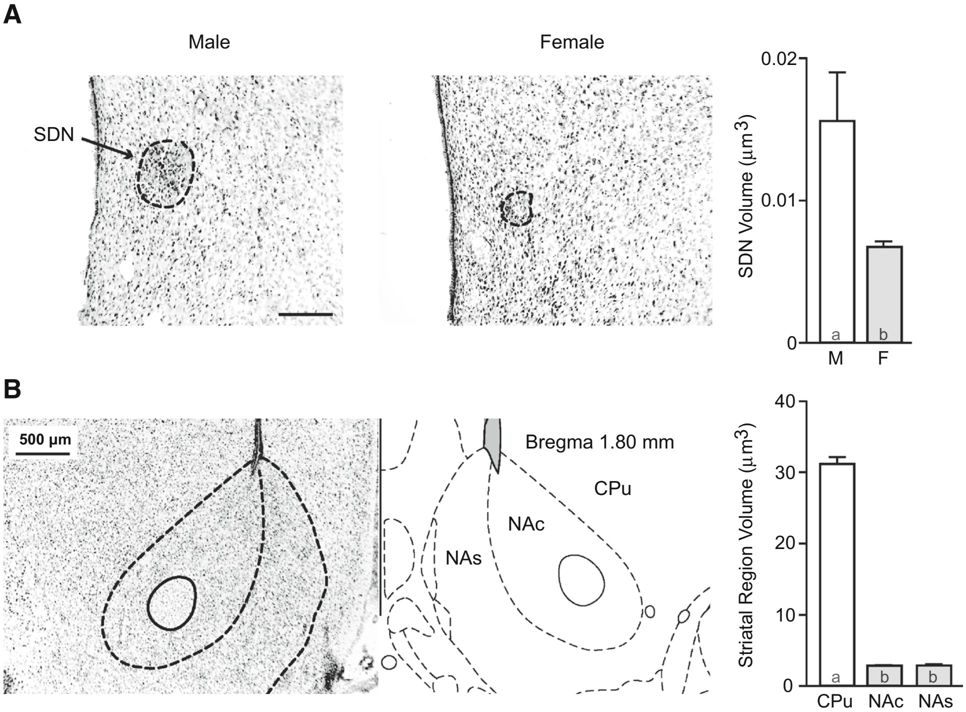

Fig. 1 Controls for volumetric measurements of sex differences and striatal regions. **a** Volumetric measurements of the sexually dimorphic nucleus of the medial preoptic area (SDN-POA). *Left* micrographs of male and female SDN-POA (scale bar 186 µm). *Right* as expected, the volume of the SDN-POA was larger in males (M) than in females (F) ($p < 0.05$). **b** Striatal region volumes considered independently of sex and hemisphere. *Left* schematic of caudate-putamen (CPu), nucleus accumbens core (NAc) and nucleus accumbens shell (NAs) (*scale bar* 500 µm). *Right* all measured volumes were consistent with those reported from earlier studies. The volume of the caudate-putamen was larger than that of the nucleus accumbens core and shell ($p < 0.0001$). The volumes of the nucleus accumbens core and shell did not differ significantly from each other ($p > 0.05$)

difference", "caudate putamen" AND "sex difference", "caudate" AND "sex difference", "putamen" AND "sex difference", or "nucleus accumbens AND "sex difference". Articles were included in the review if they analyzed the following neuroanatomical attributes by sex: volume and/or dimensionality, soma size, cell density (any aspect, including cell death counts), dendrites (including dendritic spine characteristics and chemical synapse markers), and afferent and efferent striatal anatomical projections. Excluded articles were those that were not in English, were conference proceedings or literature reviews, were not peer-reviewed, and whose subject purely involved pathologies, drug administration or recently reviewed topics such as neuromodulator/hormone action (most prominently dopamine and estradiol) (Carroll and Anker 2010; Becker et al. 2013; Yoest et al. 2014).

Results

SDN-POA volume is larger in males than females

We first performed a positive control for detecting sex differences in brain region volume by measuring the SDN-POA, which in rats is typically 2–3 times larger in males than in females (Gorski et al. 1980; Bleier et al. 1982). Consistent with earlier studies, SDN-POA volume was ~2.3 times larger in males than in females (Fig. 1a; $p < 0.05$ $t_{(6)} = 2.513$). This finding indicates that a sex difference in brain region volume can be detected using the tissue and techniques available for this study.

Caudate-putamen, nucleus accumbens core and shell volumes are similar to those reported by previous studies

As an additional control of experimental technique, we also compared the overall volumes of striatal regions independently of sex and hemisphere (Table 1). As expected, the volume of the caudate-putamen was larger than that of both the nucleus accumbens core and shell (Fig. 1b; $p < 0.0001$, $F_{(2,23)} = 713.2$). The present study's measurement of caudate-putamen volume was 30.72 ± 1.07 mm^3, similar to measurements from previous studies (Anden et al. 1966; Fentress et al. 1981; Oorschot 1996; Chakos et al. 1998; Roberts 2001; Andersson et al. 2002; Hsu et al. 2010). Regarding the nucleus accumbens, the measured volumes of the total nucleus accumbens (5.08 ± 0.53 mm^3) and the nucleus accumbens core (2.51 ± 0.09 mm^3) are also similar to those reported from previous studies (McClure et al. 2004; Wissman et al. 2012). The volumes of the nucleus accumbens core and shell did not differ significantly from each other (Fig. 1b). Collectively these measurements confirm that striatal region volumes considered

Table 1 Measurements and statistics of striatal region volumes

Volume	Caudate-putamen	Nucleus accumbens core	Nucleus accumbens shell
Global	**30.7 ± 1.1**^{a}	**2.5 ± 1.1**^{b}	**2.5 ± 0.1**^{b}
Statistics	$\boldsymbol{F_{2,23} = 713; p < 0.0001}$	$\boldsymbol{F_{2,23} = 713; p < 0.0001}$	$\boldsymbol{F_{2,23} = 713; p < 0.0001}$
Sex			
M	31.1 ± 2.2;	2.6 ± 0.1	2.4 ± 0.1
F	30.4 ± 0.5	2.4 ± 0.1	2.6 ± 0.2
Statistics	$F_{1,15} = 1.21; p = 0.313$	$F_{1,15} = 1.00; p = 0.355$	$F_{1,15} = 1.63; p = 0.249$
Hemisphere			
L	31.0 ± 1.2	**2.3 ± 0.1**	2.5 ± 0.1
R	30.4 ± 1.0	**2.7 ± 0.1**	2.5 ± 0.1
Statistics	$F_{1,15} = 1.13; p = 0.329$	$\boldsymbol{F_{1,15} = 12.59; p = 0.012}$	$F_{1,15} = 0.01; p = 0.933$
Sex × hemisphere			
ML	31.1 ± 2.5	2.4 ± 0.0	2.5 ± 0.1
MR	31.0 ± 2.5	2.9 ± 0.2	2.5 ± 0.1
FL	31.1 ± 2.0	2.2 ± 0.1	2.7 ± 0.2
FR	30.0 ± 0.7	2.5 ± 0.2	2.6 ± 0.2
Statistics	$F_{1,15} = 1.21; p = 0.313$	$F_{1,15} = 1.00; p = 0.355$	$F_{1,15} = 1.63; p = 0.249$

Striatal region volume is presented in mm^3. Bold indicates a significant finding. In the Global section, different superscript letters denote significant differences across striatal regions. A one-way repeated measures ANOVA was used to compare values across the caudate-putamen, nucleus accumbens core and shell ("Global" row). A two-way repeated measures ANOVA was used to test the contributions of sex, hemisphere, and the interaction of sex and hemisphere for the volumes of individual striatal regions. *M* male, *F* female, *L* left, *R* right independently of hemisphere and sex follow expected relationships and ranges derived from previous studies.

Hemispheric but not sex differences in select striatal region volumes

We then tested whether striatal volumes differed by hemisphere and sex (Table 1). No differences in striatal region volumes were detected between sex or the interaction between sex and hemisphere (Fig. 2a–c). Regarding hemisphere, the volume of the nucleus accumbens core was larger in the right compared to left hemisphere in both sexes (Fig. 2b; $p < 0.02$; $F = 12.59$). Similarly, the volume of the total nucleus accumbens was lateralized in the same direction (left 4.9 ± 0.1 mm^3, right 5.3 ± 0.2 mm^3; $p < 0.03$; $F = 8.11$). No difference between hemispheres was detected in caudate-putamen (Fig. 2a) or the nucleus accumbens shell (Fig. 2c). We conclude that there is evidence suggesting that the volume of the nucleus accumbens core is lateralized, and that there is no evidence for a sex difference in the volume of any striatal region, extending studies in other animals and striatal regions (Table 2).

Discussion

This study measured the overall volumes of rat caudate-putamen, nucleus accumbens core, and nucleus accumbens shell to determine whether these differed by sex or hemisphere. Additionally, SDN-POA volume was measured as a positive control for detecting sex differences in volume. Overall volumes of striatal brain regions analyzed regardless of sex or hemisphere were as expected from previous studies, without consideration of sex or hemisphere. SDN-POA volume was larger in males compared to females. No sex differences were detected in the volumes of the caudate-putamen, nucleus accumbens core or shell. Hemispheric analysis suggests that nucleus accumbens core volume was consistently larger in the right hemisphere. Here we discuss these findings first in the context of sex differences, and then with regards to hemispheric lateralization.

Sex differences in striatal-associated functions and pathologies have been extensively studied, with sex differences occurring in motivated behaviors, sensorimotor and learning tasks, responsiveness to drugs of abuse, and aspects of Parkinson’s Disease (Becker 2002; Davis et al. 2005; Haaxma et al. 2007; Zurkovsky et al. 2007; Becker and Hu 2008; Yoest et al. 2014). In certain other brain regions and/or animals, sex differences in behavior are associated with changes in overall neuroanatomical volume. Here we tested whether this was the case for striatal regions, and found no evidence for sex differences in overall volumes. These results extend and complement the existing literature on sex and estradiol-induced differences in striatal anatomical properties by being the first to test whether rat caudate-putamen and nucleus accumbens shell volume varies by sex (Table 2). Additionally, these data confirm a previous report that rat nucleus accumbens core volume does not differ

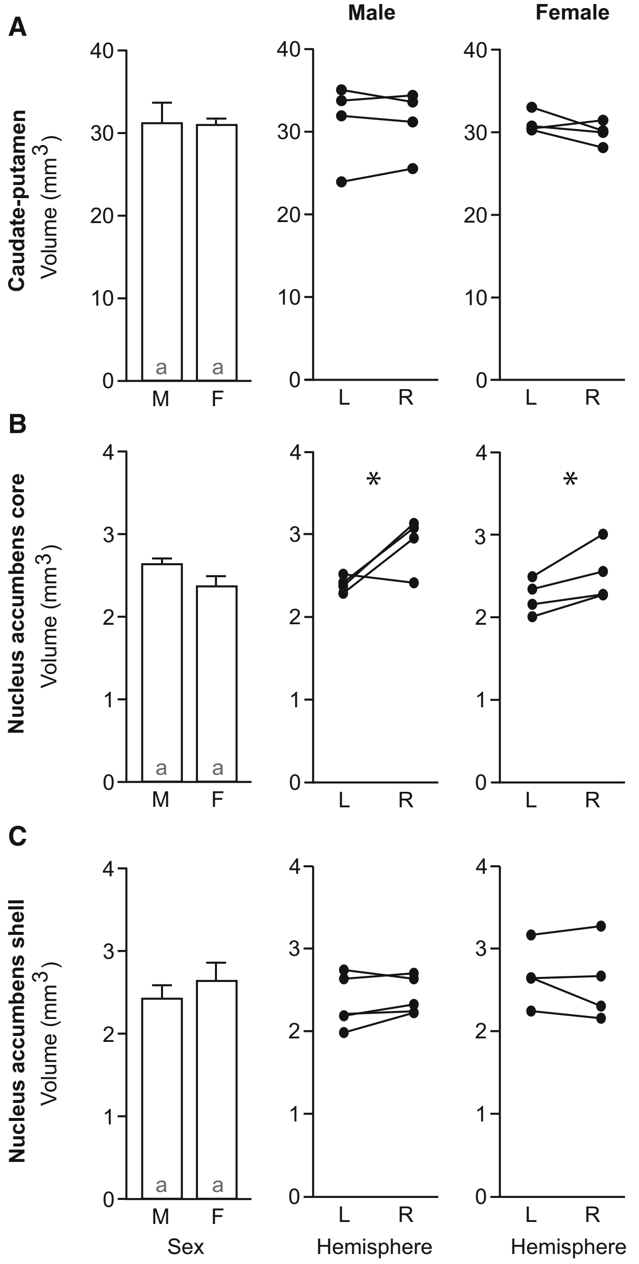

Fig. 2 Striatal region volume was lateralized in the nucleus accumbens core but otherwise did not differ by sex or hemisphere. *Left* striatal region volumes compared between males (M) and females (F). *Middle* striatal region volumes compared between hemispheres in individual males. (*L* left, *R* right). *Right* striatal region volumes compared between hemispheres in individual females. **a** Caudate-putamen. **b** Nucleus accumbens core. Nucleus accumbens core volume was significantly larger in the right hemisphere compared to the left in both males and females ($p < 0.02$). **c** Nucleus accumbens shell. Except for that noted above, for all comparisons $p > 0.05$

Table 2 Anatomical sex differences and estradiol sensitivity in striatal brain regions

Measurement	Species	Sex difference	Hormone exposure	References
Caudate-putamen				
Volume	Rat	M = F		This study
Volume	Mouse (ABF2)	M = F[a]		Rosen et al. (2009)
Volume	Mouse (C57BL/6, BXD RI, DBA/2J)	M = F		Ahern et al. (2013), Rosen et al. (2009)
Volume	**Mouse (4CG)**	**M > F[b]**		**Corre et al. (2014)**
Soma size, neuron density	Rat	M = F		Meitzen et al. (2011)
Dendritic spine density	Hamster	F only	No	Staffend et al. (2011)
Orbital frontal cortex projections	**Rat**	**M < F**		**Bayless and Daniel** (2015)
Post-natal cell death	Mouse (C57BL/6)	M = F		Ahern et al. (2013)
ΔFosB expression	**Rat**	**M ≤ F[c]**		**Sato et al.** (2011)
Caudate and/or Putamen				
Volume	Human	M = F		Ahsan et al. (2007), Brabec et al. (2003), Koikkalainen et al. (2007), Jancke et al. (2015), Sato et al. (2014), Hibar et al. (2015), Rijpkema et al. (2012)
Volume	**Human**	**M > F**		**Rijpkema et al.** (2012)**, Raz et al.** (1995)**, Tauscher-Wisniewski et al.** (2005)
Volume	**Human**	**M < F**		**Szabo et al.** (2003)**, Giedd et al.** (1997)
Volume (juvenile)	**Human**	**M > F**		**Goddings et al.** (2014)**, Dennison et al.** (2013)
Volume (juvenile)	Human	M = F		Giedd et al. (1997)
Volume (juvenile global striatum)	**Human**	**M > F**		**Raznahan et al.** (2014)
Embryonic striatum (global)				
TH-IR fiber density	**Rat**	**M < F**		**Ovtscharoff et al.** (1992)
GABA-IR cell body density				
Nucleus Accumbens (global)				
Volume	Rat	M = F		This study
Volume	Mouse (California)	M = F		Campi et al. (2013)
Volume	Human	M = F		Ahsan et al. (2007), Brabec et al. (2003), Jancke et al. (2015), Rijpkema et al. (2012)
Volume	**Human (juvenile)**	**M > F**		**Goddings et al.** (2014)**, Urosevic et al.** (2014)
Volume	**Human (juvenile)**	**M > F, M < F[d]**		**Dennison et al.** (2013)
Dimensions	Human	M = F[e]		Mavridis et al. (2011)
Y' Stereotactic coordinate	**Human**	**M > F[e]**		**Mavridis et al.** (2011)
Nucleus accumbens core				
Volume	Rat	M = F		This study, Wissman et al. (2012)
Soma size, neuron density	Rat	M = F		Meitzen et al. (2011)
Soma Size	Human	M = F		Sazdanovic et al. (2013)
Dendritic spine density	**Rat**	**F only**	**Yes, ↓**	Peterson et al. (2015)
Dendritic spine density	**Hamster**	**F only**	**Yes, ↓**	Staffend et al. (2011)
Dendritic spine density	**Rat**	**M < F**		**Forlano and Woolley** (2010)**, Wissman et al.** (2011, 2012)
Dendritic spine density	**Human**	**M < F**		**Sazdanovic et al.** (2013)
Dendrite length	Rat	M = F		Forlano and Woolley (2010)
PSD-95 puncta	Rat	M = F		Forlano and Woolley (2010)
VGLUT1 and VGLUT2 expression				
TH-IR profiles	Rat	M = F		Wissman et al. (2012), Forlano and Woolley (2010)
Large spines near TH-IR	**Rat**	**M < F**		**Wissman et al.** (2012)
ΔFosB expression	**Rat**	**M ≥ F[c]**		**Sato et al.** (2011)

Table 2 continued

Measurement	Species	Sex difference	Hormone exposure	References
Nucleus accumbens shell				
Volume	Rat	M = F		This study
Soma size, neuron density	Rat	M = F		Meitzen et al. (2011)
Soma size	Human	M = F		Sazdanovic et al. (2013)
Dendritic spine density	**Rat**	**F only**	**Yes ↑, No**[f]	**Peterson et al.** (2015)
Dendritic spine density	Hamster	F only	No	Staffend et al. (2011)
Dendritic spine density	Rat	M = F[g]		Forlano and Woolley (2010), Wissman et al. (2011)
Dendritic spine density	**Human**	**M < F**		**Sazdanovic et al.** (2013)
Dendritic large spine density	**Rat**	**M < F**		**Forlano and Woolley** (2010)
Dendrite length	Rat	M = F		Forlano and Woolley (2010)
PSD-95 puncta volume	**Rat**	**M < F**		**Forlano and Woolley** (2010)
TH-IR profiles	Rat	M = F		Forlano and Woolley (2010)
VGLUT1 and VGLUT2				
ΔFosB expression	**Rat**	**M ≥ F**[c]		**Sato et al.** (2011)

Bold indicates a significant finding as defined by the cited study. Unbold indicate data not collected. All cellular-level measurements were performed on medium spiny neurons

TH-IR tyrosine hydroxylase-immunoreactive, *PSD-95* postsynaptic density protein-95, *VGLUT* vesicular glutamate transporter

[a] Mouse caudate-putamen volume was analyzed via *t*-test using supplemental data provided by Rosen et al. (2009)

[b] This study employed a false discovery rate of 10 % or less to determine significance. The false discovery rate-corrected *p* value was 0.092 for gonadal sex for striatum

[c] Sato and colleagues further analyzed expression by regional anatomical location and cell expression subtype. Sex differences varied by these attributes

[d] Result varied by hemisphere

[e] Mavridis and colleagues published two different studies of human nucleus accumbens dimensions in 2011. One study found no sex difference. The other detected a sex difference in the Y' stereotaxic coordinate, which was interpreted to indicate that the male nucleus accumbens extends ∼1 mm more posterior than the female nucleus accumbens. Overall volume was not calculated

[f] Experiment 1 in this study did not show an effect of estradiol. However, experiment 2 did

[g] Forlano and Woolley (2010), found a trend toward a sex difference in the shell ($p = 0.06$)

between sexes (Wissman et al. 2012). Overall, this study supports the conclusion that the gross anatomical properties of the adult caudate-putamen, nucleus accumbens core and shell largely do not differ by sex, with the possible exception of volumetric changes during early development (Table 2). We also note that there is some evidence of sex differences in human caudate or putamen volume (Table 2) (Ruigrok et al. 2014). Given the divergent results of these studies, overall we conclude that there is little support for a significant sex difference in striatal region volume in adults. Striatal soma size and neuron density do not differ by sex (Meitzen et al. 2011). Instead, striatal neuroanatomical sex differences are more commonly detected in microanatomy such as dendritic spine density, and seem more robust in the nucleus accumbens than in the caudate-putamen (Forlano and Woolley 2010; Staffend et al. 2011; Wissman et al. 2011; Peterson et al. 2015), and possibly during adolescence (Hammerslag and Gulley 2015). Notable neuroanatomical information missing from the literature include studies addressing sex differences (or lack thereof) in the anatomical projections to and from striatal regions, especially regarding glutamatergic projections (Bayless and Daniel 2015). An exception to this is dopaminergic projections. In adult nucleus accumbens core and shell there is no evidence for sex differences in the magnitude of dopaminergic projections as assessed via TH-IR at the light and electron microscopy levels (Forlano and Woolley 2010; Wissman et al. 2012), though sex differences have been reported in dopaminergic projections to non-striatal brain regions in adult rodents (Kritzer and Creutz 2008). Dopaminergic projections into adult caudate-putamen have not been assessed, except within the context of Parkinson's Disease patients (Kotagal et al. 2013). However, in embryonic striatum there is evidence for increased density of dopaminergic fibers in females than in males (Ovtscharoff et al. 1992). Collectively, this body of literature and the present study indicate that striatal sex differences are likely mediated via influences on the excitatory synaptic and electrophysiological properties of striatal neurons and striatal dopaminergic terminals (Mermelstein et al. 1996; Wissman et al. 2011; Dorris et al. 2015; Tozzi et al. 2015). This is most notable within the context of interactions between estradiol and/or dopamine release, uptake and receptors (Becker 1990; Di Paolo 1994; Mermelstein et al. 1996; Xiao and Becker 1998; Becker 1999; Walker et al. 2000; Hu et al. 2006; Schultz et al. 2009; Forlano and Woolley 2010; Grove-Strawser et al. 2010; Staffend et al. 2011; Meitzen et al. 2013; Yoest et al. 2014; Peterson et al. 2015).

Analysis of hemispheric differences was initially included in this study because of the known lateralizations in the mesostriatal dopaminergic system (Molochnikov and Cohen 2014), reports of lateralized sex differences in striatal dopamine content (Robinson et al. 1980), and because lateralized sex differences in volume have been detected in other brain regions (Cooke 2006). No interactions, however, were found between sex and hemisphere in the present study (Table 1). A lateralization in nucleus accumbens core volume independent of sex was detected, with volumes consistently larger in the right compared to the left hemisphere. Similarly, the volume of the entire nucleus accumbens was significantly larger in the right compared to the left hemisphere. As far as we are aware, this is the first investigation in rodents as to whether nucleus accumbens volume is potentially lateralized, and the first report to suggest that this may be due to differences specific to the nucleus accumbens core. Multiple studies in humans have tested for hemispheric differences in nucleus accumbens volume, with divergent conclusions. Consistent with the data from the current study, one study reported larger nucleus accumbens volume in the right hemisphere in humans (Neto et al. 2008). In contrast, at least two other studies reported larger nucleus accumbens volumes in the left hemisphere in humans (Tamagaki et al. 2005; Ahsan et al. 2007). At least one study detected no lateralization in human nucleus accumbens volume (Mamah et al. 2007). Given the confusion regarding whether human nucleus accumbens volume is lateralized, and that overall nucleus accumbens structure may be susceptible to environmental influences such as stress, drug exposure and disease (McClure et al. 2004; Mamah et al. 2007; Gilman et al. 2014), broad interpretations regarding nucleus accumbens lateralizations in both humans and rodents should be cautious.

Acknowledgments Funding: NC State University Start Up Funds, NC State Faculty Research and Professional Development Grant, and an NC State University Undergraduate Research Grant. We thank Jaime Willet, Drs. Heather Patisaul, Chris Stern, and Paul Mermelstein.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent This manuscript does not contain any studies with human participants. All procedures performed in studies involving animals were approved by the Institutional Animal Care and Use Committee at the University of Minnesota.

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