Reply to: New Meta- and Mega-analyses of Magnetic Resonance Imaging Findings in Schizophrenia: Do They Really Increase Our Knowledge About the Nature of the Disease Process?

To the Editor:

In their letter to the editor, Vita and De Peri (1) question whether new meta- and mega-analyses of magnetic resonance imaging (MRI) findings in schizophrenia increase our knowledge about the nature of the disease process. In general, meta- and mega-analyses provide objective methods to critically summarize a body of evidence regarding a particular question. As there had been no coordinated meta-analysis of cortical thickness and surface area abnormalities in schizophrenia, it is our view that this new, collaboratively conducted meta-analysis (2) contributes to our knowledge on this question and offers information on the cross-site consistency of observed disease effects. Regional effects on cortical thickness and surface area can be difficult to summarize based on the traditional, literature-based, meta-analysis method, given the heterogeneity of analysis methods used in individual studies.

The Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) approach of collaboratively conducting meta-analyses offers additional benefits. First, ENIGMA's publicly available methods lend themselves well to independent replication of imaging findings (3,4), which is crucial given the "crisis of replication" in neuroscience (5–7). Second, the use of the same quality assurance, image processing, and statistical analysis methods across samples within and across ENIGMA working groups minimizes method-related heterogeneity and offers the potential for straightforward cross-disorder comparisons (8–12). Third, the use of similar meta-analytic methods across worldwide samples has generated imaging and genetics findings with sample sizes beyond the scope of any individual laboratory or consortium studying a single disorder (13–16).

Vita and De Peri (1) repeat one of the study weaknesses already listed in the discussion: that possible group differences in lateralization were not examined. This question is under investigation by the ENIGMA Laterality Working Group, which is currently examining healthy and disordered brain laterality (17,18). ENIGMA coordinates publication efforts across working groups to avoid overlap. Moreover, numerous ENIGMA studies make important contributions showing between-disorder brain differences without addressing laterality.

Vita and De Peri (1) also mention that the meta-analysis does not address possible differential longitudinal trajectories between individuals with schizophrenia and healthy volunteers, which is also correct as this cross-sectional meta-analysis did not aim to examine longitudinal trajectories. There are ongoing efforts by the ENIGMA Plasticity Working Group to study genetic influences on individual differences in longitudinal brain changes (19). We agree that further investigation of questions regarding longitudinal trajectories of brain changes across the lifespan, especially prior to illness onset, e.g., in adolescents at clinical high risk for psychosis, as well as after a first psychotic episode, will provide valuable information regarding schizophrenia pathogenesis, and several such analyses are planned or are ongoing.

Vita and De Peri (1) further state that the meta-analysis does not add relevant information about the effects of antipsychotic medication on brain morphology but qualify that the reported findings seem compatible with findings from longitudinal MRI studies that suggest different effects of first- versus second-generation antipsychotic treatments on cortical gray matter changes. We point out that prior meta-analyses did not dissociate effects of antipsychotic treatments on cortical surface area versus cortical thickness, whose product constitutes gray matter volume, and that the consistency of findings is important in the light of reports on nonreplication in neuroscience.

The comment that "the supposed huge statistical power of mega-analyses of MRI findings in schizophrenia may be undermined by the large variation of data obtained by different centers in disparate conditions" is incorrect. First, van Erp *et al.* (2) is a meta-analysis and not a mega-analysis, which, like any other meta-analysis, summarizes within-sample effects. In fact, joint meta-analyses tend to reduce method-related variation when compared with literature-based meta-analyses because similar analysis methods are applied across samples. Second, multiple imaging genetics meta-analyses replicate common genetic variants associated with measures of brain structure and find a greater number of common variants associated with these measures when additional independent samples are added (20–22). These findings suggest increased power as brain imaging data from independent samples are added. Finally, the suggestion that mega-analyses of MRI data are undermined by between-site variation is not borne out by the facts. Research from a decade ago showed the feasibility and the additional power gained by pooling legacy structural imaging data (23). More recent studies show that meta- and mega-analyses of structural imaging data, whether from prospective multiscanner or independent samples, yield significant and similar findings (24–26). Each analysis method has strengths, weaknesses, and pitfalls. Hence researchers must consider whether to conduct a meta-analysis, a mega-analysis, or both, to answer a particular question.

The suggestion that meta- and mega-analyses are not hypothesis-driven approaches is also incorrect. All published ENIGMA Schizophrenia Working Group meta-analyses list their hypotheses at the end of their introductions (2,3,27–29). Of note, nowhere in the article do we state that "meta-analyses provide better evidence than large, well-designed, hypothesis-driven, high-quality individual trials." On the contrary, all findings from meta-analyses depend on the quality of the studies on which they are based. Even so, meta-analyses can offer additional safeguards against false positive findings

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generated by individual studies with small or highly heterogeneous samples by considering each sample's error terms. We do agree that missing data for known or supposed significant moderators can be an issue. However, this is a criticism of all analyses of scientific data rather than of our study specifically.

Finally, we respectfully disagree with the statement by Vita and De Peri "that the time has come for applying new approaches to the study of the nature of the disease process underlying schizophrenia, rather than promoting redundant research on mega-databases that may even dilute or confuse established knowledge" (1). We believe there is value both in taking the relatively new approach of performing large-scale collaborative research on costly, already collected data, and also in applying other innovative approaches and experimentation in adequately powered samples. We believe that most scientists who contribute to ENIGMA or other consortia as well as the funding agencies who promote large-scale data sharing and analysis recognize that both approaches make valuable contributions to the field.

Theo G.M. van Erp
Esther Walton
Derrek P. Hibar
Lianne Schmaal
Wenhao Jiang
David C. Glahn
Godfrey D. Pearlson
Nailin Yao
Masaki Fukunaga
Ryota Hashimoto
Naohiro Okada
Hidenaga Yamamori
Vincent P. Clark
Bryon A. Mueller
Sonja M.C. de Zwarte
Roel A. Ophoff
Neeltje E.M. van Haren
Ole A. Andreassen
Tiril P. Gurholt
Oliver Gruber
Bernd Kraemer
Anja Richter
Vince D. Calhoun
Benedicto Crespo-Facorro
Roberto Roiz-Santiañez
Diana Tordesillas-Gutiérrez
Carmel Loughland
Stanley Catts
Janice M. Fullerton
Melissa J. Green
Frans Henskens
Assen Jablensky
Bryan J. Mowry
Christos Pantelis
Yann Quidé
Ulrich Schall
Rodney J. Scott
Murray J. Cairns
Marc Seal
Paul A. Tooney
Paul E. Rasser
Gavin Cooper
Cynthia Shannon Weickert
Thomas W. Weickert
Elliot Hong
Peter Kochunov
Raquel E. Gur
Ruben C. Gur
Judith M. Ford
Fabio Macciardi
Daniel H. Mathalon
Steven G. Potkin
Adrian Preda
Fengmei Fan
Stefan Ehrlich
Margaret D. King
Lieuwe De Haan
Dick J. Veltman
Francesca Assogna
Nerisa Banaj
Pietro de Rossi
Mariangela Iorio
Fabrizio Piras
Gianfranco Spalletta
Edith Pomarol-Clotet
Sinead Kelly
Simone Ciufolini
Joaquim Radua
Robin Murray
Tiago Reis Marques
Andrew Simmons
Stefan Borgwardt
Fabienne Schönborn-Harrisberger
Anita Riecher-Rössler
Renata Smieskova
Kathryn I. Alpert
Alessandro Bertolino
Aurora Bonvino
Annabella Di Giorgio
Emma Neilson
Andrew R. Mayer
Je-Yeon Yun
Dara M. Cannon
Irina Lebedeva
Alexander S. Tomyshev
Tolibjohn Akhadov
Vasily Kaleda
Helena Fatouros-Bergman
Lena Flyckt
Karolinska Schizophrenia Project
Pedro G.P. Rosa
Mauricio H. Serpa
Marcus V. Zanetti
Cyril Hoschl
Antonin Skoch
Filip Spaniel
David Tomecek
Andrew M. McIntosh
Heather C. Whalley

Christian Knöchel
Viola Oertel-Knöchel
Fleur M. Howells
Dan J. Stein
Henk S. Temmingh
Anne Uhlmann
Carlos Lopez-Jaramillo
Danai Dima
Joshua I. Faskowitz
Boris A. Gutman
Neda Jahanshad
Paul M. Thompson
Jessica A. Turner

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Article Information

From the Department of Psychiatry and Human Behavior (TGMvE, FM, SGP, AP), University of California, Irvine; Imaging Genetics Center (DPH, JIF, NJ, PMT), Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of the University of Southern California, Marina del Rey; Janssen Research and Development (DPH), San Diego; University of California Los Angeles Center for Neurobehavioral Genetics (RAO), Los Angeles; Department of Psychiatry (JMFo, DHM), University of California, San Francisco, and the San Francisco Veterans Affairs Medical Center (JMFo, DHM), San Francisco, California; Medical Research Council Integrative Epidemiology Unit and Bristol Medical School (EW), Population Health Sciences, University of Bristol; Department of Psychosis Studies (JR, RM, TRM, ASi, SC) and Department of Neuroimaging (DD), Institute of Psychiatry, Psychology and Neuroscience, King's College London; Division of Psychiatry (EN, AMM, HCW) and the Centre for Cognitive Ageing and Cognitive Epidemiology (AMM), University of Edinburgh; Department of Psychology (DD), City, University of London, London, United Kingdom; Orygen (LS), The National Centre of Excellence in Youth Mental Health, Melbourne, Victoria; Centre for Youth Mental Health (LS), The University of Melbourne; Melbourne Neuropsychiatry Centre (CP), University of Melbourne and Melbourne Health, and the Florey Institute of Neuroscience and Mental Health (CP), University of Melbourne; Hunter Medical Research Institute (FH, RJS, MJC, PAT, CL), Priority Research Centre for Brain and Mental Health (PAT, PER, GC, CL), Priority Research Centres for Brain and Mental Health and Grow Up Well (US), School of Biomedical Sciences and Pharmacy (RJS, MJC, PAT), and the Priority Research Center for Health Behaviour (FH) and the School of Medicine and Public Health (FH), The University of Newcastle, New South Wales; Murdoch Children's Research Institute (MS), Melbourne, Victoria, Australia; Queensland Brain Institute (BJM) and the Queensland Centre for Mental Health Research (BJM), University of Queensland (SC), Brisbane, Queensland; Neuroscience Research Australia (MJG, YQ, JMFu, CSW, TWW), Sydney, and the School of Medical Sciences (JMF), University of New South Wales, Sydney; School of Psychiatry (MJG, CSW, TWW, YQ), University of New South Wales, Sydney; University of Western Australia (AJ), Perth, Western Australia; and the Hunter New England Local Health District (CL), Newcastle, New South Wales, Australia; Department of Neuroscience and Physiology (CSW), State University of New York Upstate Medical University, Syracuse, New York; Department of Psychiatry and Amsterdam Neuroscience (LS), VU University Medical Center, Amsterdam; Department of Psychiatry and Brain Center Rudolf Magnus (SMCdZ, NEMvH), University Medical Center Utrecht, Utrecht; Department of Psychiatry (LDH), Academic Medical Center, University of Amsterdam, and the Department of Psychiatry (DJV), Vrije Universiteit Medical Center, Amsterdam; Department of Child and Adolescent Psychiatry/Psychology (NEMvH), Erasmus Medical Centre, Rotterdam, The Netherlands; Department of Psychology (WJ), Georgia State University, Atlanta, Georgia; Department of Psychiatry (DCG, GDP, NY), Yale University, New Haven; Olin Neuropsychiatric Research Center (DCG, GDP, NY), Institute of Living, Hartford Hospital, Hartford, Connecticut; Division of Cerebral Integration (MF), National Institute for Physiological Sciences, Okazaki, Aichi, Japan; Molecular Research Center for Children's Mental Development (RH), United Graduate School of Child Development, Osaka University, and Department of Pathology of Mental Diseases (RH), National Institute of Mental Health, National Center of Neurology and Psychiatry, and the Department of Psychiatry (RH, HY), Osaka University Graduate School of Medicine, Osaka; Department of Neuropsychiatry (NO), Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan; University of New Mexico (VPC, VDC) and the Mind Research Network (VPC, VDC, ARM, MDK, JAT), Albuquerque, New Mexico; Department of Psychiatry (BAM), University of Minnesota, Minneapolis, Minnesota; Norwegian Centre for Mental Disorders Research (OAA, TPG), K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction (OAA, TGP) and the Institute of Clinical Medicine (TPG, OAA), Oslo University Hospital, and the Department of Psychiatric Research (TPG), Diakonhjemmet Hospital, Oslo, Norway; Section for Experimental Psychopathology and Neuroimaging (OG, BK, AR), Department of General Psychiatry, Heidelberg University Hospital, Heidelberg, and the Center for Translational Research in Systems Neuroscience and Psychiatry (BK, AR), Department of Psychiatry, Georg August University, Göttingen, Germany; Department of Psychiatry (BC-F, RR-S, DT-G), University Hospital Marqués de Valdecilla, School of Medicine, University of Cantabria-Valdecilla Biomedical Research Institute, Marqués de Valdecilla Research Institute, and the Centro Investigación Biomédica en Red de Salud Mental (BC-F, RR-S, DT-G), Santander, Spain; Maryland Psychiatric Research Center (EG, PK), University of Maryland School of Medicine, Baltimore, Maryland; Department of Psychiatry (REG, RCG), University of Pennsylvania, Philadelphia, Pennsylvania; Psychiatry Research Center (FF), Beijing Huilongguan Hospital, Beijing, China; Division of Psychological and Social Medicine and Developmental Neurosciences (SE), Faculty of Medicine, TU Dresden, Dresden, Germany; Massachusetts General Hospital/Harvard Medical School (SE), Athinoula A. Martinos Center for Biomedical Imaging, Psychiatric Neuroimaging Research Program, Boston, Massachusetts; Laboratory of Neuropsychiatry (FA, NB, PdR, MI, FP, GS), Department of Clinical and Behavioral Neurology, Istituto Di Ricovero e Cura a Carattere Scientifico Santa Lucia Foundation, Rome, and Centro Fermi - Museo Storico della Fisica e Centro Studi e Ricerche "Enrico Fermi," (FA, FP), Rome, Italy; Dipartimento di Neuroscienze (PdR), Salute Mentale e Organi di Senso Department, Faculty of Medicine and Psychology, and the Department of Neurology and Psychiatry (PdR), Sapienza University of Rome, Rome, Italy; Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry (GS), Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas; Fundación para la Investigación y Docencia Maria Angustias Giménez Germanes Hospitalaries Research Foundation (EP-C, JR) and the Centro Investigación Biomédica en Red de Salud Mental (JR), Barcelona, Spain; Department of Psychiatry (SK), Beth Israel Deaconess Medical Center, and the Psychiatry Neuroimaging Laboratory (SK), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Department of Clinical Neuroscience (JR), Centre for Psychiatric Research, Karolinska Institutet, Stockholm, Sweden; University of Basel Psychiatric Hospital (SB, FS-H, AR-R, RS), Basel, Switzerland; Department of Psychiatry and Behavioral Sciences (KIA), Northwestern University Feinberg School of Medicine, Chicago, Illinois; Department of Basic Medical Science (AB), Neuroscience and Sense Organs, University of Bari "Aldo Moro," Bari, Italy; Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico Casa Sollievo della Sofferenza (AB, ADG), San Giovanni Rotondo, Italy; Seoul National University Hospital (J-YY) and the Yeongeon Student Support Center (J-YY), Seoul National University College of Medicine, Seoul, Republic of Korea; Centre for Neuroimaging and Cognitive Genomics (DMC), Clinical Neuroimaging Laboratory, National Centre for Biomedical Engineering Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland

Galway, Galway, Ireland; Mental Health Research Center (IL, AST, VK), and the Children's Clinical and Research Institute of Emergency Surgery and Trauma (TA), Moscow, Russia; Centre for Psychiatry Research (HF-B, LF), Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, and the Karolinska Schizophrenia Project, Stockholm, Sweden; Laboratory of Psychiatric Neuroimaging (PGPR, MHS, MVZ), Department of Psychiatry, Faculty of Medicine, and the Center for Interdisciplinary Research on Applied Neurosciences (PGPR, MHS, MVZ), University of São Paulo, São Paulo, Brazil; National Institute of Mental Health (CH, AS, FS, DT), Klecany, Czech Republic; Magnetic Resonance Unit (AS), Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Prague; Institute of Computer Science (DT), Czech Academy of Sciences, and the Faculty of Electrical Engineering (DT), Czech Technical University in Prague, Prague, Czech Republic; Department of Psychiatry (CK, VO-K), Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; Department of Psychiatry, Groote Schuur Hospital (FMH, DJS, HST, AU) and Medical Research Council Unit on Risk & Resilience in Mental Disorders (DJS), and Department of Psychiatry (AU), MRC Unit on Risk & Resilience in Mental Disorders, Stellenbosch University, Cape Town, South Africa; Research Group in Psychiatry (CL-J), Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellín, Colombia; Department of Biomedical Engineering (BAG), Illinois Institute of Technology, Chicago, Illinois; Imaging Genetics and Neuroinformatics Laboratory (JAT), Department of Psychology, Georgia State University, Atlanta, Georgia; Neuroimaging Unit Technological Facilities (DT-G), Valdecilla Biomedical Research Institute, Santander, Cantabria, Spain; and the Institut d'Investigacions Biomediques August Pi i Sunyer (JR), Barcelona, Spain.

Karolinska Schizophrenia Project members include Lars Farde, Lena Flyckt, Helena Fatouros-Bergman, Simon Cervenka, Karin Collste, and Pauliina Victorsson from the Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm County Council, Stockholm; Göran Engberg, Sophie Erhardt, Lilly Schwieler, Anna Malmqvist, Mikael Hedberg, and Funda Orhan from the Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm; Fredrik Piehl from the Neuroimmunology Unit, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; and Ingrid Agartz from NORMENT, K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, University of Oslo, and the Department of Psychiatry Research, Diakonhjemmet Hospital, Oslo, Norway.

Address correspondence to Theo G.M. van Erp, Ph.D., Clinical Translational Neuroscience Laboratory, Department of Psychiatry and Human Behavior, School of Medicine, University of California Irvine, 5251 California Ave, Ste 240, Irvine, CA 92617; E-mail: tvanerp@uci.edu.

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