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Evidence of an *IFN*-γ by early life stress interaction in the regulation of amygdala reactivity to emotional stimuli

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ABSTRACT

Introduction: Since numerous studies have found that exposure to early life stress leads to increased peripheral inflammation and psychiatric disease, it is thought that peripheral immune activation precedes and possibly mediates the onset of stress-associated psychiatric disease. Despite early studies, IFNγ has received little attention relative to other inflammatory cytokines in the context of the pathophysiology of affective disorders. Neuroimaging endophenotypes have emerged recently as a promising means of elucidating these types of complex relationships including the modeling of the interaction between environmental factors and genetic predisposition. Here we investigate the GxE relationship between early-life stress and genetic variants of IFNγ on emotion processing.
Methods: To investigate the impact of the relationship between genetic variants of IFNγ (rs1861494, rs2069718, rs2430561) and early life stress on emotion processing, a sample of healthy adults ($n = 409$) undergoing an emotional faces paradigm in an fMRI study were genotyped and analysed. Information on early life stress was obtained via Childhood Trauma Questionnaire (CTQ).
Results: A positive association between early life stress and amygdala reactivity was found. Specifically, the main effect of genotype of rs1861494 on amygdala reactivity indicates a higher neural response in C allele carriers compared to T homozygotes, while we did not find main effects of rs2069718 and rs2430561. Importantly, interaction analyses revealed a specific interaction between IFNγ genotype (rs1861494) and early life stress affecting amygdala reactivity to emotional faces, resulting from a positive association between CTQ scores and amygdala reactivity in C allele carriers while this association was absent in T homozygotes.
Conclusions: Our findings indicate that firstly the genetic variant of IFNγ (rs1861494) is involved with the regulation of amygdala reactivity to emotional stimuli and secondly, that this genetic variant moderates effects of early life stress on emotion processing. These findings reiterate the importance that inflammatory genes play in the interaction with early life stress and the regulation of emotion processing.

1. Introduction

Childhood maltreatment is highly prevalent, affecting between 30% and 40% of the adult population in western countries (Scher et al., 2004). Extensive research has shown that childhood maltreatment and traumatic life events constitute major risk factors for multiple psychiatric disorders including affective disorders and post traumatic stress disorders (Caspi and Moffitt, 2006). Importantly, research has also shown that common genetic variation is capable of moderating the effects of early life stress, which can ulti-

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mately influence an individual's susceptibility to the development of psychiatric disease later in life. A particularly prominent example of this phenomenon concerns the moderation of early life stress effects by the serotonin transporter (*SLC6A4*) within the context of major depressive disorder (MDD) and other affective disorders (Caspi et al., 2003).

When investigating affective disorders and childhood maltreatment, inflammatory genes constitute particularly promising candidates for gene by environment effects due to the association of inflammatory processes with both depression and childhood maltreatment (Baune et al., 2012a,b). Indeed, research over the last decade or so has shown that exposure to early life stress can have significant and long lasting effects on peripheral inflammation in both animals and humans. For example, a recent animal study found evidence of a perturbed immune system in 4-month old rhesus macaques that had been reared under adverse social conditions, manifesting as enhanced expression of inflammatory genes in basal leukocytes (Cole et al., 2012).

In humans, a recent study of children reported an increase in both the relative and absolute numbers of activated T cells (CD4 + helper and CD8 + cytotoxic) in maltreated children compared to healthy control children (Bielas et al., 2012). Likewise, a large life-course study revealed that individuals maltreated as children exhibited increased serum levels of C-reactive protein (CRP) 20 years later as adults—an effect that was not only independent of additional stressors during adulthood but also particularly pronounced in individuals who were diagnosed as being depressed at the time of CRP assessment (Danese et al., 2007, 2008). Furthermore, in a more recent retrospective study using a sample of healthy adults, it was found that high levels of early life trauma were associated with increased serum levels of interleukin 6 (IL-6), IL-1β, and TNFα (Hartwell et al., 2013). For a more comprehensive accounting of this line of research we refer readers to (Coelho et al., 2014; Nusslock and Miller, 2015).

Thus, persistent low-grade peripheral inflammation has been widely hypothesized to precede the development of stress-related psychiatric disease (Känel et al., 2007; Wium-Andersen et al., 2013). Indeed, numerous recent studies have highlighted the immune system as an important factor in various stress-related psychiatric disorders including post-traumatic stress disorder (Wieck et al., 2014) and MDD (Dowlati et al., 2010). However, the precise mechanisms in the central nervous system (CNS) that might mediate this apparent relationship between stress, peripheral inflammation, and psychiatric disease are not yet clear. Nevertheless, a primary candidate region that may play a central role here is the amygdala, which is widely regarded as being (i) a neurobiological substrate for stress and fear, (ii) a hub for emotion processing circuits (Davis and Whalen, 2001), and (iii) involved in the pathogenesis of MDD (Dannlowski et al., 2007; Phillips et al., 2003a,b).

Accordingly, imaging genetics studies utilising functional magnetic resonance imaging (fMRI) have shown that numerous affective disorder risk genes such as the serotonin transporter (*SLC6A4*) influence amygdala reactivity to emotional stimuli (Dannlowski et al., 2013; Grotegerd et al., 2014; Hall et al., 2014; Hariri et al., 2002; Loth et al., 2014; Stuhrmann et al., 2013). Furthermore, studies have also shown that early life stress appears to moderate the effects of *SLC6A4* and other genes on amygdala reactivity during emotion processing (Hsu et al., 2012; Williams et al., 2009). However, inflammatory and immune-related genes have not yet been widely studied within the context of amygdala reactivity, though there is precedence with one study revealing a significant association between *IL1β* genotype and amygdala responsiveness during emotion processing (Baune et al., 2010).

Other inflammatory markers such as Interferon γ (*IFNγ*), a type II interferon that plays diverse roles in both innate and adaptive immunity (Gough et al., 2008), have been related to clinical depression (Hernández et al., 2008; Pavón et al., 2006) and therefore constitute inflammatory gene candidates for a role in affective disorders. Indeed, behavioural phenotyping of *IFNγ*$^{-/-}$ mice has recently revealed an anxiogenic profile relative to wild type controls (Campos et al., 2014), whilst genetic variation in human *IFNγ* has been shown to modify risk to IFN-α-induced depression (Oxenkrug et al., 2011). Furthermore, *IFNγ* may interact with monoaminergic mechanisms underlying depression by promoting transcription of the indoleamine 2,3-dioxygenase (IDO) enzyme responsible for degrading tryptophan, which in turn can lead to serotonin depletion (Myint et al., 2013). Given that other monoaminergic-regulating genes such as the serotonin transporter (*SLC6A4*) have previously been heavily implicated in amygdala reactivity, *IFNγ* represents an additional attractive candidate.

Thus, in order to investigate a possible role for *IFNγ* in (i) regulating amygdala reactivity during emotion processing and (ii) moderating the effects of early life stress on amygdala reactivity, we have performed an imaging genetics study using the negative faces fMRI paradigm in a sample of healthy control adults (Dannlowski et al., 2012; Glahn et al., 2007). We selected the *IFN*γ SNPs rs1861494, rs2069718 and rs2430561 based on previous research showing they are not only functional but also significantly associated with various disease phenotypes like harm avoidance, tuberculosis, asthma or inflammatory bowel disease (Gonsky et al., 2014; Kumar and Ghosh, 2008; Lee et al., 2014; MacMurray et al., 2013). We hypothesized significant main effects of childhood maltreatment and *IFNγ* genotype, mirrored in elevated amygdala responsiveness in maltreated subjects as well as *IFNγ* risk allele carriers. Since environmental factors like childhood adversity are thought to trigger an underlying genetic vulnerability, we further expected an interaction of maltreatment and genotype showing elevated amygdala responsiveness only in risk allele carriers who experienced maltreatment during childhood. To the best of our knowledge, this is the first study investigating the association between early life stress and *IFNγ* genotype using fMRI.

2. Materials and methods

2.1. Participants

The complete dataset comprised 409 healthy volunteers. All subjects performed an emotional processing task whilst undergoing functional magnetic resonance imaging (fMRI). Data were collected in the context of a large ongoing study (Münster Neuroimaging Cohort) investigating the neurobiology of emotional processes. For all analyses, 5 subjects had to be excluded due to anatomical abnormalities, 2 additional subjects due to genotyping failures. Furthermore, 25 subjects had to be excluded due to excessive head movement (exclusion criterion >3° or >3 mm) leaving 377 subjects (mean age = 36.46, SD = 11.59 years; 218 women, 159 men) for all analyses.

All participants were recruited from the general population by public notices and newspaper announcements. Participants had no history of psychiatric illness, according to the SCID-Interview (Wittchen et al., 1997), no neurological conditions, they were free of psychotropic medication, had normal or corrected-to-normal vision, and had adequate knowledge of German and cognitive abilities [verbal IQ > 80; multiple-choice vocabulary intelligence test MWT-B (Lehrl, 2005)]. All subjects were carefully screened for ethnicity and fulfilled the criteria for caucasian ethnicity. The Childhood Trauma Questionnaire (CTQ) was administered before the MRI scan to assess maltreatment during childhood. The CTQ is a 25-item retrospective self-report questionnaire designed to assess five types of negative childhood experiences (Bernstein et al., 1994). The analysis of the whole sample yielded a mean CTQ