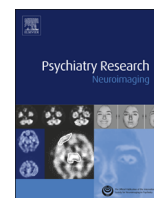




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Pallidum and lateral ventricle volume enlargement in autism spectrum disorder



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ABSTRACT

Studies on structural brain abnormalities in individuals with autism spectrum disorders (ASD) have been of limited size and many findings have not been replicated. In the largest ASD brain morphology study to date, we compared subcortical, total brain (TBV), and intracranial (ICV) volumes between 472 subjects with DSM-IV ASD diagnoses and 538 healthy volunteers (age range: 6–64 years), obtained from high-resolution structural brain scans provided by the Autism Brain Imaging Data Exchange (ABIDE). Compared to healthy volunteers, we found significantly larger pallidum (Cohen's $d=0.15$) and lateral ventricle volumes (Cohen's $d=0.18$) in ASD. These enlargements were independent of total brain volume and IQ, passed FDR correction for multiple comparisons, and were observed in overall, male-only, and medication-free subjects. In addition, intracranial, hippocampal, and caudate volumes were enlarged in ASD at a nominal statistical threshold of $p < 0.05$. This study provides the first robust evidence for pallidum enlargement in ASD independent from TBV and encourages further study of the functional role of the pallidum in individuals with autism spectrum disorder.

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1. Introduction

Autism spectrum disorders (ASD) –as defined by the DSM-IV– comprise a range of developmental disorders, including Autistic Disorder, Asperger's Syndrome and Pervasive Developmental Disorder Not Otherwise Specified (Levy et al., 2009), characterized by social, communication, and stereotypical behaviors and/or interests. However, the recently published DSM-5 no longer includes these three sub diagnoses and characterizes ASD by two criteria: 1) social communication/interaction and 2) restricted and repetitive behavior symptoms (Hyman, 2013).

Brain morphological abnormalities have been observed in autism spectrum disorders but studies are mostly small and their findings inconsistent (Amaral et al., 2008). A meta-analysis of region of interest (ROI) brain volumes showed larger total brain (TBV), intracranial (ICV), cerebral hemispheres, cerebellum, and caudate volumes as well as smaller corpus callosum volumes in ASD subjects compared to healthy controls; with the number of

patients and controls in the individual studies ranging from between 6 and 67 patients and 8–83 controls, respectively (Stanfield et al., 2008). In addition, one recent study showed larger putamen volume in 29 adults (ages 18–46) with ASD compared with 29 healthy controls (Sato et al., 2014) and another showed smaller pallidum volumes in 72 children (ages 4–18) with ASD compared with 138 healthy children (Sussman et al., 2015).

To address the issue of small sample sizes in ASD brain imaging studies, the Autism Brain Imaging Data Exchange (ABIDE, http://fcon_1000.projects.nitrc.org/indi/abide) made available a collection of 20 international data sets including high-resolution structural imaging and resting state functional magnetic resonance imaging (rsfMRI) of ASD patients and healthy volunteers. Initial findings comparing brain connectivity (Di Martino et al., 2013), cortical thickness (Valk et al., 2015), corpus callosum size (Lefebvre et al., 2015), and region of interest volumes (Haar et al., 2014) between ASD subjects and controls using ABIDE data have been published. With regard to subcortical volumes, the ABIDE studies found evidence for enlarged ventricular volumes and a smaller central segment of the corpus callosum (Haar et al., 2014); though the latter was not replicated in a second study (Lefebvre et al., 2015).

Given limited comprehensive examination of subcortical

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volumes in the ASD literature and in the ABIDE sample, as well as meta-analytic evidence for subcortical volume (caudate) enlargement in ASD (Stanfield et al., 2008), here we examined total brain, intracranial, and subcortical volumes in 472 ASD patients and 538 healthy volunteers (ages 6–64 years old) with brain imaging data obtained from the ABIDE. Based on a meta-analysis (Stanfield et al., 2008), we hypothesized larger TBV, ICV, lateral ventricle, and caudate volumes in individuals with ASD compared with healthy volunteers.

2. Methods

2.1. Subjects

This study includes 472 (mean age \pm SD = 17.7 \pm 8.6, 418 males) subjects with a DSM-IV-TR ASD diagnosis and 538 healthy volunteers (HV; mean age \pm SD 17.3 \pm 7.7, 443 males) with high-resolution T1-weighted imaging data. The patient and control groups were similar in mean age and handedness distribution but the ASD group included a higher proportion of males, had lower IQ, lower social skills, and higher proportion of medication use (see Table 1). Analysis of the anonymous ABIDE data was approved as non-human subjects research by the University of California, Irvine Institutional Review Board.

2.2. Image acquisition

One-thousand-one-hundred-and-two, anonymous, high-resolution, whole brain, structural imaging scans were downloaded from the ABIDE website (http://fcon_1000.projects.nitrc.org/indi/abide). The ABIDE structural imaging scans were acquired at 20 sites using a variety of scanners and acquisition protocols (for summary of scan parameters, see Table 1S available online).

2.3. Quality assurance and image processing

Based on visual inspection of the T1-weighted images, blind to diagnosis (only subject identifiers were known at time of visual inspection), we excluded 84 out of the 1102 scans due to significant motion artifacts (see Table 10S). FreeSurfer failed to complete recon-all and extract subcortical volumes on an additional 8 scans resulting in a total of 92 excluded scans (see Table 10S). Left and right lateral ventricle, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens volumes as well as total brain and intracranial volumes (Table 2) were obtained using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>, Version 5.1.0).

Table 1

Sample demographics.

	Autism spectrum disorder (n=472)	Healthy volunteers (n=538)	Statistics
DSM-IV-TR Diagnosis			
Autism	304		
Aspergers Syndrome (AS)	86		
PDD-NOS	35		
AS or PDD-NOS	5		
Sex (M/F)	418/54	443/95	$\chi^2_1 = 7.73, p = 0.005$
Age at Scan in Years (SD)	17.7 (8.6)	17.3 (7.7)	$t_{1008} = 0.83, p = 0.41$
Handedness (L/R/M/A)	32/277/3/8	29/334/3/5	$\chi^2_3 = 2.41, p = 0.49$
FSIQ (SD)	106.02 (16.9)	111.37 (12.3)	$t_{938} = -5.61, p < 0.0001$
VIQ (SD)	104.83 (18.1)	111.56 (13.0)	$t_{829} = -6.21, p < 0.0001$
PIQ (SD)	105.62 (16.9)	108.20 (13.2)	$t_{841} = -2.49, p = 0.01$
FSIQ (SD) Autism	103.78 (15.6)	111.37 (12.3)	$t_{776} = -7.29, p < 0.0001$
FSIQ (SD) AS	112.86 (16.1)	111.37 (12.3)	$t_{568} = -1.04, p = 0.30$
FSIQ (SD) PDD-NOS	100.97 (21.2)	111.37 (12.3)	$t_{520} = -4.22, p < 0.0001$
ADI ^a -R Social (SD)	19.77 (5.6)	...	
ADI ^a -R Verbal (SD)	15.93 (4.66)	...	
ADI ^a -R RRB	6.03 (2.6)		
Vineland ^b Social	75.10 (1.8)	111.72 (2.3)	$t_{108} = 12.84, p < 0.0001$
Vineland ^b Communication (SD)	78.60 (15.5)		
Vineland ^b ABC	77.09 (1.6)	108.53 (2.0)	$t_{108} = 12.64, p < 0.0001$
Medication Status (taking/not taking)	108/232	2/391	$\chi^2_1 = 139.62, p < 0.0001$

PDD-NOS: Pervasive Developmental Disorder – Not Otherwise Specified

Handedness: L=Left; R=Right, M=Mixed; A=Ambidextrous

FSIQ=Full Scale Intelligence Quotient; VIQ=Verbal Intelligence Quotient; PIQ=Performance Intelligence Quotient

^a ADI=Autism Diagnostic Interview-Revised (Rutter et al., 2008)

^b Vineland=Vineland Adaptive Behavioral Scale (Cabrera et al., 1999)

Table 2
Absolute Volumes.

Region	Autism spectrum disorder (n=472)	Healthy volunteer (n=538)
Hippocampus		
Left	4234(561)	4167 (494)
Right	4302(536)	4221 (512)
Amygdala		
Left	1759 (316)	1717 (285)
Right	1823 (304)	1795 (306)
Caudate		
Left	4140 (595)	4074 (560)
Right	4240 (625)	4186 (570)
Putamen		
Left	6821 (878)	6748 (832)
Right	6541 (882)	6441 (805)
Pallidum		
Left	2020 (277)	1974 (254)
Right	1808 (258)	1776 (241)
Thalamus		
Left	7501 (895)	7485 (813)
Right	7651 (876)	7611 (832)
Lateral ventricle		
Left	6143 (3614)	5428 (3110)
Right	5696 (3468)	5011 (2844)
Nucleus accumbens		
Left	797 (171)	779 (170)
Right	818 (174)	800 (169)
Total brain volume	1224 (132)	1213 (120)
Intracranial volume	1383 (239)	1365 (220)

The absolute volumes are presented as mean mm³ (SD) except for the Total brain volume which is presented as mean cm³ (SD).

Methods used to obtain subcortical volumes have been described in previous publications (Fischl et al., 2002; Fischl, 2012). After FreeSurfer analysis, all regions of interest with a volume larger or smaller than 1.5 times the inter quartile range (IQR) were identified and visually inspected by overlaying them on the subject's anatomical images. Based on these inspections, between 0 and 5 data points for each of the regions were removed from the final analyses due to poor segmentation (see Table 11S). All data exclusions were based on consensus of visual inspections performed by authors AHT and TGMvE.

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