Subcortical Morphometric Differences and Heterogeneity in Autism Spectrum Disorder

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David N. MacDonald[1,2], Saashi A. Bedford[1,2,8], Emily Olafson[2,3], Min Tae M. Park[4], Gabriel A. Devenyi[2,5], Stephanie Tullo[1,2], Raihaan Patel[2,6], Evdokia Anagnostou[7], Simon Baron-Cohen[8], Edward T. Bullmore[9], Lindsay R. Chura[8], Michael C. Craig[10,11], Christine Ecker[10,12], Dorothea L. Floris[8,13], Rosemary J. Holt[8], Rhoshel Lenroot[14], Jason P. Lerch[15,16,17], Michael V. Lombardo[8,18], Declan G. M. Murphy[10], Armin Raznahan[19], Amber N. V. Ruigrok[8], Elizabeth Smith[20], Russell T. Shinohara[21, 22], Michael D. Spencer[8], John Suckling[9], Margot J. Taylor[23], Audrey Thurm[20], MRC AIMS Consortium, Meng-Chuan Lai[8,15,24,25,26], M. Mallar Chakravarty[1,2,5,6]

1. Integrated Program in Neuroscience, McGill University; 2. Cerebral Imaging Centre, Douglas Mental Health University Institute; 3. Department of Neuroscience, Weill Cornell Graduate School of Medical Sciences; 4. Department of Psychiatry, Schulich School of Medicine and Dentistry, Western University; 5. Department of Psychiatry, McGill University; 6. Department of Biological and Biomedical Engineering, McGill University; 7. Holland Bloorview Kids Rehabilitation Hospital; 8. Autism Research Centre, Department of Psychiatry, University of Cambridge; 9. Brain Mapping Unit, Department of Psychiatry, University of Cambridge; 10. Institute of Psychiatry, Psychology and Neuroscience, King's College London; 11. National Autism Unit, Bethlem Royal Hospital, London, UK, 12. Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, Goethe University; 13. Hassenfeld Children's Hospital at NYU Langone Department of Child and Adolescent Psychiatry, Child Study Center; 14. Dept. of Psychiatry and Behavioral Sciences, University of New Mexico; 15. Program in Neurosciences and Mental Health, The Hospital for Sick Children; 16. Department of Medical Biophysics, University of Toronto; 17. Wellcome Centre for Integrative Neuroimaging, University of Oxford; 18. Department of Psychology, University of Cyprus; 19. Developmental Neurogenomics Unit, Human Genetics Branch, National Institute of Mental Health; 20. Section on Behavioral Pediatrics, National Institute of Mental Health; 21. Penn Statistics in Imaging and Visualization Center, Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania; 22. Center for Biomedical Image Computing and Analytics, Department of Radiology, Perelman School of Medicine, University of Pennsylvania; 23. Diagnostic Imaging, The Hospital for Sick Children; 24. The Margaret and Wallace McCain Centre for Child, Youth & Family Mental Health and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health; 25. Department of Psychiatry, University of Toronto; 26. Department of Psychiatry, National Taiwan University Hospital and College of Medicine

Introduction

- The striatum, thalamus, and globus pallidus are critical mediators of behaviours affected in Autism Spectrum Disorder (ASD)
- Neuroanatomical ASD studies have produced inconsistent and contradictory results[1].
- We examined volume and shape differences in ASD using a large (n=3145), cross-sectional dataset of structural MRI scans.
- We studied the impact of sex, age, and intelligence quotient (IQ) in neuroanatomical heterogeneity in ASD

Methods

- Rigorous motion & segmentation quality control (QC)
- MAGeTbrain[2] segmentation of bilateral thalamus, striatum and globus pallidus.
- Reducing impact of site effects
  - Identical processing and segmentation for all scans
  - Per-site data processing and analysis
  - Prospective, random-effects meta-analysis to pool effect sizes measures.[3]
- Structure volume, vertex wise surface area and displacement (convexity) models:
  - Multiple linear regression, controlling for structure volume/total brain volume (TBV), age, sex, IQ
  - Vertex-wise regression and meta-analysis at 3000-13 000 vertices per structure
  - Corrected for multiple comparisons with FDR at .05
- Assessed the importance of age, sex, and IQ with AIC

Data

- 3145 T1w scans from 5 datasets, 33 sites.
- Sites with fewer than 4 females in either group after motion QC were excluded.

Name*	# Sites	Age (IQ)	Total ASD M	Total ASD F	Total Control M	Total Control F	# Sites	Included after QC ASD M	Included after QC ASD F	Included after QC Control M	Included after QC Control F
ABIDE I & II	28	5-64 (49-148)	880	137	854	274	7	194	46	268	135
UK-AIMS	2	18-52 (73-137)	72	54	73	54	2	56	46	69	56
CFSA	1	12-18 (73-146)	39	17	20	20	1	19	13	11	14
Toronto	1	4-65 (69-149)	106	25	196	194	1	69	20	148	166
NIMH	1	2-9 (N/A)	68	17	29	16	0				
Total	**33**	**2-65 (49-149)**	**1135**	**250**	**1172**	**558**	**11**	**338**	**125**	**496**	**371**
			1415		**1730**			**463**		**867**	
Grand Total			**3145**					**1330**			

* ABIDE: Autism Brain Imaging Data Exchange, Releases I and II[4,5]
* NIMH: National Institute of Mental Health (USA)
* Toronto: The Hospital for Sick Children (Canada)
* CFSA: Cambridge Family Study of Autism (UK)
* UK-AIMS: UK Medical Research Council Autism Imaging Multicentre Study

Results

- Between 1045 and 1318 scans, from 11 sites, passed segmentation QC, depending on structure.
- All figures show Hedges' *g** effect sizes, pooled across sites using random effects meta-analysis, with multiple comparisons correction using the False Discovery Rate (FDR) at .05. Cool colours represent negative effects; warm colours are positive.

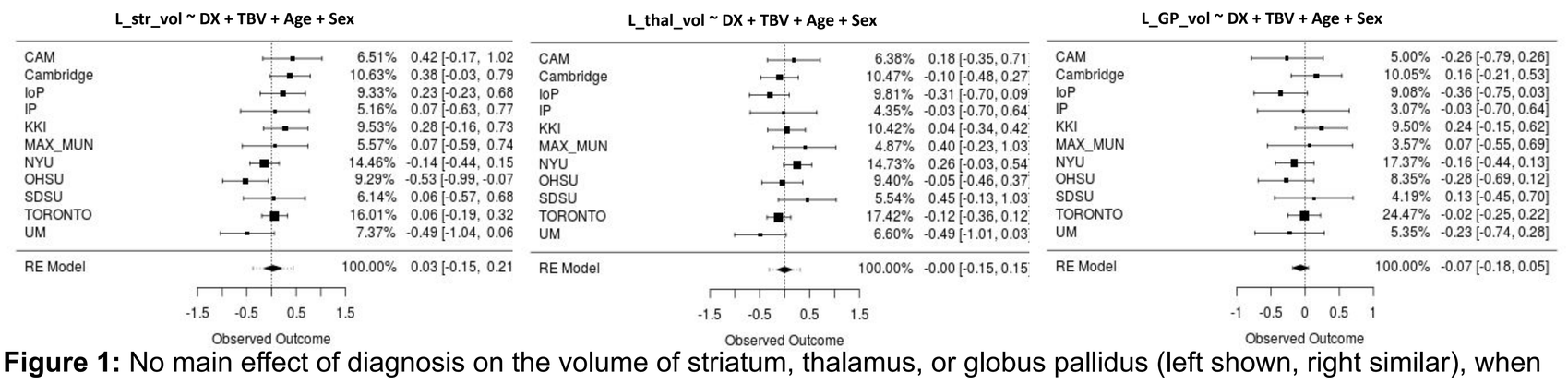

Figure 1: No main effect of diagnosis on the volume of striatum, thalamus, or globus pallidus (left shown, right similar), when controlling for TBV, age and sex. Results were similar with FIQ, and in sex-stratified, age-centered, and IQ-centered analyses.

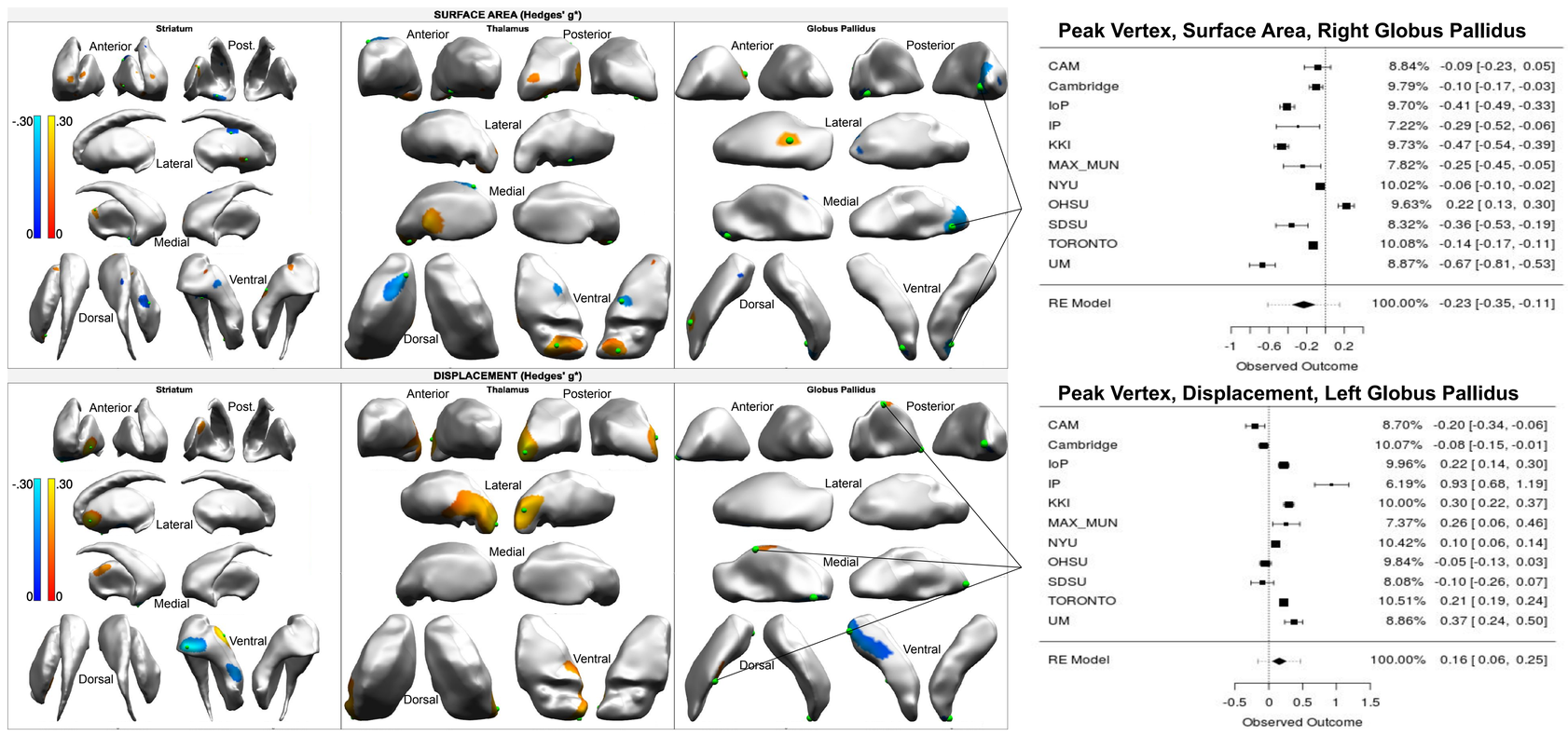

Figure 2: Main effect of diagnosis on vertex-wise surface area (top) and displacement (bottom) in striatum, thalamus, and globus pallidus. Green spheres indicate vertices with peak effect sizes. Forest plots show meta-analytic results at sample peak vertices for pallidal surface area (negative, top) and pallidal displacement (positive, bottom).

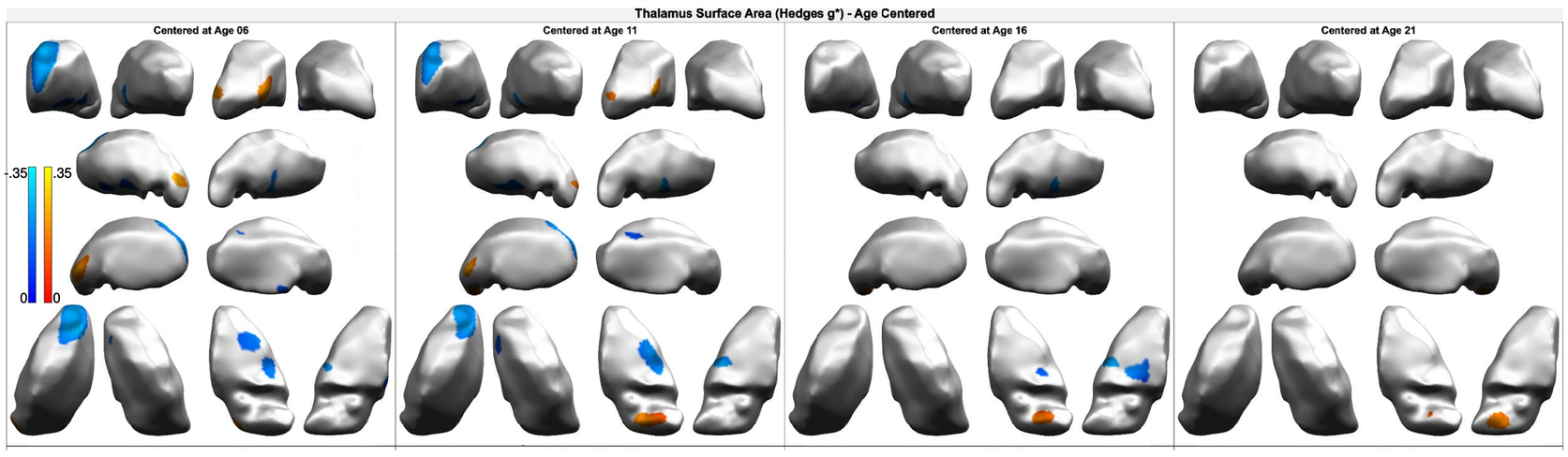

Figure 3: Main effect of diagnosis on vertex-wise surface area in the thalamus at 5 year intervals from age 6 to age 21 (striatum and globus pallidus not shown, ages 31-61 not shown). IQ-centered and sex-stratified analyses not shown, as AIC-based model selection indicated that IQ and sex improved model fit at fewer than 50% of vertices in all structures.

Conclusions

- No evidence of an effect of ASD diagnosis on striatal, thalamic, or pallidal volume was found, when controlling for TBV, age, and sex, or when also controlling for FIQ.
- Sex-stratified, age-centered, and IQ-centered analyses similarly showed no evidence of a main effect of ASD diagnosis on structure volume.
- Localized effects of ASD diagnosis on surface area and displacement (convexity/concavity) were detected that were not apparent in volumetric analysis.
- Age was an important source of neuroanatomical heterogeneity in ASD in the striatum, thalamus, and globus pallidus. This effect was not apparent when analyzing only structure volumes. At most vertices, AIC-based model selection did not indicate a similar role for sex or IQ.
- The localized effects of ASD diagnosis on surface-based measures are highly age-dependent, and are more pronounced in childhood and adolescence.

Acknowledgements and References

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