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Linking genetic variants of the mineralocorticoid receptor and negative memory bias: Interaction with prior life adversity

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Summary Substantial research has been conducted investigating the association between life adversity and genetic vulnerability for depression, but clear mechanistic links are rarely identified and investigation often focused on single genetic variants. Complex phenotypes like depression, however, are likely determined by multiple variants in interaction with environmental factors. As variations in the mineralocorticoid receptor gene (*NR3C2*) have been related to a higher risk for depression, we investigated whether *NR3C2* variance is related to negative memory bias, an established endophenotype for depression, in healthy participants. Furthermore, we explored the influence of life adversity on this association.

We used a set-based analysis to simultaneously test all measured variation in *NR3C2* for an association with negative memory bias in 483 participants and an interaction with life adversity. To further specify this interaction, we split the sample into low and high live adversity groups and repeated the analyses in both groups separately.

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NR3C2 variance was associated with negative memory bias, especially in the high life adversity group. Additionally, we identified a functional polymorphism (rs5534) related to negative memory bias and demonstrating a gene × life adversity interaction.

Variations in *NR3C2* are associated with negative memory bias and this relationship appears to be influenced by life adversity. As negative memory bias is implicated in the susceptibility to depression, our findings provide mechanistic support for the notion that variations in *NR3C2* — which could compromise the proper function of this receptor — are a risk factor for the development of mood disorders.

1. Introduction

Mood disorders such as major depressive disorder (MDD) result in increased mortality risk and an immense burden for patients, their families, and society. The lifetime prevalence for depression in the US amounts to 16.5% (Kessler et al., 2005) and further increase is predicted (Mathers and Loncar, 2006). Thus, the search for risk factors for mood disorders is of particular importance (Collins et al., 2011).

To find genetic risk factors for heterogeneous and complex diseases such as MDD, the endophenotype approach has gained increasing recognition (Franke et al., 2009; Hasler et al., 2004). Endophenotypes represent heritable phenotypic constructs which are presumably more directly affected by genetic variations than disease categories or symptoms (Gottesman and Gould, 2003). In contrast to overt clinical phenotypes, they appear less complex and more homogenous (Kendler and Neale, 2010). Endophenotypes can be conceptualized and measured on different levels. For example, they can be found at the level of cell functioning, variations of brain function or structure, or at the level of behavior (Franke et al., 2009). Several endophenotypes have been proposed for MDD, among them negative memory bias (Beck, 2008; Hasler et al., 2004; Mathews and MacLeod, 2005), i.e. the tendency of depressed individuals to show enhanced memory for sad and pessimistic information. This bias forms a main cognitive risk and maintenance factor for MDD (Mathews and MacLeod, 2005), persists after remission (Leppanen, 2006) and is heightened in individuals with vulnerability to develop MDD (Chan et al., 2007; van Oostrom et al., 2013). Negative memory bias has also been associated with comparable structural brain variations as frequently found in MDD, i.e. increased amygdala volume and decreased hippocampal volume (Gerritsen et al., 2011).

Using negative memory bias as endophenotype for MDD, we investigated specifically whether genetic variation in a receptor for the stress hormone cortisol, the mineralocorticoid receptor (MR), is associated with higher vulnerability for MDD. MRs act together with glucocorticoid receptors (GRs) regulating the hypothalamus–pituitary–adrenal (HPA) axis, one of the major stress systems, which is altered in MDD (Joels et al., 2008). In the nuclear version, MRs have such a high affinity for glucocorticoids that they appear to be substantially activated even at baseline levels of cortisol (Joels et al., 2008). For a long time, research therefore primarily focused on the lower-affinity GRs (Anacker et al., 2011). However, it was recently shown that MRs also locate in the membrane of neurons. There, MRs appear to have a lower affinity, so that they respond to stress-induced increases of cortisol and play a functional role in mediating stress effects (Joels et al., 2008). In terms of psychopathology, brain MR expression is reduced in depressed patients (Klok et al., 2011a) and administration of MR agonists accelerates pharmacotherapeutic effects in MDD (Otte et al., 2010). Variations of the MR gene (also called nuclear receptor subfamily 3, group C, member 2, *NR3C2*) are associated with loss-in-function or reduced expression and have been related to hopelessness and higher MDD rates in pre-menopausal women (Klok et al., 2011b), neuroticism (DeRijk et al., 2011), HPA axis responsiveness (van Leeuwen et al., 2011) and higher amygdala reactivity (Bogdan et al., 2012).

Beyond genome-wide approaches, most previous studies investigating the influence of a candidate gene on MDD used single-SNP-based testing. More complex phenotypes like MDD or memory bias, however, are likely determined by several SNPs which each contribute small effects (Franke et al., 2009). Single-SNP analyses could therefore not optimally explain the heritability of such traits (Schwender et al., 2011). A newer approach is testing the combined effect of all genetic variations within a set of SNPs in a single analysis (Bralten et al., 2011; Deelen et al., 2011). This approach needs less power than genome-wide testing and also allows unbiased identification of SNPs within this set that were not yet known to be associated with the phenotype of interest.

It has repeatedly been shown for psychiatric disorders including MDD that genes might not link directly to disease, but instead genes modulate the vulnerability for such diseases. Thus, gene × environment interaction seems to be the prototypical mechanism leading to the development of several mental disorders (Caspi et al., 2003; Karg and Sen, 2012). This idea is in contrast to a genetic main-effect hypothesis that assumes the direct causation of a disorder by a specific genetic variation. The gene × environment interaction framework postulates that environmental factors cause disorders to occur and that genetic variants influence vulnerability as well as resilience to these factors, leading to psychopathology in some individuals only.

It is well established that the experience of life adversity is an important environmental factor in the etiology of MDD (Klengel and Binder, 2013). For example, a study by Kendler and colleagues demonstrated a causal relationship between stressful life events and the onset of MDD (Kendler et al., 1999). Cortisol has been implicated in mediating this interaction between life adversity and MDD (Wilkinson and Goodyer, 2011). The MR may play a particular role in this interaction as it