Response to Dr Fried & Dr Kievit, and Dr Malhi et al

Citation for published version:

Digital Object Identifier (DOI):
10.1038/mp.2016.9

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Molecular Psychiatry

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
LETTER TO THE EDITOR

Response to Dr Fried & Dr Kievit, and Dr Malhi et al.

We thank Dr. Fried & Dr. Kievit, and Dr. Malhi and colleagues for their insightful comments. Here we further clarify the design and outcome of our meta-analysis of subcortical volume differences between patients with major depressive disorder (MDD) and controls.

Fried and Kievit and Malhi et al. commend the collaborative achievement of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) MDD consortium in analyzing sample sizes unprecedented in neuroimaging of depression. They also raise some concerns and provide additional interpretations of our results. Malhi et al. suggest that we should better exploit this vast data set to study the heterogeneity of MDD. MDD is a heterogeneous disorder, and the scope and extent of brain alterations depends on specific clinical characteristics of the sample studied. That is why we reported meta-analytic results of subcortical volume differences in depressed patients stratified by stage of illness (first episode versus recurrent) and age of onset (early versus late). Compared to controls, hippocampal volume was lower in recurrent and early-onset patients, on an average, but not in first-episode patients or patients diagnosed after age 21. These findings indeed raise interesting questions: for instance, whether hippocampal volume reductions are detectable in early-onset first-episode patients. Malhi et al. suggest partitioning our sample into finer subgroups to study these interactions. We agree that it is important to analyze between-subject differences across these complex interactions, but our study design did not allow for delineating these more complex interactions (for example, diagnosis x recurrence x age of onset). Our meta-analysis comprised standardized processing, statistics and quality control to harmonize methods in a sample of unprecedented size. In a mega-analysis, one can access all participant-level data. By contrast, our initial meta-analysis distributed work efficiently across many sites, and we meta-analyzed summary statistics at a central site. Coordinated analyses at this scale must consider what is feasible and achievable, to motivate more fine-grained analysis. So far, partitioning patients into fine-grained subgroups has not been feasible in most individual samples, as the numbers per cell quickly become too small to assess more complex clinical interactions. As ENIGMA grows, several analyses are showing consistency worldwide. A mega-analysis may be feasible with a subsample of participating sites who meet legal and ethical requirements for the sharing of individual subject data at a central site.

Our study is the largest meta-analysis to date and reveals the profile of subcortical volume alterations in MDD, and some factors that affect it. Brain structure was consistently altered across: (1) MDD patients residing in the community or primary care, and (2) patients recruited from specialized mental health services, many of whom had more severe and recurrent MDD. Unlike smaller studies, we found no consistent subcortical brain alterations beyond the hippocampus, and even this was observed only in specific patient subgroups: this is, unquestionably, new information from a worldwide sample offering very high power. As Fried and Kievit note, subcortical abnormalities in MDD are moderate, but consistent. Past claims reporting smaller volumes of (for example) the amygdala in MDD patients were not robust across the cohorts we analyzed. As with any other study, ours has limitations. Not all individual studies had detailed information on duration, number of episodes and treatment history. When combining already collected data across worldwide samples, data collection protocols are not prospectively harmonized. Clinical assessments therefore differed across studies, which limits the analysis of sources of heterogeneity. For instance, different instruments were used to assess depression symptom severity across the studies included in the meta-analysis. New subprojects were recently initiated within our ENIGMA MDD consortium specifically focused on how severity impacts neural changes in MDD, which intend to (1) establish a common metric for depressive symptoms for various questionnaires, and (2) explore different ways of defining symptom and disease severity and their association with brain measures. Regarding the effects of antidepressants (cf., the letter to the editor by Malhi et al.), a cross-sectional study design such as ours cannot determine how antidepressant medication affects brain structure. Interventional studies comparing patients pre- and post-treatment are required to establish how antidepressants affect brain structure.

Fried and Kievit rightly note that hippocampal volume reduction in the MDD group and its subgroups is known to be small (Cohen’s d between 0.14 and 0.21) and not specific to MDD. As our colleagues found in the ENIGMA Schizophrenia Working Group, larger effects are observed in schizophrenia, motivating cross-disorder comparisons across ENIGMA eventually. However, our finding is robust: the hippocampus was consistently smaller, on average, across a large number of samples encompassing the broad heterogeneity of MDD (p2 scores showed low heterogeneity of findings across studies). Smaller hippocampal volume has been associated with executive function impairments, learning and memory deficits and poorer treatment response in MDD; so the hippocampal volume reduction is important despite its small effect size. Establishing the degree of hippocampal volume difference in MDD, and its modulators, with this precision is crucial, as the disorder affects billions of people worldwide.

Indeed we did not estimate any form of classification accuracy. Researchers in the field of neuroimaging already realize that no single univariate data point differentiates MDD patients from controls. If classification were the goal, one could include other subcortical regions whose effects do not reach the significance threshold, but within a multivariate analysis could boost classification accuracy. Moreover, cortical regions or other imaging measures could be included. Ultimately, consortia such as ENIGMA may discover multivariate patterns predictive of diagnosis, but progress is unlikely without first publishing studies of measures that are easier to harmonize. It is widely known that findings based on group-level (univariate and mass-univariate) approaches may not offer sufficient predictive value for individual patients within a multivariate classification approach. Measures from future ENIGMA MDD projects studying cortical thickness, surface area, shape, hippocampal subfields, diffusion tensor imaging or functional measures may help multivariate prediction methods, eventually. Moreover, the harmonization of processing, statistics and quality control protocols across ENIGMA disease working groups will eventually allow classification across different psychiatric disorders.

Fried and Kievit discuss some alternative mechanisms that may drive hippocampal volume reduction in MDD. In our original paper, we did not claim ‘that depression causes structural changes’
(cf. letter to the editor by Fried and Kievit). In fact, not only patients with recurrent episodes, but also the group with early age of onset (consisting of almost 50% of first-episode patients) showed smaller hippocampal volumes; so structural changes are not merely a consequence of depression. We speculated that hippocampal volume reductions may be promoted by a chronic hyperactivity of the hypothalamic–pituitary–adrenal axis via remodelling and downregulation of growth factors including brain-derived neurotrophic factor, associated with (chronic) stress.10 Stressors include multiple episodes of depression, early-life stress and a family history of depression, which are all linked to early-onset depression,11–13 higher risk for recurrent depression,14–16 an overactive hypothalamic–pituitary–adrenal axis17,18 and smaller hippocampal volume.19 As we stated in our article, smaller hippocampal volume may even be a risk factor for depression: ‘morphological hippocampal alterations may represent risk markers for depression, recurrence and chronicity’ and ‘Clearly, there is a continued need for longitudinal studies tracking hippocampal volume changes over the disease course, to further elucidate whether hippocampal abnormalities result from prolonged duration of chronic stress (i.e. ‘scarring’), represent a vulnerability factor for MDD, or both’, which agrees with Fried and Kievit.

CONSORTIUM MEMBERS
The members of the ENIGMA-Major Depressive Disorder Working Group consortium are listed at http://enigma.ini.usc.edu/ongoing/enigma-mdd-working-group/.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGMENTS
The ENIGMA-Major Depressive Disorder working group gratefully acknowledges support from the NIH Big Data to Knowledge (BD2K) award (USA EB020403 to Paul Thompson).

L Schmaal1, DJ Veltman1, TGM van Erp2, PG Sämann3, T Frodl4,5, N Jahanshad6, E Loehr7, MW Vernooij3,8,9, WJ Niessen3,9,10,11, MA Ikram9,12, K Wittfeld13, HJ Grabe3,14,15, A Block14, K Hegenscheid16, D Hoehn3, M Czisch3, J Lagopoulos17, SN Hatton17,18, IB Hickie17, R Goya-Maldonado19, B Krämer17,18, O Gruber19, B Couvy-Duchesne20, O21,22, ME Rentería23, LT Strike20, MJ Wright20,21, GI de Zubicaray24, KL McMahon21,22, SE Medland25, AM McIntosh39,40, HC Whalley39, JE Sussmann39, BR Godlewksa41, FH Fischer42,43, BWJH Penninx1, PM Thompson5, DP Hibar3; for the ENIGMA-Major Depressive Disorder Working Group
1Department of Psychiatry and Neurosciences Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands;
2Department of Psychiatry and Human Behavior, University of California, Irvine, CA, USA;
3Max Planck Institute of Psychiatry, Neuroimaging Research Group, Munich, Germany;
4Department of Psychiatry and Psychotherapy, Otto von Guericke University of Magdeburg, Magdeburg, Germany;
5Department of Psychiatry, Trinity College, University of Dublin, Dublin, Ireland;
6Imaging Genetics Center, Department of Neurology, Keck School of Medicine, University of Southern California, Marina del Rey, CA, USA;
7Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA;
8Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands;
9Department of Radiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands;
10Department of Medical Informatics, Erasmus MC University Medical Center, Rotterdam, The Netherlands;
11Faculty of Applied Sciences, Delft University of Technology, Delft, The Netherlands;
12Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands;
13German Center for Neurodegenerative Diseases (DZNE), Rostock/Greifswald, Germany;
14Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany;
15Helios Hospital Stralsund, Stralsund, Germany;
16Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, Germany;
17Clinical Research Unit, Brain and Mind Centre, University of Sydney, Camperdown, NSW, Australia;
18Center for Translational Research in Systems Neuroscience and Psychiatry, Department of Psychiatry and Psychotherapy, University Medical Center (UMG), G"ottingen, Germany;
19Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University Hospital, Heidelberg, Germany;
20Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia;
21Center for Advanced Imaging, The University of Queensland, Brisbane, QLD, Australia;
22Queensland Institute of Medical Research Berghofer, Brisbane, QLD, Australia;
23Department of Genetic Epidemiology, Queensland Institute of Medical Research Berghofer, Brisbane, QLD, Australia;
24Faculty of Health, The Institute of Health and Biomedical Innovation, Queensland University of Technology (QUT), Brisbane, QLD, Australia;
25Department of Quantitative Genetics, Queensland Institute of Medical Research Berghofer, Brisbane, QLD, Australia;
26Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA;
27Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, ON, Canada;
28Imaging Research Centre, St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada;
29Department of Neuroscience, Neuroimaging Center, Groningen, The Netherlands;
30Department of Psychiatry, Leiden University Medical Center, Leiden University, Leiden, The Netherlands;
31Leiden Institute for Brain and Cognition, Leiden, The Netherlands;
32Division of Mind and Brain Research, Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Berlin, Germany;
33Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Freiburg, Germany;
34Psychiatric University Clinic, Basel, Switzerland;
35Department of Psychiatry, University of Bonn, Bonn, Germany;
36Department of Psychiatry and Psychotherapy, Agaplesion Diakoniklinikum, Rotenburg, Germany;
37Department of Psychiatry and Psychotherapy, Philipp-Universität Marburg, Marburg, Germany;
38Center for Integrative Psychiatry, University of Lübeck, Lübeck, Germany;
39Division of Psychiatry, University of Edinburgh, UK;
40Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, UK;
41Department of Psychiatry, Warneford Hospital, Oxford, UK;
42Department of Psychosomatic Medicine, Center for Internal Medicine and Dermatology, Charité Universitätsmedizin Berlin, Germany and
REFERENCES

1 Fried EI, Kievit RA. The volumes of subcortical regions in depressed and healthy individuals are strikingly similar: a reinterpretation of the results by Schmaal et al. Mol Psychiatry 2015; e-pub ahead of print 15 December 2015.


Letter to the Editor

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/