Full-length Article

Interaction between childhood maltreatment on immunogenetic risk in depression: Discovery and replication in clinical case-control samples

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ARTICLE INFO

ABSTRACT

Major depressive disorder (MDD) is a prevalent disorder with moderate heritability. Both MDD and interpersonal adversity, including childhood maltreatment, have been consistently associated with elevated inflammatory markers. We investigated interaction between exposure to childhood maltreatment and extensive genetic variation within the inflammation pathway (CRP, IL1b, IL-6, IL11, TNF, TNFR1, and TNFR2) in relation to depression diagnosis. The discovery RADIANT sample included 262 cases with recurrent DSM-IV/ICD-10 MDD, and 288 unaffected controls. The replication Münster cohort included 277 cases with DSM-IV MDD, and 316 unaffected controls. We identified twenty-five single nucleotide polymorphisms (SNPs) following multiple testing correction that interacted with childhood maltreatment to predict depression in the discovery cohort. Seven SNPs representing independent signals (rs1818879, rs1041981, rs4149576, rs616645, rs17882988, rs1061622, and rs3093077) were taken forward for replication. Meta-analyses of the two samples presented evidence for interaction with rs1818879 (IL6) (RD = 0.059, SE = 0.016, $p < 0.001$), with the replication Münster sample approaching statistical significance in analyses restricted to recurrent MDD and controls following correction for multiple testing ($q = 0.066$). The CRP locus (rs3093077) showed a similar level of evidence for interaction in the meta-analysis (RD = 0.092, SE = 0.029, $p = 0.002$), but less compelling evidence in the replication sample alone (recurrent MDD $q = 0.198$; all MDD $q = 0.126$). Here we present evidence suggestive of interaction with childhood maltreatment for novel loci in IL-6 (rs1818879) and CRP (rs3093077), increasing risk of depression. Replication is needed by independent groups, targeting these specific variants and interaction with childhood maltreatment on depression risk.

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1. Introduction

Major depressive disorder (MDD) is a highly prevalent disorder that represents a substantial economic as well as clinical burden (Mortality and Causes of Death, 2016). Heritability has been well-established and estimates from population-based studies range between 31 and 42% (Sullivan et al., 2000), with higher estimates of around 70% based on clinical or more severe cases (McGuffin et al., 2007). Many studies have attempted to identify genes associated with the disorder, however despite significant improvements in genotyping platforms, and large-scale increases in sample sizes, consistently replicated genetic variants remain elusive (Major Depressive Disorder Working Group of the Psychiatric Consortium et al., 2013). This may be for multiple

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reasons, including failure of most association studies to take into account the role of stress in the development of MDD (Cohen-Woods et al., 2013; Hosang et al., 2012; Thapar et al., 2012).

The first reported specific gene–environment (GE) interaction in MDD was with the serotonin transporter polymorphism, *5HTTLPR* and this has proven controversial (Uher and McGuffin, 2010). Recent meta-analyses indicate that the variable being measured (i.e. childhood stress vs. adult recent stress vs. medical illness) can impact findings, and highlight the need for replication (Karg et al., 2011), with the most recent failing to confirm a robust GE interaction with the *5HTTLPR* and life events (Culverhouse et al., 2017). GE studies face significant methodological challenges with recommendations for future candidate gene-environment studies including: reporting *all* statistical tests conducted for a novel candidate GE study, applying appropriate corrections for statistical testing, and replication (Duncan et al., 2014).

Elevated inflammation has been associated with both MDD and exposure to childhood traumatic events. Our study focuses on genes where proteins in the periphery have been associated with both MDD *and* childhood maltreatment (*CRP*, *IL-6*, *TNF*), genes where GE interactions have previously been reported that include childhood or adolescent stressors (*IL-1b*, *IL6*), or genes associated with anti-depressant response in caucasian MDD patients (*IL-11*); poor anti-depressant response has been reported in individuals with a history of childhood maltreatment (Williams et al., 2016). Elevations of many inflammatory proteins have been reported in patients with MDD including C-reactive protein (CRP), tumour necrosis factor (TNF), and interleukin-6 (IL-6) (Dowlati et al., 2010; Howren et al., 2009). Further, psychological stressors, including early-life maltreatment, have been consistently associated with elevated inflammatory markers (Baumeister et al., 2016; Danese et al., 2008; Fagundes et al., 2013; Kiecolt-Glaser et al., 2011), supported by animal models (Ganguly and Brenhouse, 2015).

Most studies to date have focused on protein analyses, and are limited in number; many more studies have genetic data available rather than serum or plasma, which is necessary for peripheral protein analyses. For this reason investigating genetic variants that have potential to impact gene- and protein-expression in the context of stressful life events is of value. There is also some evidence for interaction with genetic variants in IL-1b and IL-6 and chronic recent stress exposure predicting depressive scores in Australian youth (Tartter et al., 2015), and IL-1b predicting depressive symptoms in preschoolers exposed to childhood maltreatment (Ridout et al., 2014), and IL-11 with anti-depressant response (Uher et al., 2010). Other genes in the inflammation pathway have been associated with anti-depressant response (e.g. (Barnes et al., 2017; Wong et al., 2008), however as our populations are caucasian, for this study we restricted to genes identified in Caucasian populations. Thus overall there are sound reasons for exploring genes involved in inflammation in GE research, looking at depressive disorder onset, course and exposure to stressors including childhood maltreatment (Baumeister et al., 2016; Grosse et al., 2016; Kiecolt-Glaser et al., 2015; Miller and Raison, 2016).

In this paper we present the first investigation of the interaction between exposure to childhood stress and genetic variation, as captured by array, within the inflammation pathway. We focus on genes based on proteins and/or genes previously implicated in depression *and* with childhood maltreatment directly (*CRP*, *IL1b*, *IL-6*, *IL11*, and *TNF*), and indirectly (*TNFR1*, *and TNFR2*) (Camara et al., 2015; Danese et al., 2008; Goldsmith et al., 2016; Kiecolt-Glaser et al., 2015). This study aimed to address the recommendations by Duncan et al. (Duncan et al., 2014): including previously implicated GE loci (IL-6 (rs1800795) and IL-1b (rs16944)) (Tartter et al., 2015), by clearly reporting *all* statistical tests run,

robust multiple testing correction and reporting, and independent replication, extended to a meta-analysis.

2. Material and methods

2.1. Participants

2.1.1. Discovery sample

Individuals were drawn from the Radiant MDD cohort recruited in the United Kingdom from three sites (Birmingham, Cardiff, and London), described in detail previously (Fisher et al., 2013; Lewis et al., 2010). In brief, MDD cases experienced a minimum of two DSM-IV/ICD-10 depressive episodes of moderate to severe severity (First, 1994), ascertained by interview in person with the Schedules Clinical Assessments Neuropsychiatry (SCAN) (Wing et al., 1990); DNA was extracted from whole blood. Exclusion criteria were history of substance-related disorders, mania or hypomania, mood-incongruent psychosis, and a first or second-degree relative with bipolar or psychotic disorder. Control individuals were screened to ensure they had no psychiatric history themselves, or in their first-degree relatives. The Radiant sample assessed for childhood trauma consisted of 262 cases (190 females, and 72 males; mean age = 44.79 (±12.38)) and 288 controls (119 females, and 169 males; mean age = 47.49 (±9.24)); DNA was extracted from saliva. Controls were excluded if they had a personal or first-degree relative with a history of any psychiatric disorder. All participants were white European, with parents and grandparents of white European origin, and aged 18 years or over. This study was approved by the local University and NHS Ethics Committees at each site and conformed to the Declaration of Helsinki (1975). All participants provided written informed consent.

2.1.2. Replication sample

To replicate findings, we used an independent cohort, the Münster Depression cohort described in detail elsewhere (Power et al., 2016). In brief, MDD cases were identified to have experienced a minimum of one DSM-IV/ICD-10 depressive episode, ascertained using the Structured Clinical Interview for DSM Disorders (SCID) (Wing et al., 1990). Exclusion criteria were any neurologic abnormalities, substance-related disorders, psychotic symptoms, and/or a history of mania or hypomania. Control individuals were screened to have no psychiatric history themselves, also using the SCID. Exclusion criteria were scores $\geq$ 10 on the Beck Depression Inventory (BDI), any neurological abnormalities, history of seizures, head trauma or unconsciousness, intake of any psychotropic medication. The replication cohort included 277 adult cases (159 females, and 118 males; mean age = 40.27 (±11.89)) and 316 adult controls (177 females, and 139 males; mean age = 34.30 (±11.21)). Of the cases, 78% (n = 215) had experienced recurrent episodes of depression (125 females, and 90 males; mean age = 40.62 (±11.74)) which represented our primary replication sample as this most closely reflected our discovery sample. All participants were white European, with parents and grandparents of white European origin, and aged 18 years or over. DNA was extracted from whole blood for all participants. This study was approved by the local University Ethics Committees and conformed to the Declaration of Helsinki (1975). All participants provided written informed consent.

2.2. Measures

2.2.1. Childhood maltreatment

Self-reported emotional (EA), physical (PA), and sexual (SA) abuse, emotional (EN) and physical (PN) neglect during childhood