A Common Mineralocorticoid Receptor Polymorphism (I180V) Interacts with Life Events in Relation to Perfectionism in Eating Disorders: A Pilot Study

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Abstract

The stress response is regulated by the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). When the balance between GR and MR signalling is disturbed, one’s capacity to cope with a stressful event is diminished. In this pilot study, we tested the hypothesis that an interaction between common variants in the MR (rs5522) or GR gene (rs41423247) and stressful life events influences perfectionism levels in a group of patients with an eating disorder (ED; n = 113). Patients carrying the minor G allele of rs5522 had a higher perfectionism score if more stressful life events were experienced [β = 0.95, t(109) = 3.75, p < 0.01]. This effect was not found for patients carrying the AA genotype. These results suggest that rs5522 G allele carriers might be vulnerable to stressful life events. When patients with an ED are carriers and experience multiple life events, this might fuel their insecurity, which in turn may engender higher levels of perfectionism. Further studies are necessary to replicate and expand our findings. Copyright © 2014 John Wiley & Sons, Ltd and Eating Disorders Association.

Keywords

eating disorder; G×E interactions; mineralocorticoid receptor; life events; perfectionism

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Introduction

A personality feature that plays an important role in the onset and maintenance of eating disorders (EDs) is perfectionism (for a review, see Bardone-Cone et al., 2007). Perfectionism consistently characterizes patients with an ED, with minimal differences between the subtypes (Cassin & von Ranson, 2005; Bardone-Cone et al., 2007). High levels of perfectionism remain present after recovery and appear to be familial in nature, suggesting an underlying genetic risk factor (Bardone-Cone et al., 2007). More importantly, high levels of perfectionism precede the onset of EDs (Bardone-Cone et al., 2007; Halmi et al., 2012). Harsh, perfectionist parenting is associated with the development of perfectionism in children, especially in those who are sensitive and feel insecure (Enns, Cox, & Clara, 2002; Frost, Lahart, & Rosenblade, 1991; Hollender, 1965). Boone, Soenens, Vansteenkiste, and Braet (2012) recently showed in an experimental study that levels of ‘state’ perfectionism could be induced in people, irrespective of their ‘trait’ perfectionism level. This suggests that perfectionism may be a personality feature that is relatively malleable and open to the influence of environmental factors.

An example of an environmental factor that could influence both perfectionism and EDs is the experience of stressful life events. Patients with an ED have experienced more major life events before the onset of their ED compared with healthy controls (Jacobi, Hayward, de Zwaan, Kraemer, & Agras, 2004). Stressful life events have also been linked with disordered eating behaviours, like extreme weight control behaviours and binge eating, in community samples of adolescents and young adults (Smyth, Heron, Wonderlich, Crosby, & Thompson, 2008; Loth, van den Berg, Eisenberg, & Neumark-Sztainer, 2008). In a longitudinal study, Johnson, Cohen, Kasen, and Brook (2002) found that a wide range of childhood adversities were associated with elevated risk for problems in eating or weight during adolescence and early adulthood.

Physical and psychological threats such as life events evoke a stress response, which includes activation of the hypothalamic–pituitary–adrenal (HPA) axis (de Kloet, Joels, & Holsboer, 2005), resulting in elevated levels of cortisol. Cortisol coordinates neuroendocrine and behavioural responses leading to adaptive coping with the stressor. Two related cortisol receptors, the low-affinity glucocorticoid receptor (GR) and the high-affinity mineralocorticoid receptor (MR), are
involved in the regulation of the stress response. When the balance between GR and MR signalling is disturbed, appraisal processes, HPA axis activation and autonomic responses will be suboptimal, and the capacity of an individual to cope with a stressful event is diminished (de Kloet et al., 2005). HPA axis dysregulation appears to be a trait vulnerability to mood disorder and possibly anxiety disorder (Van Santen et al., 2011). Changes in the regulation of the HPA axis have also been reported in patients with an ED (for a review, see Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008; Bruce et al., 2012; Ginty, Phillips, Higgs, Heaney, & Carroll, 2012; Monteleone et al., 2011).

The genes encoding GR (NR3C1) and MR (NR3C2) harbour several polymorphisms, including two common variants within the GR gene and the MR gene, the so-called BclI and MR I180V, respectively. Both variants are associated with changes in regulation of the HPA axis (Derijk et al., 2006; Kumsta et al., 2007) and susceptibility to psychiatric disorders, including post-traumatic stress disorder and depression (Hauer et al., 2011; Klok et al., 2011). The BclI restriction fragment length polymorphism (rs41423247) is located in exon B of the GR gene and involves a C-to-G conversion, with a frequency of 35%. Homozygous G allele carriers had an altered cortisol response after psychosocial stress (Wust et al., 2004; Kumsta et al., 2007), were at increased risk for traumatic memories and post-traumatic stress disorder symptoms (Hauer et al., 2011) and showed increased emotional memory performance (Ackermann, Hech, Rasch, Papassotiropoulos, & de Quervain, 2013). The functional polymorphism I180V (rs5522) is located in exon 2 of the MR gene and changes the primary structure of the MR protein. It involves an A-to-G conversion, with a frequency of 12%. Carriers of the rs5522 G allele showed higher cortisol and heart rate responses after psychosocial stress (Derijk et al., 2006).

In this pilot study, we tested the hypothesis that interactions between the common variants GR BclI (rs41423247) and MR I180V (rs5522) and stressful life events are associated with perfectionism levels in a group of patients with an ED (n = 113). We predict a higher level of perfectionism due to an interaction between genetic susceptibility and experiencing more stressful life events, with possible consequences for the development of EDs.

**Method**

**Participants**

This study was approved by the ethics committee for mental health institutions in the Netherlands. All participants gave written informed consent.

At 10 specialist ED units throughout the Netherlands, consecutive patients who were seeking treatment for their ED were asked to participate in the GenED study (Slof-Op’t Landt et al., 2011). Of the 389 female patients who took part in this study, patients with a current diagnosis of anorexia nervosa (AN) or bulimia nervosa (BN; n = 215) were invited to participate in the second part of the study. Of these, 113 patients (71 AN and 42 BN) consented. This subsample completed additional self-report questionnaires and was assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1997) and the Eating Disorder Examination (EDE; Fairburn & Cooper, 1993).

**Measures**

**Phenotypes**

The Multidimensional Perfectionism Scale (MPS; Frost, Marten, Lahart, & Rosenblate, 1990) is a 36-item questionnaire that distinguishes six dimensions of perfectionism (concern over mistakes, personal standards, parental expectations, parental criticism, doubt about actions and organization). In the current study, three forms of perfectionism were distinguished, on the basis of the MPS: global perfectionism (sum score of all subscales except organization), healthy perfectionism (comprising of personal standards and organization) and unhealthy perfectionism (comprised of concern over mistakes, parental expectations, parental criticism and doubt about actions; Stumpf & Parker, 2000).

A life events scale from the longitudinal survey studies of the Young Netherlands Twin Register (van Beijsterveldt et al., 2013) was used. This scale consists of 13 items and was derived from other existing scales (Van der Velden, Van der Burg, Steinmetz, & Van den Bout, 1992; Middeldorp, Cath, Vink, & Boomsma, 2005; Kaprio, Pulkkinnen, & Rose, 2002) to assess stressful life events. Patients were asked if they experienced the following life events: moving to another neighbourhood or town, change of school, having an illness or severe accident, a close friend moving away, illness of a significant other, death of a significant other, conflicts between parents, divorce or break-up of parents, a new partner of one of the parents moving in, a sibling leaving home, one of the parents losing their job, one of the parents started working again or the birth of a sibling. Response categories were ‘never’, ‘less than 2 years ago’ and ‘more than 2 years ago’. For the current study, the total number of life events (regardless of when they happened) was calculated.

The EDE (Fairburn & Cooper, 1993) is a semi-structured interview that measures the complete range of psychopathology and behaviours specific to EDs. A global score can be calculated, providing a measure of overall severity.

The Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is a 21-item self-report rating inventory measuring characteristic attitudes and symptoms of depression. Each item contains four self-evaluative statements rated on severity. Total scores range from 0 to 63, with high scores indicating more severe depression symptoms.

The State–Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) is designed to differentiate between the temporary condition of ‘state anxiety’ and the more general and long-standing quality of ‘trait anxiety’ in adults. Each of the two sections contains 20 items. The STAI evaluates feelings of apprehension, tension, nervousness and worry, which increase in response to physical danger and psychological stress. Total scores per subscale range from 20 to 80, with higher scores correlating with greater anxiety.

**Genotypes**

Genomic DNA was isolated from buccal swabs. In 63 samples, genotyping of rs41423247 and rs5522 was performed by mass spectrometry (homogeneous MassARRAY system, Sequenom, San Diego, CA) using standard conditions. Polymerase chain reactions (PCRs) were carried out in a final volume of 5 μl and contained standard reagents and 2.5 ng of genomic DNA. Genotyping was successful for 100% of the samples. In 53 samples, Taqman assays...
(Applied Biosystems, Foster City, CA) were used. For rs41423247, a custom TaqMan® SNP Genotyping Assay was designed, whereas a predesigned assay (C_1_12007869_20) was used for determining rs5522. All PCR assays were performed in 5-μl volume (5 ng DNA) in 384-well PCR plates using a GeneAmp® PCR System 9700 according to manufacturer’s specifications. The PCR plates were post-read and analysed using the LightCycler® 480 Real-time PCR System and Endpoint Genotyping module of the LightCycler® 480 software version 1.5 (Roche, Germany). The genotype call rates for rs5522 and rs41423247 were respectively 100% and 96%.

**Statistical analyses**

First, independent t-tests were performed to discover whether the two ED groups differed in age, body mass index (BMI), perfectionism levels and life events. In addition, genotype frequencies (rs41423247 and rs5522) were compared between patients with AN and BN using a χ² test. In the combined ED group, the χ² test for Hardy–Weinberg equilibrium (HWE) was calculated using the HWE program of LINKUTIL (http://linkage.rockefeller.edu/ott/linkutil.htm).

Next, in the combined ED group, the associations between rs41423247 and rs5522 and the number of life events and perfectionism scores (global, healthy and unhealthy) were tested using t-test statistics. In previous studies, changes in regulation of the HPA axis (Derijk et al., 2008; Wust et al., 2004; Kumsta et al., 2007) and/or in regulation of emotional memory (Hauer et al., 2011; Ackermann et al., 2013) were found solely in rs41423247 GG genotype carriers and rs5522 G allele carriers. We therefore only expected an effect in carriers of these specific genotypes, so a recessive model for rs41423247 (CC/CG vs GG genotypes) and a dominant model for rs5522 (AA vs AG/GG genotypes) were used.

Finally, stepwise linear regression analyses were performed to test for the interaction effects between rs41423247 or rs5522 and stressful life events on perfectionism level. In the first model, the main effects of genotype (rs41423247 GG or rs5522 G allele) and life events on perfectionism (dependent variable) were tested. In the second model, the GxE interaction between genotype and life events was entered into the analysis. In the third step, ED severity (EDE), depression (BDI) and anxiety (STAI ‘state’ and STAI ‘trait’) scores were entered into the model, to correct for possible effects on the interaction. Regression analyses were performed, first with global perfectionism as the dependent variable and then with healthy and unhealthy perfectionism as the dependent variables. All the statistical analyses were carried out in SPSS version 19 (IBM SPSS statistics, Armonk, NY).

**Results**

Body mass index, age, perfectionism and stressful life events for the total ED group and the patients with AN and BN are shown in Table 1. Patients with AN had a significantly lower BMI than patients with BN. In addition, healthy perfectionism and number of reported stressful life events were significantly higher in patients with AN than in patients with BN. Age, global perfectionism and unhealthy perfectionism did not differ between the two patient groups. Genotype frequencies (presented in Table 2) for NR3CI rs41423247 and NR3C2 rs5522 did not differ significantly between the two ED diagnoses [χ²(1) = 0.08, n.s., and χ²(1) = 1.52, n.s.]. No deviation from HWE was found for either rs41423247 or rs5522 [χ²(1) = 1.97, n.s., and χ²(1) = 0.55, n.s. respectively].

Table 2 presents the perfectionism levels and number of life events in the total ED group per genotype. Because changes in regulation of the HPA axis (Derijk et al., 2008; Wust et al., 2004; Kumsta et al., 2007) and/or in regulation of emotional memory (Hauer et al., 2011; Ackermann et al., 2013) were found solely in rs41423247 GG genotype carriers and rs5522 G allele carriers, genotype and GxE interaction effects were only expected for these specific genotype carriers. Hence, a recessive model for rs41423247 (CC/CG vs GG carriers) and a dominant model for rs5522 (AA vs AG/GG carriers) were used. Neither of the two polymorphisms was associated with perfectionism level or number of stressful life events (p > 0.3). There were no significant correlations between perfectionism level (global, healthy or unhealthy) and number of stressful life events.

Table 3 lists the stepwise linear regression analyses with global perfectionism as the dependent variable and life events and genotype (rs41423247 CC/CG vs GG or rs5522 AA vs AG/GG) as the independent variables. No interaction effect was found for NR3CI rs41423247 and stressful life events [β = −0.14, t (107) = −0.67, n.s.] on global perfectionism score. For rs5522, however, there was a significant interaction effect with life events on global perfectionism score [β = 0.95, t(109) = 3.75, p < 0.01]. In AA homozygotes of this polymorphism, no differences in

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### Table 1 Descriptives in total ED group, in patients with AN and in patients with BN

<table>
<thead>
<tr>
<th></th>
<th>Total ED</th>
<th>AN</th>
<th>BN</th>
<th>t-test</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (SD)</td>
<td>18.1 (4.3)</td>
<td>15.5 (1.8)</td>
<td>22.4 (3.6)</td>
<td>−11.57</td>
<td>53.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>28.2 (10.1)</td>
<td>28.9 (10.8)</td>
<td>26.9 (8.9)</td>
<td>1.00</td>
<td>111</td>
<td>0.32</td>
</tr>
<tr>
<td>Global perfectionism (SD)</td>
<td>89.6 (21.0)</td>
<td>91.6 (18.9)</td>
<td>86.3 (23.9)</td>
<td>1.33</td>
<td>111</td>
<td>0.19</td>
</tr>
<tr>
<td>Healthy perfectionism (SD)</td>
<td>50.4 (9.7)</td>
<td>52 (9.1)</td>
<td>47.6 (10.2)</td>
<td>2.38</td>
<td>111</td>
<td>0.02</td>
</tr>
<tr>
<td>Unhealthy perfectionism (SD)</td>
<td>65 (16.2)</td>
<td>64.3 (15.1)</td>
<td>60.8 (18.1)</td>
<td>1.10</td>
<td>111</td>
<td>0.27</td>
</tr>
<tr>
<td>Life events (SD)</td>
<td>5.8 (2.6)</td>
<td>6.2 (2.6)</td>
<td>5.2 (2.4)</td>
<td>2.00</td>
<td>111</td>
<td>0.05</td>
</tr>
</tbody>
</table>

AN, anorexia nervosa; BMI, body mass index; BN, bulimia nervosa; ED, eating disorder; SD, standard deviation.

*a*-test, equal variances not assumed.
Table 2: Perfectionism levels and number of life events in the total eating disorder group per genotype for rs41423247 and rs5522, including association analyses using a recessive model for rs41423247 and a dominant model for rs5522

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>CC</th>
<th>CG</th>
<th>GG</th>
<th>Global (SD)</th>
<th>Healthy (SD)</th>
<th>Unhealthy (SD)</th>
<th>Life events (SD)</th>
<th>t-test</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs41423247</td>
<td>90.8 (17.1)</td>
<td>89.4 (24.7)</td>
<td>82.3 (20.2)</td>
<td>90.9 (20.0)</td>
<td>89.0 (25.6)</td>
<td>90.3 (14.6)</td>
<td>0.95</td>
<td>109</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>rs5522</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recessive</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td>0.01</td>
<td>0.01</td>
<td>0.62</td>
<td>0.45</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

Table 3: Stepwise linear regression analyses to test for G×E interactions between genotype (rs41423247 or rs5522) and life events for global perfectionism

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>SE B</td>
<td>β</td>
</tr>
<tr>
<td>rs41423247 (CC/CG vs GG) Life events</td>
<td>1.59</td>
<td>0.78</td>
</tr>
<tr>
<td>rs41423247 (recessive) Life events × rs41423247 (recessive)</td>
<td>-10.31</td>
<td>8.24</td>
</tr>
<tr>
<td>rs5522 (AA vs AG/GG) Life events</td>
<td>1.45</td>
<td>0.78</td>
</tr>
<tr>
<td>rs5522 (dominant) Life events × rs5522 (dominant)</td>
<td>-0.43</td>
<td>4.62</td>
</tr>
<tr>
<td>EDE Life</td>
<td>-0.3</td>
<td>2.26</td>
</tr>
<tr>
<td>BDI STAI ‘state’</td>
<td>0.73</td>
<td>0.20</td>
</tr>
<tr>
<td>STAI ‘trait’</td>
<td>-0.3</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Analyses of rs41423247: R^2 = 0.05 for Model 1; ΔR^2 = 0.004 for Model 2, F(1, 107) = 0.45, n.s. Analyses of rs5522: R^2 = 0.03 for Model 1; ΔR^2 = 0.11 for Model 2, F(1, 109) = 14.03, p < 0.01; ΔR^2 = 0.23 for Model 3, F(4, 95) = 8.90, p < 0.01.

Discussion

In this pilot study, we found a significant interaction between the functional MR variant rs5522 and life events for the level of perfectionism in patients with an ED. Carriers of the minor G allele of rs5522 showed an elevated perfectionism level if they experienced more life events, in contrast to carriers of the AA genotype where no such relation was found. No interaction effect was observed with the GR Be/l variant.

All living organisms strive for homeostasis, a dynamic equilibrium. Physical and psychological events can threaten this equilibrium (de Kloet et al., 2005). A well-functioning stress system is a prerequisite to deal with these situations. The balance between the GR and MR determines an organism's capacity to cope with a stressful event (de Kloet et al., 2005). MR plays an essential role in the appraisal process of an event and the onset of the stress response.
response (de Kloet et al., 2005; Oitzl & de Kloet, 1992; Schwabe, Tegenthoff, Hoffken, & Wolf, 2013). The MR rs5522 G allele has been found to be associated with susceptibility to depression (Kuningas et al., 2007; Klok et al., 2011). Two recent studies on the functional rs5522 found G×E interactions (Luijk et al., 2011; Bogdan, Williamson, & Hariri, 2012). Luijk et al. (2011) found that the association between sensitive responsiveness of the mother and attachment security in the infant was moderated by this variant. In addition, rs5522 was found to moderate the association between previous childhood emotional neglect and amygdala reactivity (Bogdan et al., 2012). In our study, rs5522 moderated the association between stressful life events and the level of perfectionism. DeRijk et al. (2006) found that carriers of the rs5522 G allele had a higher cortisol response after psychological stress. Therefore, G allele carriers of this variant might be less capable of coping adaptively with stressful life events. The experience of multiple stressful life events in combination with the incapacity to cope with them might fuel the feelings of insecurity of people carrying the rs5522 G allele, and this in turn may engender higher levels of perfectionism.

In the current study, we tested for G×E interaction effects on perfectionism level in a combined sample of patients with AN or BN. Because the two ED groups differed in their level of healthy perfectionism and number of reported life events, it is possible that this could have influenced our findings. However, the interaction effect between rs5522 and life events on global or unhealthy perfectionism was also found in the two patient groups separately. For healthy perfectionism, the interaction between rs5522 and life events was only significant in the patients with BN (data not shown).

In combination with another functional variant, the −2G/C (rs2070951) polymorphism, rs5522 distinguishes three common haplotypes in the MR gene. These haplotypes modulate neuroendocrine responses and vulnerability to depression (Ising et al., 2008; Kuningas et al., 2007; Klok et al., 2011). The minor allele of rs5522 represents the third MR haplotype. No interaction effect with either the rs2070951 variant or the other two haplotypes was found in the current study (data not shown). This was expected, because the rs5522 G allele defines MR haplotype 3, independent of the rs2070951 variant. In addition, the three MR haplotypes extend into the 5′ promoter region and show different in vitro activities (Klok et al., 2011). Traumatic life events could therefore affect the three MR haplotypes in a unique manner, leading to haplotype-specific interaction effects. Because no interaction was observed with rs2070951, the data suggest a unique interaction between MR haplotype 3 (rs5522) and stressful life events.

Previous studies on G×E interaction in EDs have mainly focused on the promoter polymorphism of the serotonin transporter gene (Akkermann et al., 2012; Karwautz et al., 2011; Stoltenberg, Anderson, Nag, & Anagnostopoulos, 2012). However, with our current study, we followed up on a recent tendency to focus on polymorphisms that, in relation to the environment, could affect the stress response more directly like the MR and GR variants. Steiger et al. (2011, 2012) recently found a G×E interaction for the GR rs41423247 (BclI) polymorphism and childhood abuse in BN. The risk of developing BN was highest in C allele carriers who also experienced childhood abuse. In the current study, no G×E interaction was found for this polymorphism. The low minor allele frequency of rs41423247 in our sample (only seven patients carried the GG genotype) might explain why no effect was found for this variant.

The observed interaction between rs5522 and stressful life events for perfectionism level should be seen in the light of some limitations. First, the sample size of our study was small for evaluating G×E interactions. Second, a healthy control group was lacking in our study. Because our sample consisted solely of patients with an ED, we can only postulate that the interaction between this MR variant and stressful events in relation to

**Figure 1** G×E interaction between mineralocorticoid receptor (NR3C2) variant rs5522 and number of experienced stressful life events for the level of global perfectionism
perfectionism might be of aetiological relevance. Although the effects of stressful life events through MR rs5522 on perfectionism seem to be present in both patients with AN and BN, the statistical power to test this was limited. In addition, it is not certain whether the effects found in our subsample are representative of the entire ED sample from the GenED study (Slof-Op’t Landt et al., 2011). Ideally, this finding should be replicated in larger studies consisting of both patients with different types of EDs and controls. Finally, the life events scale used in this study was a self-report questionnaire and primarily focused on events that took place when the individuals were living with their parents. This scale only assessed the experience of 13 common life events, and not the impact these events might have had on the lives of the patients. Moreover, some major life events, such as physical or sexual abuse, were not represented. It is not clear if a similar G×E interaction would have been found when these major life events would have been assessed by the scale as well. The most frequently reported life events were death or illness of a significant other and moving to another neighbourhood or town. Yet an interaction with rs5522 was still observed, which suggests a high sensitivity of this specific MR gene variant to environmental influences. In previous studies, childhood emotional neglect and maternal responsiveness were also shown to interact with this variant (Luijk et al., 2011; Bogdan et al., 2012). But future studies that assess a complete range of life events (preferably by interview) in a larger sample are required to confirm the results of our study. In summary, this pilot study has demonstrated an interaction between a common functional MR gene variant and relatively common life events that increases the level of perfectionism. This higher level of perfectionism may confer increased susceptibility to ED.

Conflict of interest

Author R. H. D. is a consultant at Dynacortics Therapeutics B.V. (a company that aims to develop a drug that targets the mineralocorticoid receptor as a treatment for depression).


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