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Subcortical brain volume, regional cortical thickness, and cortical surface area across disorders: findings from the ENIGMA ADHD, ASD, and OCD Working Groups

Article

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Boedhoe, P. S. W., van Rooij, D., Hoogman, M., Twisk, J. W. R., Schmaal, L., Abe, Y., Alonso, P., Ameis, S. H., Anikin, A., Anticevic, A., Aherson, P., Arango, C., Arnold, P. D., Assogna, F., Auzias, G., Banaschewski, T., Baranov, A., Batistuzzo, M. C., Baumeister, S., Baur-Streubel, R., Behrmann, M., Bellgrove, M. A., Benedetti, F., Beucke, J. C., Biederman, J., Bollettini, I., Bose, A., Bralten, J., Bramati, I. E., Brandeis, D., Brem, S., Brennan, B. P., Busatto, G. F., Calderoni, S., Calvo, A., Calvo, R., Castellanos, F. X., Cercignani, M., Chaim-Avancini, T. M., Chantiluke, K. C., Cheng, Y., Cho, K. I. K., Christakou, A. ORCID: https://orcid.org/0000-0002-4267-3436, Coghill, D., Conzelmann, A., Cubillo, A. I., Dale, A. M., Dallaspezia, S., Daly, E., Denys, D., Deruelle, C., Di Martino, A., Dinstein, I., Doyle, A. E., Durston, S., Earl, E. A., Ecker, C., Ehrlich, S., Ely, B. A., Epstein, J. N., Ethofer, T., Fair, D. A., Fallgatter, A. J., Faraone, S. V., Fedor, J., Feng, X., Feusner, J. D., Fitzgerald, J., Fitzgerald, K. D., Fouche, J.-P., Freitag, C. M., Fridgeirsson, E. A., Frodl, T., Gabel, M. C., Gallagher, L.,

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Gogberashvili, T., Gori, I., Gruner, P., Gürsel, D. A., Haar, S., Haavik, J., Hall, G. B., Harrison, N. A., Hartman, C. A., Heslenfeld, D. J., Hirano, Y., Hoekstra, P. J., Hoexter, M. Q., Hohmann, S., Høvik, M. F., Hu, H., Huyser, C., Jahanshad, N., Jalbrzikowski, M., James, A., Janssen, J., Jaspers-Fayer, F., Jernigan, T. L., Kapilushniy, D., Kardatzki, B., Karkashadze, G., Kathmann, N., Kaufmann, C., Kelly, C., Khadka, S., King, J. A., Koch, K., Kohls, G., Kohls, K., Kuno, M., Kuntsi, J., Kvale, G., Kwon, J. S., Lázaro, L., Lera-Miguel, S., Lesch, K.-P., Hoekstra, L., Liu, Y., Lochner, C., Louza, M. R., Luna, B., Lundervold, A. J., Malpas, C. B., Marques, P., Marsh, R., Martínez-Zalacaín, I., Mataix-Cols, D., Mattos, P., McCarthy, H., McGrath, J., Mehta, M. A., Menchón, J. M., Mennes, M., Martinho, M. M., Moreira, P. S., Morer, A., Morgado, P., Muratori, F., Murphy, C. M., Murphy, D. G.M., Nakagawa, A., Nakamae, T., Nakao, T., Namazova-Baranova, L., Narayanaswamy, J. C., Nicolau, R., Nigg, J. T., Novotny, S. E., Nurmi, E. L., Weiss, E. O., O'Gorman Tuura, R. L., O'Hearn, K., O'Neill, J., Oosterlaan, J., Oranje, B., Paloyelis, Y., Parellada, M., Pauli, P., Perriello, C., Piacentini, J., Piras, F., Piras, F., Plessen, K. J., Puig, O., Ramos-Quiroga, J. A., Janardhan Reddy, Y. C., Reif, A., Reneman, L., Retico, A., Rosa, P. G.P., Rubia, K., Rus, O. G., Sakai, Y., Schrantee, A., Schwarz, L., Schweren, L. J. S., Seitz, J., Shaw, P., Shook, D., Silk, T. J., Simpson, H. B., Skokauskas, N., Soliva Vila, J. C., Solovieva, A., Soreni, N., Soriano-Mas, C., Spalletta, G., Stern, E. R., Stevens, M. C., Stewart, S. E., Sudre, G., Szeszko, P. R., Tamm, L., Taylor, M. J., Tolin, D. F., Tosetti, M., Tovar-Moll, F., Tsuchiyagaito, A., van Erp, T. G. M., van Wingen, G. A., Vance, A., Venkatasubramanian, G., Vilarroya, O., Vives-Gilabert, Y., von Polier, G. G., Walitza, S., Wallace, G. L., Wang, Z., Wolfers, T., Yoncheva, Y. N., Yun, J.-Y., Zanetti, M. V., Zhou, F., Ziegler, G. C., Zierhut, K. C., Zwiers, M. P., Thompson, P. M., Stein, D. J., Buitelaar, J., Franke, B. and van den Heuvel, O. A. (2020) Subcortical brain volume, regional cortical thickness, and cortical surface area across disorders: findings from the ENIGMA ADHD, ASD, and OCD

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The American Journal of Psychiatry

Subcortical brain volume, regional cortical thickness and cortical surface area across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) – findings from the ENIGMA-ADHD, -ASD, and -OCD working groups

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Complete List of Authors:	Boedhoe, Premika; VU medisch centrum School of Medical Sciences, Department of Psychiatry; VU medisch centrum School of Medical Sciences, Department of Anatomy & Neurosciences van Rooij, Daan; Donders Centre for Cognitive Neuroimaging, Radboud University Medical Center, Cognitive Neuroscience Hoogman, Martine; Radboud university medical centre, Human Genetics; Radboud University Donders Institute for Brain Cognition and Behaviour Twisk, Jos; Amsterdam UMC Vrije Universiteit, Department of Epidemiology and Biostatistics Schmaal, Lianne; Orygen, The National Centre of Excellence in Youth Mental Health, ; The University of Melbourne, Centre for Youth Mental Health Abe, Yoshinari; 4. Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine Alonso, Pino; Hospital de Bellvitge, Department of Psychiatry; Centro de Investigación Biomèdica en Red de Salud Mental-CIBERSAM; University of Barcelona, Department of Clinical Sciences Ameis, Stephanie; The Margaret and Wallace McCain Centre for Child, Youth & Family Mental Health, Campbell Family Mental Health Research Institute, The Centre for Addiction and Mental Health, Department of Psychiatry; The Hospital for Sick Children, Centre for Brain and Mental Health Anikin, Anatoly; National Medical Research Center for Children's Health, Department of magnetic resonance imaging and densitometry, Moscow Anticevic, Alan; Yale University, Psychiatry Arango, Celso; Instituto de Investigación Sanitaria Gregorio Marañón, IiSGM. Hospital General Universitario Gregorio Marañón, CIBERSAM,, Child and Adolescent Psychiatry Arnold, Paul; Cumming School of Medicine, University of Calgary, The Mathison Centre for Mental Health Research and Education; Cumming School of Medicine, University of Calgary, Department of Psychiatry Asherson, Phil; King's College London, Social, Genetic and Developmental Psychiatry Centre; Institute of Psychiatry, Psychology and Neuroscience Assogna, Francesca; IRCCS Santa Lucia Foundation, Department of

	Clinical and Behavioral Neurology, Laboratory of Neuropsychiatry Auzias, Guillaume ; Aix Marseille Université, Institut de Neurosciences de la Timone Banaschewski, Tobias; Central Institute of Mental Health, Department of Child and Adolescent Psychiatry and Psychotherapy Baranov, Alexander; Russian Academy of Sciences, Central Clinicl Hospital Batistuzzo, Marcelo; Hospital das Clinicas, IPQ HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Departamento e Instituto de Psiquiatria Baumeister, Sarah; Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Department of Child and Adolescent Psychiatry and Psychotherapy Baur, Ramona; University of Würzburg, Institute of Psychology Behrmann, Marlene; Carnegie Mellon University, Department of Psychology Bellgrove, Mark; Monash University, Monash Institute for Cognitive and Clinical Neurosciences (MICCN) and School of Psychological Sciences Benedetti, Francesco; Istituto Scientifico Universitario Ospedale San Raffaele, Division of Neuroscience, Psychiatry and Clinical Psychobiology Beucke, Jan; Humboldt-Universität zu Berlin, Department of Psychology Biederman, Joseph; Massachusetts General Hospital, Department of Psychiatry, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD; Harvard Medical School, Department of Psychiatry Bollettini, Irene; Scientific Institute Ospedale San Raffaele, Division of Neuroscience, Clinical Research Group Psychiatry and Clinical Psychobiology Bose, Anushree; NIMHANS, Department of Psychiatry, Obsessive-Compulsive Disorder (OCD) Clinic Bralten, Janita; Radboud University Medical Center, Department of Human Genetics; Donders Institute for Brain, Cognition and Behaviour, Radboud University Bramati, Ivanei; D'Or Institute for Research and Education (IDOR), Brandeis, Daniel; Psychiatric University Hospital Zurich, Department of Child and Adolescent Psychiatry and Psychotherapy; Heidelberg University, Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health; University of Zurich and ETH Zurich, Neuroscience Center Zurich Brem, Silvia; Psychiatric Hospital, University of Zurich, Department of Child and Adolescent Psychiatry and Psychotherapy; University of Zurich and ETH Zurich, Neuroscience Center Zurich Brennan, Brian; McLean Hospital/Harvard Medical School, Biological Psychiatry Laboratory Busatto, Geraldo; University of São Paulo Medical School, Laboratory of Psychiatric Neuroimaging (LIM21), Hospital das Clinicas HCFMUSP; University of Sao Paulo Medical School, Department and Institute of Psychiatry; University of Sao Paulo, Center for Interdisciplinary Research on Applied Neurosciences (NAPNA) Calderoni, Sara; IRCCS Fondazione Stella Maris; University of Pisa, Department of Clinical and Experimental Medicine Calvo, Anna; IDIBAPS, Magnetic Resonance Image Core Facility Calvo, Rosa; Institute of Neurosciences, Hospital Clínic Universitari, Department of Child and Adolescent Psychiatry and Psychology; University of Barcelona, Department of Medicine; Centro de Investigación Biomédica en red de Salud Mental (CIBERSAM) Castellanos, Francisco; Hassenfeld Children's Hospital, Department of Child and Adolescent Psychiatry; Nathan S Kline Institute for Psychiatric Research Cercignani, Mara; Brighton& Sussex Medical School, Department of Neuroscience

Chaim-Avancini, Tiffany; Universidade de Sao Paulo Faculdade de Medicina, Department and Institute of Psychiatry, Laboratory of Psychiatric Neuroimaging (LIM-21); University of São Paulo, Center for Interdisciplinary Research on Applied Neurosciences (NAPNA)
Chantiluke, Kaylita; Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London
Cheng, Yuqi; First affiliated hospital of Kunming medical university, Department of Psychiatry
Cho, Kang Ik; Seoul National University College of Natural Sciences
Christakou, Anastasia; King's College London, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience; University of Reading, School of Psychology and Clinical Language Sciences
Coghill, Prof David; University of Melbourne, Departments of Paediatrics and Psychiatry; Murdoch Childrens Research Institute; University of Dundee, Division of Neuroscience
Conzelmann, Annette; University of Tübingen, Department of Child and Adolescent Psychiatry and Psychotherapy; University of Wurzburg, Department of Biological Psychology, Clinical Psychology and Psychotherapy
Cubillo, Ana; Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London; University of Zurich, Jacobs Center for Productive Youth Development, Zurich Center for Neuroeconomics
Dale, Anders; University of California, Departments of Neurosciences and Radiology; University of California, Center for Multimodal Imaging and Genetics (CMIG)
Dallaspezia, Sara; Istituto Scientifico Universitario Ospedale San Raffaele, Division of Neuroscience, Psychiatry and Clinical Psychobiology
Daly, Eileen; King’s College London, Institute of Psychiatry, Department of Forensic and Neurodevelopmental Sciences London
Denys, Damiaan; Amsterdam UMC, University of Amsterdam, Department of Psychiatry; Netherlands Institute for Neuroscience
DeRuelle, Christine; Aix-Marseille Université, nstitut de Neurosciences de la Timone
Di Martino, Adriana; The Child Mind Institute, Autism Center
Dinstein, Ilan; Ben-Gurion University of the Negev, Department of Psychology and Zlotowski Center for Neuroscience
Doyle, Alysa; Harvard Medical School, Massachusetts General Hospital, Center for Genomic Medicine; Harvard Medical School, Department Of Psychiatry
Durston, Sarah; UMC Utrecht, Brain Center Rudolf Magnus, Department of Psychiatry
Earl, Eric; Department of Behavioral Neuroscience, Oregon Health & Science University, Portland OR, USA
Ecker, Christine; Goethe-Universitat Frankfurt am Main, Department of Child and Adolescent Psychiatry Psychosomatics and Psychotherapy ; University of Southern California, Imaging Genetics Center, Mark & Mary Stevens Institution for Neuroimaging & Informatics
Ehrlich, Stefan; TU Dresden Faculty of Medicine Carl Gustav Carus, Division of Psychological and Social Medicine and Developmental Neurosciences; TU Dresden Faculty of Medicine Carl Gustav Carus, Department of Child and Adolescent Psychiatry, Eating Disorders Research and Treatment Center
Ely, Benjamin; Icahn School of Medicine at Mount Sinai, Department of Neurosciences
Epstein, Jeff; Cincinnati Children's Hospital Medical Center, Division of Behavioral Medicine and Clinical Psychology; Cincinnati Children's Hospital Medical Center, Pediatrics
Ethofer, Thomas; Department of Psychiatry and Psychotherapy,

	University Hospital of Tübingen; University of Tuebingen, Department of Biomedical Magnetic Resonance Duran, Fabio; University of São Paulo Hospital of Clinics of the Medical School Institute of Psychiatry, Department and Institute of Psychiatry, Laboratory of Psychiatric Neuroimaging (LIM-21); University of São Paulo, Center for Interdisciplinary Research on Applied Neurosciences (NAPNA) Fair, Damien; Oregon Health and Science University, Department of Behavioral Neuroscience; Oregon Health and Science University, Department of Psychiatry Fallgatter, Andreas; University of Tuebingen, Psychiatry and Psychotherapy; University of Tuebingen, LEAD Graduate School Faraone, Stephen; State University of New York Upstate Medical University, the Department of Psychiatry and of Neuroscience and Physiology Fedor, Jennifer; University of Pittsburgh, Pittsburgh, PA, USA, Department of Psychiatry Feng, Xin; Jilin University, BioKnow Health Informatics Lab, College of Computer Science and Technology, and Key Laboratory of Symbolic Computation and Knowledge Engineering of Ministry of Education Feusner, Jamie; UCLA, Department of Psychiatry and Biobehavioral Sciences Fitzgerald, Jacqueline; Trinity College Dublin, Psychiatry ; Trinity College Institute of Neuroscience Fitzgerald, Kate; University of Michigan, Department of Psychiatry Fouche, Jean-Paul; University of Cape Town, Department of Psychiatry and Mental Health Freitag, Christine; JW Goethe University, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Fridgeirsson, Egill; Amsterdam UMC, University of Amsterdam, Department of Psychiatry Frodl, Thomas; Otto von Guericke University Magdeburg, Department of Psychiatry and Psychotherapy; Trinity College Dublin, Department of Psychiatry; German Centre for Neurodegenerative Diseases Gabel, Matt; Department of Neuroscience, Brighton and Sussex Medical School, Falmer, Brighton Gallagher, Louise; Trinity College Dublin, Department of Psychiatry; Trinity College, The Trinity College Institute of Neuroscience Gogberashvili, Tinatin; National Medical Research Center for Children's Health, Laboratory of Neurology and Cognitive Health, Moscow Gori, Ilaria; National Institute for Nuclear Physics, Pisa Division Gruner, Patricia; Yale University School of Medicine, Department of Psychiatry Gürsel, Deniz; Klinikum rechts der Isar, Technische Universität München, Department of Neuroradiology; Technische Universität München, TUM-Neuroimaging Center (TUM-NIC) of Klinikum rechts der Isar Haar, Shlomi; Imperial College London, Department of Bioengineering Haavik, Jan; K.G.Jebsen Centre for Neuropsychiatric Disorders, University of Bergen, Biomedicine; Haukeland University Hospital, Division of Psychiatry Hall, Geoffrey; McMaster University, Department of Psychology Harrison, Neil; Brighton and Sussex Medical School, Department of Neuroscience; Sussex Partnership NHS Foundation Trust Hartman, Catharina; University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE) Heslenfeld, Dirk; VU University Amsterdam, Faculty of Behavioral and Movement Sciences Hirano, Yoshiyuki; Chiba University, Research Center for Child Mental Development Hoekstra, Liesbeth; Donders Institute for Brain, Cognition and Behavior,

	Radboud University Medical Centre, Department of Cognitive Neuroscience; Karakter Child and Adolescent Psychiatry, Radboud University Medical Centre Hoekstra, Pieter; University Medical Center Groningen, Department of Child and Adolescent Psychiatry Hoexter, Marcelo; University of São Paulo Medical School, Departamento e Instituto de Psiquiatria do Hospital das Clinicas, IPQ HCFMUSP Hohmann, Sarah; Central Institute of Mental Health, Clinical Faculty Mannheim, University of Heidelberg, Mannheim, Department of Child and Adolescent Psychiatry and Psychotherapy Høvik, Marie; University of Bergen, Dept. of Clinical Medicine, Faculty of Medicine and Health Sciences; Haukeland University Hospital, Department of Psychiatry Hu, Hao; Shanghai Jiao Tong University School of Medicine, Shanghai Mental Health Center Huyser, Chaim; De Bascule, Academic Center for Child and Adolescent Psychiatry; Amsterdam UMC, University of Amsterdam, Department of Child and Adolescent Psychiatry Jahanshad, Neda; Imaging Genetics Center, Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, Marina del Rey, CA, 90292 jalbrzikowski, maria; University of Pittsburgh School of Medicine, Department of Psychiatry James, Anthony; Univeristy of Oxford, Department of Psychiatry Janssen, Joost; Gregorio Marañón General University Hospital, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM, Department of Child and Adolescent Psychiatry Jaspers-Fayer, Fern; University of British Columbia, Department of Psychiatry Jernigan, Terry; University of California, San Diego, Center for Human Development Kapilushniy, Dmitry; National Medical Research Center for Children's Health, Department of Information Technologies Kardatzki, Bernd; University of Tuebingen, Department of Biomedical Magnetic Resonance Karkashadze, Georgii; National Medical Research Center for Children's Health, Laboratory of Neurology and Cognitive Health, Moscow Kathmann, Norbert; Humboldt University Berlin, Department of Psychology Kaufmann, Christian; Humboldt-Universität zu Berlin, Department of Psychology Kelly, Clare; School of Psychology and Department of Psychiatry at the School of Medicine, Trinity College Dublin; Trinity College Dublin, Trinity College Institute of Neuroscience; NYU Langone Medical Center, Department of Child and Adolescent Psychiatry Khadka, Sabin; Olin Neuropsychiatry Research Center, Hartford Hospital, Hartford, CT, USA King, Joseph; TU Dresden Faculty of Medicine Carl Gustav Carus, Division of Psychological and Social Medicine and Developmental Neurosciences Koch, Kathrin; Technical University Munich, Neuroimaging Center (TUM-NIC), Department of Neuroradiology; Technische Universität München, TUM-Neuroimaging Center (TUM-NIC) of Klinikum rechts der Isar Kohls, Gregor; University Hospital Aachen, Child Neuropsychology Section, Department of Child and Adolescent Psychiatry Konrad, Kerstin; University Hospital Aachen, Child Neuropsychology Section; Research Center Juelich, Institute of Neuroscience and Medicine, JARA Institute Molecular Neuroscience and Neuroimaging (INM-11) Kuno, Masaru; Chiba University, Research Center for Child Mental Development

	Kuntsi, Jonna; King's College London, Institute of Psychiatry, Psychology and Neuroscience, Social, Genetic and Developmental Psychiatry Centre Kvale, Gerd; Haukeland University Hospital; University of Bergen, Department of Clinical Psychology Kwon, Jun Soo; Seoul National University College of Medicine, Department of Psychiatry; Seoul National University College of Natural Sciences, Department of Brain & Cognitive Sciences Lázaro, Luisa; Hospital Clínic Universitari, Department of Child and Adolescent Psychiatry and Psychology; IDIBAPS; University of Barcelona, Department of Medicine Lera-Miguel, Sara; Hospital Clínic Universitari, Department of Child and Adolescent Psychiatry and Psychology; Universitat de Barcelona, Institute of Neuroscience Lesch, K. Peter; University of Würzburg, Division of Molecular Psychiatry, Center of Mental Health; I M Sechenov First Moscow State Medical University, Institute of Molecular Medicine, Laboratory of Psychiatric Neurobiology; Universiteit Maastricht School for Mental Health and Neuroscience, Department of Neuroscience Liu, Yanni; University of Michigan, Department of Psychiatry Lochner, Christine; Stellenbosch University, SA MRC Unit on Anxiety & Stress Disorders, Department of Psychiatry Louzã, Mario; Universidade de Sao Paulo Faculdade de Medicina, Department and Institute of Psychiatry Luna, Beatriz; University of Pittsburgh, Department of Psychiatry, Laboratory of Neurocognitive Development Lundervolt, Astri; University of Bergen, Department of Biological and Medical Psychology; University of Bergen, K.G. Jebsen Centre for Neuropsychiatric Disorders, Department of Biomedicine Malpas, Charles; Melbourne Health, Clinical Outcomes Research Unit (CORe), Department of Medicine; Murdoch Childrens Research Institute, Developmental Imaging Group; University of Melbourne, Melbourne School of Psychological Sciences Marques, Paulo; University of Minho, Life and Health Sciences Research Institute (ICVS), School of Medicine Marsh, Rachel; Columbia University, Columbia University Irving Medical Center; New York State Psychiatric Institute and the College of Physicians & Surgeons, Columbia University, The Division of Child and Adolescent Psychiatry in the Department of Psychiatry Martinez-Zalacain, Ignacio; Hospital de Bellvitge-IDIBELL, Department of Psychiatry; University of Barcelona, Department of Clinical Sciences Mataix-Cols, David; Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research Mattos, Paulo; D'Or Institute for Research and Education (IDOR); Federal University of Rio de Janeiro McCarthy, Hazel; Trinity College Dublin, Department of Psychiatry; St James's Hospital, Centre of Advanced Medical Imaging McGrath, Jane; School of Medicine, Trinity College Dublin, Department of Psychiatry Mehta, Mitul; King’s College London, Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience Menchon, Jose; Hospital de Bellvitge, Department of Psychiatry; CIBERSAM; University of Barcelona, Department of Clinical Sciences Mennes, Maarten; Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, Netherlands Martinho, Maurício ; Universidade Federal de Santa Maria, Department of Neuropsychiatry Moreira, Pedro; University of Minho, Life and Health Sciences Research Institute (ICVS), School of Medicine; Clinical Academic Center Braga morer, astrid; Hospital Clinic Universitari of Barcelona, Child and Adolescent Psychiatry and Psychology Department; IDIBAPS; University of Barcelona, Department of Medicine; CIBERSAM

	Morgado, Pedro; Life and Health Sciences Research Institute; Clinical Academic Center Braga Muratori, Filippo; IRCCS Foundation Stella Maris; University of Pisa, Department of Clinical and Experimental Medicine Murphy, Clodagh; King's College London, Institute of Psychiatry, Department of Forensic and Neurodevelopmental Sciences; South London and Maudsley NHS Foundation Trust, Behavioural Genetics Clinic, Adult Autism and ADHD Service, Behavioural and Developmental Psychiatry Clinical Academic Group Murphy, Declan; King's College London, The Sackler Institute for Translational Neurodevelopment, Institute of Psychiatry, Psychology & Neuroscience; South London and Maudsley NHS Foundation Trust, Behavioural Genetics Clinic, Adult Autism Service, Behavioural and Developmental Psychiatry Clinical Academic Group Nakagawa, Akiko; Chiba University, Research Center for Child Mental Development Nakamae, Takashi; Graduate School of Medical Science Kyoto Prefectural University of Medicine, Department of Psychiatry NAKAO, TOMOHIRO; Graduate School of Medical Sciences, Kyushu University, Department of Neuropsychiatry Namazova-Baranova, Leyla; Russian National Research Medical University, Central Clinical Hospital, Russian Academy of Science Narayanaswamy, Janardhanan; National Institute of Mental Health and Neuro Sciences, Obsessive-Compulsive Disorder (OCD) Clinic Department of Psychiatry Nicolau, Rosa; Department of Child and Adolescent Psychiatry and Psychology, Institut of Neurosciencies, Hospital Clínic, Barcelona Nigg, JT; Oregon Health and Science University, Department of Psychiatry; Oregon Health and Science University, Department of Behavioral Neuroscience Novotny, Stephanie; Olin Neuropsychiatry Research Center, Hartford Hospital, Hartford, CT, USA Nurmi, Erika; University of California Los Angeles, Department of Psychiatry and Biobehavioral Sciences O'Gorman, Ruth; University of Zurich, Center for MR-Research ; University of Zurich and ETH Zurich, Neuroscience Center Zurich O'Neill, Joseph; UCLA, Division of Child and Adolescent Psychiatry, Jane & Terry Semel Institute For Neurosciences O'Hearn, Kirsten; Wake Forest Medical School, Department of Physiology and Pharmacology Oberwelland Weiß, Eileen; University Hospital RWTH Aachen, Translational Neuroscience, Child and Adolescent Psychiatry; Jülich Research Center, Institute of Neuroscience and Medicine, Cognitive Neuroscience (INM-3); Jülich Research Center, Institute for Neuroscience and Medicine, JARA Institute Molecular Neuroscience and Neuroimaging (INM-11) Oosterlaan, Jaap; VU University, Amsterdam, The Netherlands, Clinical Neuropsychology Section; Amsterdam UMC Emma Children's Hospital, Emma Neuroscience Group, Department of Pediatrics Oranje, Bob; Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht Paloyelis, Yannis; King's College London, Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience Parellada, Mara; Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM. Madrid, Spain.; CIBERSAM, Biomedical Research Networking Centre Consortium on Mental Health, 28029, Madrid, Spain Pauli, Paul; University of Würzburg, Department of Psychology and Center of Mental Health Perriello, Chris; Harvard Medical School, McLean Hospital ; University of

	Illinois at Urbana-Champaign Piacentini, John; UCLA , Department of Psychiatry and Biobehavioral Sciences Piras, Fabrizio; IRCCS Santa Lucia Foundation, Laboratory of Neuropsychiatry, Department of Clinical and Behavioral Neurology Piras, Federica; IRCCS Santa Lucia Foundation, Department of Clinical and Behavioral Neurology, Laboratory of Neuropsychiatry Plessen, Kerstin; University of Copenhagen, Dept. of Clinical Medicine, Faculty of Medical and Health Sciences; University Hospital of Lausanne, Division of Child and Adolescent Psychiatry, Department of Psychiatry Puig, Olga; Hospital Clinic de Barcelona, Department of Child and Adolescent Psychiatry and Psychology; CIBERSAM Ramos-Quiroga, Josep; Hospital Universitari Vall d'Hebron, Department of Psychiatry; CIBERSAM; Universitat Autonoma de Barcelona, Department of Psychiatry and Forensic Medicine Reddy, Y.C.; National Institute of Mental Health & NeuroSciences, Obsessive-Compulsive Disorder (OCD) Clinic Department of Psychiatry Reif, Andreas; University Hospital Frankfurt, Psychiatry, Psychosomatic Medicine and Psychotherapy Reneman, Liesbeth; Amsterdam UMC, University of Amsterdam, Department of Radiology and Nuclear Medicine; Amsterdam UMC, University of Amsterdam, Brain Imaging Center Retico, Alessandra; National Institute for Nuclear Physics, Pisa Division Rossa, Pedro; Laboratory of Neuroimaging, University of São Paulo Medical School, Brazil; University of Sao Paulo, Center for Interdisciplinary Research on Applied Neurosciences (NAPNA) Rubia, Katya; King's College London, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience Rus-Oswald, Oana; University of Zürich, Dept. Neuroradiology; University Center for Medicine of Aging Sakai, Yuki; Graduate School of Medical Science Kyoto Prefectural University of Medicine, Psychiatry; ATR Brain Information Communication Research Laboratory Group Schrantee, Anouk; Amsterdam UMC, University of Amsterdam, Department of Radiology and Nuclear Medicine Schwarz, Lena; Department of Psychiatry and Psychotherapy, University Hospital of Tübingen Schweren, Lizanne; University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE) Seitz, Jochen; University Hospital Aachen, Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics Shaw, Philip; National Human Genome Research Institute; National Institute of Mental Health, Child Psychiatry Shook, Devon; UMC Utrecht Brain Center Rudolf Magnus, Department of Psychiatry Silk, Tim; Deakin University, School of Psychology, Geelong; Murdoch Childrens Research Institute, Developmental Imaging; University of Melbourne, Department of Paediatrics Simpson, Helen; Columbia University, Columbia University Irving Medical Center; New York State Psychiatric Institute, Center for OCD and Related Disorders Skokauskas, Norbert; Norges teknisk-naturvitenskapelige universitet, Centre for child and youth mental health; Norwegian University of Science and Technology, Institute of Mental Health Soliva, Joan Carles; Universitat Autònoma de Barcelona, Department of Psychiatry and Legal Medicine, Solovieva, Anastasia; National Medical Research Center for Children's Health, Moscow Soreni, Noam; McMaster University, Pediatric OCD Consultation service,

	Anxiety Treatment and Research Center, St. Joseph's HealthCare Soriano-Más, Carles; Hospital de Bellvitge-IDIBELL, Psychiatry; CIBERSAM; Universitat Autònoma de Barcelona, Department of Psychobiology and Methodology of Health Sciences Spalletta, Gianfranco; IRCCS Santa Lucia, Laboratory of Neuropsychiatry, Department of Clinical and Behavioral Neurology; Baylor College of Medicine, Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry, Department of Psychiatry and Behavioral Sciences Stern, Emily; New York University School of Medicine, Psychiatry; Nathan S Kline Institute for Psychiatric Research Stevens, Michael; Institute of Living, Olin Neuropsychiatry Research; Yale University School of Medicine, Department of Psychiatry Stewart, Evelyn; University of British Columbia; British Columbia Children's Hospital Sudre, Gustavo; National Human Genome Research Institute Szeszko, Philip; Icahn School of Medicine at Mount Sinai, Psychiatry; James J Peters VA Medical Center Tamm, Leanne; Department of Pediatrics, Cincinnati Children's Hospital Medical Center; University of Cincinnati, College of Medicine Taylor, Margot; The Hospital for Sick Children, Diagnostic Imaging Research Tolin, David; Institute of Living, Hartford Hospital, Anxiety Disorders Center; Yale University School of Medicine Tosetti, Michela; IRCCS Foundation Stella Maris Tovar-Moll, Fernanda; D'Or Institute for Research and Education (IDOR); Federal University of Rio de Janeiro, Morphological Sciences Program Tsuchiyagaito , Aki; Chiba University, Research Center for Child Mental Development; Laureate Institute for Brain Research van Erp, Theo; University of California, Irvine, Department of Psychiatry and Human Behavior; University of California Irvine, Center for the Neurobiology of Learning and Memory van Wingen, Guido; Amsterdam UMC, University of Amsterdam, Department of Psychiatry Vance, Alasdair; University of Melbourne, Paediatrics Venkatasubramanian, Ganesan ; National Institute of Mental Health and Neurosciences, Bangalore, 560029, India, , Schizophrenia Clinic, Department of Psychiatry & Translational Psychiatry Laboratory, Neurobiology Research Centre Vilarroya, Oscar; Universitat Autònoma de Barcelona, Psychiatry and Forensic Medicine; Hospital del Mar Institute for Medical Research Vives-Gilabert, Yolanda; Universitat Politècnica de València, Instituto ITACA von Polier, Georg; University Hospital Aachen, Child Neuropsychology Section, Department of Child and Adolescent Psychiatry,; Research Centre Jülich, Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7) Walitza, Susanne; Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zürich Wallace, Gregory; George Washington University, Department of Speech, Language, and Hearing Sciences wang, zhen; Shanghai Mental Health Center, Shanghai Jiao Tong University; Shanghai Key Laboratory of Psychotic Disorders Wolfers, Thomas; Radboud university medical center, Human Genetics; Radboud University, Donders Institute for Brain, Cognition and Behaviour Yoncheva, Yuliya; Hassenfeld Children's Hospital at NYU Langone, Department of Child and Adolescent Psychiatry Yun, Je-Yeon; Seoul National University College of Medicine, Department of Psychiatry; Seoul National University College of Medicine, Yeongeon Student Support Center Zanetti, Marcus; Department of Psychiatry, Faculty of Medicine, University of São Paulo, Laboratory of Psychiatric Neuroimaging (LIM-

	21); University of São Paulo, Center for Interdisciplinary Research on Applied Neurosciences (NAPNA; Hospital Sírio-Libanês, Instituto de Ensino e Pesquisa Zhou, Fengfeng; Jilin University, College of Computer Science and Technology, and Key Laboratory of Symbolic Computation and Knowledge Engineering of Ministry of Education Ziegler, Georg ; Division of Molecular Psychiatry, Center of Mental Health, University of Würzburg Zierhut, Kathrin; University of Würzburg, Department of Psychology I Zwiers, Marcel; 1. Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging Thompson, Paul; University of Southern California, Imaging Genetics Center, Stevens Institute for Neuroimaging & Informatics, Keck School of Medicine Stein, Dan; University of Cape Town, SAMRC Unit on Anxiety & Stress Disorders, Department of Psychiatry and Mental Health Buitelaar, Jan; Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Cognitive Neuroscience; Karakter Child and Adolescent Psychiatry University Center Franke, Barbara; Radboud University Medical Centre, Department of Human Genetics; Radboud University Donders Institute for Brain Cognition and Behaviour Van Den Heuvel, Odile; Amsterdam UMC, Vrije Universiteit, Department of Psychiatry; Amsterdam UMC, Vrije Universiteit, Department of Anatomy & Neurosciences
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Subcortical brain volume, regional cortical thickness and cortical surface area across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD)

– findings from the ENIGMA-ADHD, -ASD, and -OCD working groups

Premika S.W. Boedhoe, Ph.D.*, Daan van Rooij, Ph.D. *, Martine Hoogman, Ph.D., Jos W.R. Twisk Ph.D., Lianne Schmaal, Ph.D., Yoshinari Abe, M.D., Ph.D., Pino Alonso, M.D., Ph.D., Stephanie H. Ameis, M.D., M.Sc., Anatoly Anikin, Ph.D., Alan Anticevic, Ph.D., Celso Arango, M.D., Ph.D., Paul D. Arnold, M.D., Ph.D., Philip Asherson, Ph.D., Francesca Assogna, Ph.D., Guillaume Auzias, Ph.D., Tobias Banaschewski, M.D., Ph.D., Alexander Baranov, Ph.D., Marcelo C. Batistuzzo, Ph.D., Sarah Baumeister, Ph.D., Ramona Baur-Streubel, Ph.D., Marlene Behrmann, Ph.D., Mark A. Bellgrove, Ph.D., Francesco Benedetti, M.D., Jan C. Beucke, Ph.D., Joseph Biederman, M.D., Irene Bollettini, Ph.D., Anushree Bose, Ph.D., Janita Bralten, Ph.D., Ivanei E. Bramati, Ph.D., Daniel Brandeis, Ph.D., Silvia Brem, Ph.D., Brian P. Brennan, M.D., M.M.Sc., Geraldo F. Busatto, Ph.D., Sara Calderoni, M.D., Ph.D., Anna Calvo, M.Sc., Rosa Calvo, M.D., Ph.D., Francisco X. Castellanos, M.D., Mara Cercignani, Ph.D., Tiffany M. Chaim-Avancini, Ph.D., Kaylita C. Chantiluke, Ph.D., Yuqi Cheng, Ph.D., Kang Ik K. Cho, Ph.D., Anastasia Christakou, Ph.D., David Coghill, M.D., Annette Conzelmann, M.D., Ph.D., Ana I. Cubillo, Ph.D., Anders M. Dale, Ph.D., Sara Dallaspezia, M.D., Eileen Daly, Ph.D., Damiaan Denys, M.D., Ph.D., Christine Deruelle, Ph.D., Adriana Di Martino, Ph.D., Ilan Dinstein, Ph.D., Alysa E. Doyle, Ph.D., Sarah Durston, Ph.D., Eric A. Earl, B.Sc., Christine Ecker, Ph.D., Stefan Ehrlich, M.D., Ph.D., Benjamin A. Ely, B.S., Jeffrey N. Epstein, Ph.D., Thomas Ethofer, Ph.D., Damien A. Fair, Ph.D., Andreas J. Fallgatter, M.D., Stephen V. Faraone, Ph.D., Jennifer Fedor, B.Sc., Xin Feng, M.Sc., Jamie D. Feusner, M.D., Jackie Fitzgerald, Ph.D., Kate D. Fitzgerald, M.D., Jean-Paul Fouche, M.Sc., Christine M. Freitag, Ph.D., Egill A. Fridgeirsson, M.Sc., Thomas Frodl, M.D., Ph.D., Matt C. Gabel, Ph.D., Louise Gallagher, M.D., Ph.D., Tinatin Gogberashvili, Ph.D., Ilaria Gori, M.Sc., Patricia Gruner, Ph.D., Deniz A. Gürsel, M.Sc., Shlomi Haar, Ph.D., Jan Haavik, M.D., Ph.D., Geoffrey B. Hall, Ph.D., Neil A. Harrison, Ph.D., Catharina A. Hartman, Ph.D., Dirk J. Heslenfeld, Ph.D., Yoshiyuki Hirano, Ph.D., Pieter J. Hoekstra,M.D., Ph.D., Marcelo Q. Hoexter, M.D., Ph.D., Sarah Hohmann, M.D., Marie F. Høvik, M.D., Hao Hu, Ph.D., Chaim Huyser, M.D., Ph.D., Neda Jahanshad, Ph.D., Maria Jalbrzikowski, Ph.D., Anthony James, M.R.C.P., M.R.Psych., Joost Janssen, Ph.D., Fern Jaspers-Fayer, Ph.D., Terry L. Jernigan, Ph.D., Dmitry Kapilushniy, Ph.D., Bernd Kardatzki, M.Sc., Georgii Karkashadze, Ph.D., Norbert Kathmann, Ph.D., Christian Kaufmann, Ph.D., Clare Kelly, Ph.D., Sabin Khadka, M.Sc., Joseph A. King, Ph.D., Kathrin Koch, Ph.D., Gregor Kohls, Ph.D., Kerstin Kohls, Ph.D., Masaru Kuno, M.D., Ph.D., Jonna Kuntsi, Ph.D., Gerd Kvale, Ph.D., Jun Soo Kwon, M.D., Ph.D., Luisa Lázaro, M.D., Ph.D , Sara Lera-Miguel, Ph.D., Klaus-Peter Lesch, M.D., Ph.D., Liesbeth Hoekstra, M.Sc., Yanni Liu, Ph.D., Christine Lochner, Ph.D., Mario R. Louza, M.D., Ph.D., Beatriz Luna, Ph.D., Astri J. Lundervold, Ph.D., Charles B. Malpas, Ph.D., Paulo Marques, Ph.D., Rachel Marsh, Ph.D., Ignacio Martínez-Zalacaín, M.Sc., David Mataix-Cols, Ph.D., Paulo Mattos, M.D., Ph.D., Hazel McCarthy, Ph.D., Jane McGrath, Ph.D., Mitul A. Mehta,

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Ph.D., José M. Menchón, M.D., Ph.D., Maarten Mennes, Ph.D., Mauricio Moller Martinho, M.D., M.S., Pedro S. Moreira, M.Sc., Astrid Morer, M.D. Ph.D., Pedro Morgado, M.D., Ph.D., Filippo Muratori, Ph.D., Clodagh M. Murphy, M.R.C.Psych., Ph.D., Declan G.M. Murphy, M.D., F.R.C.Psych., Akiko Nakagawa, M.D., Ph.D., Takashi Nakamae, M.D., Ph.D., Tomohiro Nakao, M.D., Ph.D., Leyla Namazova-Baranova, Ph.D., Janardhanan. C. Narayanaswamy, M.D., Rosa Nicolau, B.Sc., Joel T. Nigg, Ph.D., Stephanie E. Novotny, M.Sc., Erika L. Nurmi, M.D., Ph.D., Eileen Oberwelland Weiss, Ph.D., Ruth L. O'Gorman Tuura, Ph.D., Kirsten O'Hearn, Ph.D., Joseph O'Neill, Ph.D., Jaap Oosterlaan, Ph.D., Bob Oranje, Ph.D., Yannis Paloyelis, Ph.D., Mara Parellada, M.D., Ph.D., Paul Pauli, Ph.D., Chris Perriello, B.Sc., John Piacentini, Ph.D., Fabrizio Piras, Ph.D., Federica Piras, Ph.D., Kerstin J. Plessen, M.D., Ph.D., Olga Puig, Ph.D., J. Antoni Ramos-Quiroga, M.D., Ph.D., Y.C. Janardhan Reddy, M.D., Andreas Reif, M.D., Liesbeth Reneman, M.D., Ph.D., Alessandra Retico, Ph.D., Pedro G.P. Rosa, M.D., Katya Rubia, Ph.D., Oana Georgiana Rus, Ph.D., Yuki Sakai, M.D., Ph.D., Anouk Schrantee, Ph.D., Lena Schwarz, M.D., Lizanne J.S. Schweren, Ph.D., Jochen Seitz, M.D., Philip Shaw, M.D., Ph.D., Devon Shook, Ph.D., Tim J. Silk, Ph.D., H. Blair Simpson, M.D., Ph.D., Norbert Skokauskas, M.D., Ph.D., Juan Carlos Soliva Vila, Ph.D., Anastasia Solovieva, Ph.D., Noam Soreni, M.D., Carles Soriano-Mas, Ph.D., Gianfranco Spalletta, M.D., Ph.D., Emily R. Stern, Ph.D., Michael C. Stevens, Ph.D., S. Evelyn Stewart, M.D., Gustavo Sudre, Ph.D., Philip R. Szeszko, Ph.D., Leanne Tamm, Ph.D., Margot J. Taylor, Ph.D., David F. Tolin, Ph.D., Michela Tosetti, Ph.D., Fernanda Tovar-Moll, M.D., Ph.D., Aki Tsuchiyagaito, Ph.D., Theo G.M. van Erp, Ph.D., Guido A. van Wingen, Ph.D., Alasdair Vance, M.D., Ganesan Venkatasubramanian, M.D., Ph.D., Oscar Vilarroya, Ph.D., Yolanda Vives-Gilabert, Ph.D., Georg G. von Polier, M.D., Susanne Walitza, M.D., M.Sc., Gregory L. Wallace, Ph.D., Zhen Wang, M.D., Ph.D., Thomas Wolfers, M.Sc., Yuliya N. Yoncheva, Ph.D., Je-Yeon Yun, M.D., Ph.D., Marcus V. Zanetti, Ph.D., Fengfeng Zhou, Ph.D., Georg C. Ziegler, M.D., Kathrin C. Zierhut, Ph.D., Marcel P. Zwiers, Ph.D., the ENIGMA-ADHD working group[#], the ENIGMA-ASD working group[#], the ENIGMA-OCD working group[#],
Paul M. Thompson, Ph.D., Dan J. Stein, M.D., Ph.D., Jan Buitelaar, M.D., Ph.D., Barbara Franke, Ph.D., Odile A. van den Heuvel, M.D., Ph.D.

*equal contribution first authors
[#] see excel sheet for full list of authors

Corresponding author: Daan van Rooij, PhD d.vanrooij@donders.ru.nl

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Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common neurodevelopmental disorders that frequently co-occur. We aimed to directly compare all three disorders. The ENIGMA consortium is ideally positioned to investigate structural brain differences across these disorders.

Methods: Structural T1-weighted whole-brain MRI of controls (*n*=5,827) and patients with ADHD (n=2,271), ASD (n=1,777), and OCD (n=2,323) from 151 cohorts worldwide were analyzed using standardized processing protocols. We examined subcortical volume, cortical thickness and surface area differences within a mega-analytical framework, pooling measures extracted from each cohort. Analyses were performed separately for children, adolescents, and adults using linear mixed-effects models adjusting for age, sex and site (and intra-cranial volume (ICV) for subcortical and surface area measures).

Results: We found no shared differences among all three disorders, while shared differences between any two disorders did not survive multiple comparisons correction. Children with ADHD compared to those with OCD had smaller hippocampal volumes, possibly influenced by IQ. Children and adolescents with ADHD also had smaller ICV than controls and those with OCD or ASD. Adults with ASD showed thicker frontal cortices compared to adult controls and other clinical groups. No OCD-specific differences across different age-groups and surface area differences among all disorders in childhood and adulthood were observed.

Conclusion

Our findings suggest robust but subtle differences across different age-groups among ADHD, ASD, and OCD. ADHD-specific ICV and hippocampal differences in children and adolescents, and ASD-specific cortical thickness differences in the frontal cortex in adults support previous work emphasizing structural brain differences in these disorders.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common neurodevelopmental disorders with a lifetime prevalence of 2.5-5%, ~1%, and 2.3%, respectively (1-3). Symptoms mostly develop early in life (ADHD, ASD) or later in childhood (OCD) and often persist into adulthood. Characteristic symptoms include inattentiveness, impulsivity and hyperactivity for ADHD; impairments in social communication and restricted and stereotyped behaviors for ASD; and repetitive thoughts (obsessions) and behaviors or mental acts (compulsions) that cause distress or anxiety for OCD. Although each disorder is distinguished by its own core symptoms, the disorders frequently co-occur and share overlap in phenomenology and pathophysiology (4,5).

There are parallels between the uncontrollable impulsive behaviors of ADHD and the excessive and compulsive rituals of OCD and ASD. Impaired response inhibition and cognitive control processes may underlie the cross-disorder traits within the impulsive-compulsive spectrum (6), implicating cortico-striato-thalamo-cortical and fronto-parietal networks (7). It remains unclear which morphological brain abnormalities within these networks are shared (non-specific) versus distinct (specific to one disorder).

Imaging studies, including meta-analyses, have generally compared one of the three disorders to healthy controls (8-12). Large-scale studies generally yielded small to moderate effect sizes, indicating that disorder-associated differences are subtle (13-17). Few structural imaging studies have directly compared these three disorders (18,19), mostly in small numbers and with inconsistent results (20). A meta-analysis including 931 patients with ADHD and 928 with OCD reported shared smaller ventromedial prefrontal cortex gray matter volume, ADHD-specific smaller gray matter volume in basal ganglia and insula, and OCD-specific smaller volume of rostral and dorsal anterior cingulate and medial prefrontal cortex (21). Another meta-analysis comparing structural brain differences in 911 patients with ASD and 928 with OCD reported shared differences in the dorsal medial prefrontal cortex and OCD-specific differences in the basal ganglia (22). However, despite their clinical overlap, no structural gray matter study so far compared all three disorders.

The ENIGMA consortium (23) includes the largest samples for ADHD, ASD, and OCD worldwide (13-17). The consortium also improves on earlier meta-analyses by using harmonized protocols for brain segmentation and quality control procedures across ENIGMA working groups, and by pooling extracted individual participant data. The ENIGMA consortium is therefore ideally positioned to investigate overlap and specificity of structural brain differences across disorders.

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Here, we present the largest comparative study investigating subcortical and cortical differences across ADHD, ASD, and OCD. We extracted subcortical volumes, cortical thickness, and cortical surface area estimates of 12,198 individuals from 151 cohorts worldwide, using harmonized data processing protocols. Based on previous meta- and mega-analyses, we expected to find ADHD-specific differences in frontal and temporal surface areas and basal ganglia volumes in children (14,15), ASD-specific differences in frontal and temporal cortical thickness (13), and OCD-specific differences in the thalamus of pediatric patients and the pallidum of adult patients (16). We expected that differences in the striatum and dorsomedial prefrontal cortex would be observed across disorders (21,22).

Methods

Samples

The ENIGMA-ADHD working group includes 48 cohorts from 34 research institutes, with neuroimaging and clinical data from patients with ADHD and healthy controls. The ENIGMA-ASD working group includes 56 cohorts from 38 research institutes, with neuroimaging and clinical data from patients with ASD and healthy controls. The ENIGMA-OCD working group includes 47 cohorts from 34 research institutes, with neuroimaging and clinical data from patients with OCD and healthy controls..

All working groups included data from subjects across the lifespan. As prior results suggested differential effects between pediatric (<12 years), adolescent (12-18 years), and adult (≥18 years) patients, we performed separate mega-analyses for these three age-groups. In total, we analyzed data from 2,271 patients with ADHD, 1,777 with ASD, 2,323 with OCD, and 5,827 healthy controls. All local institutional review boards permitted the use of measures extracted from the coded data for mega-analyses.

Image Acquisition and Processing

Structural T_1-weighted whole-brain Magnetic Resonance Spectroscopy (MRI) was acquired and processed locally. Image acquisition parameters for each cohort are listed in Supplementary Tables S1-S3. All cortical parcellations were performed with the fully automated segmentation program FreeSurfer, version 5.3, following standardized ENIGMA protocols to harmonize analyses and quality control (QC) procedures across multiple sites (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Segmentations of seven bilateral subcortical and 34 bilateral cortical regions of interest according to the Desikan-Killiany atlas were statistically evaluated for outliers, and subsequenlty visually inspected for segmentation success. Individual volumes with poor segmentation were removed, as well as subjects with overall poor segmentation quality. All the quality control was performed locally on each site, and only data of sufficient quality was send for inclusion in the ENIGMA cohorts. All reported group sizes in this manuscript are after QC. Details on image exclusion criteria

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and quality control are presented in Supplementary Information SI1. All cohorts of each working group underwent identical processing and quality control procedures.

Statistical Analysis

We pooled extracted subcortical volumes, cortical thickness and cortical surface area measures from individual subjects across all cohorts from the different working groups into one database to perform a mega-analysis. We examined differences among patients groups and controls using linear mixed-effects models in STATA; mixed models are used to take into account the differences between sites. The means of the left and right hemisphere of 34 cortical regions (separately for cortical thickness and cortical surface area), whole-hemisphere measures (average thickness and total surface area), and seven subcortical regions were used in the mega-analyses. To obtain comparable standardized regression coefficients (effect sizes) for all comparisons the z-scores for each of the cortical and subcortical regions-of-interest served as the outcome measures, and the diagnoses (ADHD, ASD, OCD, and HC) were included as separate independent variables of interest, using three dummy variables. Disorder specific differences were assessed by alternating the different diagnoses as reference category. Shared differences were assessed using the HC as a reference category. A random intercept for cohort was entered to account for clustering within cohorts; if necessary (i.e. when there was a significant improvement of the model fit), a random slope for diagnosis*cohort was included to account for different effect sizes between cohorts within the different working groups (24). Age and sex were included as covariates (25,26); for the surface area and subcortical volume analyses, ICV was also added as a covariate, since these measures scale with head size (27). The standard formula with a putative random slope therefore looks as follows: ***MRI_feature_zscore ~ Dx1 + Dx2 + Dx3 + Age + Sex + (Dx*cohort), with Dx1-3 referring to Diagnostic groups.***

To detect potentially different effects of disorder with age, we performed all analyses separately for pediatric, adolescent, and adult patients. Because only a limited number of cohorts had data on IQ and medication use, sensitivity analyses were performed to investigate how IQ and psychotropic medication use might have influenced the disorder differences. For medication use (yes/no at time of scanning), stratified analyses according to medication status were performed. With respect to IQ, we included the variable as an additional covariate in the analyses. The Benjamini-Hochberg false discovery rate (FDR) was used to control for multiple comparisons within each model, with p-values adjusted separately for each age-group and for each modality (cortical thickness, surface area and subcortical volume). Results were considered significant if the FDR-corrected p-value (q) was ≤0.05.

To quantify the robustness of the main between group comparisons, additional leave-one-site-out cross validation was performed for each of the models (see supplementary table 3-13). For this cross-validation, the same model was repeatedly performed, each time removing one of the individual sites from the cohort. We report the distribution of the p-values (mean, min and max p-value after all iterations), indicating how strongly the p-value of the comparison was influenced by single-site effects.

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Results

The demographic and clinical characteristics of participants are summarized per age category in Table 1a-c (entire sample Supplementary Table S4), these are also the final numbers of subjects used in each of the analyses. Results not surviving multiple comparison correction, but with p-values <0.05 were considered trends and are described for the main analyses in Supplemental Information SI2. Based on our statistical tests, indicating an effect is *specific* means we observe a significant difference between a diagnostic group and the control group but not necessarily between a diagnostic group, and each of the three other groups, but not the others. It should be noted this is distinct from diagnostic specificity based on a full interaction model as recommended in (43)"

Shared subcortical and cortical differences across clinical groups compared to healthy controls

Children with ADHD and those with ASD showed some overlap in *subcortical volume* and *cortical thickness* differences compared to controls (Supplementary Information SI2), however none of these results survived multiple comparison correction (Supplementary Tables S5-S6). In *adolescents*, we did not observe shared *subcortical and cortical* differences among any of the disorders (Supplementary Tables S7-S9). *Adult* patients with OCD and those with ASD showed smaller hippocampal volumes compared to adult controls, however this finding did not survive multiple comparison correction in adults with ASD (Supplementary Table S10). Adult patient groups showed no overlap in *cortical* differences (Supplementary Tables S11-S12). Details on differences compared to healthy controls per patient group can be found in Supplementary Tables S5-S13.

Disease-specific subcortical and cortical differences

Children: Figure 1a depicts the pattern of *subcortical volume* differences in children. Children with ADHD showed significantly smaller ICV compared to those with ASD (effect size=-0.23) or OCD (effect size=-0.28). Children with ADHD (effect size=-0.22) also showed smaller hippocampal volumes compared to children with OCD. No significant *cortical* differences among disorders survived multiple comparison correction (Supplementary Tables S15-S16 & Supplementary Information SI2).

Adolescents: Adolescents with ADHD had significantly smaller ICV compared to those with ASD (effect size=-0.22) or OCD (effect size=-0.19), shown in Figure 1b (Supplementary Table S17). However, the latter did not survive multiple comparison correction. Group differences in *cortical thickness* did not survive multiple comparison correction (Supplementary Table S18 & Supplementary Information SI2). *Surface area* analysis revealed significantly lower surface area of the medial orbitofrontal cortex (effect size=-0.22) in patients with OCD compared to patients with ADHD (Supplementary Table S19).

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Adults: None of the *subcortical* volumes differed significantly among adult patient groups (Figure 1c & Supplementary Table S20). *Cortical thickness* analysis revealed significantly thicker cortical gray matter in several frontal regions in adults with ASD compared to adults with OCD or ADHD (Figure 2) with effect sizes varying between 0.17 and 0.30. Adults with OCD did not differ significantly from those with ADHD (Supplementary Table S21). *Surface area* analysis revealed that none of the regions differed significantly among patient groups (Supplementary Table S22).

Influence of medication on cross-disorder effects

Medication status information was incomplete. Table 1a-c lists the numbers of patients for whom information about medication status at the time of scanning was available.

Children: The smaller ICV between children with ADHD and those with OCD (effect size=-0.32) or those with ASD (effect size=-0.19) may be driven by the unmedicated children (Supplementary Table S23) since ICV did not significantly differed among disorders when comparing the medicated children (Supplementary Tables S24). No *cortical* differences survived multiple comparison correction when comparing unmedicated children among disorders (Supplementary Tables S25 and S26).

Medicated children with OCD had larger amygdala volumes than medicated children with ADHD (effect size=0.43) (Supplementary Table S24). Medicated children with ASD showed a thicker cuneus cortex (effect size=0.60) compared to medicated children with OCD and a thinner middle temporal gyrus (effect size=-0.44) compared to medicated children with ADHD (Supplementary Table S27). No differences in *surface area* differences survived multiple comparison correction when comparing medicated children among disorders (Supplementary Tables S28).

Adolescents & Adults: Except for significantly larger *surface area* of the parahippocampal gyrus in unmedicated adults with ASD (effect size=0.33) compared to unmedicated adults with ADHD (Supplementary Table S29), no significant *subcortical* and *cortical* differences survived multiple comparison correction when comparing unmedicated (Supplementary Tables S30–S34) or medicated (Supplementary Tables S35–S40) adults and adolescents among disorders. Details on disease-specific differences for unmedicated or medicated patients compared to controls can be found in Supplementary Tables S41-S58.

Adjusting for Individual Differences in IQ

Information about IQ was incomplete. Table 1a-c shows the number of patients for whom IQ scores were available. We did not have sufficient IQ data to include *adult* patients with OCD into the analysis (Table 1a). Therefore, results for *adults* are based on ASD, ADHD, and HC only.

Adjusting for IQ resulted in similar findings as the main results across all age-groups (Supplementary Tables S59-S67). However, *subcortical volume* analysis did not show smaller hippocampal volumes in children with ADHD and children with ASD compared to those with OCD (Supplementary Table S59). *Cortical thickness* analysis additionally revealed significant thicker cortices

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of pars orbitalis (effect size=0.20), superior frontal gyrus (effect size=0.22), and frontal pole (effect size=0.23) in adults with ASD compared to adults with ADHD (Supplementary Table S67). Details on disease-specific differences compared to healthy controls adjusted for IQ can be found in Supplementary Tables S65-S73.

Supplementary robustness analyses

The leave-one-site-out cross-validation analyses (supplementary table 3-13) indicated that the main effects of diagnostic group in all age-bins was not influenced by single outlying site effects. Further scatterplots with polynomial age-fits for several selected key MRI features can be viewed in SI3, demonstrating the full distribution of data points over the lifespan for each diagnostic group.

SI4 shows for several key MRI features the Estimated Marginal Means for each diagnostic group after the main group comparisons model has been run, as well as full distributions of the residuals (with and without correction for site). These figures demonstrate that the inclusion of random slopes per site leads to more normally distributed residuals.

SI5-7 show meta-analytic results for several key MRI features for each age-bin, containing both forest plots per site as well as the average meta-analytic results. These plots demonstrate considerable heterogeneity in the effect size between site, as well as overall smaller effect sizes in the mean meta-analysis result per MRI feature than those reported in our main mega-analysis.

As previous studies have shown field-strength may influence FreeSurfer segmentations (42), we have repeated the main between-group comparisons, split by sites employing either 1.5T or 3T scanner. As demonstrated in supplementary table 75, we mostly have a much larger sample of 3T scans. The results of these comparisons (see supplementary tables 75-84) indicate that the between-group results are mostly stable across field-strengths.

Discussion

This study comprised the largest neuroimaging investigation to date of structural brain alterations across ADHD, ASD and OCD. Results revealed differing patterns of subcortical and cortical differences among the disorders across childhood, adolescence, and adulthood. We found ADHD-specific smaller ICV in children and adolescents, and ASD-specific thicker frontal cortices in adults. We did not find OCD-specific differences across the different age-groups. No brain differences were shared among all three disorders.

Previous ENIGMA disease working group results, comparing patients with distinct disorders to controls, were mostly replicated, albeit not always using an FDR-corrected threshold. The current study included more patients and considerably more controls than the previously published working group studies (13-17). Accordingly, the present investigation may more accurately represent the normal heterogeneity in the control population. Importantly, our method allowed different mean control group outcomes per cohort, meaning that it statistically accounted for the heterogeneity amongst controls from

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different cohorts (24).

Overall, results were subtle with small to moderate effect sizes. These effect sizes emerge even after combining dozens of different scanner types and rise above the noise. Large-scale studies like those of the ENIGMA consortium convey another important message mainly by not replicating the extremely large effect sizes that have been found in previous research with smaller samples. Small clinical samples are often rather homogeneous samples carefully selected on the basis of a specific set of in- and exclusion criteria. Homogeneous samples can increase statistical power to discover larger effect sizes, but are typically not representative of the broader population, and such effect sizes are less likely to generalize to the population where patient groups are highly heterogeneous.

Smaller amygdala volume and thinner frontal and temporal cortices might be shared differences in children with ASD and ADHD (Supplementary Information SI2). We did not observe similar shared differences in the adolescents and adults with ASD and ADHD. These findings may be indicative of a more general delayed brain development (18,29). Smaller hippocampus volume might be a shared alteration in adults with ASD and OCD (Supplementary Information SI2). Hippocampal differences are also described in other psychiatric disorders, such as major depressive disorder, schizophrenia and bipolar disorder (30,31). Decreased hippocampal volume may reflect a disorder non-specific effect, potentially related to chronic stressors (32).

Deficits in social communication and interaction are hypothesized to be related to a thinner temporal cortex (33). Our results fit with the involvement of the temporal cortex in ASD compared to controls, but we did not detect temporal cortex differences in patients with ASD compared to those with ADHD or OCD. A thicker cortex of several frontal regions was specific to patients with ASD and has been linked to impaired cognitive control and executive dysfunction (13,34). The pattern of thinner temporal and thicker frontal cortices in patients with ASD has been reported in longitudinal studies and suggests accelerated expansion in early childhood, accelerated thinning in later childhood and adolescence, and decelerated thinning in adulthood (35). Although executive dysfunction is present in all three patient groups (4,5), diagnostic categories might differ in executive functioning profiles. Future studies, such as the COMPULS study (36), that focus on neural correlates of executive functioning in all three patient groups will give more insight in this.

Inattention, hyperactivity and impulsivity are the main symptoms of ADHD, presumably modulated by abnormal fronto-striatal circuits (37). Our study confirms frontal surface area and striatal volume differences in children with ADHD compared to controls, but we did not detect these fronto-striatal differences in patients with ADHD compared to those with ASD or OCD. Smaller ICV did appear specific to children and adolescents with ADHD. These results support the hypothesis that differences in ADHD may be due to a delay in brain maturation (29), which possibly normalizes in adulthood. These results are also in line with the genetic correlation between risk for ADHD and smaller ICV (38).

Children with ASD (Supplementary Info SI2) and ADHD seemed to have smaller hippocampal

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volumes compared to children with OCD. This effect was not detected when adjusting for IQ. Although the sensitivity analysis adjusting for IQ was performed in a smaller subgroup, these findings indicate that the hippocampal volume differences may be driven by IQ differences among patient groups. Indeed, previous studies have shown an association between IQ and hippocampal volume (39). Further cross-disorder analyses adjusted for IQ revealed similar results as the main analyses across all age-groups.

Cross-disorder main effects were not detected when comparing medicated patients and unmedicated patients separately. However, these analyses may have been underpowered to detect the small effect sizes we observed in the larger combined group due to smaller sample sizes when stratifying patients according to medication status.

Two studies performed VBM meta-analyses and reported shared differences and disease specific differences between patients with ASD and OCD, and patients with ADHD and OCD, respectively (21,22). Our findings do not corroborate with these findings. This inconsistency might reflect reporting bias in these meta-analyses of published studies and/or differences in analytical methods. FreeSurfer segments brain regions based on probabilistic information from a predefined atlas compared to VBM's voxel-wise registration. The differences in these methodological approaches may lead to diverging results. Mainly global or regional differences in structure can be inferred from atlas-based FreeSurfer analyses, as opposed to voxel-level morphology with VBM. Thus local morphological differences may not be detected when averaging across regions (40).

Strengths and Limitations of the study

This study has several strengths and limitations. As the largest mega-analysis to date, sample size is an obvious strength. Another strength is harmonization of segmentation protocols across all participating sites, reducing variation caused by differences in methods. QC procedures were also harmonized across site, however, given the large datasets involved, QC was largely based on automated outlier detection before visual inspection. This means that more subtle biases (for instance limited head motion) may have remained unnoticed.

Another key limitation is the variation attributable to different scanners and acquisition protocols across cohorts. This issue was mitigated by the formal consideration of potential site differences in all statistical analyses. We have included comparisons of 1.5 vs 3 Tesla field strength in the supplement (see SI2), indicating that our main group effects are largely unaffected by field strength. However, other acquisition parameters like RF coil or imaging sequence were not available from sufficient sites to run sensitivity analyses, which must be considered a limitation of the current study, as these factors may influence segmentation results (41).

Another strength of the study was the use of mega- as opposed to meta-analysis. The comprehensive evaluation of missing data and greater flexibility in control of confounds at the level of individual patients and specific studies are significant advantages. Mega-analyses are also

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recommended as they avoid the assumptions of within-study normality and known within-study variances, which are especially problematic when including small samples. Within supplementary materials 5-7 we demonstrate forest plots of the main group effects split by site, together with overall meta-analysis effects and I2 heterogeneity statistics. These results indicate substantial heterogeneity in the effect sizes between individual sites. Indeed our recent study comparing meta- and mega-analytical methods showed that the mega-analytical framework appears to be the better approach for investigating structural neuroimaging data in multi-center studies (24).

We did not perform stratified analyses for reported sex even though ADHD and ASD have a strong sex bias. This issue was mitigated by adjusting for sex in all statistical analyses. Moreover the independent working groups did not observed sex specific effects in their patient groups (13-17).

We chose to differentiate children**,** adolescents, and adults; cut-offs might not have been optimal, given different disorder onsets. Our rationale was to minimize differences in average age among disorders – in addition to age as a nuisance covariate – and thus to minimize the detection of age effects rather than disease effects. Separate analysis by age group also avoids the difficulties in modeling possibly complex – yet unknown, a priori – nonlinear age effects that might also differ among groups. The primary focus of this manuscript was cross-disorder comparisons. Yet such analyses of age effects are of great interest and should be addressed in future research using multivariate pattern recognition e.g., the support vector machine that can detect informative patterns in the data that may not be identified by traditional linear analyses.

Structural differences among disorders did not show any significant association with medication use and IQ. Nonetheless, we did not have data on medication use and IQ for all patients, indicating insufficient statistical power to address this issue with confidence. We also lacked detailed information on psychotropic treatment. Further efforts are required to draw valid conclusions on the impact of psychotropic medication use on brain structure.

Effects of comorbidity or general phenotypic overlap among ADHD, ASD, and OCD could not be analyzed, because this was not systematically addressed across the cohorts of the different working groups. Presence of comorbidities might have reduced disorder-specific findings. However, excluding comorbid conditions would have ignored complex interactions that are often integral to the disorder. Future studies should test to what extent the comorbid cases differ from the "pure" disorders. Greater consideration of how data may be used in international collaborations such as ENIGMA may influence the collection of data in future studies, which may increase their impact beyond their primary focus.

Conclusion

To conclude, we found subcortical and cortical differences across different age categories among ADHD, ASD and OCD. We found ASD-specific cortical thickness differences in the frontal cortex of adult patients and ADHD-specific subcortical differences in children and adolescents. We did not find shared differences among the three disorders and shared differences across any two disorders did not

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survive multiple comparison corrections. Further work, e.g., multivariate pattern recognition analyses and normative modeling incorporating neural correlates, cognitive and genetic variables will be useful in understanding the mechanisms underlying distinct and shared deficits in these neurodevelopmental disorders.

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ADHD working group

Disclosures

David Coghill served in an advisory or consultancy role for Lilly, Medice, Novartis, Oxford outcomes, Shire and Viforpharma. He received conference support or speaker's fee by Janssen McNeil, Lilly, Medice, Novartis, Shire and Sunovian. He is/has been involved in clinical trials conducted by Lilly & Shire. The present work is unrelated to the above grants and relationships. *Jonna Kuntsi* has given talks at educational events sponsored by Medice; all funds are received by King's College London and used for studies of ADHD. *Anders Dale* is a Founder of CorTechs Labs, Inc. He serves on the Scientific Advisory Boards of CorTechs Labs and Human Longevity, Inc., and receives research funding through a Research Agreement with General Electric Healthcare. *Paulo Mattos* was on the speakers' bureau and/or acted as consultant for Janssen-Cilag, Novartis, and Shire in the previous five years; he also received travel awards to participate in scientific meetings from those companies. The ADHD outpatient program (Grupo de Estudos do Déficit de Atenção/Institute of Psychiatry) chaired by Dr. Mattos has also received research support from Novartis and Shire. The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. *Tobias Banaschewski* served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Lundbeck, Medice, Neurim Pharmaceuticals, Novartis and Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire & Viforpharma. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. 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With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. *Joseph Biederman* is currently receiving research support from the following sources: AACAP, Feinstein Institute for Medical Research, Food & Drug Administration, Genentech, Headspace Inc., Lundbeck AS, Neurocentria Inc., NIDA, Pfizer Pharmaceuticals, Roche TCRC Inc., Shire Pharmaceuticals Inc., Sunovion Pharmaceuticals Inc., and NIH. Dr. Biederman has a financial interest in Avekshan LLC, a company that develops treatments for attention deficit hyperactivity disorder (ADHD). His interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. 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ASD working group

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OCD working group

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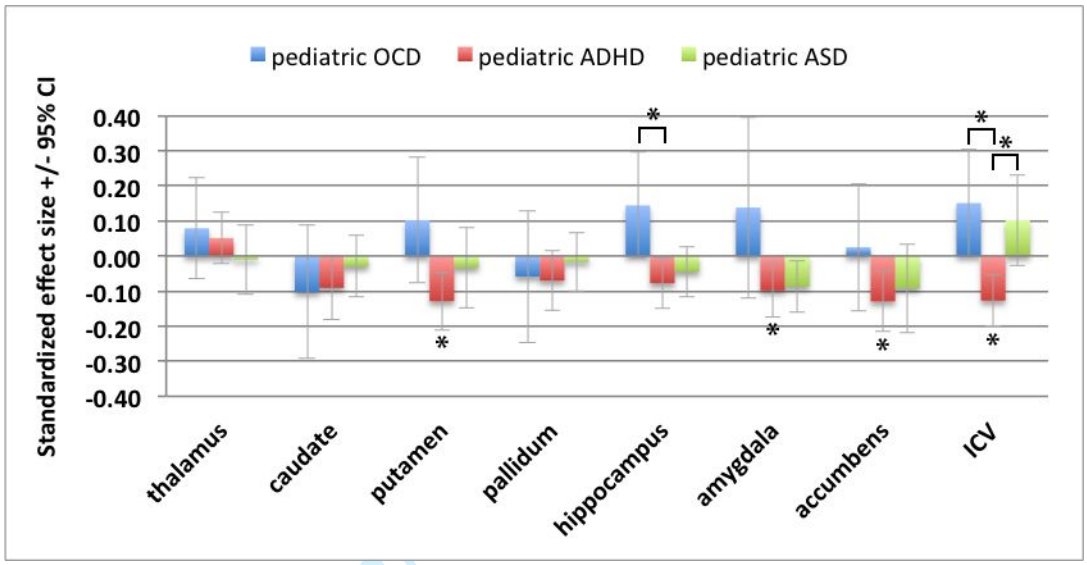
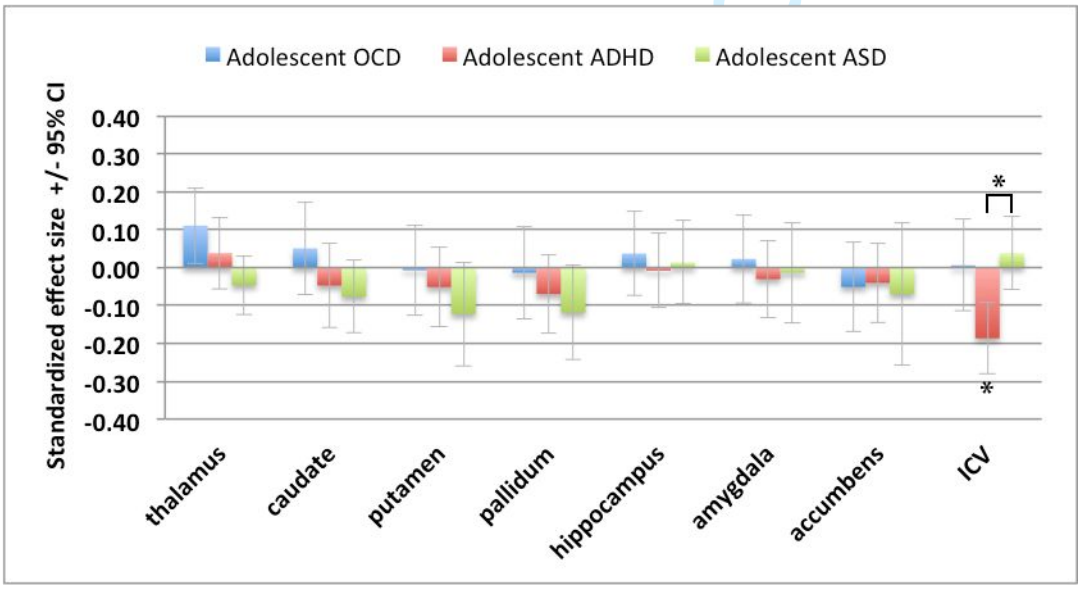
Figure 1a: Subcortical volume differences in children with ADHD, ASD, or OCD compared to controls



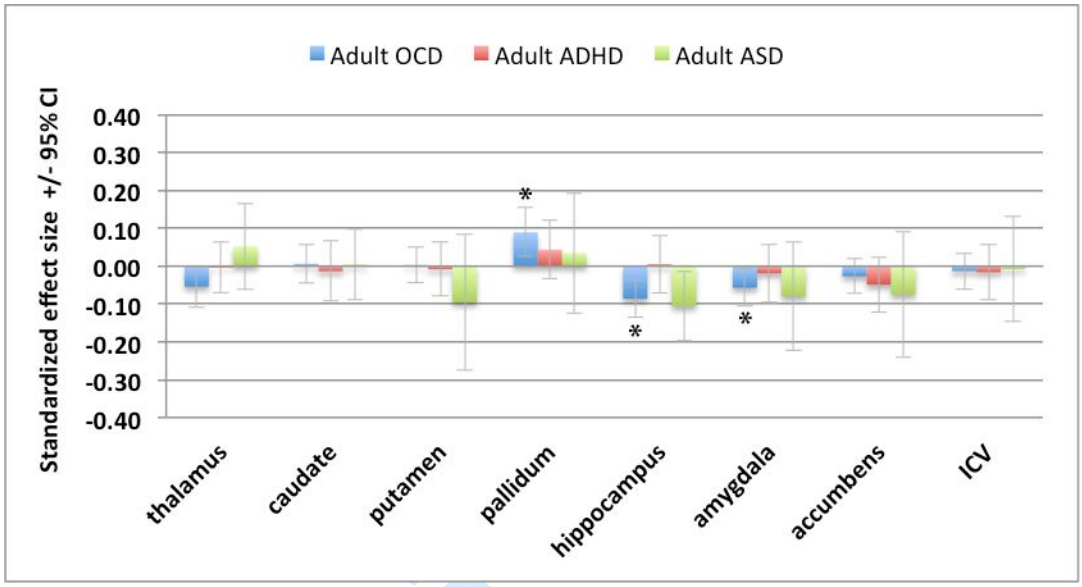
Significant results (FDR q ≤ 0.05) are indicated by an asterisk (Supplementary Table S5). For Effect size values across disorders see Supplementary Table S14. Abbreviations: Confidence Interval (CI); Intracranial volume (ICV)

Figure 1b: Subcortical volume differences in adolescents with ADHD, ASD, or OCD compared to controls



Significant results (FDR q ≤ 0.05) are indicated by an asterisk (Supplementary Table S7). For Effect size values across disorders see Supplementary Table S17. Abbreviations: Confidence Interval (CI); Intracranial volume (ICV)

Figure 1c: Subcortical volume differences in adults with ADHD, ASD, or OCD compared to controls



Significant results (FDR q ≤ 0.05) are indicated by an asterisk (Supplementary Table S10). For Effect size values across disorders see Supplementary Table S20. Abbreviations: Confidence Interval (CI); Intracranial volume (ICV)

Figure 2: Thicker cortices of several frontal regions in adults with ASD compared to those with OCD or ADHD

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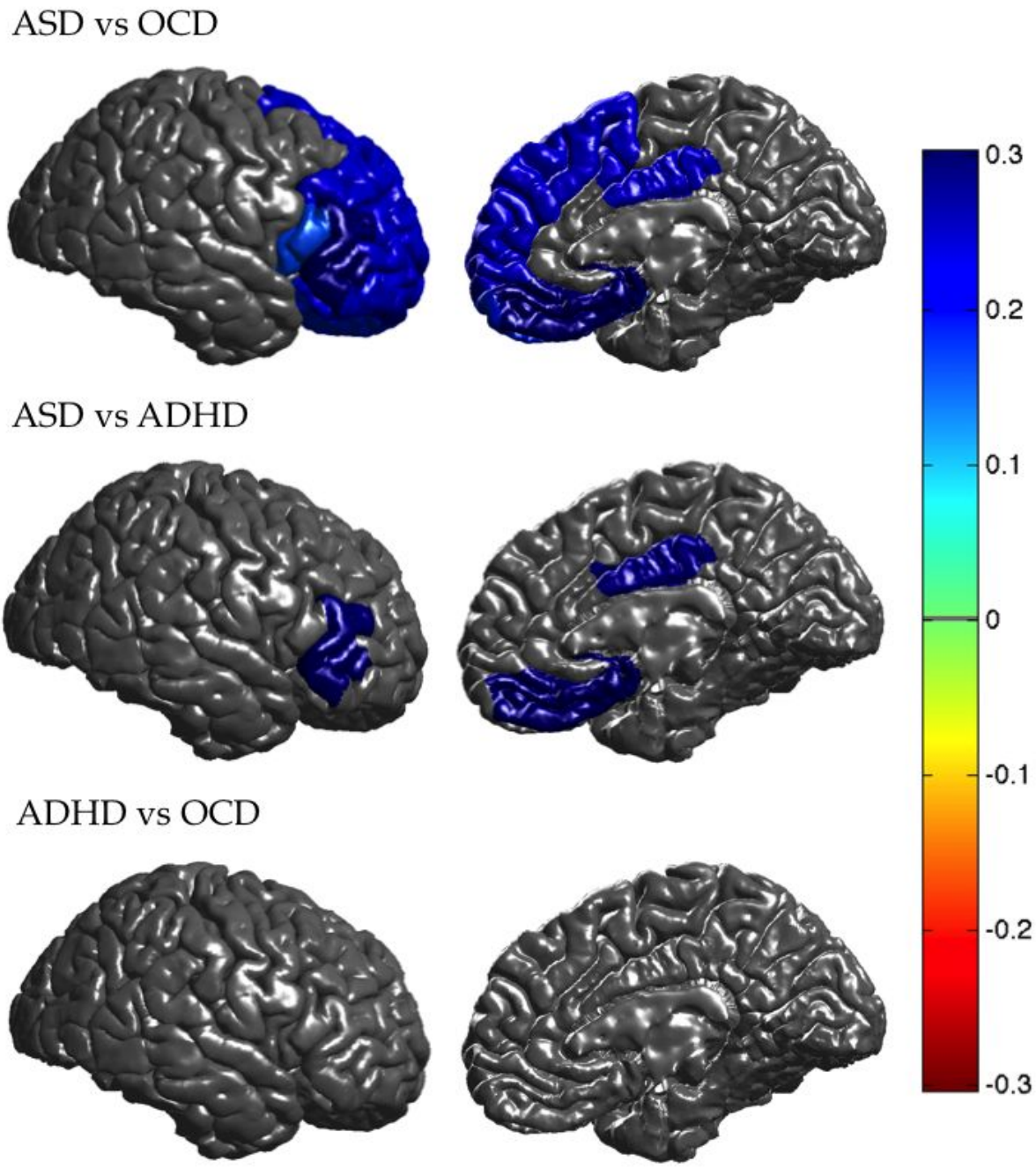

Regions that showed a significant (FDR q ≤ 0.05) difference in cortical thickness among adults with ASD, ADHD or OCD. Positive effect sizes *d* (blue) indicate thicker cortices in adults with ASD patients compared to those with ADHD or OCD.