Collaborative meta-analyses and mega-analyses of magnetic resonance imaging data increase our knowledge about brain disorders

Reply to: New meta-analyses and mega-analyses of MRI findings in schizophrenia: do they really increase our knowledge about the nature of the disease process?

Theo GM van Erp[1*], Esther Walton[2], Derrek P Hibar[3,4], Lianne Schmaal[5,6,7], Wenhao Jiang[8], David C Glahn[9,10], Godfrey D Pearlson[9,10], Nailin Yao[9,10], Masaki Fukunaga[11], Ryota Hashimoto[12,13], Naohiro Okada[14], Hidenaga Yamamori[13], Vincent P Clark[15,16], Bryon A Mueller[20], Sonja MC de Zwarte[21], Roel A Ophoff[21,22], Neeltje EM van Haren[21,116], Ole A Andreassen[17,23], Tiril P Gurholt[17,18], Oliver Gruber[28,29], Bernd Kraemer[28,29], Anja Richter[28,29], Vince D Calhoun[15,16], Benedicto Crespo-Facorro[31,32], Roberto Roiz-Santiañez[31,32], Diana Tordesillas-Gutiérrez[31,32,68], Carmel Loughland[47,49,115], Stanley Catts[36], Janice M Fullerton[38,39], Melissa J Green[34,38], Frans Henskens[40,123,47], Assen Jablensky[41], Bryan J Mowry[42,43], Christos Pantelis[37,45], Yann Quidé[34,38], Ulrich Schall[46,47], Rodney J Scott[33,47], Murray J Cairns[33,47], Marc Seal[48], Paul A Tooney[33,47,49], Paul E Rasser[49], Gavin Cooper[49], Cynthia Shannon Weickert[34,38], Thomas W Weickert[34,38], Elliot Hong[52], Peter Kochunov[52], Raquel E Gur[53], Ruben C Gur[53], Judith M Ford[57,58], Fabio Macciardi[1], Daniel H Mathalon[57,58], Steven G Potkin[1], Adrian Preda[1], Fengmei Fan[61], Stefan Ehrlich[66,67], Margaret D King[16], Lieuwe De Haan[70], Dick J Veltman[72], Francesca Assogna[73,74], Nerisa Banaj[73], Pietro de Rossi[73,75,76], Mariangela Iorio[73], Fabrizio Piras[73,74], Gianfranco Spalletta[73,77], Edith Pomarol-Clotet[78,79], Sinead Kelly[80,81], Simone Ciufolini[83], Joaquim Radua[19,78,79,83,119], Robin Murray[83], Tiago Reis Marques[83], Andrew Simmons[83], Stefan Borgwardt[85], Fabienne Schönborn-Harrisberger[85], Anita Riecher-Rössler[85],

Renata Smieskova[85], Kathryn I Alpert[86], Alessandro Bertolino[88], Aurora Bonvino[89], Annabella Di Giorgio[89], Emma Neilson[90], Andrew R Mayer[16], Je-Yeon Yun[93,94], Dara M Cannon[95], Irina Lebedeva[96], Alexander S Tomyshev[96], Tolibjohn Akhadov[97], Vasily Kaleda[96], Helena Fatouros-Bergman[98], Lena Flyckt[98], Karolinska Schizophrenia Project (KaSP)[99], Pedro GP Rosa[100,101], Mauricio H Serpa[100,101], Marcus V Zanetti[100,101], Cyril Hoschl[102], Antonin Skoch[102,103], Filip Spaniel[102], David Tomecek[102,120,121], Andrew M McIntosh[90,104], Heather C Whalley[90], Christian Knöchel[106], Viola Oertel-Knöchel[106], Fleur M Howells[107], Dan J Stein[107,108], Henk S Temmingh[107], Anne Uhlmann[107,109], Carlos Lopez-Jaramillo[110], Danai Dima[111,112], Joshua I Faskowitz[3], Boris A Gutman[122], Neda Jahanshad[3], Paul M Thompson[3], Jessica A Turner[16,118]

[1]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA

[2]Medical Research Council Integrative Epidemiology Unit and Bristol Medical School, Population Health Sciences, University of Bristol, United Kingdom

[3]Imaging Genetics Center, Mark and Mary Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of the University of Southern California, Marina del Rey, CA, USA

[4]Janssen Research & Development, San Diego, CA, USA

[5]Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, VIC, Australia

[6]Centre for Youth Mental Health, The University of Melbourne, Melbourne, VIC, Australia

[7]Department of Psychiatry and Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands

[8]Department of Psychology, Georgia State University, Atlanta, GA, USA

[9]Department of Psychiatry, Yale University, New Haven, CT, USA

[10]Olin Neuropsychiatric Research Center, Institute of Living, Hartford Hospital, Hartford, CT, USA

[11]Division of Cerebral Integration, National Institute for Physiological Sciences, Okazaki, Aichi, Japan

[12]Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Suita, Osaka, Japan

[13]Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

[14]Department of Neuropsychiatry, Graduate school of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

[15]University of New Mexico, Albuquerque, NM, USA

[16]Mind Research Network, Albuquerque, NM, USA

[17]Norwegian Centre for Mental Disorders Research (NORMENT), K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[18]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

[19]Department of Clinical Neuroscience, Centre for Psychiatric Research, Karolinska Institutet, Stockholm, Sweden

[20]Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

[21]Department of Psychiatry and Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

[22]University of California Los Angeles Center for Neurobehavioral Genetics, Los Angeles, CA,

USA

[23]Norwegian Centre for Mental Disorders Research (NORMENT), K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

[28]Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University Hospital, Heidelberg, Germany

[29]Center for Translational Research in Systems Neuroscience and Psychiatry, Department of Psychiatry, Georg August University, Göttingen, Germany

[31]Department of Psychiatry, University Hospital Marqués de Valdecilla, School of Medicine, University of Cantabria-Valdecilla Biomedical Research Institute, Marqués de Valdecilla Research Institute (IDIVAL), Santander, Spain

[32]Centro Investigación Biomédica en Red de Salud Mental (CIBERSAM), Santander, Spain

[33]School of Biomedical Sciences and Pharmacy, The University of Newcastle, Newcastle, NSW, Australia

[34]School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

[36]University of Queensland, Brisbane, QLD, Australia

[37]Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne, VIC, Australia

[38]Neuroscience Research Australia, Sydney, NSW, Australia

[39]School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia

[40] Priority Research Center for Health Behaviour, The University of Newcastle, Newcastle,

NSW, Australia

[41]University of Western Australia, Perth, WA, Australia

[42]Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia

[43]Queensland Centre for Mental Health Research, The University of Queensland, Brisbane, QLD, Australia

[45]Florey Institute of Neuroscience and Mental Health, University of Melbourne, VIC, Australia

[46]Priority Research Centres for Brain & Mental Health and Grow Up Well, The University of Newcastle, Newcastle, NSW, Australia

[47]Hunter Medical Research Institute, Newcastle, NSW, Australia

[48]Murdoch Children's Research Institute, Melbourne, VIC, Australia

[49]Priority Research Centre for Brain & Mental Health, The University of Newcastle, Newcastle, NSW, Australia

[52]Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA

[53]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

[57]Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA

[58]San Francisco VA Medical Center, San Francisco, CA, USA

[61]Psychiatry Research Center, Beijing Huilongguan Hospital, Beijing, China

[66]Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Germany, Dresden, Germany

[67]Massachusetts General Hospital/ Harvard Medical School, Athinoula A. Martinos Center for

Biomedical Imaging, Psychiatric Neuroimaging Research Program

[68]Neuroimaging Unit.Technological Facilities, Valdecilla Biomedical Research Institute IDIVAL, Santander, Cantabria, Spain

Dresden, Dresden, Germany

[70]Department of psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[72]Department of Psychiatry, Vrije Universiteit Medical Center, Amsterdam, The Netherlands

[73]Laboratory of Neuropsychiatry, Department of Clinical and Behavioral Neurology, Istituto Di Ricovero e Cura a Carattere Scientifico Santa Lucia Foundation, Rome, Italy

[74]Centro Fermi - Museo Storico della Fisica e Centro Studi e Ricerche "Enrico Fermi", Rome, Italy

[75]Dipartimento di Neuroscienze, Salute Mentale e Organi di Senso (NESMOS) Department, Faculty of Medicine and Psychology, University "Sapienza" of Rome, Rome, Italy

[76]Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy

[77]Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Tx USA.

[78]Fundación para la Investigación y Docencia Maria Angustias Giménez (FIDMAG) Germanes Hospitalaries Research Foundation, Barcelona, Spain

[79]Centro Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain

[80]Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

[81]Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[83]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

[85]University of Basel Psychiatric Hospital, Basel, Switzerland

[86]Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[88]Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy

[89] Istituto Di Ricovero e Cura a Carattere Scientifico Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

[90]Division of Psychiatry, University of Edinburgh, Edinburgh, United Kingdom

[93]Seoul National University Hospital, Seoul, Republic of Korea

[94]Yeongeon Student Support Center, Seoul National University College of Medicine, Seoul, Republic of Korea

[95]Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, National Centre for Biomedical Engineering Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway, H91 TK33 Galway, Ireland.

[96]Mental Health Research Center, Moscow, Russia

[97]Children's Clinical and Research Institute of Emergency Surgery and Trauma, Moscow,

Russia

[98]Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, & Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

[99]Members of the Karolinska Schizophrenia Project (KaSP) are listed at the end of the manuscript as collaborators

[100]Laboratory of Psychiatric Neuroimaging (LIM 21), Department of Psychiatry, Faculty of Medicine, University of São Paulo, São Paulo, Brazil

[101]Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, São Paulo, Brazil

[102]National Institute of Mental Health, Klecany, Czech Republic

[103]MR Unit, Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

[104]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, United Kingdom

[106]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany

[107]University of Cape Town Dept of Psychiatry, Groote Schuur Hospital (J2), Cape Town South Africa

[108]Medical Research Council Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry, University of Cape Town, Cape Town, South Africa

[109]MRC Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry, Stellenbosch

University, Cape Town, South Africa

[110]Research Group in Psychiatry, Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellin, Colombia

[111]Department of Psychology, City, University of London, London, United Kingdom

[112]Department of Neuroimaging, IOPPN, King's College London, London, United Kingdom

[115]Hunter New England Local Health District, Newcastle, NSW, Australia

[116]Department of child and adolescent psychiatry/psychology, Erasmus Medical Centre, Rotterdam, The Netherlands

[118]Imaging Genetics and Neuroinformatics Lab, Department of Psychology, Georgia State University, Atlanta, GA, USA

[119]Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[120]Institute of Computer Science, Czech Academy of Sciences, Prague, Czech Republic

[121]Faculty of Electrical Engineering, Czech Technical University in Prague, Prague, Czech Republic

[122]Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, Illinois

[123]School of Medicine and Public Health, The University of Newcastle, Newcastle, NSW, Australia

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*Corresponding Author:

Theo G.M. van Erp

Clinical Translational Neuroscience Laboratory

Department of Psychiatry and Human Behavior

School of Medicine

University of California Irvine

5251 California Avenue, Suite 240

Irvine, CA 92617

voice: (949) 824-3331

email: tvanerp@uci.edu

To the Editor:

In their letter to the editor, Vita and De Peri question whether new meta-analyses and mega-analyses of magnetic resonance imaging (MRI) findings in schizophrenia increase our knowledge about the nature of the disease process. In general, meta-analyses 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 (1) 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 (2, 3), which is crucial given the 'crisis of replication' in neuroscience (4–6). Second, 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 (7–11). Third, 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 (12–15).

Vita and De Peri repeat one of the study weaknesses already listed in the discussion, namely 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 (16, 17). ENIGMA coordinates publication efforts across working groups in order to avoid overlap. Moreover, numerous ENIGMA studies make important contributions showing between-disorder brain differences without addressing laterality.

Vita and De Peri 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 (18). 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 with regard to schizophrenia pathogenesis and several such analyses are planned or already ongoing.

Vita and De Peri 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 non-replication 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. (2018) 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 to 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 (19–21). 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 (22). More recent studies show that meta-analyses and mega-analyses of structural imaging data, whether from prospective multi-scanner or independent samples, yield significant and very similar findings (23–25). 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-analyses 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 (1, 2, 26–28). Of note, nowhere in the manuscript 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 generated by individual studies with small or highly heterogeneous samples by taking into account 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 really new approaches to the study of the nature of the disease process underlying schizophrenia, rather than promoting redundant research on mega-databases which may even dilute or confuse established knowledge". We believe there is value both in the relatively new approach of large-scale collaborative research on costly, already collected data, as

well as 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.

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Division of Mental Health and Addiction, University of Oslo, Oslo, Norway; [5]Department

of Psychiatry Research, Diakonhjemmet Hospital, Oslo, Norway.

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