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# Childhood adversity impacts on brain subcortical structures relevant to depression

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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.



## 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'Keane, 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'Keane, 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 Ravnkilde, 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 continuously 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.