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BYLINE: Martine Hoogman*, PhD[1,2], Ryan Muetzel*, PhD[3,4], Joao P. Guimaraes,MSc[1,5], Elena Shumskaya, PhD[1,2], Maarten Mennes, PhD[6], Marcel P. Zwiers, PhD[5], Neda Jahanshad, PhD[7], Gustavo Sudre, PhD[8], Jeanette Mostert, PhD[1,2], Thomas Wolfers, MSc[1,2], Eric A. Earl, BSc[9], Juan Carlos Soliva Vila, PhD[10], Yolanda Vives-Gilabert, PhD[11], Sabin Khadka, MSc[12], Stephanie E. Novotny, MSc[12], Catharina A. Hartman, PhD[13], Dirk J. Heslenfeld, PhD[14], Lizanne J.S. Schweren, PhD[15], Sara Ambrosino, MD[16], Bob Oranje, PhD[16], Patrick de Zeeuw, PhD[16], Tiffany M. Chaim-Avancini, PhD[17,18], Pedro G. P. Rosa, MD[17,18], Marcus V. Zanetti, PhD[17,18], Charles B. Malpas, PhD[19,20,21], Gregor Kohls, PhD[22], Georg G. von Polier, MD[23], Jochen Seitz, MD[23], Joseph Biederman, MD[24,25], Alysa E. Doyle, PhD[26,25], Anders M. Dale, PhD[27,28], Theo G.M. van Erp, PhD[29], Jeffrey N. Epstein, PhD[30,31], Terry L. Jernigan, PhD[32], Ramona Baur-Streubel, PhD[33], Georg C. Ziegler, MD[34], Kathrin C. Zierhut, PhD[33], Anouk Schrantee, PhD[35], Marie F. Høvik, MD[36,37], Astri J. Lundervold, PhD[38,39], Clare Kelly, PhD[40,41,42], Hazel McCarthy, PhD[43,44], Norbert Skokauskas, MD, PhD[43,45], Ruth L. O'Gorman Tuura, PhD[46,47], Anna Calvo, MSc[48], Sara Lera-Miguel, PhD[49], Rosa Nicolau, BSc[49], Kaylita C. Chantiluke, PhD[50], Anastasia Christakou, PhD[50,51], Alasdair Vance, MD[52], Mara Cercignani, PhD[53], Matt C. Gabel, PhD[53], Philip Asherson, PhD[54], Sarah Baumeister, PhD[55], Daniel Brandeis, PhD[55,56,57], Sarah Hohmann, MD[55], Ivanei E. Bramati, PhD[58], Fernanda Tovar-Moll, MD, PhD[58,59], Andreas J. Fallgatter, MD[60,61], Bernd Kardatzki, BSc[62], Lena Schwarz, MD[60], Anatoly Anikin, PhD[63], Alexandr Baranov, PhD[64],Tinatin Gogberashvili, PhD[65], Dmitry Kapilushniy, PhD[66], Anastasia Solovieva, PhD[64], Hanan El Marroun, PhD[3,67,68], Tonya White, MD, PhD[3,69], Georgii Karkashadze, PhD[65], Leyla Namazova-Baranova, PhD[64], Thomas Ethofer, PhD[60,62], Paulo Mattos, MD, PhD[58,70], Tobias Banaschewski, MD, PhD[55], David Coghill, MD[52,71,72,73], Kerstin J. Plessen, MD, PhD[74,75], Jonna Kuntsi, PhD[54], Mitul A. Mehta, PhD[76], Yannis Paloyelis,

PhD[76], Neil A. Harrison, PhD[53,77], Mark A. Bellgrove, PhD[78], Tim J. Silk, PhD[52,72,79], Ana I. Cubillo, PhD[50], Katya Rubia, PhD[50], Luisa Lazaro, MD, PhD[49,80], Silvia Brem, PhD[56,81], Susanne Walitza, MD[56], Thomas Frodl, MD, PhD[43,82,83], Mariam Zentis, MD[84], Francisco X. Castellanos, MD[42,85,86], Yuliya N. Yoncheva, PhD[42], Jan Haavik, MD, PhD[37,39], Liesbeth Reneman, MD, PhD[35,87], Annette Conzelmann, MD, PhD[88,89], Klaus-Peter Lesch, MD, PhD[34,90,91], Paul Pauli, PhD[89], Andreas Reif, MD[92], Leanne Tamm, PhD[30,31], Kerstin Konrad, PhD[22,93], Eileen Oberwelland Weiss, PhD[94,95], Geraldo F. Busatto, PhD[17,96], Mario R. Louza, MD, PhD[96], Sarah Durston, PhD[16], Pieter J. Hoekstra, PhD[13], Jaap Oosterlaan, PhD[97,98,99], Michael C. Stevens, PhD[12,100], J. Antoni Ramos-Quiroga, MD, PhD[10,101,102], Oscar Vilarroya, PhD[10,103], Damien A. Fair, PhD[9,104], Joel T. Nigg, PhD[9,104], Paul M. Thompson, PhD[7], Jan K. Buitelaar, MD, PhD[2,105], Stephen V. Faraone , PhD[106], Philip Shaw, MD, PhD[8, 107], Henning Tiemeier, PhD[3,108], Janita Bralten, PhD[1,2], Barbara Franke, PhD[1,2].

*shared first author

AFFILIATIONS

1. Department of Human Genetics, Radboud university medical center, Nijmegen, Netherlands

2. Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, Netherlands

3. Department of Child and Adolescent Psychiatry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

4. Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

5. Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Nijmegen, The Netherlands

6. Radboud University, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, Netherlands

7. Imaging Genetics Center, Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, Marina del Rey, CA, USA

8. National Human Genome Research Institute, Bethesda, MD, USA

9. Department of Behavioral Neuroscience, Oregon Health & Science University, Portland OR, USA

10. Department of Psychiatry and Forensic Medicine, Universitat Autonoma de Barcelona, Spain

11. Instituto ITACA, Universitat Politècnica de València, València, Spain

12. Olin Neuropsychiatry Research Center, Hartford Hospital, Hartford, CT, USA

13. University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), Groningen, The Netherlands

14. Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

15. University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry, Groningen, The Netherlands

16. NICHE Lab, Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands

17. Laboratory of Psychiatric Neuroimaging (LIM-21), Department and Institute of Psychiatry, Faculty of Medicine, University of São Paulo, Sao Paulo, Brazil.

18. Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Sao Paulo, Brazil

19. Developmental Imaging Group, Murdoch Children's Research Institute, Melbourne, Australia

20. Clinical Outcomes Research Unit (CORe), Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Melbourne, Australia

21. Melbourne School of Psychological Sciences, The University of Melbourne, Melbourne, Australia

22. Child Neuropsychology Section, University Hospital RWTH Aachen, Aachen, Germany

23. Child and Adolescent Psychiatry, University Hospital RWTH Aachen, Aachen, Germany

24. Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Department of Psychiatry, Massachusetts General Hospital, USA

25. Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, USA

26. Center for Genomic Medicine, Massachusetts General Hospital, Harvard Medical School, USA

27. Departments of Neurosciences, Radiology, and Psychiatry, UC San Diego, USA

28. Center for Multimodal Imaging and Genetics (CMIG), UC San Diego, CA, USA

29. Clinical and Translational Neuroscience Laboratory, Department of Psychiatry and Human Behavior, University of California Irvine, Irvine, CA, USA

30. Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

31. Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

32. Center for Human Development, UC San Diego, USA

33. Department of Psychology I, University of Würzburg, Würzburg, Germany

34. Division of Molecular Psychiatry, Center of Mental Health, University of Würzburg, Würzburg, Germany

35. Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Amsterdam; the Netherlands

36. Department of Clinical Medicine, University of Bergen, Bergen, Norway

37. Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

38. Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

39. K.G. Jebsen Centre for Neuropsychiatric Disorders, Department of Biomedicine, University of Bergen, Bergen, Norway

40. School of Psychology and Department of Psychiatry at the School of Medicine, Trinity College Dublin, Ireland

41. Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland

42. Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New York, NY, USA

43. Department of Psychiatry, Trinity College Dublin, Ireland

44. Centre of Advanced Medical Imaging, St James's Hospital, Dublin, Ireland

45. Institute of Mental Health, Norwegian University of Science and Technology, Norway

46. Center for MR Research, University Children's Hospital, Zurich, Switzerland

47. Zurich Center for Integrative Human Physiology (ZIHP), Zurich, Switserland

48. Magnetic Resonance Image Core Facility, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

49. Department of Child and Adolescent Psychiatry and Psychology, Institute of Neurosciencies, Hospital Clínic, Barcelona, Spain

50. Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

51. School of Psychology and Clinical Language Sciences, Centre for Integrative Neuroscience and Neurodynamics, University of Reading, Reading, UK

52. Department of Paediatrics, University of Melbourne, Australia

53. Department of Neuroscience, Brighton and Sussex Medical School, Falmer, Brighton, UK

54. Social, Genetic and Developmental Psychiatry Centre; Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

55. Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Medical Faculty Mannheim / Heidelberg University, Mannheim, Germany

56. Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Zurich, Switzerland

57. Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland

58. D'Or Institute for Research and Education, Rio de Janeiro, Brazil

59. Morphological Sciences Program, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

60. Department of Psychiatry and Psychotherapy, University Hospital of Tuebingen, Tuebingen, Germany

61. LEAD Graduate School, University of Tuebingen, Germany

62. Department of Biomedical Magnetic Resonance, University of Tuebingen, Tuebingen, Germany

63. National Medical Research Center for Children's Health, Department of magnetic resonance imaging and densitometry, Moscow, Russia

64. National Medical Research Center for Children's Health, Moscow, Russia

65. National Medical Research Center for Children's Health, Laboratory of Neurology and Cognitive Health, Moscow, Russia

66. National Medical Research Center for Children's Health, Department of Information Technologies, Moscow, Russia

67. Department of Paediatrics, Erasmus MC - Sophia, Rotterdam, the Netherlands

68. Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, Rotterdam, the Netherlands

69. Department of Radiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

70. Federal University of Rio de Janeiro, Brazil

71. Departments of Psychiatry, University of Melbourne, Melbourne, Australia

72. Murdoch Children's Research Institute, Melbourne, Australia

73. Division of Neuroscience, University of Dundee, Dundee, UK

74. Child and Adolescent Mental Health Centre, Capital Region Copenhagen, Denmark

75. Division of Child and Adolescent Psychiatry, Department of Psychiatry, University Hospital Lausanne, Switzerland

76. Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

77. Sussex Partnership NHS Foundation Trust, Swandean, East Sussex, UK

78. Monash Institute for Cognitive and Clinical Neurosciences (MICCN) and School of Psychological Sciences, Monash University, Melbourne, Australia

79. Deakin University, School of Psychology, Geelong, Australia

80. Department of Medicine, University of Barcelona, Spain

81. University of Zurich and ETH Zurich, Neuroscience Center Zurich, Zurich, Switzerland

82. Department of Psychiatry and Psychotherapy, Otto von Guericke University Magdeburg, Germany

83. German Center for Neurodegenerative Diseases (DZNE), Germany

84. Bezirksklinikum Regensburg, Germany

85. Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

86. Section of Biomedical Image Analysis, Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA

87. Brain Imaging Center, Amsterdam University Medical Centers, Amsterdam; the Netherlands

88. Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Tübingen, Germany

89. Department of Biological Psychology, Clinical Psychology and Psychotherapy, Würzburg, Germany

90. Laboratory of Psychiatric Neurobiology, Institute of Molecular Medicine, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

91. Department of Neuroscience, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, The Netherlands

92. Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt, Germany

93. JARA Institute Molecular Neuroscience and Neuroimaging (INM-11), Institute for Neuroscience and Medicine, Research Center Jülich, Germany

94. Translational Neuroscience, Child and Adolescent Psychiatry, University Hospital RWTH Aachen, Aachen, Germany

95. Cognitive Neuroscience (INM-3), Institute for Neuroscience and Medicine, Research Center Jülich, Germany

96. Department of Psychiatry, Faculty of Medicine, University of São Paulo, São Paulo, Brazil

97. Clinical Neuropsychology Section, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands.

98. Emma Children's Hospital Amsterdam Medical Center, Amsterdam, The Netherlands

99. Department of Pediatrics, VU Medical Center, Amsterdam, The Netherlands

100. Department of Psychiatry, Yale University School of Medicine, USA

101. Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain

102. Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Catalonia, Spain

103. Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

104. Department of Psychiatry, Oregon Health & Science University, Portland OR, USA

105. Karakter Child and Adolescent Psychiatry University Center, Nijmegen, The Netherlands

106. SUNY Upstate Medical University, Syracuse, NY, USA

107. National Institute of Mental Health, Bethesda, MD, USA

108. Department of Social and Behavioral Science, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

LOCATION OF WORK AND ADDRESS FOR REPRINTS

Barbara Franke, PhD

Radboud University Medical Center

Department of Human Genetics (855)

PO Box 9101

6500 HB Nijmegen

The Netherlands

Tel: +31-24-3614017

e-mail: barbara.franke@radboudumc.nl

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Jan Haavik: K.G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway

Steve Faraone: K.G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway

ABSTRACT

Objective: Neuroimaging studies show structural alterations of various brain regions in children and adults with ADHD, although non-replications are frequent. Our aim is to identify cortical characteristics related to ADHD using large-scale studies. **Methods:** Cortical thickness and surface area (based on the Desikan–Killiany atlas) were compared between cases (n=2246) and controls (n=1934) for children, adolescents, and adults separately in ENIGMA-ADHD, a consortium of 36 centers. To assess familial effects on cortical measures, cases, unaffected siblings, and controls in the NeuroIMAGE study (n=506) were compared. Associations of the attention scale from the Child Behavior Checklist with cortical measures were determined in a pediatric population sample (Generation-R, n=2707). **Results:** In ENIGMA-ADHD, lower surface area values were found in children with ADHD, mainly in frontal, cingulate, and temporal regions; the largest effect was for total surface area (Cohen's *d*=-0.21; p_{FDR}=<0.001). Fusiform gyrus and temporal pole cortical thickness was also lower in children with ADHD. Neither surface area nor thickness differences were found in the adolescents/adult groups. Familial effects were seen for surface area in several regions. In an overlapping set of regions, surface area, but not thickness, was associated with attention problems in Generation-R. **Conclusion:** Subtle differences in cortical surface area are widespread in children, but not in adolescents and adults with ADHD, confirming involvement of frontal cortex and highlighting regions deserving further attention. Importantly, the alterations behave like endophenotypes in families and are linked to ADHD symptoms in the population, extending evidence that ADHD behaves as a continuous trait in the population. Future longitudinal studies should clarify individual lifespan trajectories that lead to non-significant findings in adolescent/adult groups despite presence of an ADHD diagnosis.

KEYWORDS: ADHD, cortical thickness, cortical surface area, lifespan, meta-analysis, imaging

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder characterized by age-inappropriate levels of inattention and/or hyperactivity and impulsivity. ADHD occurs in around 5-7% of children and 2.5% of adults (1, 2). ADHD can negatively affect multiple aspects of daily life of patients, and represents a major public health challenge (3). Neuroimaging studies in ADHD show differences between the brains of people with ADHD and those of healthy individuals in structure (4-9), function (8, 10, 11), and connectivity (12-14), albeit with small effect sizes (9). While informative, existing studies have several major limitations. First, most ADHD neuroimaging studies have been cross-sectional and performed during childhood; studies that either consider ADHD throughout the lifespan or have a longitudinal design are rare. In one such lifespan study, we recently showed that differences in intracranial volume (ICV) and subcortical volumes between patients and healthy individuals were largely restricted to childhood (9). Furthermore, an earlier longitudinal study showed slower, delayed development of cortical thickness and surface area in children with ADHD, especially in frontal-temporal regions (15). Nonetheless, large-scale studies of cerebral cortical architecture throughout the lifespan are lacking.

A second major limitation in the neuroimaging literature is that most studies on ADHD have small sample sizes and show limited reproducibility (16). Combining data from existing research by means of meta-/mega-analysis can produce more reliable results. For ADHD, meta-/mega-analyses of structural brain phenotypes are available for subcortical structures (9, 17), but the cortex has only been assessed in meta-analyses of brain-wide voxel-based morphometry (VBM) studies (5-8). The largest VBM study (931 patients and 822 controls) reported case-control differences for anterior cingulate, medial prefrontal cortex, ventromedial orbitofrontal cortex, and the insula (8). Here, we further the field by providing the first large-scale, mega-analytic examination of cortical measures across the lifespan in ADHD. We analyzed cortical surface area and thickness separately, as recent large-scale studies show that the biological mechanisms underlying such measures overlap only partially (18). Our large sample size also provides the power needed to examine clinical factors such as common comorbid disorders.

Neuroimaging analyses of ADHD have also largely not addressed a major question: are the observed brain differences a consequence of living with the disorder, or do the brain differences reflect underlying risk for the disorder? Different study

designs can help us begin to address this question. Family-based studies can indicate if cortical changes are present in unaffected siblings of cases to indicate the involvement of shared genetic and/or environmental risk factors that underlie the cortical characteristics associated with the disorder. Several family studies (e.g. (19)) suggest that at least some of the brain alterations seen in patients are also present in their unaffected siblings and are associated with symptom severity in healthy individuals. Population-based studies can determine whether individuals with traits of ADHD show similar cortical changes to those associated with the full syndrome. The largest population study published to date (n=776 children) showed that higher levels of ADHD symptoms were associated with a thinner cortex in caudal middle frontal, temporal, and occipital regions (20). While this and similar studies (21) showed that brain alterations extend beyond the clinical disorder, no attempts have yet been made to directly assess the overlap between studies in clinical samples and the general population. Combined, family and population-based findings suggest that the brain differences seen in those with ADHD are not simply markers of the disorder, but larger studies, directly comparing brain phenotypes across different informative study designs, are needed to shed more light on this.

Here, we present a mega-analysis of cortical thickness and surface area in participants with ADHD and healthy controls across the lifespan from the ENIGMA-ADHD Working Group, a world-wide collaboration aiming to characterize the characteristics of the brain of people with ADHD. All partners used standardized methods (segmentation protocols and quality control procedures), limiting methodological heterogeneity more than in previous meta-analyses. In addition to assessing case-control differences in children, adolescents, and adults, we investigated cortical brain correlates of clinical features, assessed familiality of effects, and mapped the dimensionality of affected cortical regions in the large, independent pediatric Generation-R population study (22).

MATERIALS AND METHODS

Contributing studies

The ENIGMA-ADHD Working Group currently consists of 36 cohorts from around the world (http://enigma.ini.usc.edu/ongoing/enigma-adhd-working-group/). All cohorts have structural imaging data available for individuals with an ADHD diagnosis, and most sites also include data from healthy controls. An overview of the sites is given in **ST1**; details of image acquisition and study protocols are provided in **ST2** and **SA1**. The dataset for the cortical analysis comprised 4,180 individuals: 2,246 people with ADHD with mean age of 19.22 years (SD= 11.31), age range of 4-62 years, 74.1% males; 1,934 healthy controls with mean age of 18.05 years (SD=11.26), age range of 4-63 years, 59.8% males.

For the analysis of dimensionally-assessed ADHD traits in the general population we used data from 2,707 individuals with mean age of 10.11 (SD=0.57) years, age range of 8.5-11.9 years, 49.4% males (**ST3**) from the Generation-R cohort (22).

For all participating cohorts, approval for the analysis was available from the responsible ethics committees.

Neuroimaging

Structural T1-weighted brain MRI data were acquired and processed at the individual sites. The images were analyzed using standardized protocols to harmonize analysis and quality control processes (http://enigma.ini.usc.edu/protocols/imaging-protocols/ and **SA2**) (23-25). Fully-automated and validated neuroimaging segmentation algorithms based on FreeSurfer versions 5.1 or 5.3 were used (**ST2**). Regions based on the Desikan–Killiany atlas were segmented, which resulted in cortical thickness and surface area values for 34 left and 34 right hemisphere regions. Two whole-hemisphere values for average thickness and average surface area were also computed. For further analysis, we used the mean of the bilateral values ((R+L)/2).

The Generation-R data were collected using a single, study-dedicated MRI scanner and processed using FreeSurfer version 6.0 on a high-performance computing system (Cartesius, surfsara.nl), for scanner sequence please see **SA3**. All imaging data were visually inspected for inaccuracies in the surface-based reconstruction. Data not suitable for analysis were excluded (for a flowchart see **SF1**), providing n=2707. For a non response analysis, please see **SA4.**

Case-control differences in cortical thickness and surface area in children, adolescents, and adults

Based on the age-specificity of earlier findings (9), three age groups were assessed: children: 4-14 years, 1081 cases, 1048 controls; adolescents: 15-21 years, 432 cases, 347 controls; adults: 22-63 years, 733 cases, 539 controls. As there are marked developmental changes across the 4 to 14 year age range, we also performed supplemental analyses on age tertiles of the childhood group. For each of the age groups we determined differences between participants with ADHD and healthy controls using mixed-effect models with 'site' as a random factor in the nlme package in R. Age and sex were included as additional covariates; for the surface area analysis, intracranial volume (ICV) was also added, as surface area scales with head size (24-26). We also include analyses without ICV as a covariate given the debate over whether it should be included as a covariate (see **SA5**). To calculate Cohen's d effect size estimates, adjusting for the appropriate covariates, we used the t-statistic from the Diagnosis (ADHD=1, control=0) predictor in the equation(27). To correct for multiple comparisons, we used a false discovery rate (FDR) at q=0.05.

Split-half validation of case-control findings

To ensure stability of effects, we performed a validation of our mega-analysis in age groups with significant results. Data were split into two halves, statistically matched for age, sex, and ICV within each site. Validation was defined as $p_{FDR}<0.05$ in the first half and $p_{uncorrected}<0.05$ in the second half, with matching effect directions(28).

Exploration of the influence of sex, IQ and clinical factors on cortical regions affected in ADHD

For regions and age groups showing validated case-control differences, we examined potential effects of sex, IQ, comorbid disorders, medication use and ADHD symptoms (severity) (see details in **SA6**). Given the exploratory nature of these analyses, we report uncorrected p-values in the Results section.

Family study

Two subsets of the ENIGMA-ADHD sample (NeuroIMAGE Amsterdam and Nijmegen (29)) had collected brain data from patients (n=211), their unaffected siblings (n=175), and unrelated controls (n=120). To determine familial effects on ADHD-affected cortical regions, unaffected siblings were compared with healthy controls in those cortical regions. Levels of ADHD symptoms in the unaffected siblings had been shown to not differ from those of controls (19). Multiple comparisons correction was performed based on the effective number of independent tests (M_{eff}) (30); differences between unaffected siblings and controls were considered significant at $p<0.01$ ($M_{eff}=5$, for details please see **SA7**).

Association between ADHD symptoms and the cortex in the general population

ADHD symptoms were assessed in children from Generation-R using the Child Behavior Checklist (CBCL)(31). Both attention problems (Syndrome Scale) and ADHD problems (DSM-oriented scale) were examined for associations with surface/thickness in regions with validated case-control differences in ENIGMA-ADHD. R statistical software (version 3.3.3) was used to fit multiple linear regressions to model these associations. Primary analyses were adjusted for age at MRI scan, sex, ICV and ethnicity. In supplemental analyses, models were additionally adjusted for non-verbal IQ, ADHD medication status, MR-scanner software version, and motion during scanning (**SA8**).

RESULTS

Case-control differences in cortical surface area and thickness in children, adolescents, and adults

In children with ADHD versus control children, lower values of cortical surface area were widespread, with 24 out of 34 regions and total surface area being smaller in patients (**Table 1, Figure 1, ST4**). The largest effect was found for total surface area: d= -0.21, p_{FDR}=<0.001. When the child group was further subdivided in post-hoc analyses, this effect size increased to d=-0.35, p_{FDR}=<0.001 in the youngest tertile (4-9 years), which comprised 317 cases and 340 controls (**ST5**).

Also more generally, the youngest group showed the largest case-control differences (**ST5**). No case-control differences were found in the adolescent and adult groups (**ST6** and **ST7**; **ST8** shows combined analysis of age groups). For results of the model without ICV, please see **ST9.**

Cortical thickness was affected in four regions (fusiform, parahippocampal, and precentral gyrus and temporal pole) in children, all being thinner in patients than controls (**Table 2**, **Figure 1 and ST10**). Further subdivision of the child group retained significant effects for fusiform gyrus (*d*= -0.31, p_{FDR}=0.002) and temporal pole (*d*=-0.25, p_{FDR}=0.02) in the group of children aged 10 and 11 (356 cases, 365 controls); in younger (4-9 years) and older (12-14 years) children, effects did not survive multiple comparisons correction(**ST11**). In adolescents and adults, no case-control differences were found (**ST12** and **ST13**; **ST14** shows combined analysis of age groups).

Validation of case-control findings

The split-half validation analysis showed seven regions for surface area and two regions for thickness to be significant in both halves (**Table 1 & 2**, **ST15 & ST16**, **Figure1**). For all other regions, the direction of effects was the same in both split-halves.

Effect sizes of the validated cortical differences across the age groups are plotted in **Figure 1**, together with the effect sizes of subcortical brain volumes from our earlier work (9). Post-hoc analysis by adding the term Agegroup*Diagnosis to the main model indicated differences in effect sizes across the lifespan for surface area of the superior frontal gyrus and thickness of the fusiform gyrus (**ST17**).

Exploration of effects of sex, IQ, comorbidity, psychostimulant medication, and ADHD severity

Extending the main findings, we investigated several factors linked to ADHD, which have shown to influence brain volume in their own right. No significant interaction effects of diagnosis-by-sex were found (**ST18**). Correcting for IQ in surface area

analyses only led to minor changes in the level of significance in the case-control comparisons. In all thickness analyses, IQ was a non-significant contributor (**ST19**).

For comorbidity analyses, we had information on cases of the childhood subset (n=1081) available (comorbidity *ever* versus *never,* lifetime) for almost 50% of participants (**ST20**). In total, 194 children with ADHD (39%) were ever or currently diagnosed with a comorbid psychiatric disorder. The three most frequently co-occurring disorders were oppositional defiant disorder (ODD, present in n=79 cases (16.0%)), anxiety disorders (observed in n=39 (8.6%)), and mood disorders (seen in n=13 (3.0%)). Presence versus absence of comorbid disorders did not affect cortical surface area; a nominal effect of ever being diagnosed with a comorbid psychiatric disorder was found for fusiform gyrus thickness, with a thinner fusiform gyrus in cases with an additional disorder in the past or present (**ST21**).

Current stimulant use versus no current use had a nominally significant association with surface area of two regions in frontal cortex, with those taking medication having lower surface areas (**ST21**).

Hyperactivity/impulsivity severity ratings on Conners' questionnaires, available for n=240 childhood patients, but not inattention, showed nominally significant correlation with surface area in rostral anterior cingulate cortex (r=-0.18, p=0.01), superior frontal gyrus (r=-0.19, p=0.01), and with total surface area (r=-0.15, p=0.03) (**ST22)**.

Family study

Among the validated ADHD-associated cortical features, surface area of caudal middle frontal, lateral orbital frontal, and superior frontal gyrus and the total surface area were significantly smaller in the unaffected siblings as compared with controls (**Figure 2**, **ST23**), indicating familial effects. A similar trend was seen for the majority of the other cortical measures (**SF2**).

Effects of ADHD symptoms in the general population on the validated brain phenotypes

Population-based analysis showed caudal middle frontal gyrus, middle temporal gyrus, and total surface area to be associated with the attention problems scale of the CBCL (**Table3, SF3**); higher levels of dimensional ADHD symptoms were associated with smaller surface areas. No associations were found with the two cortical thickness measures (**Table 3**). To ensure a linear fit was optimal and that the more severe end of the symptom continuum was not driving findings, models with quadratic and cubic symptom terms were also tested. AIC and BIC values were highly similar across models, suggesting little to no improvement over the simpler linear term (**ST24**).

Adding non-verbal IQ or ADHD medication status to the analysis model of the attention problems, did not influence results (**ST25**). Results also remained stable when we tested the effect of MRI scanner software version and image quality (**ST25**). The quantitative amount of motion in the T1-weighted scan (32) did not seem to affect analyses (**ST26**).

DISCUSSION

Here, we report the largest study to date of ADHD and cortical surface area and thickness in clinical samples and a pediatric population sample. Compared with healthy controls, children with ADHD showed smaller surface area in frontal, temporal, and cingulate regions, with the effects being most prominent in the youngest children (4-9 years). Case control differences had small effect sizes, but survived validation. Differences in thickness were limited to the temporal pole and fusiform gyrus, which were thinner in children with ADHD. These differences were most prominent in the group aged 10 and 11 years. The influence of comorbidity and symptom ratings, available from subsamples, appeared limited. None of these covariates of interest showed effects surviving multiple testing correction. There were no significant associations between cortical alterations and either stimulant treatment or IQ. Family-based analyses revealed familial effects for four surface area regions, but not for any thickness measures. A set overlapping with family-based analyses (caudal middle frontal gyrus, total surface area) and/or severity rating analyses (total surface area) showed associations with CBCL-based ratings of attention problems, in the population-based sample; no such effects were found for thickness.

The regions affected in ADHD were widespread across the cortex. The frontal cortex differences in orbital, middle, and superior regions nicely confirmed earlier work (e.g. (8, 15)). These regions are important in cognitive processes related to

reward and punishment, emotional processing, response inhibition, and attention - all known to be deficient in ADHD (33-35). Few studies yet have implicated structural differences in the cingulate cortex, an important structure linked to executive functioning and emotion (36), in ADHD (7, 37). Findings for the temporal cortex are particularly interesting, because both surface area and thickness were affected. The functions of this region are diverse, it seems to be involved in semantic memory, processing of abstract concepts, but also in attention, emotion processing and control (38). Integrating the current findings with our earlier subcortical results (9), the multitude of findings for brain regions involved in emotion processing is intriguing. In view of this, the network of orbito-frontal cortex, cingulate, and amygdala could be particularly interesting for future research (39, 40), as it may underlie the deficient emotional self-regulation often observed among ADHD patients (33).

Effect sizes of the observed brain differences were small, which is similar to our earlier findings for subcortical volumes and ICV in ADHD (**Figure 1**) and comparable to effect sizes seen in other psychiatric disorders studied in ENIGMA (23, 24). Whether this reflects phenotypic heterogeneity, with only a subgroup of patients showing reduced brain structure of large(r) effect size, or homogeneously small effects existing in the majority of patients remains to be investigated. Effects were not driven by IQ. Findings in several areas seemed to scale with the severity of hyperactivity/impulsivity in patients, but the heterogeneity of assessment instruments limited the power of this analysis. As in our earlier analysis of subcortical volumes and ICV, we did not find any significant associations between psychostimulant medication and cortical dimensions, neither in case-control nor in population-based designs. However, given our observational design and reliance on legacy data, we would not want to draw any definite conclusions from those results.

Looking across the lifespan, all case-control differences were most pronounced in children and non-significant in adolescents and adults. The same phenomenon, albeit attenuated, was seen in our recent cross-sectional study of ICV and subcortical structures (9) (**Figure 1**). Post-hoc analysis of potential differences in effect sizes across the three age groups in the current study confirmed age-related attenuation of effects for several structures. Those findings are in line with an earlier longitudinal study, where case-control differences in cortical thickness observed in children attenuated with increasing age, suggesting a delayed cortical maturation (41). An alternative explanation for the age-related differences might be the existence of subgroups; the childhood patient group is likely to consist of a mix of individuals who will persist

and remit in adulthood, while the adult group consists largely of persisters. We cannot yet rule out low power as a reason for not detecting significant effects in the older subgroups, which were half the size of the children's group, and these initial findings concerning apparent differences across the lifespan should be confirmed in longitudinal studies.

The case-control differences observed in the childhood sample did not seem to be influenced by comorbidity. However, we noticed that the comorbidity rate in this subset was relatively low (39%). There could be several reasons for that. First, the sample we used in our analysis of comorbidity was very young (4-14 years), as we only focused on the subsample with significant case-control differences. The relatively young age could explain the lower than expected comorbidity rate, as children might simply not yet have developed some of the frequent comorbid psychiatric disorders (e.g. substance use disorders). In comparison, Taurines and coworkers (2010) (42) described in their review that 73% of 6-18 year olds with ADHD had one or more comorbid disorders. A second reason could lie in the fact that we are dealing with research diagnoses, in which comorbidity assessments were often limited to checking in- and exclusion criteria for a specific study aim. This is a clear limitation of dealing with legacy data from multiple different sites, where different protocols and different instruments of assessment of comorbidity and symptom severity were used. We adjusted our design accordingly and concentrated only on the three most frequent comorbidities, defining those as ever or never experienced.

Although our study was not designed to study causality, our results may shed some light on the issue of whether brain differences are a consequence of living with the disorder, or are a risk factor for the disorder. Our family analysis showed unaffected siblings of cases, i.e. those without a diagnosis and with levels of ADHD symptoms comparable to healthy controls, to have similar surface area differences from controls as their affected siblings. In addition, the relationship between ADHD symptoms and cortical phenotypes also held in the general population. Here, the dimensional assessment of attention problems was related to brain morphology in a linear fashion, suggesting the phenotype and underlying brain morphology to be independent of clinical diagnosis, operating along a continuum. The two different approaches show cortical alterations in ADHD-related regions to occur independent of diagnosis. The overlap between the findings from the different approaches was, however, not complete. Future studies could perform more direct comparisons between case-control and population samples using e.g. conjunction analysis (43). The two different approaches show cortical alterations in ADHD-related regions to occur independent of diagnosis, indicating that they are neither necessary nor sufficient to

cause the disorder. The overlap between the findings from the different approaches was, however, not complete. Future studies could perform more direct comparisons between case-control and population samples using e.g. conjunction analysis (41). In such a design it would be interesting to test the liability-threshold model, to better understand which factors contribute to liability for the disorder. Also, whether the observed brain differences relative to controls are indeed risk factors for ADHD, remains to be investigated in prospective longitudinal designs. Future imaging genetics studies might further clarify the neurobiological pathways and mechanisms underlying cortical differences in ADHD. While genetic information is not available in sufficient numbers from ENIGMA-ADHD, the ENIGMA Genetics Working Group recently identified genetic factors determining cortical surface area and thickness in a largely healthy population (18). Those genetic factors might in turn constitute risk factors for ADHD given recent finding of genetic overlap between the genetic contribution to ADHD and to the total surface area of the cortex. As we have recently shown for subcortical volumes and intracranial volume, further work might delineate the individual genes or gene networks underlying such genetic overlap (Klein et al., Am. J. Psychiatry, in press; see also (44)).

The current study has several strengths and limitations. Our major strength lies in the large sample sizes in both the clinical (n=4180) and population-based (n=2707) samples, along with the use of harmonized segmentation protocols, which provided unprecedented power to detect effects. Another strength is the split-half validation combined with stringent multiple comparison correction, showing that our findings – despite small effect sizes – are stable. Also, results from the population study suggest little effect of motion during scanning on our cortical regions of interest. The combination of case-control with family- and population-based designs to identify mechanisms is an additional strength. A limitation is that we relied on legacy data in ENIGMA-ADHD, so the participating studies differ somewhat in their aims, methods, and assessments. Given this heterogeneity, our findings might underestimate the true effects, and we may have missed effects of comorbidity, medication, and symptom severity due to insufficient power. The limited sample size of the family study together with the small effect sizes for brain differences is probably the reason why the results of the family study found the expected staircase effect, at a trend level only.

In light of the findings from the current and the earlier (9) ENIGMA studies of ADHD, what should future neuroimaging studies in ADHD look like? Effect sizes observed are small (i.e. Cohen's *d*=-0.21), with largest effects for measures of total

brain volume and surface area in this and our previous study (9). Also, effects are restricted to childhood despite persistent ADHD diagnosis in adolescents and adults. Future studies should answer the question, whether (regional) effect sizes are comparable in everyone, or whether subgroups exist, in which certain regional effect sizes are more pronounced. This could be examined using clustering algorithms, such as community detection, and machine learning (45). An analysis of particular interest would be the comparison between children who remit in adulthood and those who persist. In-depth analysis of adult persisters versus remitters could add to our understanding of the null findings in adults, as it seems counterintuitive that the persisters, believed to be more severely affected, show no apparent signs of brain differences in adulthood, but the mixed group of remitters and persisters in the childhood group does. Subgroups may also provide information on comorbidity and links to symptom severity in the different behavioral domains of ADHD. Most importantly, longitudinal studies are needed to study the processes that lead to the apparent reductions of case-control effects from childhood to adolescence and adulthood; only very few longitudinal samples for ADHD are currently available (15, 29). We should also not forget that the segmentation used in the current study is based on classical neuroanatomical divisions rather than a partitioning based on biological functions (44, 46). Other cortical phenotypes such as gyrification (47), or more sophisticated methods to define regional gray matter structure, and analyses of other brain measures to be captured by neuroimaging in large sample sizes (e.g., white matter integrity (48); resting state functional MRI (49)) may help us find the presumed case-control differences in adults (50, 51).

In conclusion, we identify, for the first time, cortical phenotypes affected in ADHD that are robust, and show an association with ADHD beyond narrowly-defined clinical diagnoses. Our work suggests them to behave as endophenotypes and extends the evidence for ADHD as a continuous trait in the population from behavioral measures and genetics (52) to neuroimaging phenotypes. Future studies should clarify individual lifespan trajectories and identify the underlying genetic and environmental factors shaping these trajectories.

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FIGURE LEGENDS

FIGURE 1. Subcortical and cortical brain differences across the lifespan.

A. Displayed on the y-axis are the Cohen's *d* effect sizes with error bars showing the 95% confidence intervals for case-control differences in ENIGMA-ADHD cortical and subcortical structural features stratified by age group: children of 14 years of age and younger, adolescents from age 15 to 21 years, and adults older than 21 years. All regions displayed showed significant case-control differences in children; in analyses of cortical and subcortical features, no significant effects were seen in adolescents or adults. This is reflected in the effects sizes shown, all of which are significant for children but not for adolescent and adult groups, except for the hippocampus, which shows significance also in the adolescent group. **B**. Displayed are the heatmaps of validated case-control differences in the childhood subset for both surface area (left) and thickness (right) in both hemispheres.

FIGURE 2. Bar graphs showing results of familiality analyses in the ADHD-affected cortical regions in the NeuroIMAGE datasets (n=506). Displayed are the cortical surface areas showing effects of familiality in the NeuroIMAGE datasets. For these regions, unaffected siblings differed from healthy controls (M_{eff}-corrected results). Cortical values are adjusted for age, gender, ICV and site.

Table 1. Mega-analysis of case-control cortical surface area differences in children of 14 years of age and younger in ENIGMA-ADHD.

Cortical region	Controls (N)	ADHD (N)	Cohen's *d* (standard error)	95% confidence interval	p-value	FDR p-value
total surface area[a]	1048	1081	-0.21 (0.04)	-0.29 to -0.12	<0.001	<0.001
superior frontal gyrus[a]	1044	1074	-0.19 (0.04)	-0.28 to -0.11	<0.001	<0.001
lateral orbitofrontal cortex[a]	1047	1081	-0.17 (0.04)	-0.26 to -0.09	<0.001	<0.001
medial orbitofrontal cortex	1039	1070	-0.16 (0.04)	-0.24 to -0.07	<0.001	0.002
posterior cingulate cortex[a]	1042	1078	-0.16 (0.04)	-0.25 to -0.08	<0.001	0.002
rostral anterior cingulate cortex[a]	1041	1067	-0.16 (0.04)	-0.25 to -0.08	<0.001	0.002
superior temporal gyrus	987	993	-0.15 (0.05)	-0.24 to -0.07	<0.001	0.003
caudal middle frontal gyrus[a]	1046	1077	-0.15 (0.04)	-0.23 to -0.06	<0.001	0.003
fusiform gyrus	1043	1075	-0.13 (0.04)	-0.21 to -0.04	0.004	0.01
isthmus cingulate cortex	1040	1079	-0.13 (0.04)	-0.22 to -0.05	0.002	0.008
middle temporal gyrus[a]	1001	1024	-0.13 (0.04)	-0.22 to -0.04	0.004	0.01
rostral middle frontal gyrus	1044	1079	-0.13 (0.04)	-0.21 to -0.04	0.004	0.01
supramarginal gyrus	1036	1063	-0.13 (0.04)	-0.22 to -0.05	0.002	0.008
inferior parietal cortex	1041	1078	-0.12 (0.04)	-0.20 to -0.03	0.009	0.02
inferior temporal gyrus	1041	1064	-0.12 (0.04)	-0.21 to -0.04	0.005	0.01
lateral occipital cortex	1047	1078	-0.12 (0.04)	-0.21 to -0.04	0.005	0.01
precuneus	1044	1080	-0.12 (0.04)	-0.20 to -0.03	0.008	0.02
superior parietal cortex	1045	1073	-0.12 (0.04)	-0.21 to -0.04	0.004	0.01
insula	1042	1078	-0.12 (0.04)	-0.21 to -0.04	0.006	0.01
banks of superior temporal sulcus	974	999	-0.10 (0.05)	-0.19 to -0.01	0.02	0.04
pars triangularis of inferior frontal gyrus	1048	1074	-0.10 (0.04)	-0.18 to -0.01	0.02	0.04
postcentral gyrus	1032	1060	-0.10 (0.04)	-0.18 to -0.01	0.03	0.05
precentral gyrus	1041	1064	-0.10 (0.04)	-0.19 to -0.02	0.02	0.03
temporal pole	1043	1075	-0.10 (0.04)	-0.18 to -0.01	0.03	0.04

Note: Displayed are the significant regions surviving correction for multiple comparisons with FDR q-value<0.05. Regions are sorted based on the effect size of the difference between cases and controls (Cohen's *d*), with the regions with the largest effects on top. Regions are the average of left and right hemisphere surface area. Model is adjusted for age, sex, intracranial volume (ICV), and site. [a]regions surviving validation (see also **ST15**). For the full results please see **ST4**.

Table 2. Mega-analysis of case-control cortical thickness differences in children of 14 years of age and younger in ENIGMA-ADHD.

	Controls (N)	ADHD (N)	Cohen's *d* (standard error)	95% confidence interval	p-value	FDR p-value
temporal pole[a]	1042	1075	-0.18 (0.04)	-0.27 to -0.10	<0.001	0.001
fusiform gyrus[a]	1044	1077	-0.17 (0.04)	-0.25 to -0.08	<0.001	0.003
precentral gyrus	1040	1064	-0.16 (0.04)	-0.25 to -0.07	<0.001	0.003
parahippocampal gyrus	1041	1076	-0.15 (0.04)	-0.23 to -0.06	<0.001	0.008

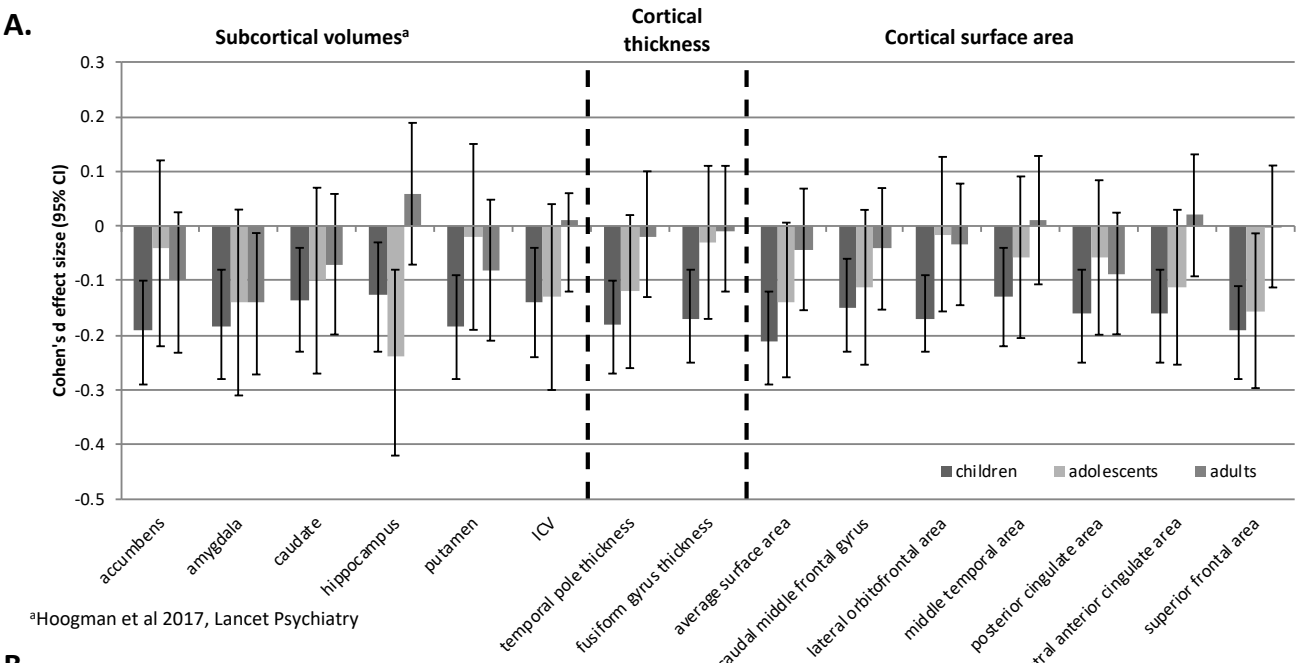
Note: Displayed are the significant regions surviving correction for multiple comparisons with FDR q-value<0.05. Regions are sorted based on the effect size of the difference between cases and controls (Cohen's *d*), with the regions with the largest effects on top. Regions are the average of left and right hemisphere thickness measures. Model is adjusted for age, sex and site. [a]regions surviving validation (see also **ST16**). For the full results please see **ST10**.

Table 3. Associations between validated cortical regions and CBCL syndrome scale attention problems in Generation-R.

Cortical region	B	SE	CI lower	CI upper	β	p-value	FDR p-value
Surface area							
caudal middle frontal gyrus	**-14.10**	**5.49**	**-24.87**	**-3.33**	**-0.04**	**0.01**	**0.03**
lateral orbitofrontal cortex	-8.28	5.01	-18.10	1.54	-0.02	0.10	0.11
middle temporal gyrus	**-13.63**	**5.86**	**-25.12**	**-2.14**	**-0.03**	**0.02**	**0.04**
posterior cingulate cortex	-5.02	2.42	-9.77	-0.27	-0.03	0.04	0.06
rostral anterior cingulate cortex	-3.50	1.93	-7.29	0.29	-0.03	0.07	0.09
superior frontal gyrus	-7.16	11.93	-30.55	16.24	-0.01	0.55	0.55
total surface area	**-323.79**	**77.50**	**-475.75**	**-171.82**	**-0.04**	**<0.001**	**<0.001**
total surface area (residualized*)	**-291.62**	**77.43**	**-443.44**	**-139.79**	**-0.07**	**<0.001**	**<0.001**
Thickness							
fusiform gyrus	0.004	0.002	0.000	0.01	0.04	0.05	0.054
temporal pole	0.01	0.01	-0.001	0.03	0.04	0.07	0.07

Note: Regions are the average of left and right hemisphere surface area, and are the regions showing significant group differences in split-half analyses (**ST15** and **ST16**). Model is adjusted for age, sex, and ethnic background. ICV is also included as a covariate in the surface area analysis. B is the unstandardized regression coefficient for the square root transformed CBCL syndrome scale attention problems score, and CI is the 95% confidence interval of that regression coefficient. β is the standardized regression coefficient. *Given the high correlation between total surface area and ICV, we also tested a model where total surface area was first regressed on ICV, and the resulting residuals were used in the model described above, but without entering ICV. This shows that multicolinearity is not driving the effects. p-values in bold are considered significant, surviving correction for multiple comparisons with FDR q-value<0.05.

Figure 1


A.
Subcortical volumes[a]
Cortical thickness
Cortical surface area
Cohen's d effect sizse (95% CI)
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
children
adolescents
adults
accumbens
amygdala
caudate
hippocampus
putamen
ICV
temporal pole thickness
fusiform gyrus thickness
average surface area
caudal middle frontal gyrus
lateral orbitofrontal area
middle temporal area
posterior cingulate area
rostral anterior cingulate area
superior frontal area
[a]Hoogman et al 2017, Lancet Psychiatry

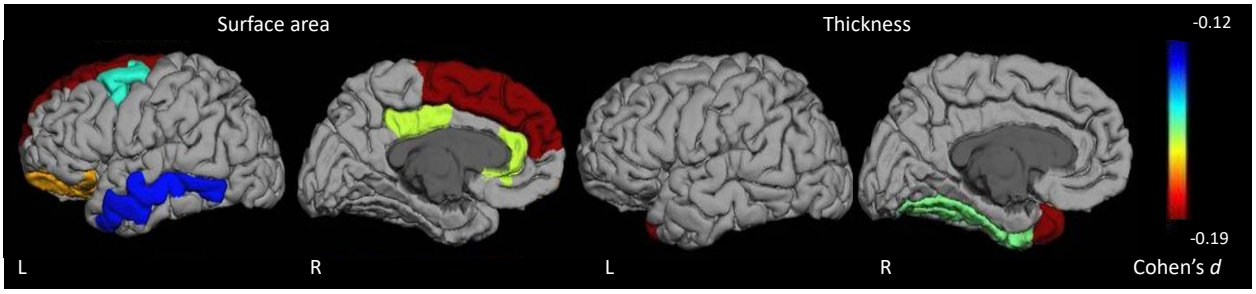
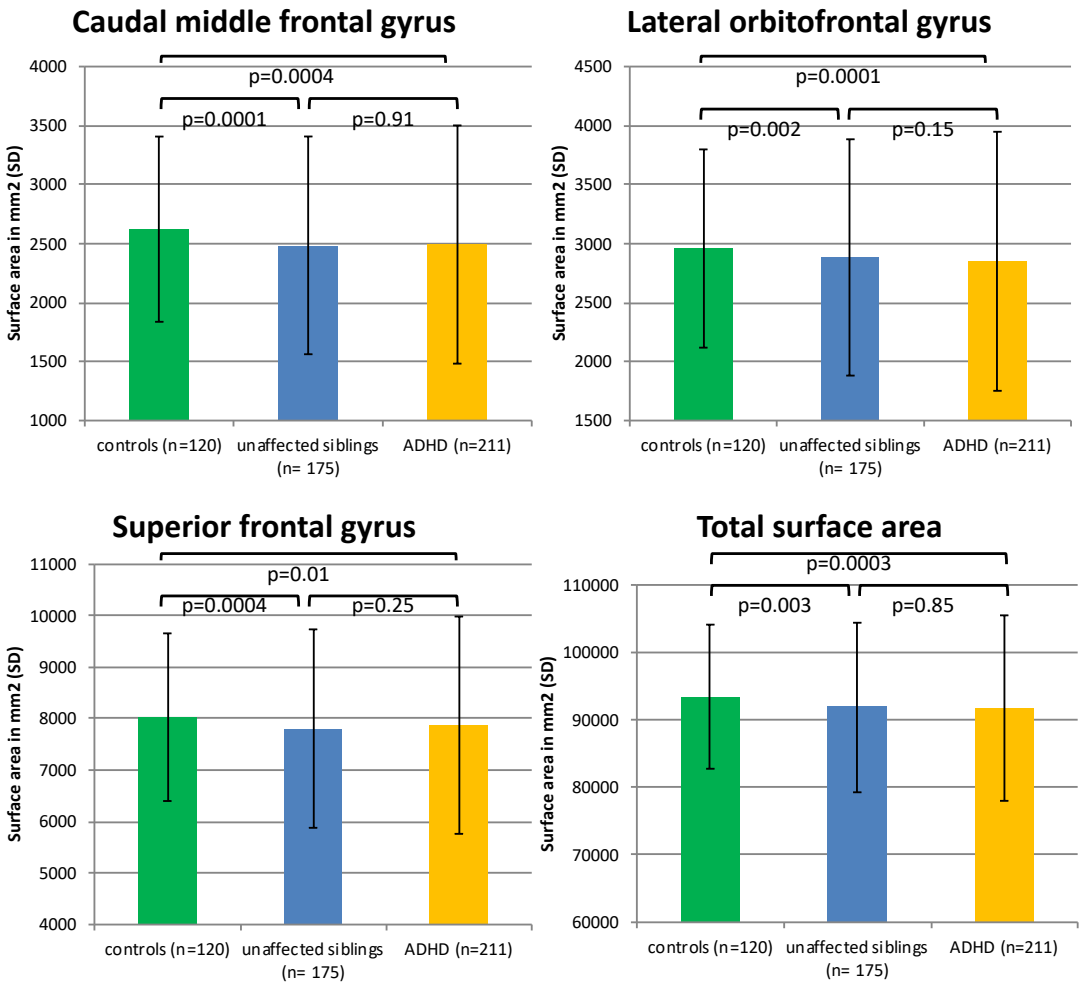

B.
Surface area
Thickness
-0.12
-0.19
L
R
L
R
Cohen's d

Figure 2


Caudal middle frontal gyrus
p=0.0004
p=0.0001
p=0.91
Surface area in mm2 (SD)
4000
3500
3000
2500
2000
1500
1000
controls (n=120)
unaffected siblings (n= 175)
ADHD (n=211)
Lateral orbitofrontal gyrus
p=0.0001
p=0.002
p=0.15
Surface area in mm2 (SD)
4500
4000
3500
3000
2500
2000
1500
controls (n=120)
unaffected siblings (n= 175)
ADHD (n=211)
Superior frontal gyrus
p=0.01
p=0.0004
p=0.25
Surface area in mm2 (SD)
11000
10000
9000
8000
7000
6000
5000
4000
controls (n=120)
unaffected siblings (n= 175)
ADHD (n=211)
Total surface area
p=0.0003
p=0.003
p=0.85
Surface area in mm2 (SD)
110000
100000
90000
80000
70000
60000
controls (n=120)
unaffected siblings (n= 175)
ADHD (n=211)