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Alterations of brain volumes in women with early life maltreatment and their associations with oxytocin

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ABSTRACT

Early life maltreatment (ELM) is associated with different neurobiological alterations. Lower oxytocin and altered grey matter volumes (GMV) in brain regions associated with the central oxytocin system, such as the hypothalamus, amygdala, and nucleus accumbens, have been reported in women with ELM. However, the association between peripheral oxytocin and brain morphometry in women with ELM has not been studied yet. We therefore collected blood samples from 33 women with and 25 women without ELM, all without current mental disorders to measure and compare oxytocin levels between the two groups. Furthermore, T1-weighted high-resolution structural magnetic resonance brain images of a subsample of these women were collected, analyzed with voxel-based morphometry, compared between the two groups, and correlated with oxytocin levels. There were no differences in oxytocin levels between the groups. However, oxytocin levels were associated with different brain regions in women with ELM compared with control women without ELM: A positive association between GMV in the nucleus accumbens and oxytocin was specific for control women but not for women with ELM. For the hypothalamus, there was a positive association between GMV and oxytocin in control women. However, the same region was negatively associated with oxytocin in women with ELM and it showed larger GMV compared to control women without ELM. For the amygdala, a negative association between GMV and oxytocin was specific for women with ELM. Results are discussed with regard to previous research on endocrine and neurostructural alterations in individuals with ELM.

1. Introduction

Early life maltreatment (ELM) which is estimated to occur in up to 30% of children worldwide (Butchart and Mikton, 2014) is known to cause alterations in grey matter volume (GMV) in specific brain regions. These include the hippocampus, nucleus caudatus, amygdala and hypothalamus. A volume reduction in the hippocampus is one of the most commonly reported ELM-related GMV alterations (Dannlowski et al., 2012; Teicher et al., 2012). The nucleus caudatus is also reported to be smaller in individuals with ELM (Dannlowski et al., 2012; Frodl and O'Keane, 2013), although one study did not find any differences (Pechtel et al., 2014). For the amygdala, findings differ between studies with some reporting smaller GMV of the amygdala in individuals with ELM (Edmiston et al., 2011; Woon and Hedges, 2008), while others found enlarged amygdala volumes (Clark et al., 2012; Pechtel et al., 2014) or no differences in GMV between individuals with ELM and controls without ELM (Gatt et al., 2010; McCrory et al., 2011). For the hypothalamus, an association between ELM and larger GMV has been reported in patients with Borderline Personality Disorder, who often report severe ELM (Kuhlmann et al., 2013). Up to date, these morphometric differences have been associated with alterations in the activity of the hypothalamic-pituitary-adrenal (HPA) axis (McCrory et al., 2011; Pruessner et al., 2010). Additionally, besides severe and lasting alterations in the HPA-stress system, alterations in other endocrine systems, such as the oxytonergic system, have been discussed as a consequence of ELM (Teicher et al., 2002).

There are only a few studies comparing endogenous oxytocin levels in adults exposed to ELM to controls without ELM. Heim et al. (2009) found a reduced concentration of oxytocin in the cerebrospinal fluid (CSF) of healthy women with ELM compared with healthy controls without ELM. In addition, CSF oxytocin concentrations were negatively associated with the severity of ELM measured with the Childhood

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Trauma Questionnaire (CTQ) (Heim et al., 2009). Similar findings have been shown for plasma oxytocin (Bertsch et al., 2013; Opacka-Juffry and Mohiyeddini, 2012).

Oxytocin is commonly known as the “love hormone” due to its role in social interaction and mother-child bonding (Feldman, 2015). Some studies have shown, that mothers with ELM are less sensitive when interacting with their child (Fuchs et al., 2015; Mielke et al., 2016), which could be related to differences in the oxytonergic system as oxytocin is crucially involved in maternal behavior and sensitivity (Kim P. et al., 2016). Oxytocin also seems to be involved in central reward processing (Groppe et al., 2013). Moreover, animal studies have shown that oxytocin specifically excites neurons in the nucleus accumbens – a region crucially involved in reward processing (Moaddab et al., 2015). Interestingly, ELM has also been associated with blunted reward responses: For example, individuals with ELM rated reward cues less positive and showed decreased activity in neuronal reward circuits in response to reward cues than healthy controls without ELM (Dillon et al., 2009). These findings raise the question whether the reported deficits in reward processing in adults with ELM might be related to lower oxytocin and/or a lower sensitivity for oxytocin in brain structures involved in reward processing, such as the nucleus accumbens in individuals with ELM. This suggestion is further supported by previous reviews indicating a link between ELM, alterations in the oxytonergic system and addiction, which is ultimately connected to abnormal reward processing (Buisman-Pijlman et al., 2014; Kim S. et al., 2016).

Oxytocin is produced in the magnocellular and parvocellular neurons of the hypothalamus. Axons of the magnocellular neurons project to the neurohypophysis, which releases oxytocin into the peripheral blood stream. In contrast, axons of the parvocellular neurons terminate in other areas of the central nervous system, such as the amygdala, hippocampus and hypothalamic nuclei, and are involved in the release of oxytocin into the CSF (Buijs et al., 1985; Sawchenko and Swanson, 1984). Oxytocin receptors have been found in several brain regions, such as the hypothalamus, amygdala, nucleus caudatus, hippocampus and nucleus accumbens (for review: Gimpl and Fahrenholz, 2001). Thus, investigating associations between peripheral oxytocin concentrations and GMV of specific brain regions that are both, associated with the central oxytonergic system and are known to be altered in individuals with a history of ELM, may contribute to understanding the relationship between neurostructural changes and the oxytonergic system in the sequelae of ELM. However, to our knowledge there has been no study up to date investigating morphometric differences related to oxytocin and ELM.

In the current study, we compared GMV and peripheral oxytocin concentrations as well as the association between them in women with and without a history of ELM. In a hypothesis-driven region-of-interest approach, GMV in regions previously reported in studies on morphometric or functional differences in individuals with ELM as well as in studies on the central oxytonergic system were correlated with plasma oxytocin concentrations, which were measured along with progesterone and estradiol to control for the menstrual cycle.

We hypothesized reduced plasma oxytocin in women with ELM compared with control women without ELM and expected to find differences in the correlation of oxytocin and GMV between the groups (ELM vs. control) in the following regions: hippocampus, nucleus caudatus, hypothalamus, amygdala, and nucleus accumbens.

2. Methods and materials

2.1. Participants

39 women with experiences of physical or sexual abuse before the age of 18 years (early life maltreatment; ELM) and 27 women without any ELM (control group; CON) took part in the study. The data of six women who reported a current mental disorder and the data of two women who were statistical outliers and on hormonal medication ($N = 1$ progesterone, $N = 1$ contraceptive coil) were excluded from the analysis. Therefore, the final data set of the current study included 33 women with ELM ($M_{age} = 38.9$, $SD = 6.1$, range: 26–50 years) and 25 women without ELM (control; $M_{age} = 39.2$, $SD = 4.8$, range: 27–47 years). In addition, a smaller subsample of these women consisting of 21 women with ELM and 20 women without ELM underwent magnetic resonance imaging (MRI). Due to poor data quality of the MRI as indicated by extreme values and artifacts in the VBM8 “check data quality” module, two data sets had to be excluded from the analysis. Therefore, the final data set for the MRI study included 19 women with ELM ($M_{age} = 38.2$, $SD = 7.0$, range: 26–50 years) and 20 women without ELM (control; $M_{age} = 38.8$, $SD = 5.1$, range: 27–47 years).

The current study was part of a large multicenter project in which effects of ELM on mother-child interaction are investigated (Understanding and Breaking the Intergenerational Cycle of Abuse; www.ubica.de). Thus, samples across UBICA studies overlap in participants. Women were recruited via advertisements in newspapers and Internet, via flyers in gynecologist and pediatric practices, as well as letters sent to participants of a former population-based study on mother-child interaction (Möhler et al., 2009) and to randomly selected samples of local inhabitants.

General exclusion criteria comprised: Any current axis I diagnosis including alcohol or drug dependence or abuse in the last six months, severe physical impairments, or dementia as well as any other neurological disorders. For the MRI subsample, an additional exclusion criterion was any contraindications for MRI measurements (e.g. implants or pregnancy). An additional exclusion criterion for the control group was any lifetime axis I diagnosis.

The study was performed in accordance to the ethical standards laid out by the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty of the University of Heidelberg. All participants gave written consent before their participation after the study procedures were fully explained to them and received a monetary compensation.

2.2. Measures

The Childhood Experience of Care and Abuse-Interview (CECA, Bifulco et al., 1994), which is regarded as the gold standard for retrospective evaluation of childhood maltreatment (Thabrew et al., 2012), was used to assess ELM. Axis I and II comorbidities were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, First et al., 2002) and a shorter Version of the International Personality Disorder Examination assessing borderline, avoidant and antisocial personality disorder (IPDE, Bronisch and Mombour, 1994).

2.2.1. Endocrine data

Two blood samples were drawn with a butterfly needle for hormonal assessment, which included oxytocin, progesterone, and estradiol. The appointment for the blood withdrawal was always set between 2 and 4:30 pm during breaks of interviews and with at least 1 h distance to any interaction with the child, who was part of the larger project. The children participating in the larger project were aged five to twelve years. In addition, participants completed a questionnaire on factors that could possibly influence plasma oxytocin such as hormone disorders, medications, contraception, sexual intercourse, and smoking. Five of the women did not complete the hormonal questionnaire.

For oxytocin analysis, 5 ml of blood was collected in EDTA vacutainer tubes, which were immediately cooled. The samples were then centrifuged at 4 °C at 4000 rpm for 5 min, 1 ml plasma was drawn and stored at −80 °C till the completion of the study, when it was send to the laboratory “RIAgnosis”, headed by R. Landgraf, on dry ice. Samples were analyzed using a sensitive radioimmunoassay (Landgraf et al., 1995; Landgraf and Neumann, 2004). The detection limit of each assay was in the 0.1 pg/sample range. There was no significant cross-reactivity with other related neuropeptides and the intra-assay variability