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Research report

The interaction of corticotropin-releasing hormone receptor gene and early life stress on emotional empathy

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ABSTRACT

Early life stress (ELS) is associated with increased vulnerability for depression, changes to the corticotropin-releasing hormone (CRH) system and structural and functional changes in hippocampus. Single nucleotide polymorphisms in the CRH receptor 1 (CRHR1) gene interact with ELS to predict depression, cognitive functions and hippocampal activity. Social cognition has been related to hippocampal function and might be crucial for maintaining mental health. However, the interaction of CRHR1 gene variation and ELS on social cognition has not been investigated yet. We assessed social cognition in 502 healthy subjects to test effects of ELS and the CRHR1 gene. Participants were genotyped for rs110402 and rs242924. ELS was assessed by Childhood Trauma Questionnaire, social cognition was measured via Multifaceted Empathy Test and Empathy Quotient. Severity of ELS was associated with decreased emotional, but not cognitive empathy. Subjects with the common homozygous GG GG genotype showed decreased implicit emotional empathy after ELS exposure regardless of its severity. The results reveal that specific CRHR1 polymorphisms moderate the effect of ELS on emotional empathy. Exposure to ELS in combination with a vulnerable genotype results in impaired emotional empathy in adulthood, which might represent an early marker of increased vulnerability after ELS.

1. Background

Early life stress (ELS) such as emotional or physical neglect and abuse considerably increase the risk of developing psychiatric disorders in later life [1]. Converging evidence from animal models and human studies indicates that ELS not only causes persisting changes to the stress system, i.e., the corticotropin-releasing hormone (CRH) system and the hypothalamic-pituitary-adrenal (HPA) axis [2], but also induces structural, functional, and epigenetic changes in brain regions involved in cognitive and emotional processing. While the pathogenic mechanisms of these alterations are still unclear, it has been suggested that early adverse experiences constantly exceeding a child's coping resources lead to persistent phases of stress and eventually result in a sensitization of the stress system [3,4]. Secondary changes in prefrontal and limbic brain regions such as reduced volume, altered neural activation patterns and decreased functional connectivity [5–7] might be crucial for subsequent impairments not only in cognitive functions, but also in social cognition [2,8,9].

Social cognition deficits are an important factor in the development, progress and treatment of psychiatric disorders such as depression [10] and schizophrenia [11]. It has been proposed that these deficits can be particularly relevant to social impairment since abilities such as emotional and cognitive empathy and theory of mind (ToM) are essential for effective and adaptive interpersonal functioning and communication [12,10]. Emotional empathy refers to the degree to which an observer experiences the affective state of another person [13], while cognitive empathy is related to inferring emotions, taking another persons' perspective and understanding another person's mental state, without necessarily being in an affective state [14,15]. Cognitive empathy therefore overlaps with the constructs of ToM and mentalizing [16,15]. Recent neurobiological studies have suggested distinct brain circuits to engage in cognitive and emotional empathic processes [17,18]. Although the development of social cognition is thought to take place during childhood, few studies have investigated associations between the respective functions and childhood adversity in humans. Emotional empathy usually evolves from basic processes of emotional contagion, i.e., the automatic adoption of a similar affective state between a child and its caregiver [19]. In the course of develop-

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ment, experiences of emotional arousal are gradually decreased by abilities of cognitive appraisal that continuously increase with age, resulting in growing capacities of mentalizing and perspective taking, which form the basis of cognitive empathy [20]. Early life stress may however hinder the development of mentalizing because of negative internal working models [21,22].

Previous studies have shown that effects of ELS are modulated by genetic factors. Particularly, single nucleotide polymorphisms (SNPs) in the CRH receptor 1 (CRHR1) gene interact with ELS to predict behavioral and neuroendocrine evidence of stress vulnerability or resilience. CRH1 receptors are abundant in areas involved in emotion processing, emotion regulation and stress response, including the prefrontal cortex, amygdala, and hippocampus [23]. The hippocampus is particularly relevant for working-memory maintenance [24], the formation and retrieval of long-term memories and declarative memory use [25]. The hallmark properties of the hippocampal declarative memory system (e.g., representational flexibility, relational binding, on-line processing capacity) might also be crucial for social cognition [26]. Accordingly, patients with hippocampal damage show lower cognitive and emotional empathy [27] and empathy, in turn, can be increased by stimulating mineralocorticoid receptors, which are highly expressed in the hippocampus [28]. Along this line, recent animal data showed that CRHR1 SNPs influence metabolic activity in the anterior hippocampus [29]. In humans, the rs110402 A and rs242924 T alleles of the CRHR1 gene seem to have a protective effect against major depressive disorder (MDD) in individuals exposed to moderate and severe ELS [30,31]. Accordingly, in healthy subjects with GG genotype on both SNPs an ELS x CRHR1 genotype interaction is reflected in an elevated cortisol response to the dexamethasone/corticotropin-releasing hormone test (DEX/CRH test) [32], impaired working memory performance [33] and lesser BOLD- responses in the medial temporal lobe/hippocampus [34]. The mechanism by which rs110402 and rs242924 affect the function of CRHR1 is presently unknown, however, variations of these polymorphisms may affect the regulation of CRHR1 receptors, resulting in increased stress vulnerability, altered neural activity and consequently impaired hippocampus dependent social cognition. Since depression has been associated with deficits in social cognition such as emotional and cognitive empathy and ToM [35,36,10], the question arises whether there are also interacting effects of genetic markers and ELS on these functions independent of depression. Social cognition plays a significant role in successful interpersonal functioning and might be crucial for maintaining mental health. Subtle deficits in healthy subjects at risk might therefore develop prior to psychopathological symptoms. We here investigated different facets of social cognition in healthy subjects to test the hypothesis that these may be influenced by functional differences in CRHR1 and thereby represent an early marker of increased vulnerability after exposure to ELS. Since the GG GG genotype has been associated with increased stress reactivity and depression vulnerability, we hypothesized that subjects with this genotype would also show stronger impairments in social cognition after ELS experience.

2. Methods

2.1. Subjects

All subjects were recruited from responses to advertising in local newspapers and mailing lists. The initial sample consisted of N = 1402. In a first step, we excluded all participants that did not meet the following inclusion criteria: age between 18 and 90 years, absence of present and past diagnosis of psychiatric or neurologic disorder, absence of major or unstable general medical conditions, and ability to participate in study procedures. Absence of present and past diagnosis of psychiatric disorders was measured using the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID). Absence of present or past neurologic disorder and major or unstable medical conditions were measured via self-report (e.g. “Have you ever been diagnosed with a neurologic disorder?” or “Do you currently take any prescribed medication, e.g. aspirin, insulin, antibiotics, thyroid hormones, and so on?”). An additional item asking about difficulties regarding sleep (both falling asleep and sleeping through) was included due to the high prevalence of disturbed sleep in individuals with any psychiatric or somatic disorder. Subjects answering “yes” to any of the screening questions of the SCID or the additional questions regarding neurologic disorders or major/unstable medical conditions were excluded from the study. Furthermore, the ability to participate in study procedures was measured using the WST with an IQ < 90 leading to exclusion. After applying these criteria, the final sample consisted of N = 541.

2.2. Ethical standards

The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of Charité Universitaetsmedizin Berlin. All subjects gave written informed consent before screening and were reimbursed for participation.

2.3. Psychological measures

Intelligence was assessed using the WST [37], which is functionally equivalent to the widely used National Adult Reading Test (NART; [38]. History of ELS experience was assessed using the Childhood Trauma Questionnaire (CTQ; [39] consisting of 28 items that are assigned to the following subscales: emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse. Subscale scores range from 5 to 25 with high scores indicating a strong exposure to early life stressors. We classified ELS exposure into four categories of severity (none, low, moderate, and severe) independent of type of abuse. Participants with a CTQ total score exceeding the 75th percentile’s score of the sample were assigned to the “severe” category. The same procedure was applied to assign participants to the “moderate” (≥50th percentile), “low” (≥25th percentile) and “none” (< 25th percentile) category [33]. Emotion regulation strategies were measured using the 10-item Emotion Regulation Questionnaire (ERQ; [40] with the subscales reappraisal and expressive suppression. Reappraisal is considered a more effective emotion regulation strategy than suppression [40].

2.4. Empathy measures

The Multifaceted Empathy Test (MET; [41] is an objective tool to measure cognitive empathy (CE), explicit emotional empathy (EEE) and implicit emotional empathy (IEE). It comprises 40 photographs of people in emotionally charged positive or negative situations. Pictures convey information on emotional mental states via facial expression, body language and context. To measure CE, subjects are asked to infer the mental state of the person in the photograph and choose which of four words provided along with the picture describes best what the person is feeling. Explicit emotional empathy (EEE) is assessed by ratings of empathic concern (‘How concerned are you for this person?’) on a visual analog scale from 1 to 9 (1 = not concerned to 9 = very concerned) while viewing the photograph. Implicit emotional empathy (IEE) is measured by arousal ratings (‘How calm/aroused does this picture make you feel?’, 1 = very calm to 9 = very aroused). The MET is implemented in Presentation (Version 14.1, Neurobehavioral Systems, Albany, CA, USA).

The Empathy Quotient (EQ; [14] questionnaire is a more subjective measure of empathy. The EQ assesses empathy on three different dimensions: cognitive empathy, emotional reactivity and social skills [42]. Cognitive empathy addresses the ability to understand affective states in other individuals, whereas emotional reactivity refers to the tendency to experience emotional reactions in response to mental states