The genetic architecture of the human cerebral cortex.

Katrina L. Grasby[1†], Neda Jahanshad[2†*], Jodie N. Painter[1‡], Lucía Colodro-Conde[1‡], Janita Bralten[3,4‡], Derrek P. Hibar[2,5‡], Penelope A. Lind[1‡], Fabrizio Pizzagalli[2‡], Christopher R.K. Ching[2,6], Mary Agnes B. McMahon[2], Natalia Shatokhina[2], Leo C.P. Zsembik[7], Ingrid Agartz[8-11], Saud Alhusaini[12,13], Marcio A.A. Almeida[14], Dag Alnæs[8,9], Inge K. Amlien[15], Micael Andersson[16,17], Tyler Ard[18], Nicola J. Armstrong[19], Allison Ashley-Koch[20], Joshua R. Atkins[21,22], Manon Bernard[23], Rachel M. Brouwer[24], Elizabeth E.L. Buimer[24], Robin Bülow[25], Christian Bürger[26], Dara M. Cannon[27], Mallar Chakravarty[28,29], Qiang Chen[30], Joshua W. Cheung[2], Baptiste Couvy-Duchesne[31-33], Anders M. Dale[34,35], Shareefa Dalvie[36], Tânia K. de Araujo[37], Greig I. de Zubicaray[38], Sonja M.C. de Zwarte[24], Anouk den Braber[39,40], Nhat Trung Doan[8,9], Katharina Dohm[26], Stefan Ehrlich[41], Hannah-Ruth Engelbrecht[42], Susanne Erk[43], Chun Chieh Fan[44], Iryna O. Fedko[39], Sonya F. Foley[45], Judith M. Ford[46], Masaki Fukunaga[47], Melanie E. Garrett[20], Tian Ge[48,49], Sudheer Giddaluru[50], Aaron L. Goldman[30], Melissa J. Green[51,52], Nynke A. Groenewold[36], Dominik Grotegerd[26], Tiril P. Gurholt[8-10], Boris A. Gutman[2,53], Narelle K. Hansell[33], Mathew A. Harris[54,55], Marc B. Harrison[2], Courtney C. Haswell[56,57], Michael Hauser[20], Stefan Herms[58-60], Dirk J. Heslenfeld[61], New Fei Ho[62], David Hoehn[63], Per Hoffmann[58,59,64], Laurena Holleran[65], Martine Hoogman[3,4], Jouke-Jan Hottenga[39], Masashi Ikeda[66], Deborah Janowitz[67], Iris E. Jansen[68,69], Tianye Jia[70-72], Christiane Jockwitz[73-75], Ryota Kanai[76-78], Sherif Karama[28,79,80], Dalia Kasperaviciute[81], Tobias Kaufmann[8,9], Sinead Kelly[82,83], Masataka Kikuchi[84], Marieke Klein[3,4,24], Michael Knapp[85], Annchen R. Knodt[86], Bernd Krämer[87,88], Max Lam[62,89], Thomas M. Lancaster[45,90], Phil H. Lee[48,91], Tristram A. Lett[43], Lindsay B. Lewis[80,92], Iscia Lopes-Cendes[37,93], Michelle Luciano[94,95], Fabio Macciardi[96], Andre F. Marquand[4,97], Samuel R. Mathias[98,99], Tracy R. Melzer[100-102], Yuri Milaneschi[103], Nazanin Mirza-Schreiber[63], Jose C.V. Moreira[93,104], Thomas W. Mühleisen[58,73,105] , Bertram Müller-Myhsok[63,106,107], Pablo Najt[27], Soichiro Nakahara[96,108], Kwangsik Nho[109], Loes M. Olde Loohuis[110], Dimitri Papadopoulos Orfanos[111], John F. Pearson[112,113], Toni L. Pitcher[100-102], Benno Pütz[63], Yann Quidé[51,52], Anjanibhargavi Ragothaman[2], Faisal M. Rashid[2], William R. Reay[21,22], Ronny Redlich[26], Céline S. Reinbold[58,59], Jonathan Repple[26], Geneviève Richard[8,9,114,115], Brandalyn C. Riedel[2,109], Shannon L. Risacher[109], Cristiane S. Rocha[37,93], Nina Roth Mota[3,4,116], Lauren Salminen[2], Arvin Saremi[2], Andrew J. Saykin[109,117], Fenja Schlag[118], Lianne Schmaal[119-121], Peter R. Schofield[122,123], Rodrigo Secolin[37,93], Chin Yang Shapland[118], Li Shen[124], Jean Shin[23,125], Elena Shumskaya[3,4,126], Ida E. Sønderby[8,9], Emma Sprooten[4], Lachlan T. Strike[33], Katherine E. Tansey[90], Alexander Teumer[127], Anbupalam Thalamuthu[128], Sophia I. Thomopoulos[2], Diana Tordesillas-Gutiérrez[129,130], Jessica A. Turner[131,132], Anne Uhlmann[36,133], Costanza Ludovica Vallerga[31], Dennis van der Meer[8,9], Marjolein M.J. van Donkelaar[3,4], Liza van Eijk[33,134], Theo G.M. van Erp[96], Neeltje E.M. van Haren[24,135], Daan van Rooij[4,97], Marie-José van Tol[136], Jan H. Veldink[137], Ellen Verhoef[118], Esther Walton[131,138], Mingyuan Wang[62], Yunpeng Wang[8,9], Joanna M. Wardlaw[54,95,139], Wei Wen[128], Lars T. Westlye[8,9,114], Christopher D. Whelan[2,12], Stephanie H. Witt[140], Katharina Wittfeld[67,141], Christiane Wolf[142], Thomas Wolfers[3], Jing Qin Wu[21], Clarissa L. Yasuda[93,143], Dario Zaremba[26], Zuo Zhang[144], Alyssa H. Zhu[2], Marcel P. Zwiers[4,97,126], Eric Artiges[145], Amelia A. Assareh[128], Rosa Ayesa-Arriola[130,146], Aysenil Belger[56], Christine L. Brandt[8,9],

Gregory G. Brown[147], Sven Cichon[58,59,73], Joanne E. Curran[14], Gareth E. Davies[148], Franziska Degenhardt[64], Michelle F. Dennis[57], Bruno Dietsche[149], Srdjan Djurovic[150,151], Colin P. Doherty[152-154], Ryan Espiritu[155], Daniel Garijo[155], Yolanda Gil[155], Penny A. Gowland[156], Robert C. Green[157-159], Alexander N. Häusler[160,161], Walter Heindel[162], Beng-Choon Ho[163], Wolfgang U. Hoffmann[127,141], Florian Holsboer[63,164], Georg Homuth[165], Norbert Hosten[166], Clifford R. Jack Jr.[167], MiHyun Jang[155], Andreas Jansen[149,168], Nathan A. Kimbrel[57,169], Knut Kolskår[8,9,114,115], Sanne Koops[24], Axel Krug[149], Kelvin O. Lim[170], Jurjen J. Luykx[24,171,172], Daniel H. Mathalon[173,174], Karen A. Mather[122,128], Venkata S. Mattay[30,175,176], Sarah Matthews[138], Jaqueline Mayoral Van Son[130,146], Sarah C. McEwen[177-179], Ingrid Melle[8,9], Derek W. Morris[27], Bryon A. Mueller[170], Matthias Nauck[180,181], Jan E. Nordvik[115], Markus M. Nöthen[64], Daniel S. O'Leary[163], Nils Opel[26], Marie - Laure Paillère Martinot[145,182], G. Bruce Pike[183], Adrian Preda[184], Erin B. Quinlan[144], Paul E. Rasser[22,185-187], Varun Ratnakar[155], Simone Reppermund[128,188], Vidar M. Steen[50,189], Paul A. Tooney[21,187], Fábio R. Torres[37,93], Dick J. Veltman[103], James T. Voyvodic[56], Robert Whelan[190], Tonya White[135,191], Hidenaga Yamamori[192], Oscar L. Lopez[193,194], Hieab H.H. Adams[193,195], Joshua C. Bis[196], Stephanie Debette[197,198], Charles Decarli[199], Myriam Fornage[200], Vilmundur Gudnason[201,202], Edith Hofer[203,204], M. Arfan Ikram[193], Lenore Launer[205], W. T. Longstreth[206], Bernard Mazoyer[207], Thomas H. Mosley[208], Gennady V. Roshchupkin[193-195], Claudia L. Satizabal[209-211], Reinhold Schmidt[212], Sudha Seshadri[209,211,,213], Qiong Yang[214], The Alzheimer's Disease Neuroimaging Initiative[#], CHARGE consortium[#], EPIGEN consortium[#], IMAGEN consortium[#], SYS consortium[#], The Parkinson's Progression Markers Initiative[#], Marina K.M. Alvim[93,143], David Ames[215,216], Tim J. Anderson[100-102,217], Ole A. Andreassen[8,9], Alejandro Arias-Vasquez[3,4,116], Mark E. Bastin[54,95], Bernhard T. Baune[218-220], John Blangero[14], Dorret I. Boomsma[39], Henry Brodaty[128,221], Han G. Brunner[3,4,222], Randy L. Buckner[223-225], Jan K. Buitelaar[4,97,226], Juan R. Bustillo[227], Wiepke Cahn[228], Murray J. Cairns[21,22,229], Vince Calhoun[230], Vaughan J. Carr[51,52,231], Xavier Caseras[90], Svenja Caspers[73,75,232], Gianpiero L. Cavalleri[233,234], Fernando Cendes[93,143], Benedicto Crespo-Facorro[130,146], John C. Dalrymple-Alford[101,102,235], Udo Dannlowski[26], Eco J.C. de Geus[39], Ian J. Deary[94,95], Chantal Depondt[236], Sylvane Desrivières[72,144], Gary Donohoe[65], Thomas Espeseth[8,114], Guillén Fernández[4,97], Simon E. Fisher[4,118], Herta Flor[237], Andreas J. Forstner[58,59,64,238], Clyde Francks[4,118], Barbara Franke[3,4,116], David C. Glahn[99,239], Randy L. Gollub[91,224,225], Hans J. Grabe[67,141], Oliver Gruber[87], Asta K. Håberg[240,241], Ahmad R. Hariri[86], Catharina A. Hartman[242], Ryota Hashimoto[192,243,244], Andreas Heinz[245], Frans A. Henskens[185,246], Manon H.J. Hillegers[135,247], Pieter J. Hoekstra[242], Avram J. Holmes[224,248], L. Elliot Hong[249], William D. Hopkins[250,251], Hilleke E. Hulshoff Pol[24], Terry L. Jernigan[35,44,147,252], Erik G. Jönsson[9,11], René S. Kahn[24,253], Martin A. Kennedy[113], Tilo T.J. Kircher[149], Peter Kochunov[249], John B.J. Kwok[122,123,254], Stephanie Le Hellard[50,189], Carmel M. Loughland[185,255], Nicholas G. Martin[32], Jean-Luc Martinot[145], Colm McDonald[27], Katie L. McMahon[256], Andreas Meyer-Lindenberg[257], Patricia T. Michie[258], Rajendra A. Morey[56,57], Bryan Mowry[33,259], Lars Nyberg[16,17,260], Jaap Oosterlaan[261-263], Roel A.. Ophoff[110], Christos Pantelis[219,220,264], Tomas Paus[265-267], Zdenka Pausova[23,268], Brenda W.J.H. Penninx[103], Tinca J.C. Polderman[68], Danielle Posthuma[68,269], Marcella Rietschel[140], Joshua L. Roffman[224], Laura M. Rowland[249], Perminder S. Sachdev[128,270], Philipp G. Sämann[63], Ulrich Schall[22,187], Gunter Schumann[72,144], Rodney J. Scott[21,271], Kang Sim[272], Sanjay M. Sisodiya[81,273], Jordan W. Smoller[48,224,274], Iris E.

Sommer[136,242,247,275], Beate St Pourcain[4,118,138], Dan J. Stein[36,276], Arthur W. Toga[18], Julian N. Trollor[128,188], Nic J.A. Van der Wee[277], Dennis van 't Ent[39], Henry Völzke[127], Henrik Walter[43], Bernd Weber[160,161], Daniel R. Weinberger[30,278], Margaret J. Wright[33,279], Juan Zhou[280], Jason L. Stein[7§]*, Paul M. Thompson[2§]*, Sarah E. Medland[1§]* on behalf of the Enhancing NeuroImaging Genetics through Meta-Analysis Consortium - Genetics working group

[1] *Psychiatric Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia.*
[2] *Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, University of Southern California, Los Angeles, USA.*
[3] *Department of Human Genetics, Radboud university medical center, Nijmegen, The Netherlands.*
[4] *Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands.*
[5] *Neuroscience Biomarkers, Janssen Research and Development, LLC, San Diego, USA.*
[6] *Graduate Interdepartmental Program in Neuroscience, University of California Los Angeles, Los Angeles, USA.*
[7] *Department of Genetics & UNC Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, USA.*
[8] *NORMENT - K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway.*
[9] *NORMENT - K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway.*
[10] *Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway.*
[11] *Centre for Psychiatric Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.*
[12] *Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland.*
[13] *Neurology Department, University of California at San Francisco, San Francisco, USA.*
[14] *Department of Human Genetics and South Texas Diabetes and Obesity Institute, University of Texas Rio Grande Valley School of Medicine, Brownsville, USA.*
[15] *Centre for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo, Oslo, Norway.*
[16] *Department of Integrative Medical Biology, Umeå University, Umeå, Sweden.*
[17] *Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden.*
[18] *Laboratory of Neuro Imaging, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of the University of Southern California, Los Angeles, USA.*
[19] *Mathematics and Statistics, Murdoch University, Murdoch, Australia.*
[20] *Duke Molecular Physiology Institute, Duke University Medical Center, Durham, USA.*
[21] *School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia.*
[22] *Priority Centre for Brain and Mental Health Research, University of Newcastle, Callaghan, Australia.*
[23] *The Hospital for Sick Children, University of Toronto, Toronto, Canada.*
[24] *Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.*
[25] *Institute for Radiology and Neuroradiology, University Medicine, Ernst-Moritz-Arndt University, Greifswald, Germany.*

[26] *Department of Psychiatry, University of Münster, Münster, Germany.*
[27] *Centre for Neuroimaging & Cognitive Genomics, National University of Ireland Galway, Galway, Ireland.*
[28] *Douglas Mental Health University Institute, McGill University, Montreal, Canada.*
[29] *Departments of Psychiatry and Biological and Biomedical Engineering, McGill University, Montreal, Canada.*
[30] *Lieber Institute for Brain Development, Baltimore, USA.*
[31] *Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia.*
[32] *Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Australia.*
[33] *Queensland Brain Institute, University of Queensland, St Lucia, Australia.*
[34] *Department of Neurosciences, University of California, San Diego, La Jolla, USA.*
[35] *Department of Radiology, University of California San Diego, San Diego, USA.*
[36] *Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa.*
[37] *Department of Medical Genetics, School of Medical Sciences, University of Campinas - UNICAMP, Campinas, Brazil.*
[38] *Faculty of Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia.*
[39] *Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[40] *Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands.*
[41] *Division of Psychological & Social Medicine and Developmental Neurosciences, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany.*
[42] *Division of Human Genetics, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa.*
[43] *Division of Mind and Brain Research, Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité - Universitätsmedizin Berlin corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany.*
[44] *Department of Cognitive Science, University of California San Diego, San Diego, USA.*
[45] *Cardiff University Brain Research Imaging Centre, Cardiff University, Cardiff, UK.*
[46] *San Francisco Veterans Administration Medical Center, San Francisco, USA.*
[47] *Division of Cerebral Integration, National Institute for Physiological Sciences, Okazaki, Japan.*
[48] *Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, USA.*
[49] *Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, USA.*
[50] *NORMENT - K.G. Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, Norway.*
[51] *School of Psychiatry, University of New South Wales, Sydney, Australia.*
[52] *Neuroscience Research Australia, Sydney, New South Wales, Australia.*
[53] *Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, USA.*
[54] *Centre for Clinical Brain Sciences and Edinburgh Imaging, University of Edinburgh, Edinburgh, UK.*
[55] *Division of Psychiatry, University of Edinburgh, Edinburgh, UK.*
[56] *Duke UNC Brain Imaging and Analysis Center, Duke University Medical Center, Durham, USA.*

[57] *Mental Illness Research Education and Clinical Center for Post Deployment Mental Health, Durham VA Medical Center, Durham, USA.*
[58] *Department of Biomedicine, University of Basel, Basel, Switzerland.*
[59] *Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland.*
[60] *Department of Genomics, Life & Brain Research Center, University of Bonn, Bonn, Germany.*
[61] *Department of Cognitive and Clinical Neuropsychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[62] *Research Division, Institute of Mental Health, Singapore, Singapore.*
[63] *Max Planck Institute of Psychiatry, Munich, Germany.*
[64] *Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany.*
[65] *Centre for Neuroimaging & Cognitive Genomics, School of Psychology, National University of Ireland Galway, Galway, Ireland.*
[66] *Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan.*
[67] *Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany.*
[68] *Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[69] *Department of Neurology, Alzheimer Center, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[70] *Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China.*
[71] *Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence (Fudan University), Ministry of Education, Shanghai, China.*
[72] *Centre for Population Neuroscience and Precision Medicine (PONS), Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.*
[73] *Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany.*
[74] *Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, RWTH Aachen University, Aachen, Germany.*
[75] *JARA-BRAIN, Jülich-Aachen Research Alliance, Jülich, Germany.*
[76] *Department of Neuroinformatics, Araya, Inc., Tokyo, Japan.*
[77] *Sackler Centre for Consciousness Science, School of Psychology, University of Sussex, Falmer, UK.*
[78] *Earth-Life Science Institute, Tokyo Institute of Technology, Tokyo, Japan.*
[79] *Department of Psychiatry, McGill University, Montreal, Canada.*
[80] *McConnell Brain Imaging Center, Montreal Neurological Institute, Montreal, Canada.*
[81] *Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK.*
[82] *Public Psychiatry Division, Massachusetts Mental Health Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA.*
[83] *Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, USA.*
[84] *Department of Genome Informatics, Graduate School of Medicine, Osaka University, Suita, Japan.*
[85] *Department of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Germany.*
[86] *Department of Psychology and Neuroscience, Duke University, Durham, USA.*
[87] *Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University Hospital, Heidelberg, Germany.*

[88] *Centre for Translational Research in Systems Neuroscience and Psychiatry, Department of Psychiatry & Psychotherapy, University Medical Center Göttingen, Göttingen, Germany.*
[89] *Human Genetics, Genome Institute of Singapore, Singapore, Singapore.*
[90] *MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK.*
[91] *Department of Psychiatry, Harvard Medical School, Boston, USA.*
[92] *McGill Centre for Integrative Neuroscience, McGill University, Montreal, Canada.*
[93] *BRAINN - Brazilian Institute of Neuroscience and Neurotechnology, Campinas, Brazil.*
[94] *Department of Psychology, University of Edinburgh, Edinburgh, UK.*
[95] *Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK.*
[96] *Department of Psychiatry and Human Behavior, School of Medicine University of California, Irvine, Irvine, USA.*
[97] *Department of Cognitive Neuroscience, Radboud university medical center, Nijmegen, The Netherlands.*
[98] *Department of Psychiatry, Yale University School of Medicine, New Haven, USA.*
[99] *Olin Neuropsychiatric Research Center, Institute of Living, Hartford Hospital, Hartford, USA.*
[100] *Department of Medicine, University of Otago, Christchurch, Christchurch, New Zealand.*
[101] *New Zealand Brain Research Institute, Christchurch, New Zealand.*
[102] *Brain Research New Zealand - Rangahau Roro Aotearoa, Christchurch, New Zealand.*
[103] *Amsterdam UMC, Vrije Universiteit, Psychiatry, Amsterdam Public Health and Amsterdam Neuroscience and GGZinGeest, Amsterdam, The Netherlands.*
[104] *IC - Institute of Computing, Campinas, Brazil.*
[105] *Cécile and Oskar Vogt Institute of Brain Research, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany.*
[106] *Munich Cluster for Systems Neurology (SyNergy), Munich, Germany.*
[107] *Institute of Translational Medicine, Liverpool, UK.*
[108] *Drug Discovery Research, Astellas Pharmaceuticals, 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan.*
[109] *Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, USA.*
[110] *Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, USA.*
[111] *NeuroSpin, CEA, Université Paris-Saclay, Gif-sur-Yvette, France.*
[112] *Biostatistics and Computational Biology Unit, University of Otago, Christchurch, Christchurch, New Zealand.*
[113] *Department of Pathology and Biomedical Science, University of Otago, Christchurch, Christchurch, New Zealand.*
[114] *Department of Psychology, University of Oslo, Oslo, Norway.*
[115] *Sunnaas Rehabilitation Hospital HT, Nesodden, Norway.*
[116] *Department of Psychiatry, Radboud university medical center, Nijmegen, The Netherlands.*
[117] *Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, USA.*
[118] *Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, The Netherlands.*
[119] *Orygen, The National Centre of Excellence for Youth Mental Health, Melbourne, Australia.*
[120] *The Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia.*

[121] *Department of Psychiatry, Vrije Universiteit University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[122] *Neuroscience Research Australia, Sydney, Australia.*
[123] *School of Medical Sciences, University of New South Wales, Sydney, Australia.*
[124] *Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, USA.*
[125] *Population Neuroscience & Developmental Neuroimaging, Bloorview Research Institute, University of Toronto, East York, Canada.*
[126] *Donders Centre for Cognitive Neuroimaging, Radboud University, Nijmegen, The Netherlands.*
[127] *Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany.*
[128] *Centre for Healthy Brain Ageing, University of New South Wales, Sydney, Australia.*
[129] *Neuroimaging Unit, Technological Facilities, Valdecilla Biomedical Research Institute IDIVAL, Santander, Spain.*
[130] *Centro Investigacion Biomedica en Red Salud Mental, Santander, Spain.*
[131] *Department of Psychology, Georgia State University, Atlanta, USA.*
[132] *Mind Research Network, Albuquerque, USA.*
[133] *Department of Psychiatry, University of Vermont, Burlington, USA.*
[134] *School of Psychology, University of Queensland, Brisbane, Australia.*
[135] *Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands.*
[136] *Cognitive Neuroscience Center, Department of Neuroscience, University Medical Center Groningen, Groningen, The Netherlands.*
[137] *Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.*
[138] *MRC Integrative Epidemiology Unit, Department of Population Health Sciences, Bristol Medical School, Bristol, UK.*
[139] *UK Dementia Research Institute, The University of Edinburgh, Edinburgh, UK.*
[140] *Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.*
[141] *German Center for Neurodegenerative Diseases Rostock/Greifswald, Greifswald, Germany.*
[142] *Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany.*
[143] *Department of Neurology, FCM, UNICAMP, Campinas, Brazil.*
[144] *Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.*
[145] *INSERM Unit 1000 - Neuroimaging & Psychiatry, Paris Saclay University,Gif sur Yvette, France.*
[146] *Department of Psychiatry, University Hospital Marqués de Valdecilla, School of Medicine, University of Cantabria–IDIVAL, Santander, Spain.*
[147] *Department of Psychiatry, University of California San Diego, San Diego, USA.*
[148] *Avera Institute for Human Genetics, Sioux Falls, USA.*
[149] *Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Marburg, Germany.*
[150] *Department of Medical Genetics, Oslo University Hospital, Oslo, Norway.*
[151] *NORMENT, Department of Clinical Science, University of Bergen, Bergen, Norway.*
[152] *Department of Neurology, St James's Hospital, Dublin, Ireland.*
[153] *Academic Unit of Neurology, TBSI, Dublin, Ireland.*
[154] *Future Neuro, Royal College of Surgeons in Ireland, Dublin, Ireland.*

[155] *Information Sciences Institute, University of Southern California, Los Angeles, USA.*
[156] *Sir Peter Mansfield Imaging Centre, University of Nottingham, Nottingham, UK.*
[157] *Brigham and Women's Hospital, Boston, USA.*
[158] *The Broad Institute, Boston, USA.*
[159] *Harvard Medical School, Boston, USA.*
[160] *Center for Economics and Neuroscience, University of Bonn, Bonn, Germany.*
[161] *Institute of Experimental Epileptology and Cognition Research, University Hospital Bonn, Germany.*
[162] *Department of Clinical Radiology, University of Münster, Münster, Germany.*
[163] *Department of Psychiatry, University of Iowa College of Medicine, Iowa City, USA.*
[164] *HMNC Holding GmbH, Munich, Germany.*
[165] *University Medicine Greifswald, Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, Greifswald, Germany.*
[166] *Institute of Diagnostic Radiology and Neuroradiology, Greifswald, Germany.*
[167] *Dept of Radiology, Mayo Clinic, Rochester, USA.*
[168] *Core-Unit Brainimaging, Faculty of Medicine, University of Marburg, Marburg, Germany.*
[169] *Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, USA.*
[170] *Department of Psychiatry, University of Minnesota, Minneapolis, USA.*
[171] *Department of Translational Neuroscience, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.*
[172] *GGNet Mental Health, Apeldoorn, The Netherlands.*
[173] *Department of Psychiatry and Weill Institute for Neurosciences, University of California San Francisco, San Francisco, USA.*
[174] *Mental Health Service 116d, Veterans Affairs San Francisco Healthcare System, San Francisco, USA.*
[175] *Department of Neurology, Johns Hopkins University, Baltimore, USA.*
[176] *Department of Radiology, Johns Hopkins University, Baltimore, USA.*
[177] *Department of Psychiatry, University of California San Diego, La Jolla, USA.*
[178] *Pacific Brain Health Center, Santa Monica, USA.*
[179] *John Wayne Cancer Institute, Santa Monica, USA.*
[180] *Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany.*
[181] *German Centre for Cardiovascular Research, Greifswald, Germany.*
[182] *Child and adolescent psychiatry department, APHP Pitié Salpêtrière hospital, Paris, France.*
[183] *Radiology and Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada.*
[184] *School of Medicine, University of California Irvine, Irvine, USA.*
[185] *School of Medicine and Public Health, University of Newcastle, Callaghan, Australia.*
[186] *Priority Centre for Stroke and Brain Injury, University of Newcastle, Callaghan, Australia.*
[187] *Hunter Medical Research Institute, Newcastle, Australia.*
[188] *Department of Developmental Disability Neuropsychiatry, University of New South Wales, Sydney, Australia.*
[189] *Dr. Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway.*
[190] *School of Psychology, Trinity College Dublin, Dublin, Ireland.*

[191] *Department of Radiology, Erasmus University Medical Centre, Rotterdam, The Netherlands.*
[192] *Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Japan.*
[193] *Department of Epidemiology, Erasmus MC Medical Center, Rotterdam, The Netherlands.*
[194] *Medical Informatics, Erasmus MC Medical Center, Rotterdam, The Netherlands.*
[195] *Department of Radiology and Nuclear Medicine, Erasmus MC Medical Center, Rotterdam, The Netherlands.*
[196] *Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, USA.*
[197] *Inserm, Bordeaux Population Health Research Center, team VINTAGE, UMR 1219, University of Bordeaux, Bordeaux, France.*
[198] *Department of Neurology, CHU de Bordeaux, Bordeaux, France.*
[199] *Department of Neurology, University of California, Davis, Sacramento, USA.*
[200] *Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, USA.*
[201] *Icelandic Heart Association, Kopavogur, Iceland.*
[202] *Faculty of Medicine, University of Iceland, Reykjavik, Iceland.*
[203] *Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria.*
[204] *Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria.*
[205] *Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute on Aging, Bethesda, USA.*
[206] *Departments of Neurology and Epidemiology, University of Washington, Seattle, USA.*
[207] *Neurodegeneratives Diseases Institute UMR 5293, CNRS, CEA, University of Bordeaux, Bordeaux, France.*
[208] *MIND Center, University of Mississippi Medical Center, Jackson, USA.*
[209] *Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, USA.*
[210] *Department of Epidemiology & Biostatistics, University of Texas Health Sciences Center, San Antonio, USA.*
[211] *Department of Neurology, Boston University School of Medicine, Boston, USA.*
[212] *Departments of Genetics and Neuroscience, Yale University School of Medicine, New Haven, USA.*
[213] *Framingham Heart Study and Department of Neurology, Boston University School of Medicine, Boston, USA.*
[214] *Department of Biostatistics, Boston University School of Public Health, Boston, USA.*
[215] *Academic Unit for Psychiatry of Old Age, University of Melbourne, Melbourne, Australia.*
[216] *National Ageing Research Institute, Melbourne, Australia.*
[217] *Department of Neurology, Canterbury District Health Board, Christchurch, New Zealand.*
[218] *University Hospital Department of Psychiatry and Psychotherapy, University of Münster, Münster, Germany.*
[219] *Department of Psychiatry, The University of Melbourne, Melbourne, Australia.*
[220] *Florey Institute for Neuroscience and Mental Health, University of Melbourne, Parkville, Australia.*
[221] *Dementia Centre for Research Collaboration, University of New South Wales, Sydney, Australia.*
[222] *Department of Clinical Genetics and School for Oncology & Developmental Biology (GROW), Maastricht University Medical Center, Maastricht, The Netherlands.*

[223] *Department of Psychology and Center for Brain Science, Harvard University, Boston, USA.*
[224] *Department of Psychiatry, Massachusetts General Hospital, Boston, USA.*
[225] *Department of Radiology, Massachusetts General Hospital, Boston, USA.*
[226] *Karakter Child and Adolescent Psychiatry University Center, Nijmegen, The Netherlands.*
[227] *Department of Psychiatry, University of New Mexico, Albuquerque, USA.*
[228] *Department of Psychiatry, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.*
[229] *Schizophrenia Research Institute, Randwick, Australia.*
[230] *Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, Emory University, Atlanta, USA.*
[231] *Department of Psychiatry, Monash University, Clayton, Australia.*
[232] *Institute for Anatomy I, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany.*
[233] *Molecular and Cellular Therapeutics, The Royal College of Surgeons In Ireland, Dublin, Ireland.*
[234] *The SFI FutureNeuro Research Centre, Dublin, Ireland.*
[235] *Department of Psychology, University of Canterbury, Christchurch, New Zealand.*
[236] *Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.*
[237] *Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.*
[238] *Department of Psychiatry (UPK), University of Basel, Basel, Switzerland.*
[239] *Tommy Fuss Center for Neuropsychiatric Disease Research, Boston Children's Hospital and Department of Psychiatry, Harvard Medical School, Boston, USA.*
[240] *Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway.*
[241] *Department of Radiology and Nuclear medicine, Trondheim, Norway.*
[242] *Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*
[243] *Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Suita, Japan.*
[244] *Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan.*
[245] *Department of Psychiatry and Psychotherapy, Charité Campus Mitte, Charité - Universitätsmedizin Berlin, Berlin, Germany.*
[246] *Health Behaviour Research Group, University of Newcastle, Callaghan, Australia.*
[247] *Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.*
[248] *Department of Psychology, Yale University, New Haven, USA.*
[249] *Maryland Psychiatry Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, USA.*
[250] *Neuroscience Institute, Georgia State University, Atlanta, USA.*
[251] *Division of Developmental and Cognitive Neuroscience, Yerkes National Primate Research Center, Atlanta, USA.*
[252] *Center for Human Development, University of California San Diego, La Jolla, USA.*
[253] *Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA.*
[254] *Neurogenetics and Epigenetics, Brain and Mind Centre, The University of Sydney, Sydney, Australia.*

[255] *Hunter New England Mental Health Service, Newcastle, Australia.*
[256] *Herston Imaging Research Facility, School of Clinical Sciences, Queensland University of Technology, Brisbane, Australia.*
[257] *Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.*
[258] *School of Psychology, University of Newcastle, Callaghan, Australia.*
[259] *Queensland Centre for Mental Health Research, The University of Queensland, Brisbane, Australia.*
[260] *Department of Radiation Sciences, Umeå University, Umeå, Sweden.*
[261] *Emma Children's Hospital Academic Medical Center, Amsterdam, The Netherlands.*
[262] *Department of Pediatrics, Vrije Universiteit Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[263] *Clinical Neuropsychology section, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[264] *NorthWestern Mental Health, Sunshine Hospital, St Albans, Australia.*
[265] *Bloorview Research Institute, University of Toronto, Toronto, Canada.*
[266] *Departments of Psychology and Psychiatry, University of Toronto, Toronto, Canada.*
[267] *Centre for Developing Brain, Child Mind Institute, New York City, USA.*
[268] *Department of Physiology, University of Toronto, Toronto, Canada.*
[269] *Department of Clinical Genetics, Vrije Universiteit Medical Centre, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.*
[270] *Neuropsychiatric Institute, The Prince of Wales Hospital, Sydney, Australia.*
[271] *Division of Molecular Medicine, John Hunter Hospital, New Lambton Heights, Australia.*
[272] *General Psychiatry, Institute of Mental Health, Singapore, Singapore.*
[273] *Chalfont Centre for Epilepsy, Chalfont-St-Peter, UK.*
[274] *Stanley Center for Psychiatric Research, Broad Institute, Boston, USA.*
[275] *Department of Medical and Biological Psychology, University of Bergen, Bergen, Norway.*
[276] *MRC Unit on Risk & Resilience in Mental Disorders, University of Cape Town, Cape Town, South Africa.*
[277] *Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands.*
[278] *Psychiatry, Neurology, Neuroscience, Genetics, Johns Hopkins University, Baltimore, USA.*
[279] *Centre for Advanced Imaging, University of Queensland, Brisbane, Australia.*
[280] *Center for Cognitive Neuroscience, Neuroscience and behavioral disorders program, Duke-National University of Singapore Medical School, Singapore, Singapore.*

The cerebral cortex underlies our complex cognitive capabilities, yet we know little about the specific genetic loci influencing human cortical structure. To identify genetic variants, including structural variants, impacting cortical structure, we conducted a genome-wide association meta-analysis of brain MRI data from 51,662 individuals. We analysed the surface area and average thickness of the whole cortex and 34 regions with known functional specialisations. We identified 255 nominally significant loci ($P \leq 5 \times 10^{-8}$); 199 survived multiple testing correction ($P \leq 8.3 \times 10^{-10}$; 187 surface area; 12 thickness). We found significant enrichment for loci influencing total surface area within regulatory elements active during prenatal cortical development, supporting the radial unit hypothesis. Loci impacting regional surface area cluster near genes in Wnt signalling pathways, known to influence progenitor expansion and areal identity. Variation in cortical structure is genetically correlated with cognitive function, Parkinson's disease, insomnia, depression and ADHD.

One Sentence Summary: Common genetic variation is associated with inter-individual variation in the structure of the human cortex, both globally and within specific regions, and is shared with genetic risk factors for some neuropsychiatric disorders.

The human cerebral cortex is the outer grey matter layer of the brain, which is implicated in multiple aspects of higher cognitive function. Its distinct folding pattern is characterised by convex (*gyral*) and concave (*sulcal*) regions. Computational brain mapping approaches use the consistent folding patterns across individual cortices to label brain regions(*1*). During fetal development excitatory neurons, the predominant neuronal cell-type in the cortex, are generated from neural progenitor cells in the developing germinal zone(*2*). The radial unit hypothesis(*3*) posits that the expansion of cortical surface area (SA) is driven by the proliferation of these neural progenitor cells, whereas thickness (TH) is determined by the number of neurogenic divisions. Variation in global and regional measures of cortical SA and TH are associated with neuropsychiatric disorders and psychological traits(*4*) (Table S1). Twin and family-based brain imaging studies show that SA and TH measurements are highly heritable and are largely influenced by independent genetic factors(*5*). Despite extensive studies of genes impacting cortical structure in model organisms(*6*), our current understanding of genetic variation impacting human cortical size and patterning is limited to rare, highly penetrant variants(*7, 8*). These variants often disrupt cortical development, leading to altered post-natal structure. However, little is known about how common genetic variants impact human cortical SA and TH.

To address this, we conducted genome-wide association meta-analyses of cortical SA and TH measures in 51,662 individuals from 60 cohorts from around the world (Tables S2–S4). Cortical measures were extracted from structural brain MRI scans in regions defined by gyral anatomy using the Desikan-Killiany atlas(*9*). We analysed two global measures, total SA and average TH, and SA and TH for 34 regions averaged across both hemispheres, yielding 70 distinct phenotypes (Fig. 1A; Table S1).

Within each cohort genome-wide association (GWAS) for each of the 70 phenotypes was conducted using an additive model. To identify genetic influences specific to each region, the primary GWAS of regional measures included the global measure of SA or TH as a covariate. To better localise the global findings, regional GWAS were also run without controlling for global measures. To estimate the multiple testing burden associated with analysing 70 phenotypes we used matrix spectral decomposition(*10*), which yielded 60 independent traits. Therefore, we adopted a significance threshold of $P \leq 8.3 \times 10^{-10}$.

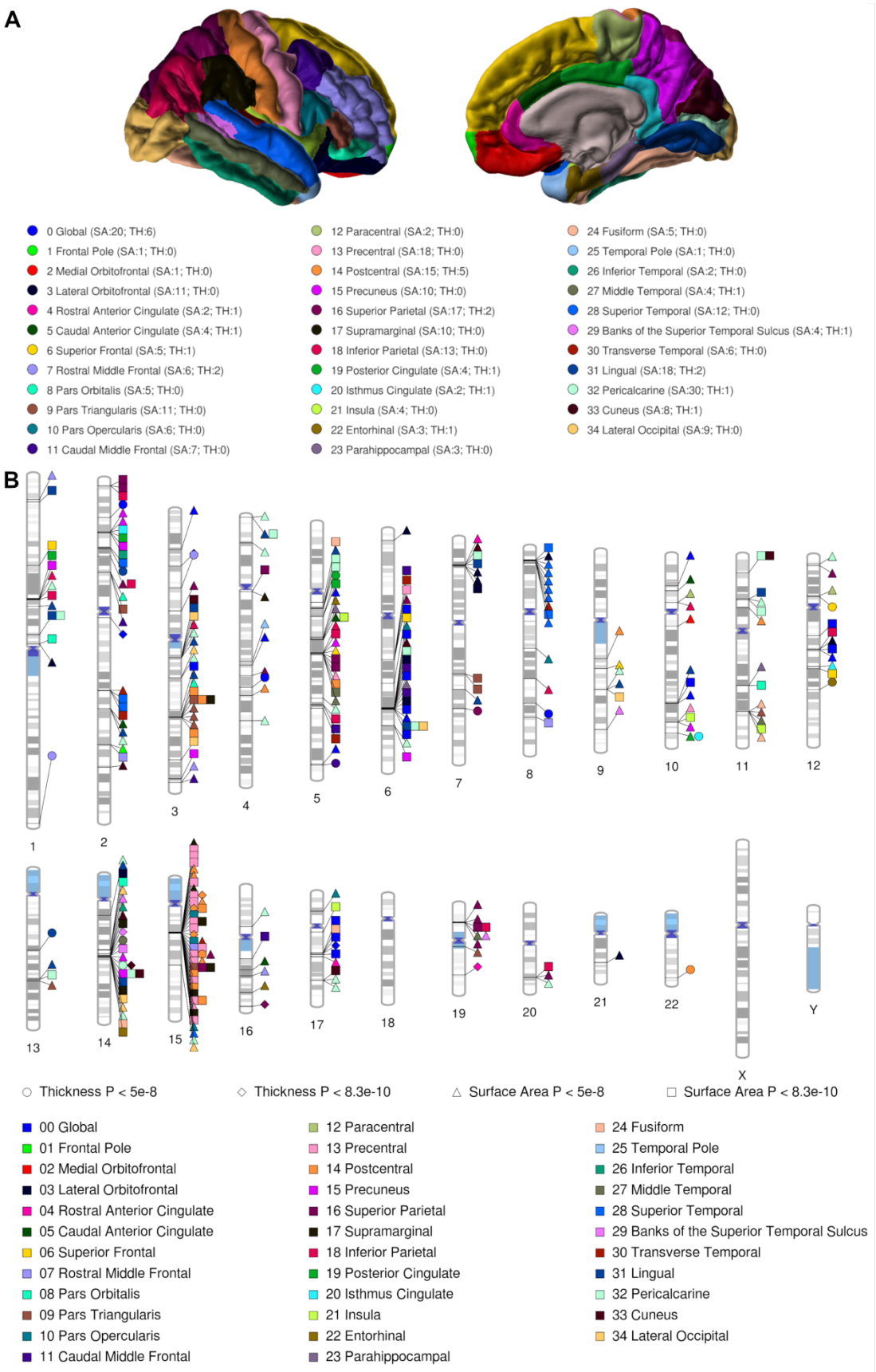

Fig. 1 | Regions of the human cortex and associated genetic loci. A, The 34 cortical regions defined by the Desikan-Killiany atlas; **B**, Ideogram of loci influencing cortical SA and TH.

The principal meta-analysis comprised results from 49 ENIGMA cohorts of European ancestry (23,909 participants) and the UK Biobank(*11*) (10,083 participants of European ancestry). We sought replication for loci reaching $P \leq 5 \times 10^{-8}$ in an additional ENIGMA cohort (777 participants) and with the CHARGE consortium(*12*) (13,950 participants, excluding UK Biobank). In addition, we meta-analysed eight cohorts of non-European ancestry (2,943 participants) to examine the generalization of these effects. High genetic correlations were observed between the meta-analysed ENIGMA European cohorts (excluding UK Biobank) and the UK Biobank cohort using LD-score regression (total SA r_G = 1.00, $P = 2.7 \times 10^{-27}$, average TH r_G = 0.91, $P = 1.7 \times 10^{-19}$), indicating consistent genetic architecture between the 49 ENIGMA cohorts and the single-site, single-scanner UK Biobank cohort.

Across the 70 cortical phenotypes we identified 306 loci that were nominally genome-wide significant in the principal meta-analysis ($P \leq 5 \times 10^{-8}$; Fig. 1B; Table S5). Of these 118 are novel, neither they nor their proxies have been associated with cortical SA or TH or volume in previous studies(*12-14*). Twenty of these were insertions or deletions (INDELs), which were not available in the replication data set. Eleven INDELs could be replicated with a proxy SNP; however, for six INDELs and one single nucleotide polymorphism (SNP) there were no proxies available to assess replication. Of the 299 loci, 255 remained genome-wide significant when the replication data were included in the meta-analysis (241 influencing SA and 14 influencing TH), with 199 passing multiple testing correction ($P \leq 8.3 \times 10^{-10}$; 187 influencing SA and 12 influencing TH). Of the 255 loci that replicated in Europeans, eleven SNPs were not available or did not pass quality control in the meta-analysis of non-European cohorts. Of the remaining 244 loci, 241 were supported in the meta-analysis with the non-European cohorts, such that the beta from the principal meta-analysis was contained within the 95% confidence intervals from the non-European meta-analysis. While most effects generalized across ancestry groups, some loci showed evidence of substantial heterogeneity. Table S5 details these results and Figure S1 sumarises these meta-analytic steps and results. Significant gene-based association was observed for 253 genes across the 70 cortical phenotypes (Table S6). Figures summarising the meta-analytic results (Manhattan, QQ, Forest, and Locus Zoom plots) are provided in the additional online materials.

Genetics of total SA and average TH

Common variants explained 34% (*SE* = 3%) of the variation in total SA and 26% (*SE* = 2%) in average TH, which approaches a third of the heritability estimated from twin and family studies(*5*) (Table S7). We observed a significant negative genetic correlation between total SA and average TH (r_G = -.32, *SE* = .05, $P = 6.5 \times 10^{-12}$; Fig. 2A), which persisted after excluding the chromosome 17 inversion region known to influence brain size(*14*) (r_G = -.31, *SE* = .05, $P = 3.3 \times 10^{-12}$). The direction of this correlation suggests that opposing genetic influences may constrain the total cortical size. The small magnitude of this correlation is consistent with the radial unit hypothesis(*3*), whereby different developmental mechanisms promote SA and TH expansion.

As expected, total SA showed a positive genetic correlation with intracranial volume (ICV); this correlation remained after controlling for height demonstrating that this relationship is not solely driven by body size (Fig. 2A; Table S8). The global cortical measures did not show significant genetic correlations with the volumes of major subcortical structures (Fig. 2A) except for total SA and the hippocampus, consistent with their shared telencephalic developmental origin. This indicates variation in cortical and subcortical structures have

predominantly independent genetic influences, consistent with known differences in cell-type composition between these structures.

To identify if common variation associated with cortical structure perturbs gene regulation during a specific developmental time period or within a given cell-type, we performed partitioned heritability analyses(*15*) using sets of gene regulatory annotations from adult and fetal brain tissues(*16*, *17*). The strongest enrichment of the heritability for global SA was seen within areas of active gene regulation (promoters and enhancers) in the mid-fetal human brain (Fig. 2B). We further identified a stronger enrichment in regions of the fetal cortex with more accessible chromatin in the neural progenitor-enriched germinal zone than in the neuron-enriched cortical plate(*16*). There was also enrichment of active regulatory elements within embryonic stem cells differentiated to neural progenitors(*17*). We conducted pathway analyses to determine if there was enrichment of association near genes in known biological pathways. Among the 998 significant gene-sets a number were involved in chromatin modification, a process guiding neurodevelopmental fate decisions(*18*) (Fig. 3C, Table S9). These findings suggest that total SA in adults is influenced by common genetic variants that may alter gene regulatory activity in neural progenitor cells during fetal development, supporting the radial unit hypothesis(*3*). In contrast, the strongest evidence of enrichment for average TH was found in active regulatory elements in the adult brain samples, which may reflect processes occurring after mid-fetal development, such as myelination, branching, or pruning(*19*).

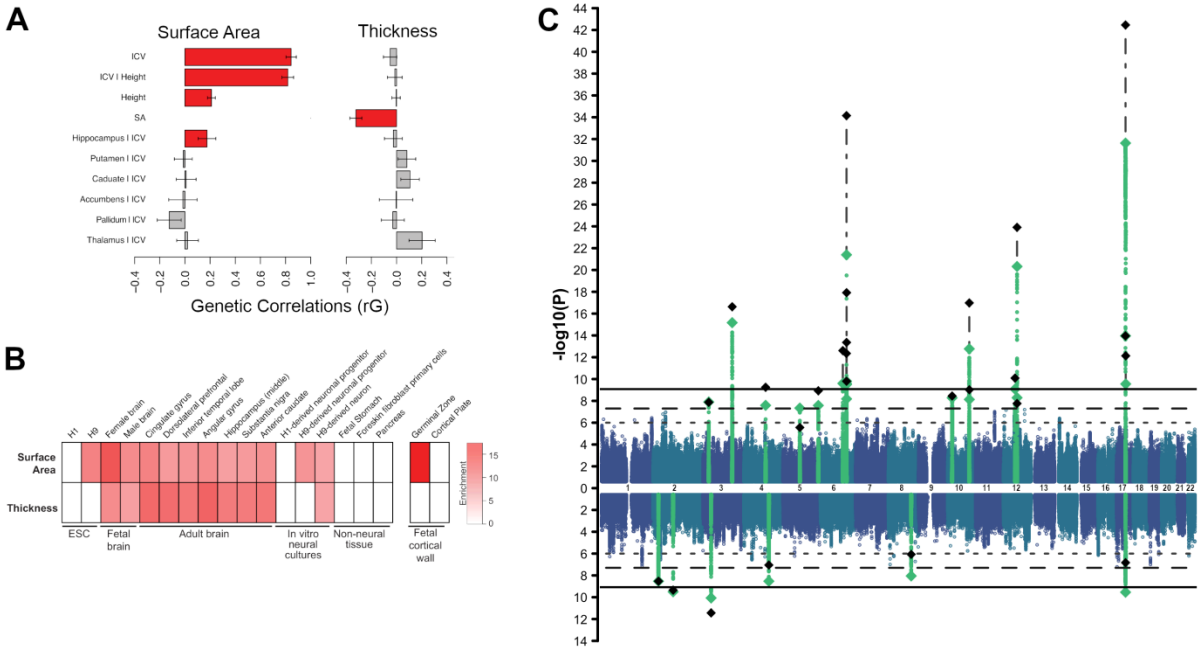

Fig. 2 | Genetics of Global Measures. A, Genetic correlations between global measures and selected traits (red indicates significant correlation, FDR<0.05); **B**, Partitioned heritability enrichment values (significant enrichments are coloured, FDR<0.05); **C**, Manhattan plot of loci associated with global SA (top) and TH (bottom), green diamonds indicate lead SNP in the principal meta-analysis, black diamonds indicate change in *P*-value after replication, dashed horizontal line is genome-wide significance, solid horizontal like is multiple-testing correction threshold.

Loci influencing total SA and average TH

Of the replicated loci, 17 loci were nominally associated with total SA; 12 survived correction for multiple testing (Fig. 2C, Table S5). Eight loci influencing total SA have been previously associated with ICV(*14*). Of these, rs79600142 (P = 2.3 x 10^{-32}; P_{rep} = 3.5 x 10^{-43}), in the highly pleiotropic chromosome 17q21.31 inversion region, has been associated with Parkinson's disease(*20*), educational attainment(*21*), and neuroticism(*22*). On 10q24.33, rs1628768 (P = 1.7 x 10^{-13}; P_{rep} = 1.0 x 10^{-17}) is a cortical expression quantitative trait locus (eQTL)(*23*) in adult cortex for *INA*, and schizophrenia candidate genes *AS3MT*, *NT5C2* and *WBP1L(24)* (P_{ADULT} = 9.0 x 10^{-3}; Tables S10–S11). This region has been associated with schizophrenia, however, rs1628768 is in low LD with the schizophrenia-associated SNP rs11191419 (r^2 = 0.15). The 6q21 locus influencing total SA is intronic to *FOXO3* (which also showed a significant gene-based association with total SA, Table S6). The minor allele of the lead variant rs2802295 is associated with decreased total SA (P = 2.5 x 10^{-10}; P_{rep} = 2.5 x 10^{-13}) and has previously been associated with lower general cognitive function(*25*) (rs2490272: $P_{Cognition}$ = 9.9 x 10^{-14}; $r^2_{rs2802295:rs2490272}$ = 1).

Of the loci not previously associated with ICV, our novel loci include rs11171739 (P = 8.4 x 10^{-10}; P_{rep} = 8.1 x 10^{-11}) on 12q13.2. In high LD with SNPs associated with educational attainment(*21*), rs11171739 is an eQTL for *RPS26* in fetal(*26*) and adult cortex (P_{FETAL} = 6.1 x 10^{-27}, P_{ADULT} = 8.8 x 10^{-49}; Tables S10–S11). This eQTL association was recently highlighted in a brain expression GWAS including subjects with Alzheimer's disease and other brain pathologies(*27*). On 2q24.2, rs13021985 (P = 3.4 x 10^{-9}; P_{rep} = 8.1 x 10^{-12}) is a fetal cortex eQTL for *TBR1* (P_{FETAL} = 1.4 x 10^{-4}; Tables S10–S11), a transcription factor specifically expressed in postmitotic projection neurons and part of the *Pax6-Tbr2-Tbr1* cascade that modulates numerous neurodevelopmental processes(*28*). On 3p24.1, rs12630663 (P = 1.3 x 10^{-8}; P_{rep} = 1.4 x 10^{-8}) is of interest due to its proximity (~200kb) to *EOMES* (also known as *TBR2*), which is expressed specifically in intermediate progenitor cells(*29*) in the developing fetal cortex(*2*). rs12630663 is located in a chromosomal region with chromatin accessibility specific to the human fetal cortex germinal zone of human(*16*). This region shows significant chromatin interaction with the *EOMES* promoter(*29*) and contains numerous regulatory elements that when excised via CRISPR/Cas9 in differentiating neural progenitor cells significantly reduced *EOMES* expression(*16*). A rare homozygous chromosomal translocation in the region separating the regulatory elements from *EOMES* (Fig. S2) silences its expression and causes microcephaly(*30*) demonstrating that rare and common non-coding variation can have similar phenotypic consequences, but to different degrees.

The two replicated loci associated with average TH, both of which are novel, survived correction for multiple testing (Fig. 2C; Table S5). On 3p22.1 rs533577 (P = 8.4 x 10^{-11}; P_{rep} = 3.7 x 10^{-12}) is a fetal cortex eQTL (P_{FETAL}= 8.9 x 10^{-6}) for *RPSA*, encoding a 40S ribosomal protein with a potential role as a laminin receptor(*31*). Laminins are major constituents of extracellular matrix, and have critical roles in neurogenesis, neuronal differentiation and migration(*32*). On 2q11.2, rs11692435 (P = 3.2 x 10^{-10}; P_{rep} = 4.5 x 10^{-10}) encodes a missense variant (p.A143V) predicted to impact ACTR1B protein function, and is an *ACTR1B* eQTL in fetal cortex (P_{FETAL} = 6.5 x 10^{-3}) (Tables S10–S11). *ACTR1B* is a subunit of the dynactin complex involved in microtubule remodeling, which is important for neuronal migration(*33*).

Genetics of regional SA and TH

Within individual cortical regions the amount of phenotypic variance explained by common variants was higher for SA (8–31%) than for TH (1–13%) (Fig. 3A–B; Table S7). With few

exceptions, the genetic correlations between SA and TH within the same region were moderate and negative (Tables S12–S13), suggesting that genetic variants contributing to the expansion of SA tend to decrease TH. Most genetic correlations between regional surface areas did not survive multiple testing correction, and those that did implied a general pattern of positive correlations between physically adjacent regions and negative correlations with more distal regions (Fig. 3A). This pattern mirrored the phenotypic correlations between regions and was also observed for TH (Fig. 3A–B). The positive genetic correlations were typically between SA of regions surrounding the major, early forming sulci (e.g., pericalcarine, lingual, cuneus, and lateral occipital regions surrounding the calcarine sulcus), which may potentially reflect genetic effects acting on the development of the sulci. However, the general pattern of correlations may, in part, depend on the regional partitioning by the Desikan-Killiany atlas(*9*) (supplementary text). Hierarchical clustering of the genetic correlations resulted in a general grouping by physical proximity (Fig. S3).

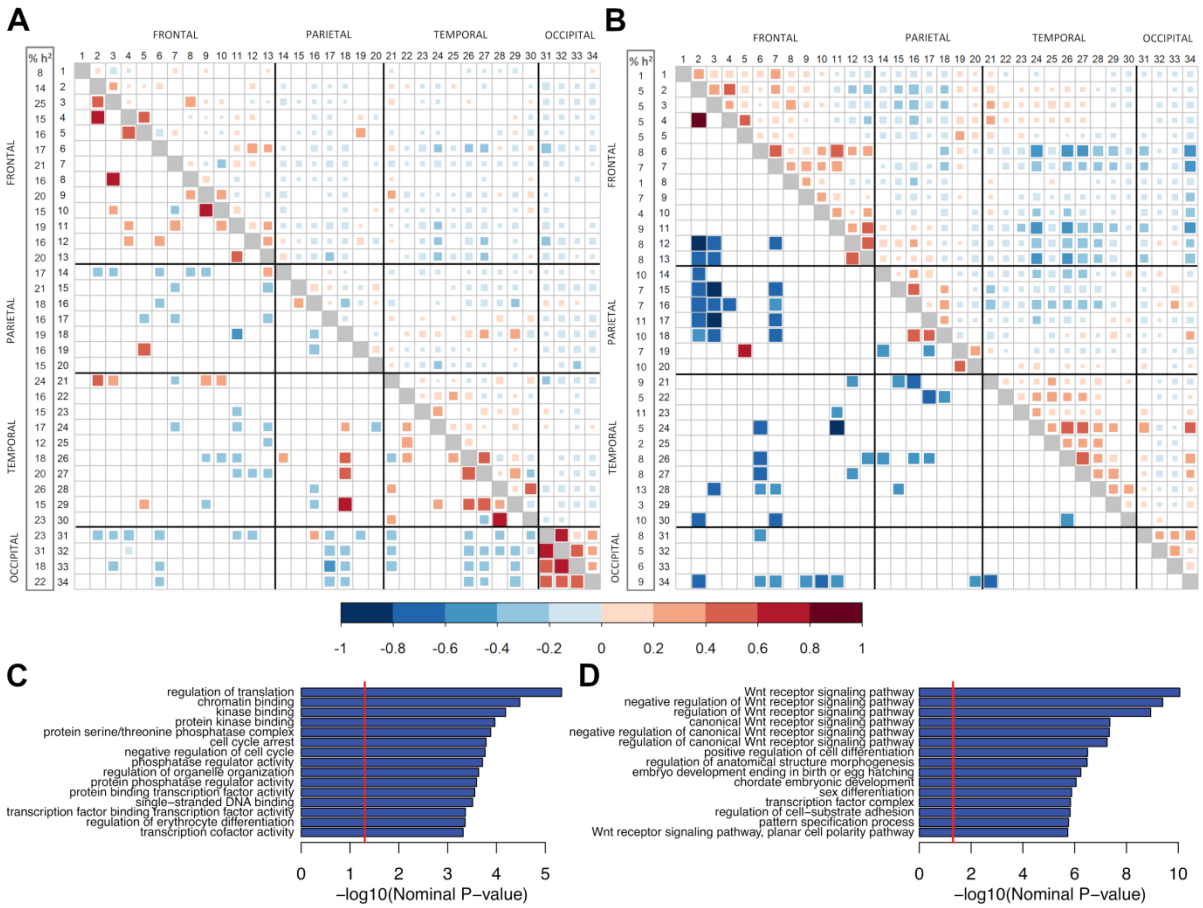

Fig. 3 | Genetic and Phenotypic Correlations Between Cortical Regions. A, Surface Area; **B**, Thickness. The regions are numbered according to the legend of Fig. 1A. The proportion of variance accounted for by common genetic variants is shown in the first column (h^2_{SNP}). Phenotypic correlations from the UK Biobank are in the upper triangle. Genetic correlations from the principal meta-analysis are in the lower triangle. Only significant correlations are shown. **C**, Enrichment of gene ontology annotations for total surface area; **D**, Enrichment of gene ontology annotations for regional surface area. The horizontal red lines (**C** and **D**) indicate nominal significance.

To further investigate biological pathways influencing areal identity, we summarised the individual regional results using multivariate GWAS analyses(*34*) separately for SA and TH

that modelled the phenotypic correlations between regions. Pathway analyses of the multivariate SA results showed significant enrichment for 903 gene sets (Fig. 3D; Table S9), many of which are involved in Wnt signalling, with the canonical Wnt signalling pathway showing the strongest enrichment (P = 8.8 x 10^{-11}). Wnt proteins regulate neural progenitor fate decisions(*35, 36*) and are expressed in spatially specific manners influencing areal identity(*6*). Pathway analyses of the multivariate TH results did not yield any findings that survived multiple testing.

Loci influencing regional SA and TH

A total of 224 loci were nominally associated with regional SA and 12 with TH; of these 175 SA and 10 TH loci survived multiple testing correction (Table S5). As shown in Fig. 1C, most loci were associated with a single cortical region. Of the loci influencing regional measures, few were also associated with global measures, and those that were showed effects in the same direction, implying that the significant regional loci were not due to collider bias(*37*) (Fig. S4).

The strongest regional association was observed on chromosome 15q14 with the precentral SA (rs1080066, P = 1.8 x 10^{-137}; P_{rep} = 4.6 x 10^{-189}; variance explained = 1.03%; Fig 4A). Across 11 traits we observed 41 independent significant associations from 18 LD blocks (r^2 threshold $\leq$ .02; see Fig. 4D, Table S5). As we observed strong association with the SA of both pre- and post-central gyri, we localised the association within the central sulcus in 5,993 unrelated individuals from the UK Biobank. The maximal association between rs1080066 and sulcal depth was observed around the *pli de passage fronto-pariétal moyen* (P = 7.9 x 10^{-21}), a region associated with hand fine-motor function in humans(*38*) and shows distinct depth patterns across different species of primates(*39*) (Fig. 4C). Variants in the rs1080066 LD block are fetal cortex eQTLs for an upsteam lncRNA *RP11-275I4.2* (P_{FETAL} = 4.0 x 10^{-4}) and a downstream gene *EIF2AK4* (P_{FETAL} = 7.4 x 10^{-3}) encoding the GCN2 protein, a negative regulator of synaptic plasticity, memory and neuritogenesis(*40*). The functional data also highlight *THBS1*, with roles in synaptogenesis and the maintenance of synaptic integrity(*41*), with chromatin interaction between the rs1080066 region and the *THBS1* promoter in neural progenitor cells and an eQTL effect in whole blood ($P_{BIOSgenelevel}$ = 1.5 x 10^{-9}). There was evidence of heterogeneity in the effect of rs1080066 across the non-European cohorts (Table S5), which might be due in part to the strength of the effect and the disparate power across ancestry groups.

At another region containing multiple regional hits, on 14q23.1, we observed 20 significant loci (Table S5) from four LD blocks. Our strongest association here was for the precuneus SA (rs73313052: P = 1.1 x 10^{-24}; P_{rep} = 2.2 x 10^{-35}; variance explained = 0.18%). These loci are located near *DACT1* and *DAAM1*, both involved in synapse formation and critical members of the Wnt signalling cascade(*42, 43*). rs73313052 and high LD proxies are eQTLs for *DAAM1* (P_{ADULT} = 9.0 x 10^{-3}) in adult cortex and for *LRRC9* (P_{FETAL} = 3.9 x 10^{-3}) in fetal cortex, *LRRC9* is primarily expressed in brain tissue but is of unknown function (Tables S10–S11).

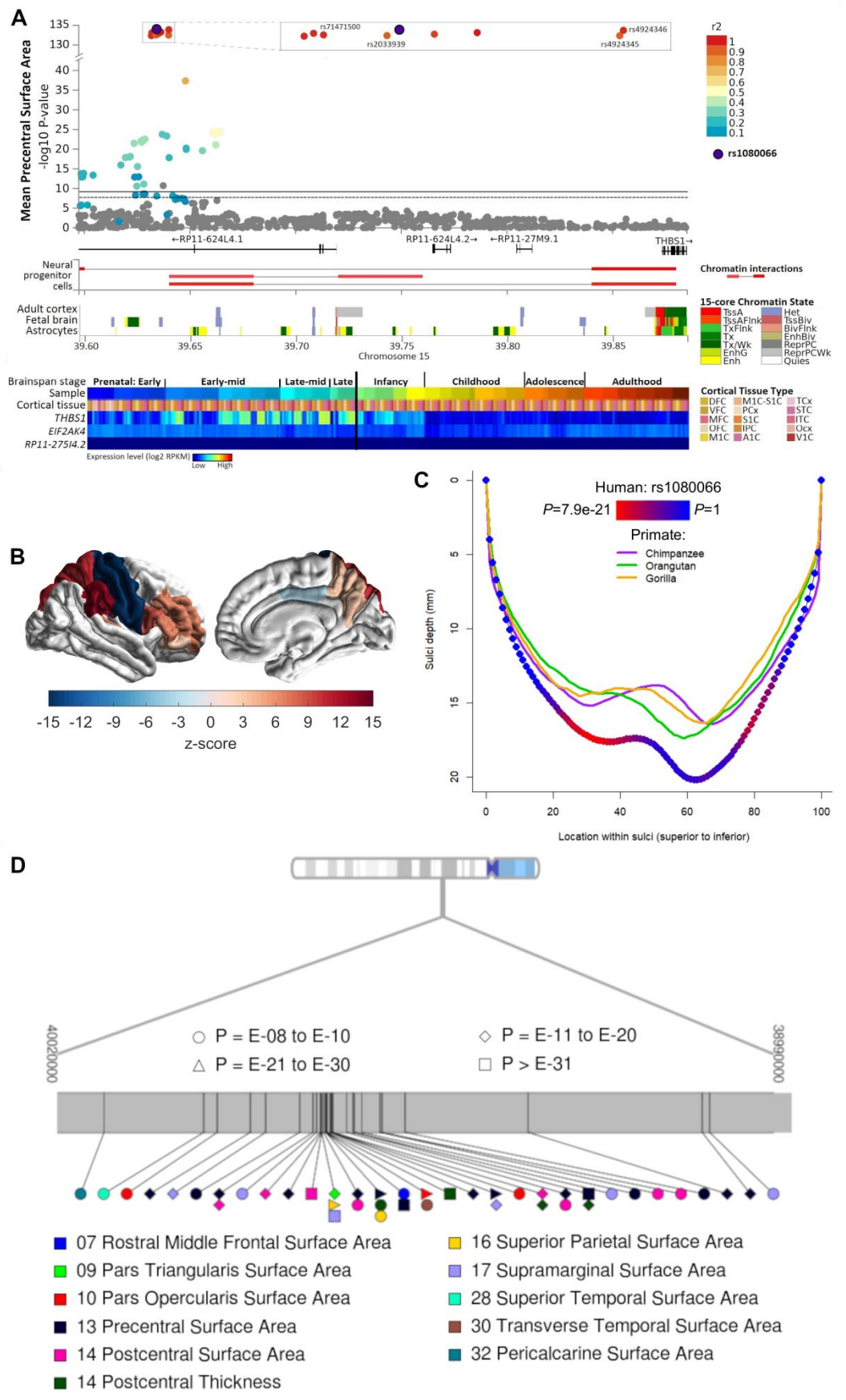

Fig. 4 | Genetics of Regional Measures. A, Regional plot for rs1080066, including additional lead SNPs within the LD block and surrounding genes, chromatin interactions in neural progenitor cells, chromatin state in RoadMap brain tissues*, and BRAINSPAN

candidate gene expression in brain tissue** (abbreviations detailed below); **B**, rs1080066 (G allele) association with SA of regions; C, rs1080066 association with central sulcus depth and depth of several primate species; **D** ideogram of 15q14, detailing the significant independent loci and cortical regions. *TssA:Active Transcription Start Site (TSS); TssAFlnk:Flanking Active TSS; TxFlnk:Transcription at gene 5' and 3'; Tx:Strong transcription; TxWk:Weak transcription; EnhG:Genic enhancers; Enh:Enhancers; Het:Heterochromatin; TssBiv:Bivalent/Poised TSS; BivFlnk:Flanking Bivalent TSS/Enhancer; EnhBiv:Bivalent Enhancer; ReprPC:Repressed; PolyComb; ReprPCWk:Weak Repressed PolyComb; Quies:Quiescent/Low; **DFC:dorsolateral prefrontal cortex; VFC:ventrolateral prefrontal cortex; MFC:anterior cingulate cortex; OFC:orbital frontal cortex; M1C:primary motor cortex; M1C-S1C:primary motor-sensory cortex; PCx:parietal neocortex; S1C:primary somatosensory cortex; IPC:posteroventral parietal cortex; A1C:primary auditory cortex; TCx:temporal neocortex; STC:posterior superior temporal cortex; ITC:inferolateral temporal cortex; Ocx:occipital neocortex; V1C:primary visual cortex.

Consistent with enrichment in the pathway analyses, a number of other loci were located in regions with functional links to genes involved in Wnt signalling, including 1p13.2, where rs2999158 (lingual SA, $P = 1.9 \times 10^{-11}$, $P_{rep} = 3.0 \times 10^{-11}$; pericalcarine SA, $P = 1.9 \times 10^{-11}$; $P_{rep} = 9.9 \times 10^{-16}$) is an eQTL for for *ST7L* and *WNT2B* (minimum $P_{ADULT} = 9.0 \times 10^{-3}$) in adult cortex (Tables S10–S11). A number of our novel regional associations occur near genes with known roles in brain development. For example, on chromosome 1p22.2, rs1413536 (inferior parietal SA: $P = 1.6 \times 10^{-10}$; $P_{rep} = 3.1 \times 10^{-14}$) is an eQTL in adult cortex for *LMO4* ($P_{ADULT} = 9.0 \times 10^{-3}$), with chromatin interactions between the region housing both this SNP and rs59373415 (precuneus SA: $P_{rep} = 5.3 \times 10^{-12}$) and the *LMO4* promoter in neural progenitor cells (Table S10–S11). *Lmo4* is one of the few genes already known to be involved in areal identity specification in mammalian brain(*44*).

Genetic correlations with other traits

To examine shared genetic effects between cortical structure and other traits, we performed genetic correlation analyses with GWAS summary statistics from 23 selected traits. We observed significant positive genetic correlations between total SA and general cognitive function(*45*), educational attainment(*21*), and Parkinson's disease(*46*). For total SA, significant negative genetic correlations were detected with insomnia(*47*), attention deficit hyperactivity disorder (ADHD)(*48*), depressive symptoms(*49*), major depressive disorder(*50*), and neuroticism(*51*)(Fig. 5A; Table S14). Genetic correlations with average TH did not survive multiple testing correction due to the weaker genetic association seen in the TH analyses. We mapped genetic correlation patterns across the cortical regions without correction for the global measures to map the magnitude of these effects across the brain (Fig. 5B). No additional neuropsychiatric or psychological traits were significant at a regional level.

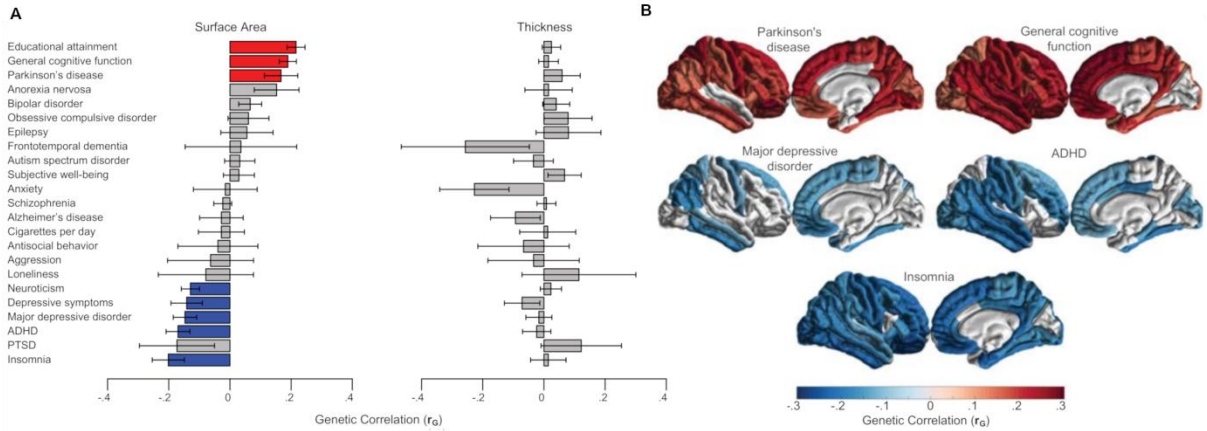

Fig. 5 | Genetic correlations with neuropsychiatric and psychological traits. A, genetic correlations with total SA and average TH positive correlations are shown in red, while negative correlations are shown in blue; **B**, regional variation in the strength of genetic correlations between regional surface area (without correction for total surface area) and traits showing significant genetic correlations with total surface area.

Discussion

Here we present a large-scale collaborative investigation of the effects of common genetic variation on human cortical structure using data from 51,662 individuals from 60 cohorts from around the world. We identify specific loci influencing cortical surface area (187 loci surviving multiple testing) and thickness (12 loci), implicating genes involved in areal patterning and cortical development. Our results support the radial unit hypothesis of surface area expansion in humans(*3*): genetic variation within regulatory elements in fetal neural progenitor cells(*16*) is associated with variability in adult cortical surface area. We also find that Wnt signalling genes influence areal expansion in humans, as has been reported in model organisms such as mice(*6*). Cortical thickness was associated with loci near genes implicated in cell differentiation, migration, adhesion, and myelination. Consequently, molecular studies in the appropriate tissues, such as neural progenitor cells and their differentiated neurons, will be critical to map the involvement of specific genes. Genetic variation associated with brain structure is functionally relevant, as evidenced by genetic correlations with a range of neuropsychiatric disorders and psychological traits, including general cognitive function, Parkinson's disease, depression, ADHD and insomnia. This work identifies novel genome-wide significant loci associated with cortical surface area and thickness based on the largest imaging genetics study to date, providing a deeper understanding of the genetic architecture of the human cerebral cortex and its patterning.

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Supplementary Materials:

Materials and Methods

Ethical approval and data availability

Participants in all cohorts in this study gave written informed consent and sites involved obtained approval from local research ethics committees or Institutional Review Boards. Ethics approval for the meta-analysis was granted by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (approval: *P2204*).

Imaging

Measures of cortical surface area (SA) and thickness (TH) were derived from *in-vivo* whole brain T1-weighted magnetic resonance imaging (MRI) scans using FreeSurfer MRI processing software(*1*) (Table S3). SA and TH were quantified for each subject within 34 distinct gyral-defined regions in each brain hemisphere according to the Desikan-Killiany atlas(*9*) (Fig. 1A). SA was measured at the grey-white matter boundary. TH was measured as the average distance between the white matter and pial surfaces. The total SA and average TH of each hemisphere was computed separately. High test-retest correlations have been reported for all measures with the exception of the frontal and temporal poles(*5*). Image processing and quality control were implemented at the cohort level following detailed, harmonized protocols (see http://enigma.ini.usc.edu/protocols/imaging-protocols/ for protocols); phenotype distributions for all traits in all cohorts were inspected centrally prior to meta-analysis. Any cohort where the phenotypic distribution for a given trait showed deviation from expectations that could not be resolved through reanalysis or outlier inspection were excluded from analyses of that trait.

Genome-wide association analyses

At each site, genotypes were imputed using either the 1000 Genomes Project(*52*) or Haplotype Reference Consortium(*53*) references (Table S4). To ensure consistency in the correction for ancestry and stability of the correction given the relatively small sample sizes, each cohort also ran the same multidimensional scaling (MDS) analysis protocol in which the data from the HapMap 3 populations were merged with the site level data and MDS components were calculated across this combined data set. Within each cohort, genome-wide association (GWAS) was conducted using an additive model including covariates to control for the effects of age, sex, ancestry (the first four MDS components), diagnostic status (when the cohort followed a case-control design), and scanner (when multiple scanners were used at the same site).

The primary GWAS of regional measures included the global measure of SA or TH as an additional covariate, to test for genetic influences specific to each region. However, to aid interpretation, the regional GWAS were also run without controlling for global measures. Cohort level GWAS results underwent quality control (excluding variants with an imputation $R^2 \leq .5$ and MAF $\leq .005$). Across all cohorts, for each phenotype, GWAS summary plots (Manhattan and QQ plots) were visually inspected by the central analysis group, if a given trait showed deviation from expectations that could not be resolved through reanalysis that cohort was excluded from analyses of that trait.

Multiple testing correction

We analysed 70 traits (total SA, average TH, and the SA and TH of 34 cortical regions averaged across right and left hemispheres). However, after accounting for the correlation between the traits in the UK Biobank (residuals correcting for sex, age, ancestry and global

measures) using matrix spectral decomposition (matSpD(*10*)) the effective number of traits was estimated to be 60. Therefore, we applied the significance threshold of $P \leq 8.3 \times 10^{-10}$ to correct for multiple testing in the GWAS meta-analysis results. Multiple testing corrections applied to each of the follow-up analyses are described below.

Meta-analysis

The initial meta-analysis was conducted on all of the ENIGMA European cohorts with genome-wide imputed data, which were then meta-anlysed with the UK Biobank European participants to give the principal results. We took the significant principal results and meta-analysed them with an additional ENIGMA cohort and results from the CHARGE consortium. In an additional replication we took these results and meta-analysed them with the ENIGMA non-European cohorts. Cohort information is provided in Table S2. All meta-analyses were conducted using METAL(*54*). The results of the meta-analysis are summarized in Table S5. For the intial and principal meta-analyses we used standard error weighted meta-analyses. In the replication steps we used sample size weighted meta-analyses, in order to include results from the CHARGE consortium for which only sample size weighted results were available. For each meta-analysis, the results were quality controlled, removing strand ambiguous SNPs and INDELs where the effect allele frequency crossed .5, and (for the initial meta-analysis) variants where the total sample size was < 10,000. Independent loci were identified by clumping significant loci in PLINK(*55*), with thresholds of 1 Mb and $r^2 < .2$. For the chromosome 17 inversion region this was increased to 10 Mb. For clumping, a random sample of 5,000 unrelated individuals from the UK BioBank were used as an LD reference.

Following Rietveld et al(*56*), we estimated the variance explained R^2 by each variant j as:

$$R_j^2 \approx \frac{2p_j q_j . \hat{\beta}_j^2}{\hat{\sigma}_y^2}$$

where p_j and q_j are the minor and major allele frequencies, $\hat{\beta}_j$ is the estimated effect of the variant within the meta-analysis and $\hat{\sigma}_y^2$ is the estimated variance of the trait (for which we used the pooled variance of the trait across all ENIGMA cohorts and UK Biobank; see Table S1). To obtain beta and standard error estimates from the results from the sample size weighted meta-analyses reported in Table S5 we used the following equations from Rietveld et al(*56*):

$$\hat{\beta}_j \approx z_j \cdot \frac{\hat{\sigma}_y}{\sqrt{N_j \cdot 2p_j q_j}} \text{ and } SE(\hat{\beta}_j) \equiv \frac{z_j}{\hat{\beta}_j}$$

Where z_j is the Z-score and SE ($\hat{\beta}_j$) is the estimated standard effect of the variant within the meta-analysis and N is the number of contributing alleles.

Analyses of UK Biobank data

Analyses of the UK Biobank cohort were conducted on the 2018 (version 3) imputed genotypes, imputed to the Haplotype Reference Consortium and merged UK10K and 1000 Genomes (phase 3) panels. UK Biobank bulk imaging data were made available for 12,962 individuals under application #11559 in July 2017. We processed the raw MRI data using the ENIGMA protocols. Following processing, all images were visually inspected. Analyses of UK Biobank participants within .02 on the first and second MDS components of the European centroid were included in the meta-analyses of the European ancestry cohorts. Analyses of participants beyond this threshold were included in the meta-analysis of non-European ancestry cohorts.

Gene-based association analyses

We conducted genome-wide gene-based association analysis using the principal meta-analytic results. We used the 19,427 protein-coding genes from the NCBI 37.3 gene definitions as the basis for the gene-based association analysis using MAGMA(*57*). For each gene we selected all SNPs within exonic, intronic and untranslated regions as well as SNPs within 50 kb upstream and downstream of the gene. After SNP annotation, there were 18,048 genes that were covered by at least one SNP. Gene-based association tests were performed taking LD between SNPs into account. We applied a Bonferroni correction to account for multiple testing, adjusting for the number of genes tested as well as the number of traits tested (60 independent traits), setting the genome-wide threshold for significance at 4.5×10^{-8}. These results are shown in Table S6.

Heritability due to common variants, genetic correlations and partitioned heritability

We used LD score regression(*58, 59*) to estimate the proportion of variance accounted for by common SNPs or SNP heritability (h^2_{SNP}) of the global measures (total SA and average TH) and the SA and TH of each of the 34 cortical regions. These results are shown in Table S7. LD score regression(*59*) was also used to estimate genetic correlations between regions and with global measures. These results are shown in Table S12–13. We used a threshold of $P \leq 8.3 \times 10^{-4}$ (.05/60) to correct for multiple testing in the genetic and phenotypic correlations shown in Fig. 3. To identify patterns of genetic correlations of SA and TH (both with and without correction for global measures), we used Mclust(*60*) for hierarchical cluster analysis, which uses expectation-maximisation to fit parameterized Gaussian mixture models to the data. The best-fitting model for number and shape of clusters was selected as the one with the largest Bayesian Information Criterion. These results are shown in Supplementary Fig. 3.

Partitioned heritability analysis was used to estimate the percentage of heritability explained by annotated regions of the genome(*61*). Annotations were derived from either Epigenomics Roadmap(*17*) or a study of chromatin accessibility in mid-fetal brains(*16*). For analyses using Epigenomics Roadmap data, chromatin states (15 state model) were downloaded for available tissue types (http://egg2.wustl.edu/roadmap/web_portal/chr_state_learning.html). For each tissue, genomic regions comprising all active regulatory elements (TssA, TssAflnk, Enh, EnhG) within each tissue type were added as an additional annotation to the baseline model provided with the LDSC package (https://github.com/bulik/ldsc). For analyses using chromatin accessibility in mid-fetal brains, the genomic coordinates of peaks more accessible in the germinal zone than the cortical plate (GZ > CP) and peaks more accessible in the cortical plate than the germinal zone (CP > GZ) were added separately to the baseline annotations. Partitioned heritability and the enrichment of heritability explained in these annotations was run using LD score regression(*61*). The significance of enrichment was corrected across all annotations used (including those not displayed) using false discovery rate (FDR) and the enrichment scores were plotted as a heatmap for those that survived significance (Fig. 2b).

Genetic correlations were calculated to determine if shared genetic influences contributed to both cortical structure and neuropsychiatric disorders or psychological traits. Summary statistics were downloaded from the following published genome-wide association studies: general cognitive function(*45*), insomnia(*47*), antisocial behavior(*62*), educational attainment(*21*), subjective well-being(*49*), depressive symptoms(*49*), neuroticism(*51*), attention deficit hyperactivity disorder (ADHD)(*48*), autism(*63*), bipolar disorder(*64*), anorexia nervosa(*65*), major depressive disorder(*50*), obsessive compulsive disorder(*66*), post-traumatic stress disorder (PTSD)(*67*), schizophrenia(*68*), anxiety disorders(*69*),

aggression(*70*), Alzheimer's disease(*71*), loneliness(*72*), cigarettes smoked per day(*73*), epilepsy(*74*), Parkinson's disease(*46*), and frontotemporal dementia(*75*). LD score regression was used to calculate genetic correlations(*58*). Significance was corrected for multiple comparisons using FDR across all genetic correlations with average TH and total SA, and significant associations were highlighted in Fig. 5A. To explore regional variability in those significant genetic correlations, genetic correlations were conducted between the trait and the cortical regions (without correcting for global measures) are depicted in Fig. 5B.

Multivariate GWAS analysis

We used TATES(*34*) to conduct two multivariate analyses: one for the 34 regional SA measures, and one for the 34 regional TH measures. These analyses were run on the meta-analytic results from the second phase of meta-analysis. Briefly, TATES combines the *p*-values from univariate GWAS while correcting for the phenotypic correlations between traits and does not require access to raw genotypic data(*34*). The power of TATES has been shown to be similar or greater than that of multivariate tests using raw data across a range of scenarios for analyses of 20 or more traits(*76*). For these analyses, we used phenotypic correlations calculated from the UK Biobank cohort (residuals correcting for sex, age, ancestry, and global brain measures).

Gene-set enrichment analyses

Gene-set enrichment analyses were performed on total SA and average TH as well as the multivariate GWAS results for SA and TH using DEPICT(*77*). Within DEPICT, groups of SNPs were assessed for enrichment in 14,462 gene-sets. These analyses were run using variants with $P \leq 1.0 \times 10^{-5}$. Gene-set enrichment analyses were considered significant if they survived FDR correction ($q \leq 0.05$)(*77*). These results are shown in Table S9.

Functional annotation

Potential functional impact was investigated for lead variants and their proxies (defined here as $r^2 > 0.6$ to the lead SNP) at each of the 306 loci nominally associated with global and regional SA and TH using a number of publicly available data sources. The majority of the SNP annotations were as provided by FUMA(*23*) which annotates:

- SNP location (e.g., genic/intergenic)
- the potential for functional effects through predicted effects as determined by CADD(*78*) and Regulome(*79*)
- expression quantitative trait (eQTL) effects. We considered eQTLs within cortical structures from GTEx v7, the UK Brain Expression Consortium (http://www.braineac.org/), and the CommonMind Consortium(*80*), and PsychENCODE(*81*) (http://resource.psychencode.org)
- chromatin state
- the presence of enhancers and promoters in SNP regions (RoadMap tissues E053, E073, E081, E082, E125)
- chromatin state (see below) and interactions in numerous brain tissues (GEO GSE87112). We included data for dorsolateral prefrontal cortex and neural progenitor cells, PsychENCODE, and adult and fetal cortex(*82*).

In the main text we provide *P*-values for adult cortical eQTLs as calculated by FUMA across tissues in which significant eQTLs were observed (Table S11). These data were used by FUMA to map coding and non-coding (e.g. lncRNA) genes to each lead SNP based on an eQTL effect with an FDR correction $P \leq .05$ in cortical tissue, and/or chromatin interactions between the region harbouring the lead SNP and a gene promoter in a second chromosomal region (including interactions with an FDR correction $P \leq 1 \times 10^{-6}$)(*23*). HaploReg(*83*) was

used to annotate transcription factor binding across multiple tissues, and whether SNPs modified transcription factor binding motifs. The potential for a detrimental effect on protein function due to lead or proxy SNPs located within gene exons was investigated using SIFT and PolyPhen as reported by SNPNexus(*80*). Fetal eQTL data were taken from O'Brien et al(*26*): we have noted only those eQTLs passing our FDR correction ($P \leq .05$) of the nomimal P-values provided in the original publication. In the main text we provide the nominal *P*-values as reported by O'Brien et al.

In Fig. 4 we annotate the genomic context of rs1080066 and high LD proxies associated with additional traits, chromatin state in relevant tissues, and gene expression in pre- and post-natal brains. Chromatin state represents the degree to which 200 bp genomic regions are accessible for transcription. Around each of our associated loci chromatin state was annotated by FUMA(*23*) utilising the core 15-state model (Table S10). In Fig. 4, genomic regions in three tissues/cells most relevant to our study (RoadMap E073 dorsolateral prefrontal cortex [Adult cortex], E081 female fetal brain [Fetal brain], and E125 NH-A Astrocytes Primary Cells [Astrocytes]) are indicated as one of the 15 possible chromatin states as predicted by Roadmap Epignomics using ChromHMM, based on data for 5 chromatin marks (H3K4me3, H3K4me1, H3K36me3, H3K27me3, H3K9me3) in 127 epigenomes(*17*). Chromatin states are as follows: TssA:Active Transcription Start Site (TSS); TssAFlnk:Flanking Active TSS; TxFlnk:Transcription at gene 5' and 3'; Tx:Strong transcription; TxWk:Weak transcription; EnhG:Genic enhancers; Enh:Enhancers; ZNF/Rpts:ZNF genes & repeats; Het:Heterochromatin; TssBiv:Bivalent/Poised TSS; BivFlnk:Flanking Bivalent TSS/Enhancer; EnhBiv:Bivalent Enhancer; ReprPC:Repressed; PolyComb; ReprPCWk:Weak Repressed PolyComb; Quies:Quiescent/Low. Pre- and post-natal gene expression data across multiple brain regions was obtained from the BrainSpan Atlas of the Developing Human Brain (http://www.brainspan.org/). These data include gene expression information for cortical tissues indicated on a scale from low (dark blue) to high (dark red) expression on a $\log_2$ RPKM scale (RPKM = Reads Per Kilobase [of transcript per] Million [mapped reads], which normalises expression levels to account for sequencing depth and gene length). The BRAINSPAN cortical tissues, organised in ontological order, are as follows: DFC:dorsolateral prefrontal cortex; VFC:ventrolateral prefrontal cortex; MFC:anterior (rostral) cingulate (medial prefrontal) cortex; OFC:orbital frontal cortex; M1C:primary motor cortex (area M1, area 4); M1C-S1C:primary motor-sensory cortex (samples); PCx:parietal neocortex; S1C:primary somatosensory cortex (area S1, areas 3,1,2); IPC:posteroventral (inferior) parietal cortex; A1C:primary auditory cortex (core); TCx:temporal neocortex; STC:posterior (caudal) superior temporal cortex (area 22c); ITC:inferolateral temporal cortex (area TEv, area 20); Ocx:occipital neocortex; V1C:primary visual cortex (striate cortex, area V1/17).

For each locus, we evaluated functional annotations for the lead SNP and for additional SNPs considered to be credible causal variants (CCVs) if they were either i) in reasonable LD ($r^2 \geq 0.6$ in individuals of European ancestry) with the lead SNP and/or ii) had *P*-values within 2 orders of magnitude of the lead SNP. As lincRNAs show considerable cell/tissue specificity, in the main text we detail SNP location based on neighbouring coding genes, but detail lincRNAs when our lead SNPs show eQTL effects and/or chromatin interactions to these non-coding transcripts. Genes at each associated locus were determined to be potential candidates by considering whether the lead SNP (or a proxy) was an eQTL for a particular gene in adult cortical tissue (e.g. BRAINEAC, CMC or GTEx cortical tissues) and/or when chromatin interactions were observed to occur between the region harbouring the lead/proxy

SNPs and a gene promoter in relevant brain tissues (dorsolateral prefrontal cortex and/or neural progenitor cells).

Analysis of the central sulcus

To follow-up the precentral surface area association with rs1080066, 10,557 UK Biobank MRI scans were further analyzed using BrainVISA-4.5 Morphologist pipeline for the extraction and parameterization of the central sulcus. Quality controlled FreeSurfer outputs (orig.mgz, ribbon.mgz and talairach.auto) were directly imported into the pipeline to use the same gray and white matter segmentations. Sulci were automatically labeled according to a predefined anatomical nomenclature of 60 sulcal labels per hemisphere(*84*, *85*). Extracted meshes for the left and right central sulcus were visually quality checked; subjects with mislabelled central sulcus were discarded from further analysis; 6,045 individuals had good quality extractions for both the left and right hemispheres. The central sulcus depth profile was measured by extending the method introduced in(*38*, *86*). The ridges at the fundus of the sulcus and at the convex hull, along with the two extremities, were automatically extracted. Using these landmarks, two coordinate fields (x and y) were extrapolated over the entire mesh surface(*87*). Sulcal depth was defined as the distance between paired points at the sulcal fundus and brain envelope that shared the same y coordinate(*88*). For each individual, the parametrized surface was divided into 100 equally spaced points along the length of the sulcus, and the depth at each point was recorded for comparison. We averaged the corresponding depth measurements across the left and right sulcus and calculated the effect of the rs1080066 G allele on the bilaterally averaged depth at each point. These results are shown in Fig. 4C.

Estimating linkage disequilibrium with the 5-HTTLPR variable number tandem repeat.

Using PLINK(*55*), we estimated the LD between rs4291964 and the 5-HTTLPR variable number tandem repeat using data from 807 unrelated founders from the QTIM sample who are genotyped for 5-HTTLPR and have rs4291964 imputed (imputation accuracy $r^2 = 0.96$). These analyses showed the two genotypes to be unlinked, $r^2 = 0.03$, $D' = 0.267$.

Supplementary Text

Sulcal development

Positive genetic correlations between the SA of neighbouring regions may also be driven by the development of the sulcus, separating the regions. The pre- and post- central regions (also known as the primary motor and sensorimotor cortices, respectively) are consistently labelled across many cortical atlases as the regions directly anterior and posterior to the central sulcus (which appears early in development(*89*)). The SA of all four regions surrounding the calcarine sulcus (the pericalcarine, lingual, cuneus, and lateral occipital region) show positive genetic correlations. The same is also true for the SA of the insula and superior temporal gyri surrounding the lateral sulcus (or Sylvian fissure). These major, early-forming sulci show positive genetic correlations between the regions that directly surround them for SA, but not TH. These observations may imply that part of the genetic influences we observe to be underlying regional SA, may actually be driving the formation of the separating folds, or sulci, during fetal development.

The Desikan-Killiany atlas

The Desikan-Killiany atlas(*9*) used here to define the 34 regions of interest is one of many possible atlases. It is one of the coarser atlases, yielding larger, more consistent regions, defined by the common folding patterns visible on standard MRI. More recent efforts partitioning the cortex into 180 regions have used high-resolution multimodal assessments

(MMPC)(*90*). It is possible that positive correlations between adjacent structures may reflect suboptimal partitioning of the cortex by the Desikan-Killiany atlas into distinct functional brain regions; for example, we see a positive genetic correlation between the inferior parietal and the superior parietal gyri, whereas in the MMPC atlas, a portion of each of these two regions is included under the *intraparietal* labels. Portions of these genetically correlated regions may in future be re-assigned based on other advanced imaging data, such as multimodal myelin mapping, which may better define cortical cellular architecture.

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Supplementary Tables

Supplementary Figures

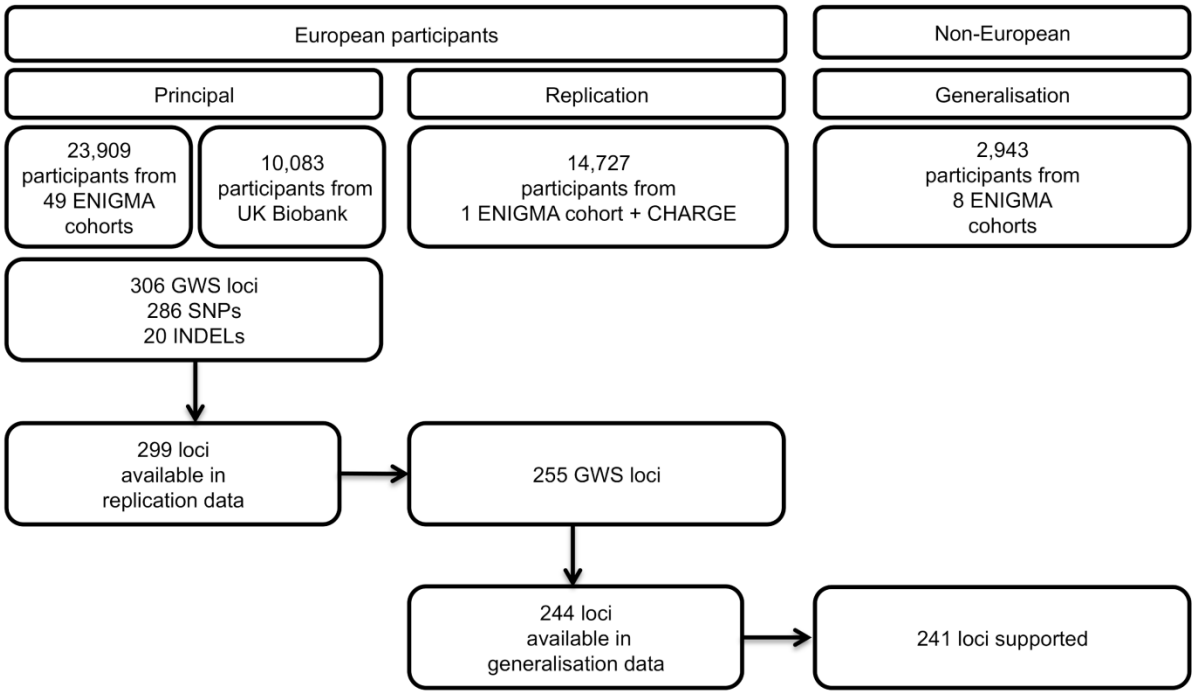

Figure S1. Flow chart summarising the phases of meta-analysis.

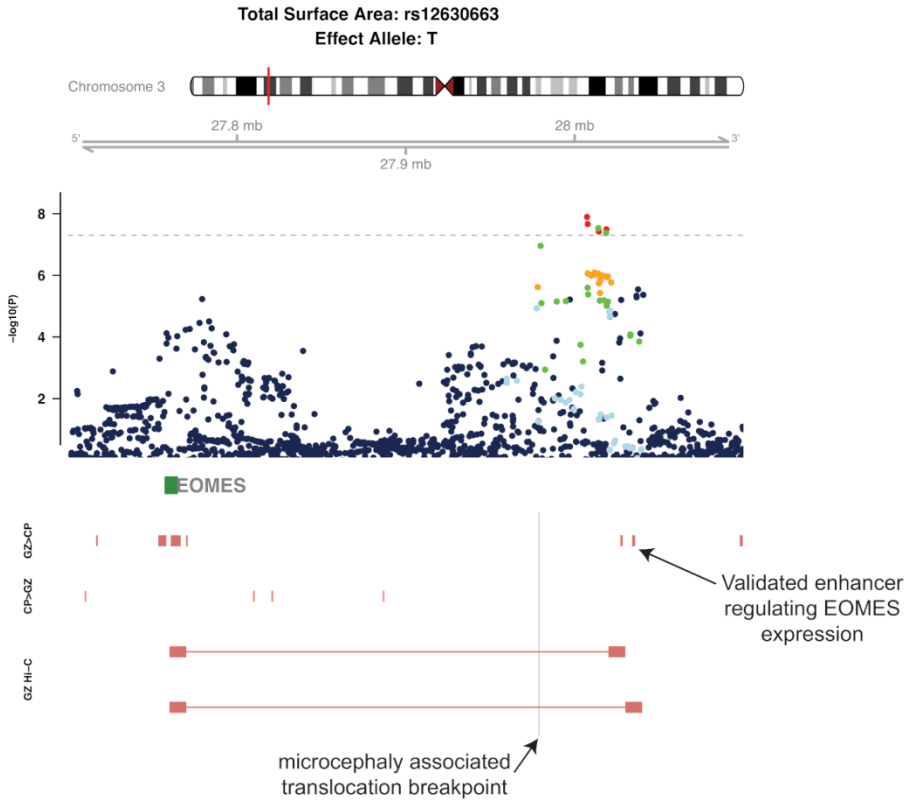

Figure S2. Regional association plot for the 3p24.1 locus (rs12630663).

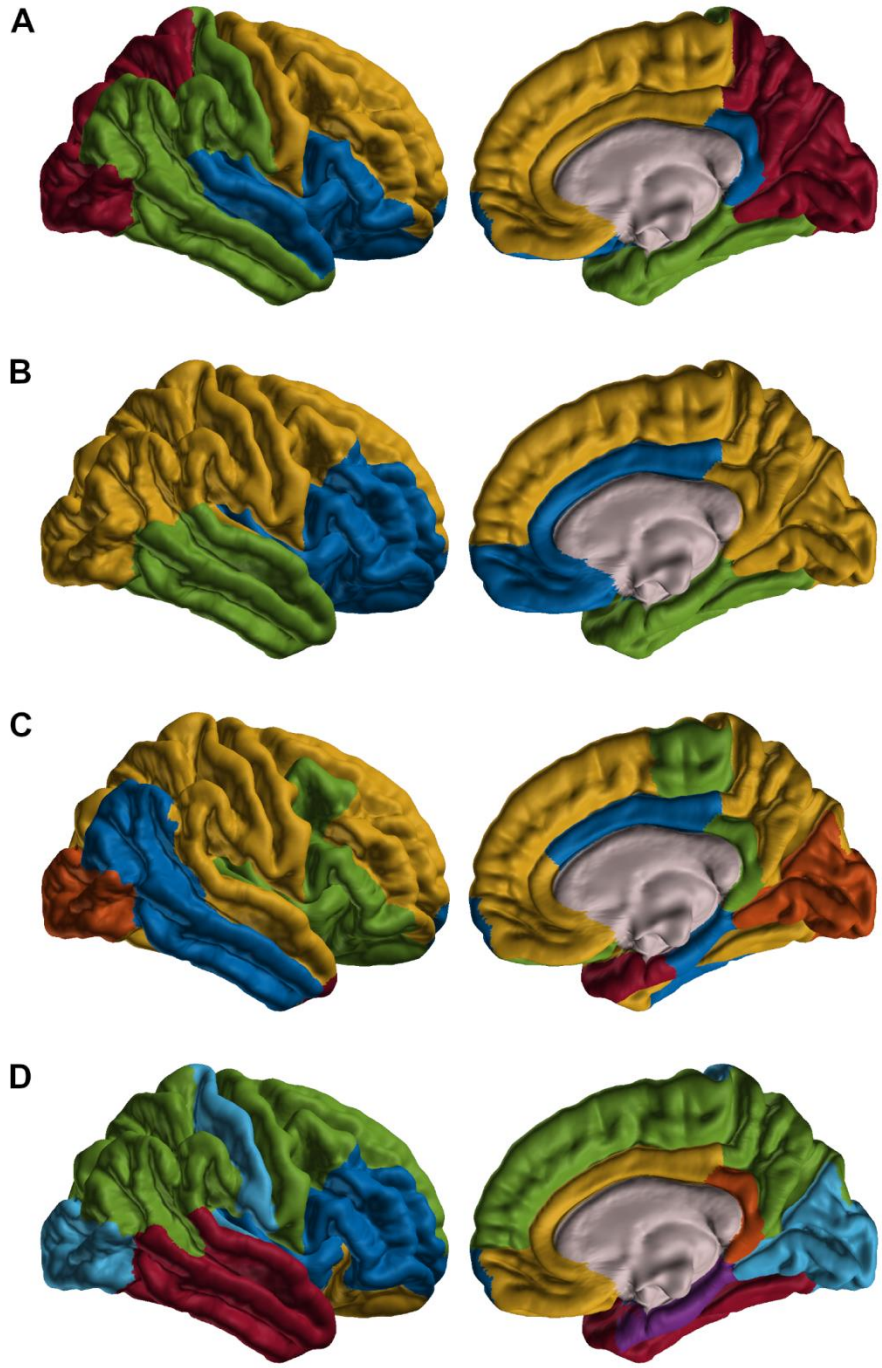

Figure S3. Clustering of genetic correlations among A) surface area and B) thickness regions after correcting for global measures. Clustering of genetic correlations among C) surface area and D) thickness regions without correcting for global measures. The best-fitting model for surface area with global correction was 4 diagonal components with varying volume and shape, and for thickness was 3 spherical components with equal volume. The best-fitting model for surface area without global correction was 5 spherical components with varying volume, and for thickness was 7 diagonal components with equal volume and shape.

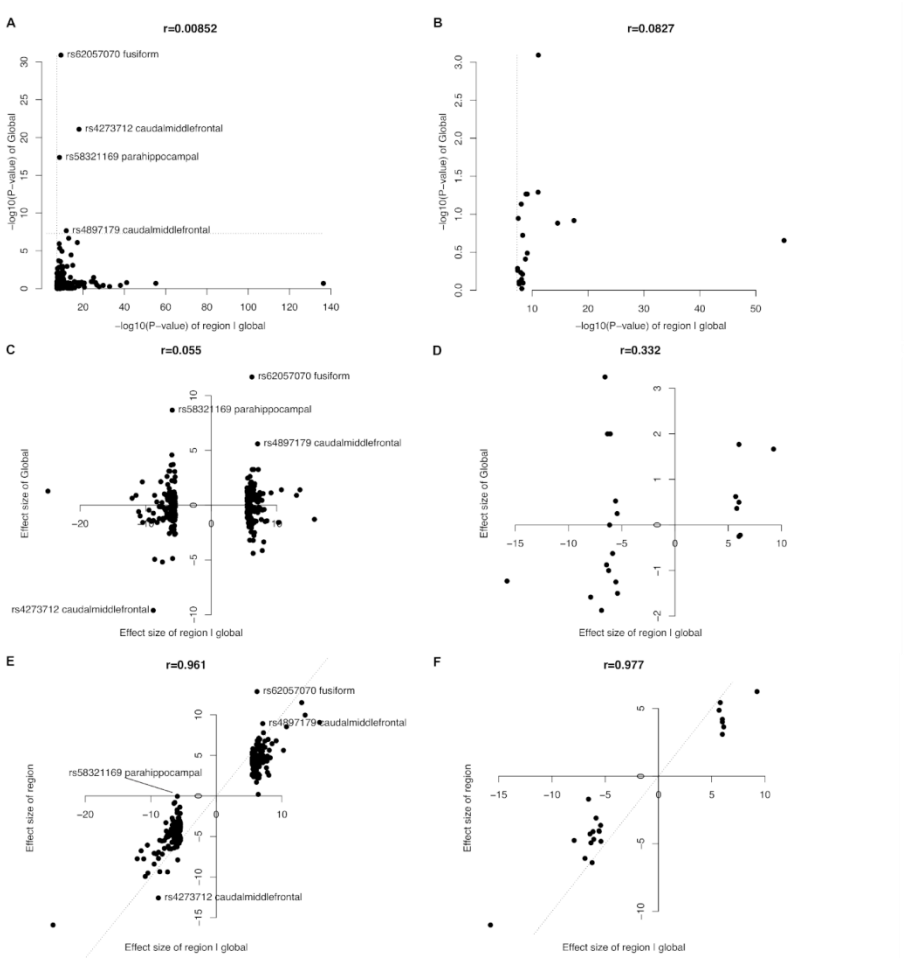

Figure S4. *P*-value of genome-wide significant regional SNPs with global control compared to their *P*-value in the global measure for A) surface area and B) thickness. Effect size of genome-wide significant regional SNPs with global control compared to their effect size in global measures for C) surface area and D) thickness. Effect size of genome-wide significant regional SNPs with global control compared to regional SNPs without global control in E) surface area and F) thickness.

Consortium Authors

Alzheimer's Disease Neuroimaging Initiative (ADNI). Data used in preparing this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, many investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators may be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

ADNI Infrastructure Investigators: Michael Weiner (UC San Francisco), Paul Aisen (University of Southern California), Ronald Petersen (Mayo Clinic, Rochester), Clifford R. Jack, Jr. (Mayo Clinic, Rochester), William Jagust (UC Berkeley), John Q. Trojanowki (U Pennsylvania), Arthur W. Toga (USC), Laurel Beckett (UC), Davis Robert C. Green (Brigham and Women's Hospital/Harvard Medical School), Andrew J. Saykin (Indiana University), John Morris (Washington University St. Louis), Leslie M. Shaw (University of Pennsylvania). *ADNI External Advisory Board (ESAB):* Zaven Khachaturian (Prevent Alzheimer's Disease 2020 (Chair)), Greg Sorensen (Siemens), Maria Carrillo (Alzheimer's Association), Lew Kuller (University of Pittsburgh), Marc Raichle (Washington University St. Louis), Steven Paul (Cornell University), Peter Davies (Albert Einstein College of Medicine of Yeshiva University), Howard Fillit (AD Drug Discovery Foundation), Franz Hefti (Acumen Pharmaceuticals), David Holtzman (Washington University St. Louis), M. Marcel Mesulam (Northwestern University), William Potter (National Institute of Mental Health), Peter Snyder (Brown University). *ADNI 3 Private Partner Scientific Board (PPSB):* Veronika Logovinsky, (Eli Lilly (Chair)). *Data and Publications Committee:* Robert C. Green (BWH/HMS (Chair)). *Resource Allocation Review Committee:* Tom Montine (University of Washington (Chair)). *Clinical Core Leaders:* Ronald Petersen (Mayo Clinic, Rochester (Core PI)), Paul Aisen (University of Southern California). *Clinical Informatics and Operations:* Gustavo Jimenez (USC), Michael Donohue (USC), Devon Gessert (USC), Kelly Harless (USC), Jennifer Salazar (USC), Yuliana Cabrera (USC), Sarah Walter (USC), Lindsey Hergesheimer (USC). *Biostatistics Core Leaders and Key Personnel:* Laurel Beckett (UC Davis (Core PI)), Danielle Harvey (UC Davis), Michael Donohue (UC San Diego). *MRI Core Leaders and Key Personnel:* Clifford R. Jack, Jr. (Mayo Clinic, Rochester (Core PI)), Matthew Bernstein (Mayo Clinic, Rochester), Nick Fox (University of London), Paul Thompson (UCLA School of Medicine), Norbert Schuff (UCSF MRI), Charles DeCArli (UC Davis), Bret Borowski (RT Mayo Clinic), Jeff Gunter (Mayo Clinic), Matt Senjem (Mayo Clinic), Prashanthi Vemuri (Mayo Clinic), David Jones (Mayo Clinic), Kejal Kantarci (Mayo Clinic), Chad Ward (Mayo Clinic). *PET Core Leaders and Key Personnel:* William Jagust (UC Berkeley (Core PI)), Robert A. Koeppe (University of Michigan), Norm Foster (University of Utah), Eric M. Reiman (Banner Alzheimer's Institute), Kewei Chen (Banner Alzheimer's Institute), Chet Mathis (University of Pittsburgh), Susan Landau (UC Berkeley). *Neuropathology Core Leaders:* John C. Morris (Washington University St. Louis), Nigel J. Cairns (Washington University St. Louis), Erin Franklin (Washington University St. Louis), Lisa Taylor-Reinwald (Washington University St. Louis – Past Investigator). *Biomarkers Core Leaders and Key Personnel:* Leslie M. Shaw (UPenn School of Medicine), John Q. Trojanowki (UPenn School of Medicine), Virginia Lee (UPenn School of Medicine), Magdalena Korecka (UPenn School of Medicine), Michal Figurski (UPenn School of Medicine). *Informatics Core Leaders and Key Personnel:* Arthur W. Toga (USC (Core PI)), Karen Crawford (USC), Scott Neu (USC). *Genetics Core Leaders and Key Personnel:* Andrew J. Saykin (Indiana University), Tatiana M. Foroud (Indiana University), Steven Potkin (UC Irvine), Li Shen (Indiana University), Kelley Faber (Indiana University), Sungeun Kim (Indiana University), Kwangsik Nho (Indiana University). *Initial Concept*

Planning & Development: Michael W. Weiner (UC San Francisco), Lean Thal (UC San Diego), Zaven Khachaturian (Prevent Alzheimer's Disease 2020). *Early Project Proposal Development:* Leon Thal (UC San Diego), Neil Buckholtz (National Institute on Aging), Michael W. Weiner (UC San Francisco), Peter J. Snyder (Brown University), William Potter (National Institute of Mental Health), Steven Paul (Cornell University), Marilyn Albert (Johns Hopkins University), Richard Frank (Richard Frank Consulting), Zaven Khachaturian (Prevent Alzheimer's Disease 2020). *NIA:* John Hsiao (National Institute on Aging). *ADNI Investigators by Site: Oregon Health & Science University*: Joseph Quinn, Lisa C. Silbert, Betty Lind, Jeffrey A. Kaye – Past Investigator, Raina Carter – Past Investigator, Sara Dolen – Past Investigator. *University of Southern California:* Lon S. Schneider, Sonia Pawluczyk, Mauricio Becerra, Liberty Teodoro, Bryan M. Spann – Past Investigator. *University of California – San Diego:* James Brewer, Helen Vanderswag, Adam Fleisher – Past Investigator. *University of Michigan:* Jaimie Ziolkowski, Judith L. Heidebrink, Joanne L. Lord – Past Investigator. *Mayo Clinic, Rochester:* Ronald Petersen, Sara S. Mason, Colleen S. Albers, David Knopman, Kris Johnson – Past Investigator. *Baylor College of Medicine:* Javier Villanueva-Meyer, Valory Pavlik, Nathaniel Pacini, Ashley Lamb, Joseph S. Kass, Rachelle S. Doody – Past Investigator, Victoria Shibley – Past Investigator, Munir Chowdhury – Past Investigator, Susan Rountree – Past Investigator, Mimi Dang – Past Investigator. *Columbia University Medical Center:* Yaakov Stern, Lawrence S. Honig, Karen L. Bell, Randy Yeh. *Washington University, St. Louis:* Beau Ances, John C. Morris, David Winkfield, Maria Carroll, Angela Oliver, Mary L. Creech – Past Investigator, Mark A. Mintun – Past Investigator, Stacy Schneider – Past Investigator. *University of Alabama - Birmingham:* Daniel Marson, David Geldmacher, Marissa Natelson Love, Randall Griffith – Past Investigator, David Clark – Past Investigator, John Brockington – Past Investigator. *Mount Sinai School of Medicine:* Hillel Grossman, Effie Mitsis – Past Investigator. *Rush University Medical Center:* Raj C. Shah, Melissa Lamar, Patricia Samuels. *Wien Center:* Ranjan Duara, Maria T. Greig-Custo, Rosemarie Rodriguez. *Johns Hopkins University:* Marilyn Albert, Chiadi Onyike, Daniel D'Agostino II, Stephanie Kielb – Past Investigator. *New York University:* Martin Sadowski, Mohammed O. Sheikh, Jamika Singleton-Garvin, Anaztasia Ulysse, Mrunalini Gaikwad. *Duke University Medical Center:* P. Murali Doraiswamy, Jeffrey R. Petrella, Olga James, Salvador Borges-Neto, Terence Z. Wong – Past Investigator, Edward Coleman – Past Investigator. *University of Pennsylvania:* Jason H. Karlawish, David A. Wolk, Sanjeev Vaishnavi, Christopher M. Clark – Past Investigator, Steven E. Arnold – Past Investigator. *University of Kentucky:* Charles D. Smith, Greg Jicha, Peter Hardy, Riham El Khouli, Elizabeth Oates, Gary Conrad. *University of Pittsburgh:* Oscar L. Lopez, MaryAnn Oakley, Donna M. Simpson. *University of Rochester Medical Center:* Anton P. Porsteinsson, Kim Martin, Nancy Kowalksi, Melanie Keltz, Bonnie S. Goldstein – Past Investigator, Kelly M. Makino – Past Investigator, M. Saleem Ismail – Past Investigator, Connie Brand – Past Investigator. *University of California Irvine IMIND:* Gaby Thai, Aimee Pierce, Beatriz Yanez, Elizabeth Sosa, Megan Witbracht. *University of Texas Southwestern Medical School:* Kyle Womack, Dana Mathews, Mary Quiceno. *Emory University:* Allan I. Levey, James J. Lah, Janet S. Cellar. *University of Kansas, Medical Center:* Jeffrey M. Burns, Russell H. Swerdlow, William M. Brooks. *University of California, Los Angeles:* Ellen Woo, Daniel H.S. Silverman, Edmond Teng, Sarah Kremen, Liana Apostolova – Past Investigator, Kathleen Tingus – Past Investigator, Po H. Lu – Past Investigator, George Bartzokis – Past Investigator. *Mayo Clinic, Jacksonville:* Neill R Graff-Radford (London), Francine Parfitt, Kim Poki-Walker. *Indiana University:* Martin R. Farlow, Ann Marie Hake, Brandy R. Matthews – Past Investigator, Jared R. Brosch, Scott Herring. *Yale University School of Medicine:* Christopher H. van Dyck, Richard E. Carson, Pradeep Varma. *McGill Univ., Montreal-Jewish General Hospital:* Howard Chertkow, Howard

Bergman, Chris Hosein. *Sunnybrook Health Sciences, Ontario:* Sandra Black, Bojana Stefanovic, Chris (Chinthaka) Heyn. *U.B.C. Clinic for AD & Related Disorders:* Ging-Yuek Robin Hsiung, Benita Mudge, Vesna Sossi, Howard Feldman – Past Investigator, Michele Assaly – Past Investigator. *Cognitive Neurology - St. Joseph's, Ontario:* Elizabeth Finger, Stephen Pasternack, William Pavlosky, Irina Rachinsky – Past Investigator, Dick Drost – Past Investigator, Andrew Kertesz – Past Investigator. *Cleveland Clinic Lou Ruvo Center for Brain Health:* Charles Bernick, Donna Muni. *Northwestern University:* Marek-Marsel Mesulam, Emily Rogalski, Kristine Lipowski, Sandra Weintraub, Borna Bonakdarpour, Diana Kerwin – Past Investigator, Chuang-Kuo Wu,– Past Investigator, Nancy Johnson – Past Investigator. *Premiere Research Inst (Palm Beach Neurology):* Carl Sadowsky, Teresa Villena. *Georgetown University Medical Center:* Raymond Scott Turner, Kathleen Johnson, Brigid Reynolds. *Brigham and Women's Hospital*: Reisa A. Sperling, Keith A. Johnson, Gad A. Marshall. *Stanford University:* Jerome Yesavage, Joy L. Taylor, Steven Chao, Barton Lane – Past Investigator, Allyson Rosen – Past Investigator, Jared Tinklenberg – Past Investigator. *Banner Sun Health Research Institute:* Edward Zamrini, Christine M. Belden, Sherye A. Sirrel. *Boston University:* Neil Kowall, Ronald Killiany, Andrew E. Budson, Alexander Norbash – Past Investigator, Patricia Lynn Johnson – Past Investigator. *Howard University:* Thomas O. Obisesan, Ntekim E. Oyonumo, Joanne Allard, Olu Ogunlana. *Case Western Reserve University:* Alan Lerner, Paula Ogrocki, Curtis Tatsuoka, Parianne Fatica. *University of California, Davis – Sacramento:* Evan Fletcher, Pauline Maillard, John Olichney, Charles DeCarli, Owen Carmichael – Past Investigator. *Neurological Care of CNY:* Smita Kittur – Past Investigator. *Parkwood Institute:* Michael Borrie, T-Y Lee, Dr Rob Bartha. *University of Wisconsin:* Sterling Johnson, Sanjay Asthana, Cynthia M. Carlsson. *Banner Alzheimer's Institute:* Pierre Tariot, Anna Burke, Joel Hetelle, Kathryn DeMarco, Nadira Trncic – Past Investigator, Adam Fleisher – Past Investigator, Stephanie Reeder – Past Investigator. *Dent Neurologic Institute:* Vernice Bates, Horacio Capote, Michelle Rainka. *Ohio State University:* Douglas W. Scharre, Maria Kataki, Rawan Tarawneh. *Albany Medical College:* Earl A. Zimmerman, Dzintra Celmins, David Hart. *Hartford Hospital, Olin Neuropsychiatry Research Center:* Godfrey D. Pearlson, Karen Blank, Karen Anderson. *Dartmouth-Hitchcock Medical Center:* Laura A. Flashman, Marc Seltzer, Mary L. Hynes, Robert B. Santulli – Past Investigator. *Wake Forest University Health Sciences:* Kaycee M. Sink, Mia Yang, Akiva Mintz. *Rhode Island Hospital:* Brian R. Ott, Geoffrey Tremont, Lori A. Daiello. *Butler Hospital:* Courtney Bodge, Stephen Salloway, Paul Malloy, Stephen Correia, Athena Lee. *UC San Francisco:* Howard J. Rosen, Bruce L. Miller, David Perry. *Medical University South Carolina:* Jacobo Mintzer, Kenneth Spicer, David Bachman. *St. Joseph's Health Care:* Elizabeth Finger, Stephen Pasternak, Irina Rachinsky, John Rogers, Andrew Kertesz – Past Investigator, Dick Drost – Past Investigator. *Nathan Kline Institute:* Nunzio Pomara, Raymundo Hernando, Antero Sarrael. *University of Iowa College of Medicine:* Delwyn D. Miller, Karen Ekstam Smith, Hristina Koleva, Ki Won Nam, Hyungsub Shim, Susan K. Schultz – Past Investigator. *Cornell University:* Norman Relkin, Gloria Chiang, Michael Lin, Lisa Ravdin. *University of South Florida: USF Health Byrd Alzheimer's Institute:* Amanda Smith, Christi Leach, Balebail Ashok Raj – Past Investigator, Kristin Fargher – Past Investigator.

CHARGE Consortium: Edith Hofer (Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria), Gennady V. Roshchupkin (Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands), Hieab H. H. Adams (Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands), Maria J. Knol (Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands), Honghuang Lin (Section of Computational Biomedicine,

Department of Medicine, Boston University School of Medicine, Boston, MA, USA), Shuo Li (Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA), Habil Zare (Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, UT Health San Antonio, San Antonio, USA), Shahzad Ahmad (Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands), Nicola J. Armstrong (Mathematics and Statistics, Murdoch University, Perth, Australia), Claudia L. Satizabal (Department of Epidemiology and Biostatistics, Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, UT Health San Antonio, San Antonio, USA), Manon Bernard (Hospital for Sick Children, Toronto, Canada), Joshua C. Bis (Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA), Nathan A. Gillespie (Virginia Institute for Psychiatric and Behavior Genetics, Virginia Commonwealth University, VA, USA), Michelle Luciano (Centre for Cognitive Epidemiology and Cognitive Ageing, University of Edinburgh, Edinburgh, UK), Aniket Mishra (University of Bordeaux, Bordeaux Population Health Research Center, INSERM UMR 1219, Bordeaux, France), Markus Scholz (Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany), Alexander Teumer (Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany), Rui Xia (Institute of Molecular Medicine and Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA), Xueqiu Jian (Institute of Molecular Medicine and Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA), Thomas H. Mosley (Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA), Yasaman Saba (Gottfried Schatz Research Center for Cell Signaling, Metabolism and Aging, Medical University of Graz, Graz, Austria), Lukas Pirpamer (Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria), Stephan Seiler (Imaging of Dementia and Aging (IDeA) Laboratory, Department of Neurology, University of California-Davis, Davis, CA, USA), James T. Becker (Departments of Psychiatry, Neurology, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA), Owen Carmichael (Pennington Biomedical Research Center, Baton Rouge, LA, USA), Jerome I. Rotter (Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Pediatrics at Harbor-UCLA Medical Center, Torrance, CA, USA), Bruce M. Psaty (Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, WA, USA), Oscar L. Lopez (Departments of Psychiatry, Neurology, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA), Najaf Amin (Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands), Sven J. van der Lee (Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands), Qiong Yang (Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA), Jayandra J. Himali (Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA), Pauline Maillard (Imaging of Dementia and Aging (IDeA) Laboratory, Department of Neurology, University of California-Davis, Davis, CA, USA), Alexa S. Beiser (Department of Neurology, Boston University School of Medicine, Boston, MA, USA), Charles DeCarli (Imaging of Dementia and Aging (IDeA) Laboratory, Department of Neurology, University of California-Davis, Davis, CA, USA), Sherif Karama (McGill University, Montreal Neurological Institute, Montreal, Canada), Lindsay Lewis (McGill University, Montreal Neurological Institute, Montreal, Canada), Mark Bastin (Centre for Cognitive Epidemiology and Cognitive Ageing, University of Edinburgh, Edinburgh, UK), Ian J. Deary (Centre for Cognitive Epidemiology and Cognitive Ageing, University of Edinburgh, Edinburgh, UK), Veronica Witte (Department of Neurology, Max Planck Institute of Cognitive and Brain Sciences, Leipzig, Germany), Frauke Beyer (Department of Neurology, Max Planck Institute of Cognitive and Brain Sciences, Leipzig, Germany),

Markus Loeffler (Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany), Karen A. Mather (Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia), Peter R. Schofield (Neuroscience Research Australia, Sydney, Australia), Anbupalam Thalamuthu (Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia), John B. Kwok (Brain and Mind Centre - The University of Sydney, Camperdown, NSW, Australia), Margaret J. Wright (Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia), David Ames (National Ageing Research Institute, Royal Melbourne Hospital, Victoria, Australia), Julian Trollor (Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia), Jiyang Jiang (Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia), Henry Brodaty (Dementia Centre for Research Collaboration, University of New South Wales, Sydney, NSW, Australia), Wei Wen (Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia), Meike W Vernooij (Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands), Albert Hofman (Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA), André G. Uitterlinden (Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands), Wiro J. Niessen (Imaging Physics, Faculty of Applied Sciences, Delft University of Technology, The Netherlands), Katharina Wittfeld (German Center for Neurodegenerative Diseases (DZNE), Site Rostock/ Greifswald, Germany), Robin Bülow (Institute for Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, Germany), Uwe Völker (Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany), Zdenka Pausova (Hospital for Sick Children, Toronto, Canada), G. Bruce Pike (Departments of Radiology and Clinial Neurosciences, University of Calgary, Calgary, Canada), Sophie Maingault (University of Bordeaux, Institut des Maladies NeurodégénrativesUMR5293, CEA, CNRS, Ubordeaux, Bordeaux, France), Fabrice Crivello (University of Bordeaux, Institut des Maladies NeurodégénrativesUMR5293, CEA, CNRS, Ubordeaux, Bordeaux, France), Bernard Mazoyer (Neurodegeneratives Diseases Institute UMR 5293, CNRS, CEA, University of Bordeaux, Bordeaux, France), Michael C. Neale (Virginia Institute for Psychiatric and Behavior Genetics, Virginia Commonwealth University, VA, USA), Carol E. Franz (Department of Psychiatry, University of California San Diego, CA, USA), Michael J. Lyons (Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA), Matthew S. Panizzon (Department of Psychiatry, University of California San Diego, CA, USA), Ole A. Andreassen (ORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway), Anders M. Dale (Departments of Radiology and Neurosciences, University of California, San Diego, La Jolla, CA, USA), Mark Logue (National Center for PTSD at Boston VA Healthcare System, Boston, MA, USA), Perminder S. Sachdev (Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia), William S. Kremen (Department of Psychiatry, University of California San Diego, CA, USA), Joanna A. Wardlaw (Centre for Cognitive Epidemiology and Cognitive Ageing, University of Edinburgh, Edinburgh, UK), Arno Villringer (Department of Neurology, Max Planck Institute of Cognitive and Brain Sciences, Leipzig, Germany), Cornelia M. van Duijn (Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands), Hans Jörgen Grabe (Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Germany), William T. Longstreth Jr (Departments of Neurology and Epidemiology, University of Washington, Seattle, WA, USA), Myriam Fornage (Institute of Molecular Medicine and Human Genetics Center, University of Texas Health Science Center at

Houston, Houston, TX, USA), Tomas Paus (Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada), Stephanie Debette (University of Bordeaux, Bordeaux Population Health Research Center, INSERM UMR 1219, Bordeaux, France), M. Arfan Ikram (Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands), Helena Schmidt (Gottfried Schatz Research Center for Cell Signaling, Metabolism and Aging, Medical University of Graz, Graz, Austria), Reinhold Schmidt (Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria), Sudha Seshadri (Department of Epidemiology and Biostatistics, Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, UT Health San Antonio, San Antonio, USA.

EPIGEN Consortium: David B. Goldstein (The Centre for Genomics and Population Genetics, Duke University Institute for Genome Sciences and Policy, Durham, North Carolina, USA), Erin L. Heinzen (The Centre for Genomics and Population Genetics, Duke University Institute for Genome Sciences and Policy, Durham, North Carolina, USA), Kevin Shianna (The Centre for Genomics and Population Genetics, Duke University Institute for Genome Sciences and Policy, Durham, North Carolina, USA), Rodney Radtke (Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA) and Ruth Ottmann (Departments of Epidemiology, Neurology, and the G.H. Sergievsky Center, Columbia University, New York, NY).

IMAGEN Consortium: Dr. Eric Artiges (INSERM), Semiha Aydin (Physikalisch-Technische Bundesanstalt), Prof. Dr. Dr. Tobias Banaschewski (Central Institute of Mental Health), Alexis Barbot (Commissariat à l'Energie Atomique), Prof. Dr. Gareth Barker (King's College London), Andreas Becker (Georg-August-Universität Göttingen), Pauline Bezivin-Frere (INSERM), Dr. Francesca Biondo (King's College London), Dr. Arun Bokde (Trinity College Dublin), Uli Bromberg (University of Hamburg), Dr. Ruediger Bruehl, Prof. Dr. Christian Büchel (University of Hamburg), Dr. Congying Chu (King's College London), Dr. Patricia Conrod (King's College London), Laura Daedelow (Charité Universitätsmedizin Berlin), Dr. Jeffrey Dalley (Cambridge University), Dr. Sylvane Desrivieres (King's College London), Eoin Dooley (Trinity College Dublin), Irina Filippi (INSERM), Dr Ariane Fillmer (Physikalisch-Technische Bundesanstalt), Prof. Dr. Herta Flor (Central Institute of Mental Health), Juliane Fröhner (Technische Universität Dresden), Vincent Frouin (Commissariat à l'Energie Atomique), Dr. Hugh Garavan (University of Vermont), Prof. Penny Gowland (University of Nottingham), Yvonne Grimmer (Central Institute of Mental Health), Prof. Dr. Andreas Heinz (Charité Universitätsmedizin Berlin), Dr. Sarah Hohmann (Central Institute of Mental Health), Albrecht Ihlenfeld (Physikalisch-Technische Bundesanstalt), Alex Ing (King's College London), Corinna Isensee (University Medical Center Göttingen), Dr. Bernd Ittermann (Physikalisch-Technische Bundesanstalt), Dr. Tianye Jia (King's College London), Dr. Hervé Lemaitre (INSERM), Emma Lethbridge (University of Nottingham), Prof. Dr. Jean-Luc Martinot (INSERM), Sabina Millenet (Central Institute of Mental Health), Sarah Miller (Charité Universitätsmedizin Berlin), Ruben Miranda (INSERM), PD Dr. Frauke Nees (Central Institute of Mental Health), Dr. Marie-Laure Paillere (INSERM), Dimitri Papadopoulos (INSERM), Prof. Dr. Tomáš Paus (Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital and Departments of Psychology and Psychatry, University of Toronto), Dr. Zdenka Pausova (University of Toronto), Dr. Dr. Jani Pentilla (INSERM), Dr. Jean-Baptiste Poline (Commissariat à l'Energie Atomique), Prof. Dr. Luise Poustka (University Medical Center Göttingen), Dr. Erin Burke Quinlan (King's College London), Dr. Michael Rapp (Charité Universitätsmedizin Berlin), Prof. Dr. Trevor Robbins (Cambridge University), Dr. Gabriel Robert (King's College London), John Rogers (Delosis),

Dr. Barbara Ruggeri (King's College London), Prof. Dr. Gunter Schumann (King's College London), Prof. Dr. Michael Smolka (Technische Universität Dresden), Argyris Stringaris (National Institute of Mental Health), Betteke van Noort (Charité Universitätsmedizin Berlin), Dr. Henrik Walter (Charité Universitätsmedizin Berlin), Dr. Robert Whelan (Trinity College Dublin), Prof. Dr. Steve Williams (King's College London).

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(The Parkinson's Institute, Sunnyvale), James Tetrud (The Parkinson's Institute, Sunnyvale), Grace Liang (The Parkinson's Institute, Sunnyvale), Alex Iranzo (Hospital Clinic of Barcelona, Barcelona), Eduardo Tolosa (Hospital Clinic of Barcelona, Barcelona), Shu-Ching Hu (University of Washington, Seattle), Gretchen Todd (University of Washington, Seattle), Laura Leary (Institute for Neurodegenerative Disorders, New Haven), Cheryl Riordan (Institute for Neurodegenerative Disorders, New Haven), Linda Rees (The Parkinson's Institute, Sunnyvale), Alicia Portillo (Oregon Health and Science University, Portland), Art Lenahan (Oregon Health and Science University, Portland), Karen Williams (Northwestern University, Chicago), Stephanie Guthrie (University of Alabama at Birmingham, Birmingham), Ashlee Rawlins (University of Alabama at Birmingham, Birmingham), Sherry Harlan (University of South Florida, Tampa), Christine Hunter (Baylor College of Medicine, Houston), Baochan Tran (University of Pennsylvania, Philadelphia), Abigail Darin (University of Pennsylvania, Philadelphia), Carly Linder (University of Pennsylvania, Philadelphia), Marne Baca (University of Washington, Seattle), Heli Venkov (University of Washington, Seattle), Cathi-Ann Thomas (Boston University, Boston), Raymond James (Boston University, Boston), Cheryl Deeley (University of Rochester, Rochester), Courtney Bishop (University of Rochester, Rochester), Fabienne Sprenger (Innsbruck Medical University, Innsbruck), Diana Willeke (Paracelsus-Elena Klinik, Kassel), Sanja Obradov (Banner Research Institute, Sun City), Jennifer Mule (Cleveland Clinic, Cleveland), Nancy Monahan (Cleveland Clinic, Cleveland), Katharina Gauss (University of Tuebingen, Tuebingen), Deborah Fontaine (University of California, San Diego), Christina Gigliotti (University of California, San Diego), Arita McCoy (Johns Hopkins University, Baltimore), Becky Dunlop (Johns Hopkins University, Baltimore), Bina Shah (Imperial College of London, London), Susan Ainscough (University of Salerno, Salerno), Angela James (Parkinson's Disease and Movement Disorders Center, Boca Raton), Rebecca Silverstein (Parkinson's Disease and Movement Disorders Center, Boca Raton), Kristy Espay (University of Cincinnati, Cincinnati), Madelaine Ranola (Macquarie University, Sydney), Thomas Comery (Pfizer, Inc., Groton), Jesse Cedarbaum (Biogen Idec, Cambridge), Bernard Ravina (Biogen Idec, Cambridge), Igor D. Grachev (GE Healthcare, Princeton), Jordan S. Dubow (AbbVie, Abbot Park), Michael Ahlijanian (Bristol-Myers Squibb Company), Holly Soares (Bristol-Myers Squibb Company), Suzanne Ostrowizki (F.Hoffmann La-Roche, Basel), Paulo Fontoura (F.Hoffmann La-Roche, Basel), Alison Chalker (Merck & Co., North Wales), David L. Hewitt (Merck & Co., North Wales), Marcel van der Brug (Genentech, Inc., South San Francisco), Alastair D. Reith (GlaxoSmithKline, Stevenage), Peggy Taylor (Covance, Dedham), Jan Egebjerg (H. Lundbeck), Mark Minton (Avid Radiopharmaceuticals, Philadelphia), Andrew Siderowf (Avid Radiopharmaceuticals, Philadelphia), Pierandrea Muglia (UCB Pharma S.A., Brussels), Robert Umek (Meso Scale Discovery), Ana Catafau (Meso Scale Discovery), Vera Kiyasova (Servier), Barbara Saba (Servier).

SYS Consortium: Tomáš Paus MD PhD (Bloorview Research Institute, University of Toronto, Canada), Zdenka Pausova, MD (The Hospital for Sick Children, University of Toronto, Canada), G. Bruce Pike PhD (Department of Radiology, University of Calgary, Canada), Louis Richer PhD (Department of Health Sciences, University of Quebec in Chicoutimi, Canada), Gabriel Leonard PhD (Montreal Neurological Institute, McGill University, Canada), Michel Perron PhD (CEGEP Jonquiere, Canada), Suzanne Veillette PhD (CEGEP Jonquiere, Canada) and Manon Bernard BComp (The Hospital for Sick Children, University of Toronto, Canada).

Additional cohort information

ADNI

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative database. The ADNI was launched in 2003 as a 5-year public–private partnership to assess and optimize biomarkers for clinical trials in Alzheimer's disease. The initial sample included older adults who were cognitive normal (CN) as well as meeting criteria for MCI and clinical AD. In 2011, ADNI-2 began to recruit an additional CN group as well as individuals with significant memory concerns (SMC), early MCI and late MCI,and AD. . These subjects, and others carried forward from ADNI-1, were scanned with an updated neuroimaging protocol. Participants were recruited from over 60 sites across the U.S. and Canada. For up-to-date information, please see www.adni-info.org.

ALSPAC

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a "Children in Focus" clinic had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper (see footnote 4 below). The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775 were live births and 14,701 were alive at 1 year of age. A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon. The data used in the present study were collected from 391 males and further description of this subset and the variables used in this study are provided in Supplementary Tables 2–4.

The study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

Further information can be found in the following papers:

Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The 'Children of the 90s'; the index offspring of The Avon Longitudinal Study of Parents and Children (ALSPAC). International Journal of Epidemiology 2013; 42: 111-127;

Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International Journal of Epidemiology 2013; 42:97-110.

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Author Contributions (in alphabetical order)

[†]K.L.G. and N.J. contributed to this work as co-first authors.
[‡]J.N.P., L.C.-C., J.B., D.P.H., P.A.L., and F.P. contributed to this work as co-second authors.
[§]J.L.S., P.M.T., and S.E.M. contributed to this work as co-last authors.
[#]Consortium authors are listed in Supplementary Materials

*N.J., J.L.S., P.M.T., and S.E.M. are corresponding authors: S.E.M. Sarah.Medland@qimrberghofer.edu.au, P.M.T. pthomp@usc.edu, J.L.S. jason_stein@med.unc.edu, N.J. njahansh@usc.edu

Central Analysis and Coordination Group
C.R.K.C., D.P.H., F.P., J.Br., J.L.S., J.N.P., K.L.G., L.C.-C., L.C.P.Z., M.A.B.M., N.J., N.S., P.A.L., P.M.T., S.E.M.

Manuscript Writing and Preparation
D.P.H., J.Br., J.L.S., J.N.P., K.L.G., L.C.-C., N.J., P.A.L., P.M.T., S.E.M.

Project Support
D.Ga., M.A.B.M., M.J., N.S., R.E., V.R., Y.G.

Cohort Principal Investigator
A.A.V., A.C., A.H., A.J.F., A.J.H., A.K.H., A.M.D., A.M.-L., A.R.H., A.W.T., B.C.-F., B.F., B.Mo., B.S.P., B.T.B., B.W., B.W.J.H.P., C.A.H., C.Dep., C.F., C.M., C.M.L., C.P., D.Am., D.C.G., D.I.B., D.J.S., D.P., D.R.W., D.v.E., E.G.J., E.J.C.d.G., E.L.H., F.A.H., F.C., G.D., G.F., G.G.B., G.L.C., G.S., H.B., H.E.H.P., H.F., H.G.B., H.J.G., H.V., H.W., I.A., I.E.Som., I.J.D., I.M., J.B.J.K., J.Bl., J.C.D.-A., J.K.B., J.-L.M., J.L.R., J.N.T., J.O., J.R.B., J.W.S., J.Z., K.L.M., K.S., L.M.R., L.N., L.R., L.T.W., M.E.B., M.H.J.H., M.J.C., M.J.W., M.K.M.A., M.R., N.D., N.J., N.J.A.v.d.W., O.A.A., O.G., P.G.S., P.J.H., P.K., P.M.T., P.S.S., P.T.M., R.A.M., R.A.O., R.H., R.J.S., R.L.B., R.L.G., R.S.K., S.Ca., S.Des., S.E.F., S.L.H., S.M.S., S.R., T.E., T.J.A., T.J.C.P., T.L.J., T.P., T.T.J.K., U.D., V.C., V.J.C., W.C., W.U.H., X.C., Z.P.

Imaging Data Collection

A.B., A.d.B., A.F.M., A.J., A.J.H., A.K., A.K.H., A.L.G., A.M.D., A.N.H., A.P., A.R.H., A.R.K., A.U., B.A.M., B.-C.H., B.D., B.F., B.Pi., B.W., B.W.J.H.P., C.B., C.D.W., C.J., C.L.B., C.L.Y., C.M., C.P., C.R.J., C.S.Re., D.Am., D.C.G., D.Gr., D.H.M., D.J., D.J.H., D.J.V., D.M.C., D.P.O., D.R.W., D.S.O., D.T.-G., D.v.E., D.v.R., D.Z., E.A., E.B.Q., E.J.C.d.G., E.L.H., E.Sh., G.B.P., G.D., G.F., G.I.d.Z., G.L.C., G.R., G.S., H.V., H.Y., I.A., I.E.Som., J.A.T., J.E.C., J.E.N., J.K.B., J.-L.M., J.-L.M., J.L.R., J.M.F., J.M.W., J.N.T., J.R., J.T.V., K.D., K.K., K.L.M., K.O.L., K.S., L.M.R., L.R., L.T.W., M.B.H., M.E.B., M.Fu., M.H.J.H., M.Ho., M.-J.v.T., M.J.W., M.-L.P.M., N.E.M.v.H., N.F.H., N.H., N.J.A.v.d.W., N.K.H., N.O., O.G., P.A.G., P.E.R., P.G.S., P.K., P.N., P.S.S., R.A.O., R.B., R.H., R.L.B., R.L.G., R.R., R.S.K., R.W., S.A., S.C.M., S.Ca., S.Er., S.Ko., S.M., S.M.S., T.G.M.v.E., T.R.M., T.Wh., T.W.M., U.D., U.S., V.C., V.J.C., V.S.M., W.D.H., W.H., W.W., X.C.

Imaging Data Analysis

A.F.M., A.H.Z., A.J.H., A.J.S., A.L.G., A.M.D., A.R., A.R.K., A.S., A.Th., A.U., B.A.G., B.C.R., B.F., B.K., B.S.P., C.B., C.C.F., C.C.H., C.D.W., C.J., C.L.Y., C.R.K.C., C.S.Ro., D.Al., D.C.G., D.Gr., D.H., D.J., D.J.H., D.M.C., D.P.H., D.P.O., D.T.-G., D.v.d.M., D.v.E., D.v.R., D.Z., E.E.L.B., E.Sh., E.Sp., E.W., F.M.R., F.P., F.S., G.I.d.Z., G.R., H.J.G., I.A., I.E.Som., I.K.A., J.A.T., J.B.J.K., J.C.V.M., J.-L.M., J.L.R., J.L.S., J.M.W., J.R., J.Z., K.D., K.L.M., K.N., K.S., K.W., L.B.L., L.H., L.Sa., L.Sc., L.Sh., L.T.S., L.T.W., L.v.E., L.C.P.Z., M.A., M.A.H., M.B.H., M.C., M.E.B., M.Fu., M.Ho., M.J.G., M.-J.v.T., M.J.W., M.Ki., M.La., M.P.Z., M.W., N.E.M.v.H., N.F.H., N.J., N.O., N.T.D., O.G., P.G.S., P.K., P.M.T., P.N., R.B., R.K., R.L.G., R.M.B., R.R., R.R.-S., S.A., S.Ca., S.Des., S.Eh., S.Er., S.F.F., S.I.T., S.Ka., S.Ke., S.L.R., S.M.C.d.Z., S.R.M., T.A., T.A.L., T.G., T.G.M.v.E., T.J., T.K., T.L.P., T.P.G., T.R.M., T.Wh., T.Wo., T.W.M., U.D., W.W., X.C., Y.Q., Z.Z.

Genetic Data collection

A.A.A., A.A.-K., A.d.B., A.J.F., A.J.H., A.J.S., A.K.H., A.M.D., A.P., A.R.H., A.R.K., B.-C.H., B.F., B.Mo., B.T.B., B.W., B.W.J.H.P., C.B., C.D.W., C.F., C.M., C.P., C.P.D., C.S.Re., D.C.G., D.H.M., D.R.W., D.W.M., D.Z., E.A., E.B.Q., E.G.J., E.J.C.d.G., E.L.H., F.D., F.M., F.R.T., G.D., G.E.D., G.F., G.H., G.L.C., G.S., H.V., H.Y., I.E.Som., I.L.-C., J.A.T., J.B.J.K., J.Bl., J.E.C., J.E.N., J.-J.H., J.J.L., J.K.B., J.-L.M., J.-L.M., J.L.R., J.M.F., J.Q.W., J.R., J.W.S., K.A.M., K.D., K.O.L., K.S., L.M.R., L.R., L.Sh., M.A.K., M.F.D., M.H.J.H., M.Ha., M.Ho., M.J.C., M.J.W., M.La., M.-L.P.M., M.M.N., M.N., N.A.K., N.E.M.v.H., N.G.M., N.J.A.v.d.W., N.K.H., N.O., O.G., P.A.T., P.H., P.K., P.R.S., P.S.S., R.A.O., R.C.G., R.H., R.L.B., R.R., R.Se., R.S.K., R.W., S.A., S.Ci., S.Dj., S.E.F., S.Eh., S.Er., S.H., S.L.H., S.M.S., T.G.M.v.E., T.J.A., T.K.d.A., T.L.P., T.W.M., U.D., V.C., V.J.C., V.M.S., X.C.

Genetic Data Analysis

A.A.-K., A.J.F., A.J.H., A.J.S., A.M.D., A.R.K., A.Te., A.Th., B.C.-D., B.F., B.K., B.M.-M., B.Pü., B.S.P., B.T.B., C.C.F., C.D.W., C.L.V., C.S.Re., C.S.Ro., C.W., C.Y.S., D.C.G., D.K., D.P.H., D.v.d.M., D.v.E., E.G.J., E.L.H., E.V., E.W., F.M., H.-R.E., I.E.J., I.E.Som., I.E.Søn., I.L.-C., I.O.F., J.Bl., J.Br., J.F.P., J.H.V., J.-J.H., J.L.R., J.L.S., J.N.P., J.Q.W., J.R.A., J.S., J.W.C., J.W.S., K.E.T., K.L.G., K.N., L.C.-C., L.M.O.L., L.Sh., L.C.P.Z., M.A.A.A., M.B., M.E.G., M.Fu., M.Ha., M.I., M.J., M.J.C., M.J.W., M.Ki., M.Kl., M.Kn., M.La., M.Lu., M.M.J.v.D., N.A.G., N.G.M., N.J., N.J.A., N.K.H., N.M.-S., N.R.M., O.G., P.A.L., P.G.S., P.H., P.H.L., P.K., P.M.T., P.R.S., Q.C., R.A.O., R.M.B., R.R., R.Se., S.Da.,

S.Des., S.E.M., S.Eh., S.G., S.H., S.H.W., S.L.H., S.M.C.d.Z., S.N., S.R.M., T.A.L., T.G., T.G.M.v.E., T.J., T.K.d.A., T.M.L., W.R.R., Y.M., Y.W.

CHARGE Study Design
B.Ma., C.Dec., C.L.S., E.H., G.V.R., H.H.H.A., H.J.G., J.C.B., L.J.L., M.A.I., M.Fo., O.L.L., Q.Y., R.Sc., S.Deb., S.S., T.H.M., V.G., W.T.L.

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