ENIGMA

Enhancing Neuro Imaging Genetics through Meta-Analysis

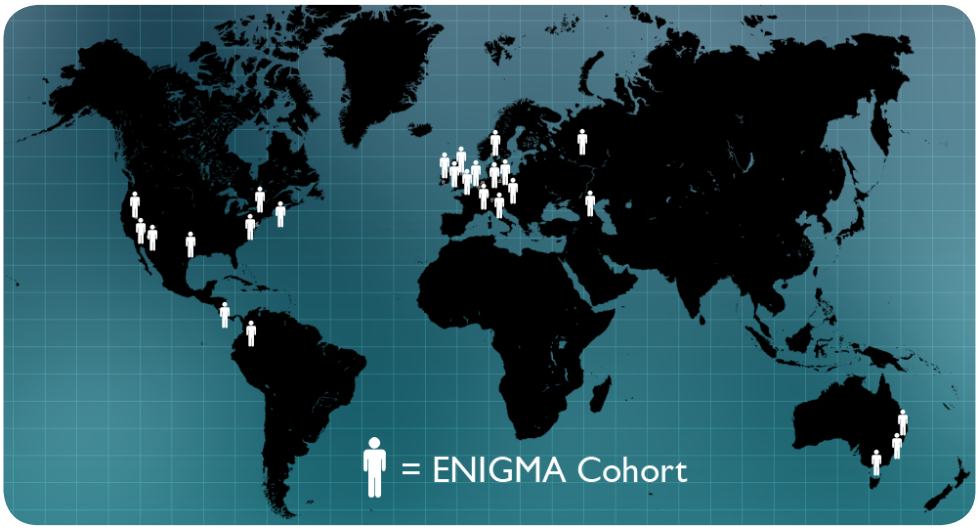
December 2012 Issue

Dear Neuroscience Community

We thank you all for your work on ENIGMA this year; it has led to some remarkable discoveries! This year has yielded new collaborations at a scale unprecedented in the imaging and neuroscience community. ENIGMA has welcomed several new members to the program, and participating members have created several highly productive Working Groups in the areas of diffusion imaging, amyloid imaging, and schizophrenia and bipolar disorder. We are now performing the largest-ever brain imaging studies of subcortical morphometry, and we have new projects on depression and ADHD planned. This update summarizes the status of our various projects now underway.

Current Participants and New Members

We have been very fortunate to work on ENIGMA with so many renowned and well-respected research centers from around the world:



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ENIGMA Founding Cohorts

Study Name	*N*
ADNI	747
BFS	220
BIG	1280
fBIRN	78
IMAGEN	1765
ImaGene	104
LBC1936	700
MooDS	309
MPIP	550
NCNG	327
QTIM	847
SHIP	800
SHIP-TREND	871
SuperStruct	442
SYS	1024
TOP	600
UMCU	279
BIG Replication	1000
CHARGE	10,779
EPIGEN	233
NESDA	216
GOBS	605
NIMH-IRP	237
TCD/NUIG	375

ENIGMA1 Founding Total 24,388

New Cohorts in ENIGMA

Study Name	*N*
BETULA	340
BPFS	575
fBIRN (Phase III)	362
GIG	272
HUBIN	220
IMpACT-NL	280
KCL	525
MAS	505
MCIC	328
NeuroIMAGE	154
NTR	677
OATS	364
PAFID	108

New Cohort Total 4,710

ENIGMA1: Hippocampal and Intracranial Volume Study

The first ENIGMA manuscript appeared in Nature Genetics on April 15, 2012. A set of four back-to-back papers appeared in the same issue, reporting newly discovered genetic variants that are consistently associated with brain measures—including intracranial volume, hippocampal volume, and brain volume—in cohorts from around the world. All authors deserve enormous credit for their concerted effort across the globe. We also thank the CHARGE consortium, whose analyses, led by Dr. Sudha Seshadri, allowed us to confirm the genome-wide significant hits in a very large independent sample.

Jason Stein
steinja@ucla.edu

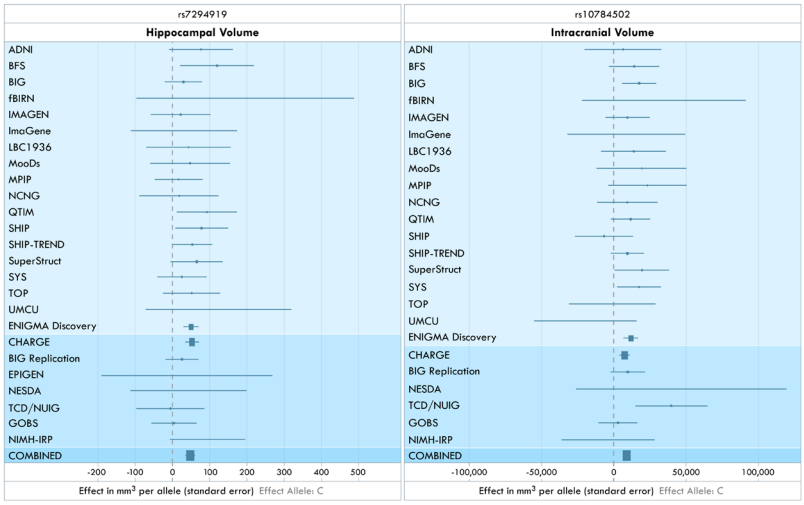

Figure 1: The effect within each sample contributing to the meta-analysis is shown in Forest plots for hippocampal volume (left) and intracranial volume (right). From: Stein JL, et al. Identification of common variants associated with human hippocampal and intracranial volumes. Nat Genet. 2012 Apr 15;44(5):552-61.

ENIGMA's first paper was covered by the international press in over 20 countries, highlighting participating members' contributions. The New York Times article, "Crowd Sourcing Expands Power of Brain Research," applauded the worldwide scope of the project as a step forward in brain research. TIME Magazine also noted the power of such studies to discover and investigate genetic risk factors for disorders, including depression, anxiety, Alzheimer's and schizophrenia. Links to these stories are found below:

The New York Times
NYTIMES.COM

Crowd Sourcing Expands Power of Brain Research

Bigger Brain and Higher IQ Linked with Specific Genetic Variants

Congratulations, and thanks to everyone again!

ENIGMA2 – Subcortical Morphometry

As a follow-up to our first successful project, ENIGMA members began a new analysis of genetic variants affecting subcortical volumes. This project also allowed new members to take part in the analyses and the update of prior results.

To streamline participation in this newest study and to standardize the analysis across cohorts, Derrek Hibar and Roberto Toro developed image processing protocols and concise QC applications for the full set of subcortical features segmented by FSL FIRST and FreeSurfer: thalamus, hippocampus, amygdala, putamen, caudate, globus pallidus and nucleus accumbens. We also thank Mark Jenkinson, Neda Jahanshad, Katharina Whittfeld, Hans Grabe, Benjamin Aribisala and Joanna Wardlaw for "beta" testing the new imaging protocols at their sites.

Alejandro A. Vasquez
a.ariasvasquez@psy.umcn.nl

Miguel Rentería
Miguel.Renteria@qimr.edu.au

Sarah Medland
medlandse@gmail.com

In addition to the imaging protocol development, we decided to move the consortium to the newest imputation reference set of the 1000 Genomes Project (phase 1, version 3). Sarah Medland and Miguel Renteria developed step-by-step protocols for performing the imputation and the association testing. The protocol development required extensive testing and we thank Derrek Hibar and Alejandro Arias Vasquez for their input. To date, approximately two-thirds of the groups participating in ENIGMA2 have uploaded association statistics for their cohorts. We are working with the remaining groups and will hopefully have the rest of the groups finished and uploaded by January 31st, the Discovery Cohort Deadline. In the meantime, we are performing QC checks on all of the uploaded data and working with groups where we find errors and inconsistencies in the results. As part of the QC process, we are excluding poorly imputed SNPs (Rsq < 0.3) and low minor allele frequency (MAF < 0.005); we are also examining QQ and Manhattan plots of individual group data. Our goal is complete the analysis and begin work on a manuscript by early Spring 2013. Groups that are ready to upload their data can contact (**support@enigma.loni.ucla.edu**) and we will coordinate with you to upload the data to the ENIGMA secure server. If you have any questions about the ENIGMA2 subcortical project, please contact one of the following people: Derrek P. Hibar - dhibar@ucla.edu; Miguel Renteria - Miguel.Renteria@qimr.edu.au; Roberto Toro - rto@pasteur.fr

Upload your data by January 31st 2013 for the Discovery Cohort

Derrek P. Hibar
dhibar@ucla.edu

Roberto Toro
rto@pasteur.fr

ENIGMA Working Groups

Neda Jahanshad
neda.jahanshad@loni.ucla.edu

Peter Kochunov
pkochunov@mprc.umaryland.edu

David Glahn
david.glahn@yale.edu

ENIGMA-DTI Working Group

The integrity of the brain's white matter can serve as an important endophenotype, and several genetic associations have already been established. However, tract measures derived from tractography or measures derived from diffusion tensor imaging (DTI), such as fractional anisotropy, can vary substantially depending on variables in the imaging acquisition protocols and the template used to define regions of interest. These variables include image voxel size, number of directional gradients used, and scanner magnetic field strength. Based on interest from David Glahn, Margie Wright, Ian Deary, Andrew McIntosh, Paul Thompson, Mark Bastin, Tom Nichols, researchers from BIG, and Hilleke Hulshoff Pol, a Working Group was formed with algorithm developments led by Neda Jahanshad, Peter Kochunov, Emma Sprooten and René Mandl. The initial goal of the Working Group has been to develop a validated protocol to obtain reliable and consistently heritable measures from images that can be easily implemented at the many ENIGMA sites that have DTI and genomic (GWAS) data.

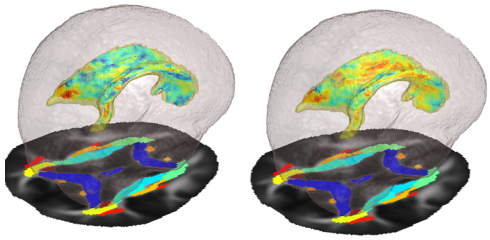

Figure 1: Meta and Mega analyzed voxelwise CC heritability

In the course of this work, the ENIGMA-DTI Protocol Working Group tested a variety of analysis protocols (based on atlas ROIs, tract-based spatial statistics or TBSS, and voxel-based analysis) to evaluate their robustness for analyzing DTI data on a large scale. To help analyze data from young and elderly cohorts, a customized brain template was created from 400 healthy adults of all ages, with data at 4 sites (GOBS, QTIM, LBC1936, BPFS). This template was then tested for registration accuracy and robustness. To prioritize measures for genetic analysis, the heritability of DTI measures from a variety of atlas-defined regions was evaluated and meta-analyzed across two family based cohorts (GOBS, QTIM). A TBSS protocol was also created and tested for voxel-wise analysis of multi-cohort DTI. New members are now actively sought to beta-test the DTI analysis protocol, and join in with analysis. The 2013 goal is to design a full genome-wide association study using both atlas-based and voxel-based methods using the ENIGMA-DTI protocol. A protocol for analyzing DTI has been developed, and several additional sites have already tested it. Note that this protocol and design are not just limited to genetic associations, but are well suited for many ROI and voxelwise DTI studies of FA.

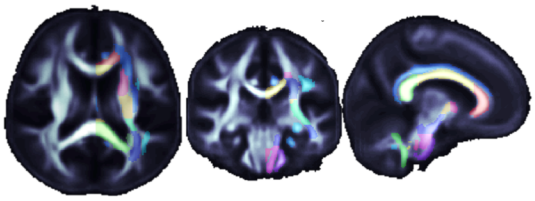

Figure 2: ENIGMA-DTI target + ROI extraction

Ian Deary
iand@staffmail.ed.ac.uk

DTI-Cognition WG

As part of the ENIGMA-DTI effort, groups have been working together to design harmonized protocols to relate DTI measures to measures of cognitive performance—such as general cognitive ability—and other data available across sites. This effort is led by Ian Deary and Tom Booth (both in Edinburgh, UK), whose initial tests show reliable associations between cognitive measures and DTI summaries derived using of the ENIGMA-DTI protocol. Initial work has focused on defining which test scores are in common across ENIGMA sites, or if similar general factors can be established from different sets of scores, and deciding a set of statistical models that can be run and meta-analyzed at each site (e.g., models with and without adjustment for age, inclusion or exclusion of disorders that may affect the white matter, etc.).

Margie Wright
Margie.Wright@qimr.edu.au

DTI-Cognition Joint GCTA

To estimate the shared heritability, PIs Andrew McIntosh and Ian Deary from the ENIGMA-DTI group, Margie Wright from QTIM, and Peter Visscher at the University of Queensland, have begun initial investigation into pooling together genetic data from multiple cohorts. Using Peter Visscher's Genome-wide Complex Trait Analysis (GCTA) tool at Queensland, the amount of shared genetic variation between FA in tract ROIs and general cognition was determined. For this ENIGMA project, the sharing of genetic data would be required. It would not, however, be required that all groups share both cognitive information and images. If you have DTI scans and are able to share FA maps and genome data for this one-of-a-kind project, please contact Margie Wright.

The GCTA Project Requires:
- FA maps
- Genome data

Dr. Barbara Franke
b.franke@gen.umcn.nl

Psychiatric GWAS Consortium WG

Dr. Barbara Franke (Nijmegen, The Netherlands) has led regular teleconference meetings on collaborative projects between ENIGMA members and the Psychiatric GWAS Consortium (PGC), led by Patrick Sullivan of UNC. The PGC is currently the largest consortium dedicated to identifying psychiatric risk genes in schizophrenia, bipolar disorder, major depression, ADHD and autism, with an extension of the number of disorders in progress. Given the rate of GWAS discoveries from the PGC, the group has been looking up top hits in the ENIGMA and PGC data to determine effects of genetic variants that affect disease risk on the brain. Analyses of three kinds have been conducted by Jason Stein, Roel Ophoff, Sarah Medland and Stephan Ripke, including: (1) reciprocal look-up of top hits from ENIGMA and PGC, focusing initially on the schizophrenia and major depression GWAS meta-analyses from PGC, (2) enrichment analyses using sets of SNPs, and (3) polygenic analyses using combinations of SNPs from each GWAS meta-analysis. More recently, this project has been further extended to include data on Alzheimer's disease genetics from the Genetic and Environmental Risk in Alzheimer's disease (GERAD), with Denise Harold as the contact person. A paper describing the analyses conducted thus far is being prepared as a joint ENIGMA-PGC effort.
Information on PGC is available at **https://pgc.unc.edu/index.php**.

Dr. Jessica Turner
jturner@mrn.org

Schizophrenia WG

Dr. Jessica Turner, from the Mind Research Network in New Mexico, has organized and led a multi-site effort to meta-analyze imaging measures across ENIGMA cohorts who have data from patients with schizophrenia. So far, this effort includes the following sites: FBIRN (Steven Potkin/Theo van Erp), MCIC (Vince Calhoun/Stefan Ehrlich), TOP (Ole Andreassen), UMCU (Hilleke Hulshoff Pol/Roel Ophoff), GIG (Oliver Gruber), and Northwestern University (John Csernansky/Lei Wang). This effort aims to rank brain measures by effect size for case-control differences, with the goal of understanding factors that affect brain volumes in schizophrenia. The MRI measures are derived using the protocol developed for ENIGMA2, the subcortical morphometry project. Derrek Hibar (UCLA) and Theo van Erp (UC Irvine) have developed and tested statistical analysis scripts that can be used in a harmonized way across participating sites. The Working Group has agreed on a common set of analyses, covariates, and inclusion criteria for the studies, and is beginning to run statistical analyses. An abstract describing the project has been submitted to the Society for Biological Psychiatry and may be found here: **http://enigma.loni.ucla.edu/ongoing/enigma-schizophrenia-working-group/**.
It is not necessary to have genetic data or GWAS to take part in this project; new cohorts with MRI or other neuroimaging data from schizophrenia patients are welcome.

Ole Andreassen
o.a.andreassen@medisin.uio.no

Bipolar Disorder WG

Dr. Ole Andreassen of the University of Oslo, Norway, has created and led an effort involving multiple ENIGMA cohorts who have data from patients with bipolar disorder. This effort involves the following cohorts: TOP - 225 cases and 250 controls (Ingrid Agartz, Ole Andreassen); Swedish BD study – 188 cases and 102 controls (Mikael Landen); GIG - 100 cases and 200 controls (Oliver Gruber); NIMH - 50 cases and 150 controls (Allison Nugent); Bipolar Family Study - 150 cases and 527 subjects (pedigree design, Scott Fears, Carrie Bearden, Nelson Freimer); Yale BD Study - 400 cases and 400 controls (David Glahn); NUI Galway - 108 cases and 122 controls (Colm McDonald, Dara Cannon). We also welcomed new participants from Pittsburgh (Mary Phillips), Cincinnati (Stephen Strakowski, Caleb Alder) and London (Sophia Frangou). As with the ENIGMA-Schizophrenia Working Group, this initiative aims to rank brain measures in order of their effect size for finding differences between bipolar disorder patients and controls. Initial efforts have developed analysis scripts and determined variables of interest for the models (e.g., bipolar I/II distinctions, medication status, etc.). To allow future joint projects with the ENIGMA-Schizophrenia Working Group, protocols have been harmonized across the two working groups, although they involve different cohorts. As with the schizophrenia group, to take part in this project, it is not necessary to have genetic data or GWAS; new cohorts with MRI or other neuroimaging data from bipolar disorder patients are welcome.

Dr. Manfred Kayser
m.kayser@erasmusmc.nl

VisiGen WG (Forming)

In October 2012, on behalf of the VisiGen Consortium, Dr. Manfred Kayser of Erasmus University Medical Center, Rotterdam, proposed a collaborative effort with ENIGMA to understand genetic variants influencing facial structure. The goal of this collaborative effort is understanding the determinants of facial dysmorphology. The VisiGen Consortium has been using facial landmarks from MRI to identify SNPs using genome-wide scans. The protocol can be applied at the site where the data was collected; neither the scans nor the genomic data need to be transferred to a central site. An initial survey of the ENIGMA PIs found that many were willing to participate. The first planning meeting of this working Group occured in December 2012. New cohorts are welcome.

Paul Thompson
thompson@loni.ucla.edu

Amyloid PET WG (Forming)

In May 2012, a group of three sites with amyloid-sensitive PET scans and GWAS discussed plans for a harmonized analysis of regional data for GWAS meta-analysis. In the Alzheimer's disease (AD) field, PET tracers have been developed that can map the build-up of amyloid in the living brain, one of the hallmarks of AD. Initial discussions focused on developing a harmonized PET analysis protocol for PIB-PET scans (Pittsburgh Compound B), including agreed common templates and normalization procedures. Several new groups expressed an interest in joining this analysis in Dec. 2012, so this group will resume meetings in Jan. 2013.

Nic Novak
nic.novak@gmail.com

Vis Group

Nic Novak, of the Laboratory of Neuro Imaging at UCLA, has developed an online web-accessible visualization program to help browse and visualize the ENIGMA meta-analysis results. Data can be viewed at: **http://enigma.loni.ucla.edu/enigma-vis/** We welcome any suggestions for new or improved features for the Vis program. Please contact Nic Novak (**nic.novak@gmail.com**) or Jason Stein (**steinja@ucla.edu**)for information

Dick Veltman
DJ.Veltman@vumc.nl

Depression WG

ENIGMA welcomes this newly formed group to the consortium.

ADHD (Attention Deficit/Hyperactivity Disorder) Working Group

Leader: Barbara Franke
Email: **b.franke@gen.umcn.nl**
ENIGMA welcomes this newly formed group to the consortium.

Solicitation of Proposals and Working Group Activities

If you would like to propose a working group or jointeffort, please send proposals to Derrek Hibar (dhibar@ucla.edu) and they will be forwarded for review by site PIs for interest in participation.

Frequently Asked Questions

Q. I have MRI or DTI data from my cohort but no genetic data; can I take part in ENIGMA?

Yes. Several of the working groups (schizophrenia, bipolar, major depression, ADHD, DTI-Cognition) are conducting analyses that do not require genetic data. If you analyze your scans with the ENIGMA analysis protocols, there are several analyses you can join in with now.

Q. My IRB restricts me from sharing genetic data or images with people outside my group. Can I take part in ENIGMA?

Yes. ENIGMA does not require that you share any images or raw genomic data with anyone else. Analyses are conducted at each site, using protocols that are developed, tested, and agreed by the ENIGMA Working Groups. Summary statistics are then uploaded to a centralized server for meta-analysis.

Q. I have imaging data but limited time and resources to analyze it. Can you help me to analyze my data?

In some cases, yes. Several of the analysis sites have personnel and computer resources for analyzing MRI, DTI, PET or genomic data on a large scale. Contact us and we will try to help.

Q. Where can I learn more about the ENIGMA project?

The ENIGMA website (http://enigma.loni.ucla.edu) has an introductory video and progress reports on all of ENIGMA's ongoing projects and Working Groups.

Figure 3: This ENIGMA video explains the process of finding genetic variants influencing brain structure in 6 steps. enigma.loni.ucla.edu

Figure 4: A Lecture on ENIGMA's Discoveries

Nick Martin and Paul Thompson, ENIGMA Members

Contributors to ENIGMA1:

Jason L Stein[1,127], Sarah E Medland[2–4,127], Alejandro Arias Vasquez[5–7,127], Derrek P Hibar[1,127], Rudy E Senstad[1], Anderson M Winkler[8,9], Roberto Toro[10–12], Katja Appel[13,14], Richard Bartecek[15], Ørjan Bergmann[16], Manon Bernard[17], Andrew A Brown[16,18], Dara M Cannon[19], M Mallar Chakravarty[21], Andrea Christoforou[22,23], Martin Domin[24], Oliver Grimm[25], Marisa Hollinshead[26,27], Avram J Holmes[26], Georg Homuth[28], Jouke-Jan Hottenga[29], Camilla Langan[20], Lorna M Lopez[30,31], Narelle K Hansell[2], Kristy S Hwang[1,32], Sungeun Kim[33,34], Gonzalo Laje[35], Phil H Lee[36,37], Xinmin Liu[35,38], Eva Loth[39], Anbarasu Lourdusamy[39], Morten Mattingsdal[16,40], Sebastian Mohnke[41], Susana Muñoz Maniega[30,42,43], Kwangsik Nho[33,44], Allison C Nugent[45], Carol O'Brien[46,47], Martina Papmeyer[48], Benno Pütz[49], Adaikalavan Ramasamy[50], Jerod Rasmussen[51], Mark Rijpkema[7,52], Shannon L Risacher[33], J Cooper Roddey[53], Emma J Rose[46,47], Mina Ryten[54], Li Shen[33,34], Emma Sprooten[48], Eric Strengman[55,56], Alexander Teumer[28], Daniah Trabzuni[54,57], Jessica Turner[58], Kristel van Eijk[55,56], Theo G M van Erp[51], Marie-Jose van Tol[59–61], Katharina Wittfeld[13], Christiane Wolf[49], Saskia Woudstra[62], Andre Aleman[61], Saud Alhusaini[63], Laura Almasy[64], Elisabeth B Binder[49], David G Brohawn[36], Rita M Cantor[65], Melanie A Carless[64], Aiden Corvin[46,47], Michael Czisch[49], Joanne E Curran[64], Gail Davies[31], Marcio A A de Almeida[64], Norman Delanty[63,66], Chantal Depondt[67], Ravi Duggirala[64], Thomas D Dyer[64], Susanne Erk[41], Jesen Fagerness[36], Peter T Fox[69], Nelson B Freimer[65], Michael Gill[46,47], Harald H H Göring[64], Donald J Hagler[70], David Hoehn[49], Florian Holsboer[49], Martine Hoogman[5,7,71,72], Norbert Hosten[24], Neda Jahanshad[1], Matthew P Johnson[64], Dalia Kasperaviciute[73], Jack W Kent Jr[64], Peter Kochunov[69,74], Jack L Lancaster[69], Stephen M Lawrie[48], David C Liewald[30], René Mandl[15], Mar Matarin[73], Manuel Mattheisen[75–77], Eva Meisenzahl[78], Ingrid Melle[16,79], Eric K Moses[64], Thomas W Mühleisen[75,76], Matthias Nauck[80], Markus M Nöthen[75,76,81], Rene L Olvera[82], Massimo Pandolfo[67], G Bruce Pike[83], Ralf Puls[24], Ivar Reinvang[84,85], Miguel E Rentería[2,86], Marcella Rietschel[25], Joshua L Roffman[37], Natalie A Royle[30,42,43], Dan Rujescu[78], Jonathan Savitz[45,87], Hugo G Schnack[15], Knut Schnell[88,89], Nina Seiferth[41], Colin Smith[90], Vidar M Steen[22,23], Maria C Valdés Hernández[30,42,43], Martijn Van den Heuvel[15], Nic J van der Wee[59,60], Neeltje E M Van Haren[15], Joris A Veltman[5], Henry Völzke[91], Robert Walker[90], Lars T Westlye[84], Christopher D Whelan[63], Ingrid Agartz[16,92], Dorret I Boomsma[29], Gianpiero L Cavalleri[63], Anders M Dale[53,70], Srdjan Djurovic[16,93], Wayne C Drevets[45,87], Peter Hagoort[7,52,72], Jeremy Hall[48], Andreas Heinz[41], Clifford R Jack Jr[94], Tatiana M Foroud[34,95], Stephanie Le Hellard[22,23], Fabio Macciardi[51], Grant W Montgomery[2], Jean Baptiste Poline[96], David J Porteous[30,97], Sanjay M Sisodiya[73], John MStarr[30,98], Jessika Sussmann[48], Arthur W Toga[1], Dick J Veltman[62], Henrik Walter[41,89], Michael W Weiner[99–102], the Alzheimer's Disease Neuroimaging Initiative (ADNI)[103], EPIGEN Consortium[103], IMAGEN Consortium[103], Saguenay Youth Study Group (SYS)[103], Joshua C Bis[104], M Arfan Ikram[105–107], Albert V Smith[108,109], Vilmundur Gudnason[108,109], Christophe Tzourio[110,111], Meike W Vernooij[105–107], Lenore J Launer[112], Charles DeCarli[113,114], Sudha Seshadri[115,116], Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium[103], Ole A Andreassen[16,79], Liana G Apostolova[1,32], Mark E Bastin[30,42,43,117], John Blangero[64], Han G Brunner[5], Randy L Buckner[26,27,37,68], Sven Cichon[75,76,118], Giovanni Coppola[32,119], Greig I de Zubicaray[86], Ian J Deary[30,31], Gary Donohoe[46,47], Eco J C de Geus[29], Thomas Espeseth[84,85,120], Guillén Fernández[7,52,71], David C Glahn[8,9], Hans J Grabe[13,121], John Hardy[54], Hilleke E Hulshoff Pol[15], Mark Jenkinson[122], René S Kahn[15], Colm McDonald[20], Andrew M McIntosh[48], Francis J McMahon[35], Katie L McMahon[123], Andreas Meyer-Lindenberg[25], Derek W Morris[46,47], Bertram Müller-Myhsok[49], Thomas E Nichols[122,124], Roel A Ophoff[15,65], Tomas Paus[21], Zdenka Pausova[17], Brenda W Penninx[59,60,62,125], Steven G Potkin[51], Philipp G Sämann[49], Andrew J Saykin[33,34,96], Gunter Schumann[39], Jordan W Smoller[36,37], Joanna M Wardlaw[30,42,43], Michael E Weale[50], Nicholas G Martin[2,125], Barbara Franke[5–7,128], Margaret J Wright[2,128] & Paul M Thompson[1,128] for the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium[126]

[1]Laboratory of Neuro Imaging, David Geffen School of Medicine, University of California, Los Angeles, California, USA. [2]Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia. [3]Quantitative Genetics Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia. [4]Broad Institute of Harvard University and MIT, Cambridge, Massachusetts, USA. [5]Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. [6]Department of Psychiatry, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. [7]Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands. [8]Olin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, Hartford, Connecticut, USA. [9]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA. [10]Laboratory of Human Genetics and Cognitive Functions, Institut Pasteur, Paris, France. [11]Centre Nationale de Recherche Scientifique (CNRS) Unité de Recherche Associée (URA) 2182 Genes, Synapses and Cognition, Institut Pasteur, Paris, France. [12]Department of Neuroscience, Université Paris Diderot, Sorbonne Paris Cité, Paris, France. [13]Department of Psychiatry and Psychotherapy, University of Greifswald, Greifswald, Germany. [14]Institute of Psychology, Department of Clinical Psychology and Psychotherapy, University of Heidelberg, Heidelberg, Germany. [15]Department of Psychiatry, Rudolf Magnus Institute, University Medical Center Utrecht, Utrecht, The Netherlands. [16]Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [17]The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. [18]Institute of Basic Medical Sciences, Department of Biostatistics, University of Oslo, Oslo, Norway. [19]Clinical Neuroimaging Laboratory, Department of Anatomy, National University of Ireland Galway, Galway, Ireland. [20]Clinical Neuroimaging Laboratory, Department of Psychiatry, National University of Ireland Galway, Galway, Ireland. [21]Rotman Research Institute, University of Toronto, Toronto, Ontario, Canada. [22]Dr Einar Martens Research Group for Biological Psychiatry, Department of Clinical Medicine, University of Bergen, Bergen, Norway. [23]Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway. [24]Department of Diagnostic Radiology and Neuroradiology, University of Greifswald, Greifswald, Germany. [25]Central Institute of Mental Health, University of Heidelberg–Medical Faculty Mannheim, Mannheim, Germany. [26]Department of Psychology, Center for Brain Science, Harvard University, Cambridge, Massachusetts, USA. [27]Howard Hughes Medical Institute, Cambridge, Massachusetts, USA. [28]Interfaculty Institute for Genetics and Functional Genomics, University of Greifswald, Greifswald, Germany. [29]Department of Biological Psychology, Neuroscience Campus Amsterdam, VU University, Amsterdam, The Netherlands. [30]Centre for Cognitive Ageing and Cognitive Epidemiology, The University of Edinburgh, Edinburgh, UK. [31]Department of Psychology, The University of Edinburgh, Edinburgh, UK. [32]Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, California, USA. [33]Department of Radiology and Imaging Sciences, Center for Neuroimaging, Indiana University School of Medicine, Indianapolis, Indiana, USA. [34]Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, Indiana, USA. [35]Mood and Anxiety Disorders Section, Human Genetics Branch, Intramural Research Program, National Institute of Mental Health (NIMH), US National Institutes of Health (NIH), US Department of Health and Human Services, Bethesda, Maryland, USA. [36]Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA. [37]Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA. [38]Taub Institute for Research on Alzheimer Disease and the Aging Brain, Columbia University Medical Center, New York, New York, USA. [39]Medical Research Council (MRC)–Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, King's College London, London, UK. [40]Research Unit, Sørlandet Hospital, Kristiansand, Norway. [41]Department of Psychiatry and Psychotherapy, Charité-Universitaetsmedizin Berlin, Campus Mitte, Berlin, Germany. [42]Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) Collaboration, UK. [43]Brain Research Imaging Centre, The University of Edinburgh, Edinburgh, UK. [44]Division of Medical Informatics, Regenstrief Institute, Indianapolis, Indiana, USA. [45]Section on Neuroimaging in Mood and Anxiety Disorders, Intramural Research Program, NIMH, NIH, US Department of Health and Human Services, Bethesda, Maryland, USA. [46]Neuropsychiatric Genetics Research Group, Department of Psychiatry, Institute for Molecular Medicine, Trinity College, Dublin, Ireland. [47]Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland. [48]Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK. [49]Max Planck Institute of Psychiatry, Munich, Germany. [50]Department of Medical & Molecular Genetics, King's College London, London, UK. [51]Department of Psychiatry and Human Behavior, University of California, Irvine, California, USA. [52]Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen, Nijmegen, The Netherlands. [53]Department of Neurosciences, University of California, San Diego, La Jolla, California, USA. [54]Department of Molecular Neuroscience, University College London, London, UK. [55]Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands. [56]Rudolf Magnus Institute, University Medical Center Utrecht, Utrecht, The Netherlands. [57]Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. [58]Mind Research Network, Albuquerque, New Mexico, USA. [59]Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands. [60]Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands. [61]Behavioural and Cognitive Neuroscience Neuroimaging Center, University Medical Center Groningen, Groningen, The Netherlands. [62]Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. [63]Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. [64]Department of Genetics, Texas Biomedical Research Institute, San Antonio, Texas, USA. [65]Center for Neurobehavioral Genetics, University of California, Los Angeles, USA. [66]Division of Neurology, Beaumont

Hospital, Dublin, Ireland. [67]Department of Neurology, Hopital Erasme, Universite Libre de Bruxelles, Brussels, Belgium. [68]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, Massachusetts, USA. [69]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA. [70]Department of Radiology, University of California, San Diego, La Jolla, California, USA. [71]Department of Cognitive Neuroscience, Radboud University Nijmegen Medical Centre, The Netherlands. [72]Max Planck Institute for Psycholinguistics, Nijmegen, The Netherlands. [73]Department of Clinical and Experimental Epilepsy, University College London, Institute of Neurology, London, UK. [74]Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland, USA. [75]Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany. [76]Institute of Human Genetics, University of Bonn, Bonn, Germany. [77]Institute for Genomic Mathematics, University of Bonn, Bonn, Germany. [78]Department of Psychiatry, Ludwig-Maximilians-University (LMU), Munich, Germany. [79]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. [80]Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Greifswald, Germany. [81]German Center for Neurodegenerative Disorders (DZNE), Bonn, Germany. [82]Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA. [83]Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada. [84]Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Oslo, Norway. [85]Centre for Advanced Study, Oslo, Norway. [86]School of Psychology, University of Queensland, Brisbane, Queensland, Australia. [87]Laureate Institute for Brain Research, Tulsa, Oklahoma, USA. [88]Department of General Psychiatry, Heidelberg University Hospital, University of Heidelberg, Heidelberg, Germany. [89]Department of Psychiatry, Division of Medical Psychology, Bonn, Germany. [90]The MRC Sudden Death Tissue Bank in Edinburgh, Department of Pathology, University of Edinburgh, Edinburgh, UK. [91]Institute for Community Medicine, University of Greifswald, Greifswald, Germany. [92]Department of Research and Development, Diakonhjemmet Hospital, Oslo, Norway. [93]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. [94]Aging and Dementia Imaging Research Laboratory, Department of Radiology, Mayo Clinic and Foundation, Rochester, Minnesota, USA. [95]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA. [96]Neurospin, Institut d'Imagerie Biomédicale (I^2BM), Commissariat à l'Energie Atomique, Gif-sur-Yvette, France. [97]Medical Genetics Section, Molecular Medicine Centre, Institute of Genetics and Molecular Medicine, The University of Edinburgh, Western General Hospital, Edinburgh, UK. [98]Geriatric Medicine Unit, The University of Edinburgh, Royal Victoria Hospital, Edinburgh, UK. [99]Departments of Radiology, University of California, San Francisco, California, USA. [100]Department of Medicine, University of California, San Francisco, California, USA. [101]Department of Psychiatry, University of California, San Francisco, California, USA. [102]Veterans Affairs Medical Center, San Francisco, California, USA. [103]A full list of members is provided in the supplementary Note. [104]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, Washington, USA. [105]Department of Epidemiology, Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands. [106]Department of Radiology, Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands. [107]Netherlands Consortium for Healthy Aging, Leiden, The Netherlands. [108]Icelandic Heart Association, Kopavogur, Iceland. [109]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [110]University of Brodeaux, U^{708}, Bordeaux, France. [111]Institut National de la Santé et la Recherche Médicale (INSERM), Neuroepidemiology, U^{708}, Bordeaux, France. [112]Laboratory of Epidemiology, Demography, and Biometry, NIH, Bethesda, Maryland, USA. [113]Department of Neurology, University of California, Davis, Sacramento, California, USA. [114]Center of Neuroscience, University of California, Davis, Sacramento, California, USA. [115]Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA. [116]National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA. [117]Division of Health Sciences (Medical Physics), The University of Edinburgh, Edinburgh, UK. [118]Institute for Neuroscience and Medicine (INM-[1]), Research Center Juelich, Juelich, Germany. [119]Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, California, USA. [120]Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, Bergen, Norway. [121]German Center for Neurodegenerative Diseases (DZNE), Rostock/Greifswald, Greifwald, Germany. [122]Functional Magnetic Resonance Imaging of the Brain (FMRIB) Centre, Oxford University, Oxford, UK. [123]Centre for Advanced Imaging, University of Queensland, Brisbane, Queensland, Australia. [124]Department of Statistics, University of Warwick, Coventry, UK. [125]Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands.

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