Childhood adversity impacts on brain subcortical structures relevant to depression

Thomas Frodl a, b, *, 1, Deborah Janowitz c, 1, Lianne Schmaal e, ab, ac, Leonardo Tozzi a, b, Henrik Dobrowolny a, Dan J. Stein b, Dick J. Veltman e, Katharina Wittfeld 1, Theo G.M. van Erp 1, Neda Jahanshad g, Andrea Block c, ad, Katrin Hegenscheid 1, Henry Völzke 1, Jim Lagopoulos k, ae, Sean N. Hatton k, Ian B. Hickie k, Eva Maria Frey 1, Angela Carballedo a, m, Samantha J. Brooksn, Daniella Vuleticn, Anne Uhlmannn, Ilya M. Veer o, Henrik Walter o, Knut Schnell P, Dominik Grotegerd q, Volker Arolt q, Harald Kugel r, Elisabeth Schramm s, t, Carsten Konrad h, v, Bartosz Zurowski w, Bernhard T. Baune x, Nic J.A. van der Wee z, Marie-Jose van Tol aa, Brenda W.J.H. Penninx e, Paul M. Thompson 8, Derrek P. Hibarg g, Udo Dannlowskiq, y, Hans J. Grabe c, d, h

* Department of Psychiatry and Psychotherapy, Otto von Guericke University of Magdeburg, Germany
1 Department of Psychiatry, University of Dublin, Trinity College, Dublin, Ireland
2 Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Germany
3 German Center for Neurodegenerative Diseases (DZNE), Rostock, Greifswald, Germany
4 Department of Psychiatry and Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
5 Department of Psychiatry and Human Behavior, University of California, Irvine, CA, USA
6 Imaging Genetics Center, Department of Neurology, Keck School of Medicine, University of Southern California, Marina del Rey, CA, USA
7 Helios Hospital Stralund, Germany
8 Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Germany
9 Institute for Community Medicine, University Medicine Greifswald, Germany
10 Brain and Mind Centre, University of Sydney, Camperdown, Australia
11 Department of Psychiatry, University of Regensburg, Regensburg, Germany
12 Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland
13 Department of Psychiatry and Mental Health, University of Cape Town, South Africa
14 Charité Universitätsmedizin Berlin, Department of Psychiatry and Psychotherapy, Division of Mind and Brain Research, Berlin, Germany
15 Department of General Psychiatry, University Hospital Heidelberg, Germany
16 Department of Psychiatry and Psychotherapy, University of Münster, Germany
17 Department of Clinical Radiology, University of Münster, Germany
18 Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Germany
19 Psychiatric University Clinic, Basel, Switzerland
20 Department of Psychiatry and Psychotherapy, Agapios Diakoniklinikum, Rotenburg, Germany
21 Department of Psychiatry and Psychotherapy, Philippus-University Marburg, Germany
22 Center for Integrative Psychiatry, University of Lübeck, Lübeck, Germany
23 Discipline of Psychiatry, School of Medicine, University of Adelaide, SA 5005 Adelaide, Australia
24 Department of Psychiatry, University of Marburg, Germany
25 Department of Psychiatry, Leiden Institute for Brain and Cognition and Leiden Center for Translational Neuroscience, Leiden, The Netherlands
26 Department of Neuroscience, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
27 Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Australia
28 Sunshine Coast Mind and Neuroscience — Thompson Institute, University of The Sunshine Coast, QLD, Australia

* Corresponding author. Department of Psychiatry and Psychotherapy, Otto von Guericke University of Magdeburg, Germany.
E-mail address: Thomas.Frodl@med.ovgu.de (T. Frodl).
1 Both authors contributed equally.

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ABSTRACT

Childhood adversity plays an important role for development of major depressive disorder (MDD). There are differences in subcortical brain structures between patients with MDD and healthy controls, but the specific impact of childhood adversity on such structures in MDD remains unclear. Thus, aim of the present study was to investigate whether childhood adversity is associated with subcortical volumes and how it interacts with a diagnosis of MDD and sex. Within the ENIGMA-MDD network, nine university partner sites, which assessed childhood adversity and magnetic resonance imaging in patients with MDD and controls, took part in the current joint mega-analysis. In this largest effort world-wide to identify subcortical brain structure differences related to childhood adversity, 3036 participants were analyzed for subcortical brain volumes using FreeSurfer. A significant interaction was evident between childhood adversity, MDD diagnosis, sex, and region. Increased exposure to childhood adversity was associated with smaller caudate volumes in females independent of MDD. All subcategories of childhood adversity were negatively associated with caudate volumes in females - in particular emotional neglect and physical neglect (independently from age, ICV, imaging site and MDD diagnosis). There was no interaction effect between childhood adversity and MDD diagnosis on subcortical brain volumes. Childhood adversity is one of the contributors to brain structural abnormalities. It is associated with subcortical brain abnormalities that are relevant to psychiatric disorders such as depression.

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1. Introduction

Exposure to neglect and abuse in childhood – here briefly called childhood adversity - plays a crucial role in the development of major depressive disorder (MDD) (Frodl and O’Kean, 2013; Nusslock and Miller, 2016; Trotta et al., 2015). The relationship between childhood adversity and depression is mediated by sex, genetic risk, parental psychopathology, stressful life events during adulthood, and social support (Pagliaccio and Barch, 2015). Childhood adversity as well as the above mentioned factors may contribute to treatment resistance in MDD (Pagliaccio and Barch, 2015; Tunnard et al., 2014). As such, understanding the role of childhood adversity is important to improve assessment and treatment of depression (Teicher and Samson, 2013).

As described in our recent review, childhood adversity also was suggested as a key factor associated with structural brain abnormalities in subjects who developed psychiatric disorders (Frodl and O’Kean, 2013). It has been demonstrated that childhood adversity and MDD are associated with structural brain changes (Dannlowski et al., 2012; Frodl et al., 2010; Gerritsen et al., 2015). Experimentally, exposure to severe chronic stressors may induce glucocorticoid-mediated pyramidal dendrite retraction in the hippocampus, and changes in dendrite arborization in the prefrontal cortex (PFC) in vulnerable individuals (Kole et al., 2004; Magarinos et al., 1996; Wellman, 2001; Woolley et al., 1990). Moreover, stress or cortisol administration may lead to neuronal atrophy in the hippocampus and to states that share features with depression (Duman, 2002).

Patients with MDD showed consistently reduced subcortical brain volumes compared to healthy controls. A recent meta-analysis, by the ENIGMA-MDD consortium, investigated subcortical volume differences between 1728 MDD patients and 7199 controls from 15 research samples worldwide. On average, the hippocampus was significantly smaller in patients compared with controls, especially in patients with early-onset or recurrent MDD (Schmaal et al., 2015). Interestingly, sample characteristics such as mean age, the proportion of antidepressant users or proportion of remitted patients and methodological characteristics did not significantly moderate these alterations of brain volumes in MDD (Schmaal et al., 2015). Previous meta-analyses also confirmed smaller hippocampal volumes (Arnone et al., 2016; Campbell et al., 2004; McKinnon et al., 2009; Videbech and Ravnlilke, 2004) and structural alterations in the hippocampus, basal ganglia, orbitofrontal cortex and the rectal gyrus (Kempton et al., 2011) in patients with MDD compared to healthy controls.

Our primary aim was to identify associations of childhood adversity and a life-time diagnosis of MDD on subcortical volumes in a large multi-center sample. Moreover, an additional goal was to assess subcortical volumes using a standardized segmentation protocol to avoid effects due to different processing and analysis techniques. Furthermore, a third aim was to consider current antidepressant treatment and to test whether this might affect subcortical volumes in the framework of the childhood adversity analyses. Using this approach, also prior methodological limitations including age and sex influences were addressed. We initiated the childhood adversity subproject within the Major Depressive Disorder (MDD) Working Group of the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium (http://enigma.ini.usc.edu/ongoing/enigma-mdd-working-group/). Nine partners in this network had addressed childhood adversity in their studies using the childhood trauma questionnaire (CTQ). Their subcortical volume measures were included in our ENIGMA-MDD analysis of childhood adversity.

2. Materials and methods

2.1. Samples

At the time when this subproject was proposed, the ENIGMA-MDD Childhood Adversity Working Subgroup included nine international samples with neuroimaging, childhood adversity, and clinical data from MDD patients and healthy controls. All of the nine research groups agreed to participate in the subgroup analysis. For future projects, new research groups around the world are encouraged to join the ongoing ENIGMA work, to increase sample size and thereby increase statistical power and evaluate the generalizability of our results on MDD. Detailed demographics for each sample are found in Table S1 and clinical characteristics in Table S2. Exclusion criteria for study enrollment in each sample are given in Table S3. In total, we analyzed data from 3036 people, including 958 MDD patients and 2078 healthy controls. All participating sites obtained approval from local institutional review boards and ethics committees. All study participants provided written, informed consent at their local institution.
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