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Investigating the relation between striatal volume and IQ.

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ORIGINAL RESEARCH

Investigating the relation between striatal volume and IQ

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Abstract The volume of the input region of the basal ganglia, the striatum, is reduced with aging and in a number of conditions associated with cognitive impairment. The aim of the current study was to investigate the relation between the volume of striatum and general cognitive ability in a sample of 303 healthy children that were sampled to be representative of the population of the United States. Correlations between the WASI-IQ and the left striatum, composed of the caudate nucleus and putamen, were significant. When these data were analyzed separately for male and female children, positive correlations were significant for the left striatum in male children only. This brain structure-behavior relation further promotes the increasingly accepted view that the striatum is intimately involved in higher order cognitive functions. Our results also suggest that the importance of these brain regions in cognitive ability might differ for male and female children.

Keywords Basal ganglia · Striatum · Cognition · IQ · Gender

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Introduction

Striatum and cognition

Despite initial conceptualizations of specialization in movement regulation, the striatum is increasingly implicated in cognitive function. The striatum, including the caudate nuclei and putamen, represents the input layer of the basal ganglia receiving projections from virtually all higher-order cortical and limbic regions. Despite being separate upon gross inspection, the caudate and putamen are indistinguishable at the microscopic level (Wickens et al. 2007) and overlap in terms of the cortical regions to which they are connected and the cognitive functions in which they have been implicated (Di Martino et al. 2008; Postuma and Dagher 2006). Via the globus pallidus, another structure belonging to the basal ganglia, and the thalamus, the striatum is recurrently connected to these cortical and limbic regions. Through these topographically-organized reciprocal connections with all regions of cortex (Middleton and Strick 2000), the striatum is ideally positioned to influence nearly every aspect of behavior, including cognition. Finally, the striatum is the main target of the midbrain nigral dopaminergic projections, with a density of dopaminergic input a hundredfold that received by the prefrontal lobes (Wickens et al. 2007). Dopamine's role in reward, learning, memory, and cognition is supported by ample, convergent empirical findings (Wickens et al. 2007; Floresco et al. 2008).

The striatum's role in cognition has been examined using a) single-cell recordings in non-human primates, b) measurements from depth electrodes in Parkinson's patients, c) tests of cognitive processing in humans with striatal lesions, Parkinson's, and Huntington's diseases, and d) functional neuroimaging techniques. These converging methods implicate the striatum in a broad range of cognitive processes spanning low-level attention to abstract reasoning and decision making (Bellebaum and Daum 2008; Degos et al. 1993; Monchi et al. 2006; Rieger et al. 2003; Kermadi and Joseph

1995; MacDonald et al. 2011; MacDonald and Monchi 2011; MacDonald et al. 2013).

Striatum structure and function investigations

Previous investigations have demonstrated that structural brain analyses can provide insights into possible functions or abilities that various brain regions might underlie (Haier et al. 2009). Striatal volumes, particularly the caudate nuclei, are reduced in a number of conditions related to abnormal cognitive processing and lowered intelligence quotients (IQ). Decreased striatal volumes have been noted in ADHD (Castellanos et al. 2002; Semrud-Clikeman et al. 2006; Silk et al. 2009), pre-term infants [(Abernethy et al. 2004; Kesler et al. 2008) but see (Skranes et al. 1997)], methamphetamine-exposed children and methamphetamine-abusing adults (Chang et al. 2005; Chang et al. 2004), dementia (de Jong et al. 2008; Looi et al. 2008), pre-clinical Huntington gene carriers and early Huntington patients with executive dysfunction (Peinemann et al. 2005; Mandelli et al. 2010). In contrast, striatal volume is normal in patient groups with normal IQs and neuropsychological profiles such as in obsessive-compulsive disorder (Rotge et al. 2009), depression [(Kim et al. 1999) but see (Kim et al. 2008)], and bipolar disorder (Ahn et al. 2007).

A recent study found no relation between subcortical gray matter volume—summing across thalamus and all segments of the basal ganglia including the striatum—and IQ in a sample of healthy children (Lange et al. 2010). Only three studies have directly investigated basal ganglia volume alone relative to cognitive performance. Andreasen and colleagues (1993) examined the relation between specific brain structures—including the caudate nucleus—and intelligence as measured by the Weschler Adult Intelligence Scale-Revised (WAIS-R) in 67 healthy adult volunteers. They found no correlation between absolute caudate nucleus size and cognitive function. Jernigan and colleagues (2001), in a study involving 53 healthy volunteers, found that caudate nucleus volume was negatively correlated with naming latency on a single-word reading task in 53 healthy adult volunteers. Although smaller caudate volumes were associated with slower reading times, they were not related to performance on a recognition or word priming task. Finally, Moffat and colleagues (2007) showed that caudate nucleus volume weighted relative to total intracranial volume was greater in young participants (mean age = 25) who performed better on a virtual spatial navigation task relative to an older group of non-demented participants (mean age = 69). A positive correlation between basal ganglia volume and performance on their spatial navigation task was noted. This correlation was calculated collapsing across groups, however. Given that younger participants performed better on the navigation task than elderly participants and that caudate volumes are known to decrease with age relative to brain volume (Raz et al. 2003), this positive correlation could simply reflect a caudate volume-age association, independent of any relation between basal ganglia and spatial navigation ability.

Current study

The aim of the current study was to directly investigate the relation between the striatum and general IQ in a large cohort of healthy children. There have been no previous studies confirming a clear relation between striatum volumes and IQ in a sample of healthy volunteers, of either adults or children. Previous investigations were possibly underpowered to detect any relation due to small sample size or due to volume estimates that summed across a number of brain regions that might be differentially related to IQ. Based on anatomical considerations and accumulating demonstrations that the striatum mediates a diverse array of cognitive functions (Bellebaum et al. 2008; Degos et al. 1993; Rieger et al. 2003; Seger et al. 2010; Kermadi and Joseph 1995; MacDonald et al. 2013; MacDonald et al. 2011; MacDonald and Monchi 2011), it is reasonable to expect a relation between striatum volume and IQ as a proxy measure for general cognitive ability.

Methods

Sampling and recruitment

The data for this study were obtained from participants in the NIH MRI Study of Normal Brain Development. The motivation for this NIH initiative was to obtain a means for studying normal brain development longitudinally in a representative sample of healthy individuals, to minimize biases and enhance generalizeability (Evans 2006). A sample of 431 participants aged 4.18 to 18.3 years was obtained from 6 pediatric study centers (Children's Hospital—Boston; Children's Hospital Medical Center—Cincinnati; University of Texas Houston Medical School—Houston; UCLA Neuropsychiatric Institute and Hospital—Los Angeles; Children's Hospital of Philadelphia—Philadelphia; and Washington University—St. Louis) across the US that matched US census demographic data with respect to age, gender, ethnicity, socioeconomic status, and family income. Recruitment was continuously monitored so that when target goals for a particular category were reached, that enrolment arm was closed. Because this is a study of healthy individuals, participants with Axis I psychiatric illness or neurological illness were excluded. Participants with any medical condition with CNS implications (e.g., malignancy, systemic rheumatological, diabetes) were also excluded. Other exclusion criteria included IQ<70, intrauterine exposure to substances with potential to alter brain structure and/or

function, family history of conditions with neurological implications. All data collected from the pediatric study centers were transferred electronically to the data coordinating center at the Montreal Neurological Institute.

Recruitment and screening proceeded in a multi-stage process as described in detail in Evans (2006). Briefly, children who were invited to participate by mail and who passed a brief screening phone interview, underwent a longer phone full screening interview that included a more detailed health and neurological history with inquiries about exclusion criteria. The Diagnostic Interview Schedule for Children (C-DISC-4, (Shaffer et al. 2000)), a structured psychiatric interview, and a Childhood Behavior Checklist (CBCL, (Achenbach and Dumenci 2001) and (Achenbach and Ruffle 2000); exclusion a T score $\geq$70 on any clinical subscale) were completed by the parent about the child. Children 11 years of age and older also completed the Diagnostic Predictive Scales (DPS, (Lucas et al. 2001)) about themselves. If the DPS interview indicated possible diagnoses, it was followed-up with the C-DISC-4 administered to the child/adolescent (Shaffer et al. 2000). Parents also completed a semi-structured interview covering first-degree family history of psychiatric disorders—the Family Interview for Genetic Studies (FIGS, Initiative NSaBDG, 1992 [MRI modified version, FIGS-MRI]).

Participants

Written informed consent was obtained from all participants or their parents when appropriate. The institutional review board of McGill University (Data Coordinating Centre) approved this study. Institutional review board approval was also obtained from the six Pediatric Study Centers: Children's Hospital, Boston; Children's Hospital Medical Center of Cincinnati; University of Texas Health Science Center at Houston/University of Houston—Texas Medical Center Annex; Washington University, St. Louis; Children's Hospital of Philadelphia; University of California, Los Angeles. Only those participants who had high quality MRI images and who completed neuropsychological testing were included. A blinded visual quality control of scans was performed by two investigators (HG and SK). Based on this visual inspection, scans were excluded if images were degraded owing to excessive movement or other sources of noise, as in Ganjavi and colleagues (2011) and Ducharme and colleagues (2012). As a result, the data collected during the first of three visits for 303 participants (142 males) with a mean age of 11.4 (range 6.0–18.3) years were entered in the current study.

IQ measurement (as a measure of general cognitive ability)

IQ measures for each participant were obtained on the day of or within a few days of brain scanning. Intelligence was measured using the four-subtest version of the Wechsler Abbreviated Scale of Intelligence, a measure of intelligence appropriate for children ages 6 and older. This test consists of matrix reasoning, block design, vocabulary, and similarities. Matrix reasoning and block design are used to calculate performance intelligence (PIQ) that is a measure of nonverbal, fluid abilities, and visuomotor skills. Vocabulary and similarities are used to calculate verbal intelligence (VIQ), a measure of crystallised abilities. VIQ and PIQ are used to calculate WASI-IQ.

MRI imaging

A 3D T1weighted (T1W) Spoiled Gradient Recalled (SPGR) echo sequence was obtained with 1 mm isotropic data acquired sagittally from the entire head. Slice thickness of approximately 1.5 mm was obtained from GE scanners due to their limit of 124 slices. T2-weighted (T2W) and proton density weighted (PDW) images were acquired using a 2D multi-slice (2 mm) dual-echo, fast-spin echo (FSE) sequence for additional structural data.

To assess inter-site variability and ensure comparable data output, two forms of calibration at each site were employed. The American College of Radiology (ACR) phantom contains various compartments which provide information on intensity non-uniformity over a flat intensity field and geometric distortion over a grid pattern was collected approximately monthly. The living phantom was collected annually and involved one normal adult volunteer who was scanned at all sites using the full MRI acquisition protocol. This database of real brain MRIs provided information on inter-site variability in brain-related measures such as tissue contrast in raw MRI signal, tissue relaxation properties and derived morphological measurements.

Anatomical regions were defined using Automated Nonlinear Image Matching and Anatomical Labelling (ANIMAL), an image registration and labelling method based on image intensity features (Collins et al. 1994). In this method, after correction for intensity non-uniformity, segmented images undergo nonlinear registration to a probabilistic atlas, acquiring an anatomical label for each voxel. The labelled images are then translated back into native space using a reverse transformation to quantify volumes of specific brain regions (Collins et al. 1994). Output measures included volumes of the caudate and putamen, as well as of the ventricles, gray, and white matter of the total cerebrum. A validation study comparing this method with manual segmentation found volumetric differences to be less than 10 % and volumetric overlap to be greater than 85 % (Collins et al. 1994).

Data analysis

Two-sample t-tests will be performed on age, WASI-IQ score, total brain volume, and bilateral striatal volumes between the female and male subgroups. For the whole group, as well as for the male and female subgroups separately,

partial correlations will be calculated between performance on the WASI-IQ and the right and left striatum volumes, adjusting for total brain volumes. Finally, a stepwise multiple regression analysis will be performed with right and left striatal volumes, total brain volumes, and age as predictors and with WASI-IQ score as the dependent measure. The significance level for these analyses was $\alpha<0.008$, after bonferonni correction for multiple comparisons.

Results

There were no significant differences between the female and male subgroups with respect to age or performance on the WASI-IQ, all $t<1$. Total brain and bilateral striatum volumes—calculated by summing left and right caudate and putamen volumes—were significantly larger for male than for female children, $t=10.67$, $p<0.001$ and $t=7.84$, $p<0.001$ respectively. Table 1 presents mean and standard deviation (SD) age, WASI-IQ score, WASI-Verbal, WASI-Performance, total brain volumes and bilateral striatum volumes, for the entire group, as well as for male and female subgroups separately.

Total group: striatal volumes and IQ correlations

Partial correlations were calculated for scores on the WASI-IQ and bilateral striatum, adjusting for total brain volume. These results are presented graphically in Fig. 1. The total brain volume measures were obtained by summing gray matter, white matter, and CSF. The correlation between the WASI-IQ and left striatal volume, correcting for total brain volume, was significant, $r=.155$, $df=300$, $p=.007$, whereas that for WASI-IQ and right striatal volume was not, $r=.098$, $df=300$, $p>.008$. All analyses were also performed correcting for age with no effect on the pattern of findings and consequently are not reported here.

A stepwise multiple regression analysis was also performed with left and right striatal volumes, total brain volumes, and age as predictors and with WASI-IQ score as the dependent measure. Only the volume of left striatum significantly predicted WASI-IQ score [$F(1, 302)=20.56$, $MSe=143.763$, $p<.001$]. Multi-collinearity was assessed. All tolerance scores were >.50 and variance inflation factor (VIF) measures were <5 save for right striatum, which had a tolerance score of .093 and a VIF measure of 9.06, reflecting a high degree of correlation between the right and left striatal volumes.

Male and female subgroups

The data were subsequently analyzed separately for male and female children and areas that significantly correlated with IQ measures for each subgroup are shown in Fig. 1. A significant positive correlation was obtained only for the volumes of the left striatum and scores on the WASI-IQ for male children ($r=.243$, $df=139$, $p=.004$). No other partial correlations were significant, $r=.191$, $df=139$, $p>.008$ for right striatum and WASI-IQ in the male subgroup, $r=.075$, $df=158$, $p>.008$ for left striatum, and $r=.030$, $df=158$, $p>.008$ for right striatum and WASI-IQ in the female subgroup (Tables 2, 3 and 4).

Discussion

In the current study, correcting for total brain volume, left striatal volumes, comprising the caudate nucleus and putamen, correlated significantly with WASI IQ scores, a measure of general cognitive ability, in a large, representative sample of healthy children aged 6 to 18 years. This finding is consistent with the increasingly supported concept that in addition to its long-understood function in movement regulation, the striatum plays an important role in cognition. The striatum is ideally positioned to affect many aspects of behaviour and empirically has been linked to a broad range of cognitive functions.

In our study, left striatum volumes were positively correlated with IQ whereas right striatum volumes were not. Although tempting to conclude that left basal ganglia is

Table 1 Age, IQ, WASI-IQ, and Striatum Volume for the total group and for male and female children separately

	Total ($n=303$)	Male ($n=142$, 47 %)	Female ($n=161$, 53 %)
Age (mean years ± SD)	11.4±3.5	11.6±3.6	11.3±3.5
WASI-IQ (mean score ± SD)	111.1±12.4	111.7±12.8	110.5±12.0
PIQ (mean score ± SD)	109.40±12.71	110.66±12.78	108.29±12.58
VIQ (mean score ± SD)	110.201±13.33	109.93±13.77	110.44±12.98
Caudate Left (mean mm^3 ± SD)	5654.7±550.4	5823.3±508.2	5506.0±544.7
Caudate Right (mean mm^3 ± SD)	5593.5±549.9	5778.2±500.1	5430.7±541.6
Putamen Left (mean mm^3 ± SD)	5295.0±625.8	5551.7±644.2	5068.6±513.2
Putamen Right (mean mm^3 ± SD)	5386.9±632.8	5677.6±629.4	5130.4±515.2

PIQ performance IQ
VIQ verbal IQ

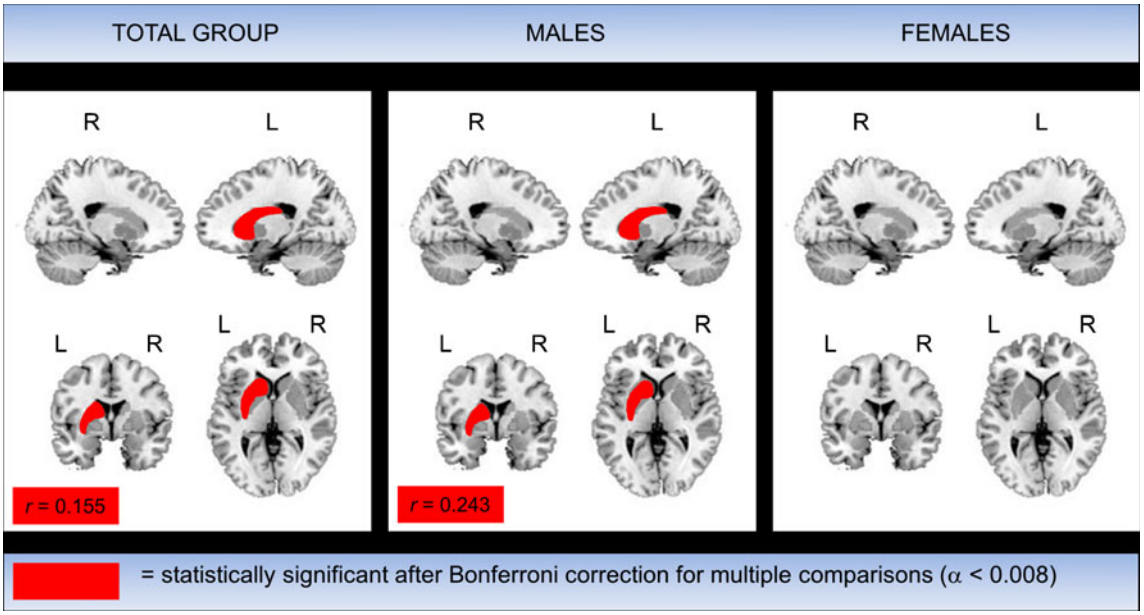

Fig. 1 Significant correlations between WASI IQ and right and left striatum, comprising caudate nucleus and striatum, controlling for total brain volume, are shown in *red* for the total group, as well as for male and female children separately

implicated to a greater extent in general cognition, our results should be viewed in light of previous findings. Overall, studies relating basal ganglia volume to conditions associated with cognitive impairment (Abernethy et al. 2004; Bloch et al. 2005; Carmona et al. 2007; Soliva et al. 2010; Chang et al. 2004; Kesler et al. 2008; Kumar et al. 2009; Peinemann et al. 2005; Reiss et al. 1993; Singer et al. 1993) find no differences comparing right and left basal ganglia. Only Looi and colleagues (2008) found significantly smaller left but not right caudate volumes in patients with dementia relative to controls. These findings are relevant to the findings in our study.

Subgroup analyses, comparing male and female children revealed significant correlations between left striatal volumes and WASI-IQ only for males. There were no correlations between striatal volumes and WASI-IQ scores for female children. Gender differences in cognitive ability (Johnson and Meade 1987), as well as in brain structure analyses (Goldstein et al. 2001; Lenroot et al. 2007) are a common finding. Overall, the literature investigating relations between caudate or putamen volumes and conditions associated with cognitive abnormalities (Abernethy et al. 2004; Chang et al. 2004; Looi et al. 2008; Peinemann et al. 2005) find similar results for male and female subgroups. Compatible with our findings, however, in all cases in the literature where findings are discrepant across genders relating structural striatal properties and cognitive impairments (Kesler et al. 2008; Peterson

Table 2 Correlation matrices between scores on WASI-IQ and subtests and a) total brain, b) left striatum, and c) right striatum for the entire group of children

	WASI-IQ	PIQ	PIQ-Block	PIQ-Matrix	VIQ-Similarity	VIQ-Vocabulary	VIQ	TBV	L Striatum	R Striatum
WASI-IQ	1.000									
PIQ	0.831	1.000								
PIQ-Block	0.695	0.861	1.000							
PIQ-Matrix	0.696	0.795	0.389	1.000						
VIQ-Similarity	0.742	0.357	0.284	0.331	1.000					
VIQ-Vocabulary	0.759	0.403	0.305	0.377	0.535	1.000				
VIQ	0.854	0.425	0.325	0.401	0.881	0.863	1.000			
TBV	0.213	0.249	0.212	0.211	0.106	0.103	0.119	1.000		
L Striatum	0.252	0.254	0.250	0.182	0.195	0.105	0.173	0.632	1.000	
R Striatum	0.209	0.222	0.220	0.155	0.146	0.082	0.134	0.630	0.952	1.000

PIQ performance IQ, *VIQ* verbal IQ, *TBV* total brain volume

Table 3 Correlation matrices between scores on WASI-IQ and subtests and a) total brain, b) left striatum, and c) right striatum for the male children

	WASI-IQ	PIQ	PIQ-Block	PIQ-Matrix	VIQ-Similarity	VIQ-Vocabulary	VIQ	TBV	L Striatum	R Striatum
WASI-IQ	1.000									
PIQ	0.841	1.000								
PIQ-Block	0.714	0.847	1.000							
PIQ-Matrix	0.665	0.783	0.344	1.000						
VIQ-Similarity	0.751	0.386	0.311	0.345	1.000					
VIQ-Vocabulary	0.785	0.452	0.395	0.338	0.555	1.000				
VIQ	0.870	0.471	0.394	0.383	0.884	0.871	1.000			
TBV	0.230	0.289	0.245	0.242	0.111	0.132	0.127	1.000		
L Striatum	0.321	0.300	0.300	0.214	0.297	0.162	0.256	0.515	1.000	
R Striatum	0.279	0.252	0.255	0.183	0.271	0.140	0.232	0.521	0.957	1.000

PIQ performance IQ, *VIQ* verbal IQ, *TBV* total brain volume

et al. 1993; Singer et al. 1993), the association holds for male participants but not for females. Our findings, in line with a number of observations in the literature, could reflect differences in the extent to which striatum mediates cognitive ability in males compared to females. An alternative explanation, however, could relate to the greater variability in basal ganglia volume for the male children in our sample relative to the female subgroup. In fact, there was a statistical trend toward larger variance for the male compared to the female subgroup on the measure of left [$F(160, 141)=0.795$, $p=0.080$] but not right [$F(160, 141)=0.848$, $p>0.150$] striatal volume.

To date, there have been few studies directly relating striatal volume to cognitive performance. None have demonstrated a clear positive relation between striatal volume and a measure of IQ. Our study differed from previous investigations in that our sample size was sufficiently large and, because it was constructed to be representative of the population of the United States, sufficiently diverse to ensure power to detect significant correlations. Lange and colleagues (2010), however, using the same dataset from which our results are derived, failed to demonstrate a significant correlation between total subcortical grey matter volumes, which included thalamus, striatum, and globus pallidus, and IQ. Ostby and colleagues (2009) found that the thalami and basal ganglia structures, comprising caudate, putamen, and globus pallidus, have significantly different developmental trajectories between the ages of 8 and 30 years. Whereas striatal volumes varied linearly with age, there was no relation between the volume of the thalamus and age. By summing the volumes of these subcortical structures, variance unrelated to IQ was increased, decreasing power to detect any true structure-function relations. Further, functions associated with these subcortical structures are unlikely entirely overlapping. These methodological differences potentially explain the discrepancy between our results and those of Lange and colleagues (2010).

Table 4 Correlation matrices between scores on WASI-IQ and subtests and a) total brain, b) left striatum, and c) right striatum for the female children

	WASI-IQ	PIQ	PIQ-Block	PIQ-Matrix	VIQ-Similarity	VIQ-Vocabulary	VIQ	TBV	L Striatum	R Striatum
WASI-IQ	1.000									
PIQ	0.822	1.000								
PIQ-Block	0.678	0.871	1.000							
PIQ-Matrix	0.725	0.807	0.427	1.000						
VIQ-Similarity	0.736	0.333	0.265	0.318	1.000					
VIQ-Vocabulary	0.739	0.366	0.232	0.418	0.516	1.000				
VIQ	0.842	0.390	0.271	0.420	0.878	0.856	1.000			
TBV	0.216	0.185	0.113	0.214	0.146	0.154	0.176	1.000		
L Striatum	0.185	0.176	0.148	0.155	0.127	0.092	0.132	0.582	1.000	
R Striatum	0.140	0.153	0.126	0.131	0.056	0.074	0.083	0.535	0.931	1.000

PIQ performance IQ, *VIQ* verbal IQ, *TBV* total brain volume

Conclusion

Given that volume of brain structures is determined by genetic as well as unique environmental effects (Draganski and May 2008; Haier et al. 2009; Johansson 2004; Ostby et al. 2009), and that the structural changes that determine brain structure volumes are known to improve or impair performance (Draganski and May 2008), studies characterizing structure-function relations have the potential to contribute in an important way to our understanding of the brain regions that underlie cognitive functions. The current study addresses a gap in the current literature by providing evidence of a positive relation between striatal volumes and IQ in a large, representative sample of healthy children, further bolstering the increasingly supported notion that striatum plays an important role in cognitive functions. In addition, our study generates a number of questions to direct future studies; chief among them whether left striatum plays a more primary role in cognition and whether males and females differ with respect to the degree to which the striatum mediates cognitive ability. We intend to explore these questions longitudinally in our sample by examining data from Visits 2 and 3. Investigating these structure-function relations in healthy adults as well as in different patient populations could also further our understanding of the role of the striatum in cognition.

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