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Full-length Article

Effects of *IL1B* single nucleotide polymorphisms on depressive and anxiety symptoms are determined by severity and type of life stress

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ABSTRACT

Interleukin-1β is one of the main mediators in the cross-talk between the immune system and the central nervous system. Higher interleukin-1β levels are found in mood spectrum disorders, and the stress-induced expression rate of the interleukin-1β gene (*IL1B*) is altered by polymorphisms in the region.

Therefore we examined the effects of rs16944 and rs1143643 single nucleotide polymorphisms (SNPs) within the *IL1B* gene on depressive and anxiety symptoms, as measured by the Brief Symptom Inventory, in a Hungarian population sample of 1053 persons. Distal and proximal environmental stress factors were also included in our analysis, namely childhood adversity and recent negative life-events.

We found that rs16944 minor (A) allele specifically interacted with childhood adversity increasing depressive and anxiety symptoms, while rs1143643's minor (A) allele showed protective effect against depressive symptoms after recent life stress. The genetic main effects of the two SNPs were not significant in the main analysis, but the interaction effects remained significant after correction for multiple testing. In addition, the effect of rs16944 A allele was reversed in a subsample with low-exposure to life stress, suggesting a protective effect against depressive symptoms, in the post hoc analysis.

In summary, both of the two *IL1B* SNPs showed specific environmental stressor-dependent effects on mood disorder symptoms. We also demonstrated that the presence of exposure to childhood adversity changed the direction of the rs16944 effect on depression phenotype. Therefore our results suggest that it is advisable to include environmental factors in genetic association studies when examining the effect of the *IL1B* gene.

1. Introduction

Depression has a consistent heritability rate (39%), which suggests a genetic predisposition to the disorder (Kendler and Prescott, 1999), but biomarker regions of specific genes for depression have begun to emerge only recently (Cohen-Woods et al., 2013; Converge-consortium, 2015). Mood disorders are highly complex clinical conditions with growing number of subcategories defined by the new DSM-V, and giving an opportunity for clinicians to refine the existing concepts about mental disorders, e.g. by including specifiers like "with anxious distress" to better distinguish between various conditions (AmericanPsychiatricAssociation, 2013). Also in genetic association studies continuous symptom scores are commonly used to assess mood disorder phenotypes in order to express more precisely the subjects state of mind, based on the observation that common psychiatric disorders, such as depression, are quantitative traits showing continuous distribution in the population (Plomin et al., 2009). The importance of using continuous variables was also highlighted by studies, which demonstrated that different subscales of tools assessing the state of mood disorder showed different associations with genetic variants, suggesting that reducing depression and anxiety state to a simple logistic variable might obscure the identification of genetic effects (Juhasz et al., 2015).

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Regarding the pathophysiology of depression, besides the well-known involvement of the monoaminergic pathways, the activation of inflammatory response has been described in the background of depression (Dantzer et al., 2011) and other psychiatric conditions (Michel et al., 2012). Elevated levels of proinflammatory cytokines, such as IL-1β in depressed individuals, have been confirmed by meta-analyses (Dowlati et al., 2010; Howren et al., 2009). The secretion of the IL-1β protein was reported to be dependent on a functional single nucleotide polymorphism (SNP) rs16944 (NM_0000576.2:c.-598T>C) in the promoter region of *IL1B* (Hall et al., 2004). The presence of the minor allele (A), which facilitates IL-1β production, was associated with elevated risk of depression in schizophrenic spectrum disorders (Rosa et al., 2004), depressive symptoms in Alzheimer disease (McCulley et al., 2004) and depressed state in breast cancer patients (Kim et al., 2013). However, other studies have shown contradictory results, in that the A allele was protective against recurrent major depression (Borkowska et al., 2011), or predicted favourable antidepressant treatment outcome (Baune et al., 2010; Yu et al., 2003). In addition, the intronic SNP rs1143643 (NM_000576.2:c.598-152G>A), which is not in linkage equilibrium with rs16944, was also reported to influence antidepressant treatment outcome and subgenual anterior cingulated cortex (ACC) activity in the same article (Baune et al., 2010). Despite these promising findings, no further studies have investigated the effect of the *IL1B* gene on mood disorder phenotypes.

Experiments with laboratory animals showed no significant effect of the IL-1 family on early brain development, however robust effects were described when various type of stressors were present (Alheim and Bartfai, 1998; Giles et al., 2014). Significant changes were detected in IL-1β expression, for example in response to chronic pain (del Rey et al., 2012), unpredictable chronic stress (Ma et al., 2013), repeated social defeat (Wohleb et al., 2014), and chronic intermittent cold stress followed by acute immunological challenge (Girotti et al., 2011). Knocking out necessary elements of the IL-1β signalling process resulted in attenuated stress response in *IL-1RI* (Wohleb et al., 2014), IL-1 receptor accessory protein (*IL-1RAcP*) (Laye et al., 2001), and IL-1β converting enzyme (*ICE*) (Lawson et al., 2013) gene knock-out models.

Exposure to stress seems to be a crucial mediator in human subjects also. All three studies mentioned above, which identified the minor A allele of rs16944 as a risk factor in depression, were carried out in patients with other severe medical conditions (Kim et al., 2013; McCulley et al., 2004; Rosa et al., 2004). By contrast, in studies finding that the A allele was associated with protective functions, or better treatment outcome, subjects with other mental or physical illness were excluded.(Baune et al., 2010; Borkowska et al., 2011; Yu et al., 2003). While IL-1β has a prominent role in the comorbidity of depression and physical conditions (Anisman and Hayley, 2012), such as post-stroke state (Pascoe et al., 2011), a recent article also reported elevated IL-1β levels in subjects exposed to psychosocial stress, particularly childhood maltreatment (Hartwell et al., 2013). The effect of different types of stress and life events, such as the influence of distal and proximal life stresses on the association of *IL1B* polymorphisms and depressive symptoms is yet poorly understood, despite the fact that on many occasions gene × environment interactions showed greater influence on mood disorder phenotypes than genetic factors alone (Juhasz et al., 2015). Moreover a recent review suggested that, considering the many aspects of cytokines' effect on the brain, a broader spectrum of neuropsychiatric conditions might be affected including neurodegenerative or personality disorders and anxiety (Capuron and Miller, 2011). Anxiety and depression has a well-established common genetic diathesis, however it is important to consider also the differences between them from genetic point of view, and include both anxiety and depression phenotype in genetic association analyses which consider novel polymorphisms or interactions (Pollack, 2005; Scott et al., 2007).

Based on the summarised research results, we hypothesised that the effects of both rs16944 and rs1143643 polymorphisms on mood related symptoms are dependent on the presence of life stressors. To test this hypothesis we analysed gene × environment interactions, taking into account both proximal (recent negative life events) and distal life stress (childhood adversity), and compared the interaction effects on depressive and anxiety symptoms.

2. Materials and methods

2.1. Population

Phenotypic and genetic data were gathered from volunteers in Budapest, Hungary during the NewMood study (New Molecules in Mood Disorders, Sixth Framework Program of the European Union LHSM-CT-2004-503474). Volunteers, aged between 18 and 60 years, were recruited through advertisement in universities and at general practices. Participants provided genetic sample and completed a questionnaire pack. The subjects' ethnicity, socio-economic background, medical and psychiatric anamnesis was assed using a background questionnaire developed and validated for that study (Juhasz et al., 2009, 2011; Lazary et al., 2008). Reported medical or psychiatric conditions were not exclusion criteria, since we aimed to investigate a general population sample. However, in order to avoid stratification bias, our analysis was performed on non-related individuals with European white ethnic origin. All participants gave written informed consent before they entered the study. Our study was approved by the local ethic committees and was carried out in accordance with the declaration of Helsinki.

2.2. Phenotypes

In our analysis, two phenotypic outcome variables and two types of environmental stress factors were used. The current depressive and anxiety state was assessed by the Brief Symptom Inventory (Derogatis and Melisaratos, 1983) depression and anxiety subscales, with the four additional items included for depression. Continuous weighted dimension scores were calculated and used in the analysis.

For interacting factors, we selected confirmed environmental stressors, namely early life stress and recent negative life stress. Early life stress was measured by the childhood adversity score (CHA), which was derived from the Childhood Trauma Questionnaire (CTQ) measuring emotional and physical abuse and neglect during childhood (Bernstein et al., 1994). An additional question asked about parental loss during childhood, and added to the total score. To define recent stressful life events, we used the List of Life Threatening Experiences questionnaire (Brugha et al., 1985), and calculated the sum of these events in the past year (Recent negative Life Events, RLE). In both cases, the sum of item scores was used in the analysis.

2.3. Genotypes

Buccal mucosa cells were collected from the participants with cytology brushes, and DNA samples were extracted according to a published validated method (Freeman et al., 2003). NanoDrop B-100 spectrophotometer was used to determine quality and quantity of DNA. Two SNPs were genotyped in the *IL1B* gene, namely rs16944 and rs1143643 in the Centre for Integrated Genomic Medical Research at The University of Manchester using Sequenom® MassARRAY technology (Sequenom Inc., San Diego, CA, USA) under the

ISO 9001:2000 quality management requirements. Primers were designed by Assay Design 3.0 software of Sequenom, and the iPLEX assay was performed by the instructions of the manufacturer. The iPLEX reaction products dispended on 384-well SpectroChip (Sequenom) were analysed in a Compact Mass Spectrometer by MassARRAY Workstation 3.3 software (Sequenom). Duplicate genotyping of 15% of random samples showed a 99.87% agreement for rs1143643, and 99.78% for rs16944.

The selected two SNPs are not in linkage equilibrium and situated in two distinct haploblocks according to the HapMap project data (http://hapmap.ncbi.nlm.nih.gov/, (Fig. 1): rs16944 is located in the functional promoter region and rs1143643 in the intronic region near to the 3′ end.

2.4. Statistical analysis

Power calculations with Quanto program (http://biostats.usc.edu/Quanto.html) were performed before testing, assuming additive heritability and R^2 = 1% explained variance. Our analysis has 86% power in the case of SNP rs16944 and 82% in the case of SNP rs1143643 to find main genetic effects. With continuous interacting environmental effects represented by CHA and RLE in Table 1, we have 86% power to detect gene-environment interaction in the case of SNP rs16944 and 83% in the case of SNP rs1143643.

PLINK 1.0.7 (http://pngu.mgh.harvard.edu/purcell/plink) was used to determine Hardy-Weinberg equilibrium and linkage disequilibrium, and to test additive, dominant and recessive models in linear regression analysis. Genetic main effects and gene-environment interactions were tested in separate models. Other statistical calculations were carried out with IBM SPSS 20.0 for Windows. Both age and gender of the subjects were used as covariates in all analyses. The nominal significance level was set at $p = 0.05$. Bias due to multiple-testing was corrected with the Bonferroni method reducing the significance-threshold to $p = 0.05/36 = 0.001389$ (2 SNP-s, 2 phenotypes, 3 heritability models, 3 types of testing), final threshold $\alpha = 1.389 \times 10^{-3}$.

In addition, a Bayesian network based multivariate modelling method, called Bayesian relevance analysis (Antal et al., 2008), was carried out in order to further investigate gene-environment interactions. This method is based on a Bayesian statistical framework (Stephens and Balding, 2009) which relies on Bayesian model averaging (Hoeting et al., 1999; Madigan et al., 1996) and thus provides a consistent handling of the multiple hypothesis problem (Antal et al., 2014). Bayesian relevance analysis computes probability scores which quantify the strong relevance of predictors with respect to a selected target (Hullam and Antal, 2013; Hullam et al., 2012). For the analysis, discrete phenotypes and environmental factors were used as follows: current depressive and anxiety symptom scores were divided into categorical variables (low = 0–<1, moderate = 1–<2, severe = 2–4), RLE and CHA scores

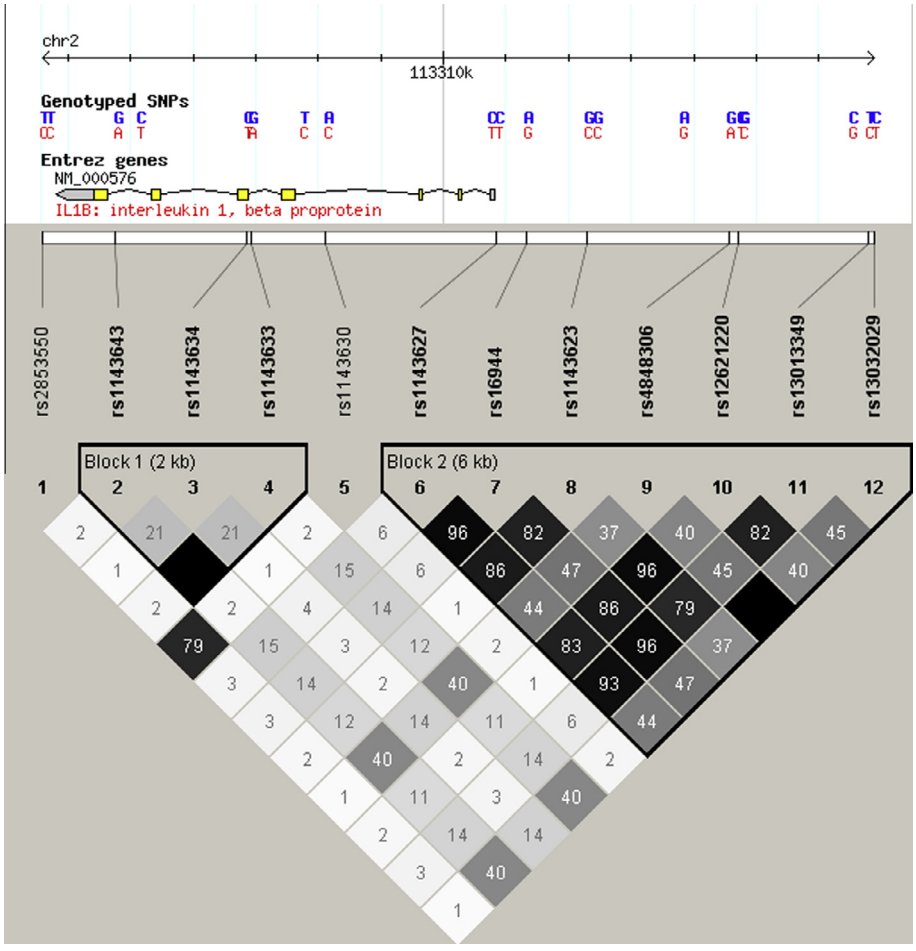

Fig. 1. Linkage disequilibrium map of the *IL1B* gene.
The LD map of the *IL1B* gene based on the CEU population data (Utah residents with ancestry from northern and western Europe) that were released at the International HapMap Project (Phase II. Release 24, 2008). LD R^2 values are visualised with the HaploView 4.2 software (https://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview).

Table 1
Descriptive statistics of the measured phenotypes.

Gender	*n*		%	
Male	320		30.40%	
Female	733		69.60%	
Reported psychiatric conditions:				
Depression	220		20.90%	
Anxiety/panic/phobia	207		19.70%	
Manic episode/disorder	18		1.70%	
Obsessive-compulsive disorder	23		2.20%	
Psychotic episode/schizophrenia	7		0.70%	
Suicide attempt/deliberate self harm	50		4.70%	
Eating disorder	72		6.80%	
Drug/alcohol problem	24		2.30%	
	Minimum	Maximum	Mean	SEM
Age	18	60	31.21	1.54
Depression score	0	4	0.554	0.683
Anxiety score	0	4	0.689	0.704
CHA	0	15	2.731	2.921
RLE	0	8	1.083	1.170

Depressive and anxiety symptom scores were measured by the Brief Symptom Inventory (BSI). CHA – Childhood Adversity; RLE – Recent negative Life Events; SEM – standard error of mean.

were grouped into three categories (RLE: low = 0–1, medium = 2, high = 3 or more; and CHA: low = 0–3, medium = 4–6, high = 7 or more) based on our previous studies (Lazary et al., 2008).

3. Results

3.1. General information and main effects of the polymorphisms

The total number of participants was 1093, but excluding non-Caucasian subjects and blood relatives, our analysis was restricted to 1053 subjects. Due to missing or low quality DNA, genetic samples of 999 subjects were genotyped. Genotyping success rate was 98.2% for rs16944, and 88.6% for rs1143643. Due to missing phenotypic data, the actual analysis was performed on 907 and 832 subjects, for rs16944 and rs1143643 respectively. Description of the study population can be seen in Table 1.

The two tested SNPs of the *IL1B* gene were in Hardy-Weinberg equilibrium, (rs16944: $p = 0.52$, rs1143643: $p = 0.60$), and not in linkage ($R^2 = 0.227$, $D = 0.856$) in our sample. The experienced minor allele frequencies (MAF) were consistent with the HAPMAP CEU (http://hapmap.ncbi.nlm.nih.gov) MAF values (A allele of rs16944: HAPMAP CEU: 0.358, measured: 0.334; and A allele of rs1143643: HAPMAP CEU: 0.392, measured: 0.379). Pearson correlation of the interacting factors CHA and RLE was significant, but acceptably low (Pearson correlation R: 0.119, $p = 0.00$).

We could not identify significant stress-independent main effects of the two SNPs on the measured phenotypes (Table 2), not even with nominal significance threshold. However, both of the mood disorder phenotypes were affected by the interaction of our SNPs with CHA and RLE as shown in Table 2.

3.2. Interactions of rs16944 with Childhood Adversity and Recent Life Events

3.2.1. Depressive symptoms

The A allele carriers scored significantly higher on BSI depression scale if they were exposed to CHA (Fig. 2A). This interaction was present in all three inheritance models, and remained significant according to the Bonferroni corrected threshold except in the recessive model. In contrast, higher RLE influenced BSI depression score at nominal significance level in A allele carriers only if additive inheritance was assumed. However this interaction did not meet the criterion of Bonferroni corrected significance threshold (Table 2).

3.2.2. Anxiety symptoms

Anxiety symptom score was elevated by the A allele-CHA interaction similarly to depressive symptoms (Fig. 2B). The significance of this interaction met the Bonferroni corrected threshold in all three inheritance models. However the interaction with RLE was only significant at nominal levels in the additive and dominant models, but none of them survived Bonferroni correction for multiple testing (Table 2).

The effect of the CHA-rs16944 A allele were stronger on anxiety, compared to depressive symptoms, in all inheritance models.

3.3. Interactions of rs1143643 with Childhood Adversity and Recent Life Events

3.3.1. Depressive symptoms

The interaction of SNP rs1143643 and CHA did not influence depression scores significantly, even at nominal levels. However the protective effect of the A allele in interaction with RLE showed high significance in the dominant heritability model, which met the Bonferroni corrected threshold; nominal significance was also detected using additive model (Fig. 3).

3.3.2. Anxiety symptoms

The A allele interaction with CHA was protective against anxiety symptoms in both additive and dominant heritability models with nominal significance, but did not survive Bonferroni correction. RLE interactions had no effect on anxiety symptoms at any significance level (Table 2).

In order to test whether the effect of these SNPs can be reversed by the exposure to life stress, we carried out post hoc genetic main effect association analysis on depressive and anxiety symptom scores, in the subgroups of our population sample who had the lowest scores on RLE and CHA respectively.

3.4. Post-hoc tests of the effects of SNPs in those with low Childhood Adversity scores

As represented above, for the main tests we had 907 and 832 subjects with sufficient data to carry out the analysis for rs16944 and rs1143643 respectively. Genetic association analysis with PLINK program for main effects of the SNPs on BSI depression and anxiety phenotype was carried out on the restricted sample of 645 and 594 subjects who scored low (0–3) on CHA using the same methods as in the main testing. Assuming recessive heritability, the rs16944 A allele had nominally significant protective effect against depressive symptoms but no other associations were identified between the two SNPs and the measured mood disorder phenotypes (Table 3).

3.5. Post-hoc tests of the effects of polymorphisms in those with low Recent Life Event scores

A total of 639 subjects (for rs16944) and 586 subjects (for rs1143643) were eligible for post hoc testing, after restricting the population samples to those subjects who reported one or less negative life events in the past year. Linear regression analysis between the two SNPs and the two outcome variables, (namely BSI depressive and anxiety symptom scores) found one significant association in subjects with the lowest scores. SNP rs16944 A allele showed protective function against depressive symptoms in the recessive heritability model (Table 3).

Table 2
Main effects and interactions with life stress of SNPs rs16944 and rs1143643 on depressive and anxiety symptom scores.

		ADD			DOM			REC		
		β	SEM	p value	β	SEM	p value	β	SEM	p value
Depressive symptom score										
rs16944	Main effect	0.009	0.035	0.787	0.048	0.047	0.3	−0.079	0.074	0.285
	CHA interaction	0.052	0.012	$\mathbf{1.61 \times 10^{-5}}$	0.057	0.018	$\mathbf{1.60 \times 10^{-4}}$	0.079	0.028	$\mathbf{4.34 \times 10^{-3}}$
	RLE interaction	0.062	0.029	**0.031**	0.071	0.039	0.064	0.103	0.059	0.08
rs1143643	Main effect	−0.018	0.036	0.61	−0.021	0.05	0.679	−0.029	0.069	0.676
	CHA interaction	−0.022	0.012	0.078	−0.032	0.017	0.054	−0.015	0.023	0.512
	RLE interaction	−0.063	0.03	**0.038**	−0.151	0.04	$\mathbf{1.80 \times 10^{-4}}$	0.091	0.062	0.141
Anxiety symptom score										
rs16944	Main effect	0.035	0.035	0.315	0.068	0.047	0.147	−0.013	0.075	0.868
	CHA interaction	0.059	0.012	$\mathbf{1.91 \times 10^{-6}}$	0.061	0.015	$\mathbf{8.89 \times 10^{-5}}$	0.103	0.028	$\mathbf{2.76 \times 10^{-4}}$
	RLE interaction	0.066	0.029	**0.022**	0.077	0.039	**0.049**	0.105	0.06	0.079
rs1143643	Main effect	−0.032	0.036	0.381	−0.035	0.051	0.494	−0.053	0.07	0.449
	CHA interaction	−0.03	0.013	**0.016**	−0.041	0.017	**0.018**	−0.03	0.024	0.207
	RLE interaction	−0.019	0.03	0.533	−0.06	0.041	0.139	0.061	0.062	0.326

Depressive and anxiety symptom scores were measured by Brief Symptom Inventory (BSI). SEM – Standard error of mean; ADD, DOM, REC – additive, dominant and recessive heritability models, respectively.

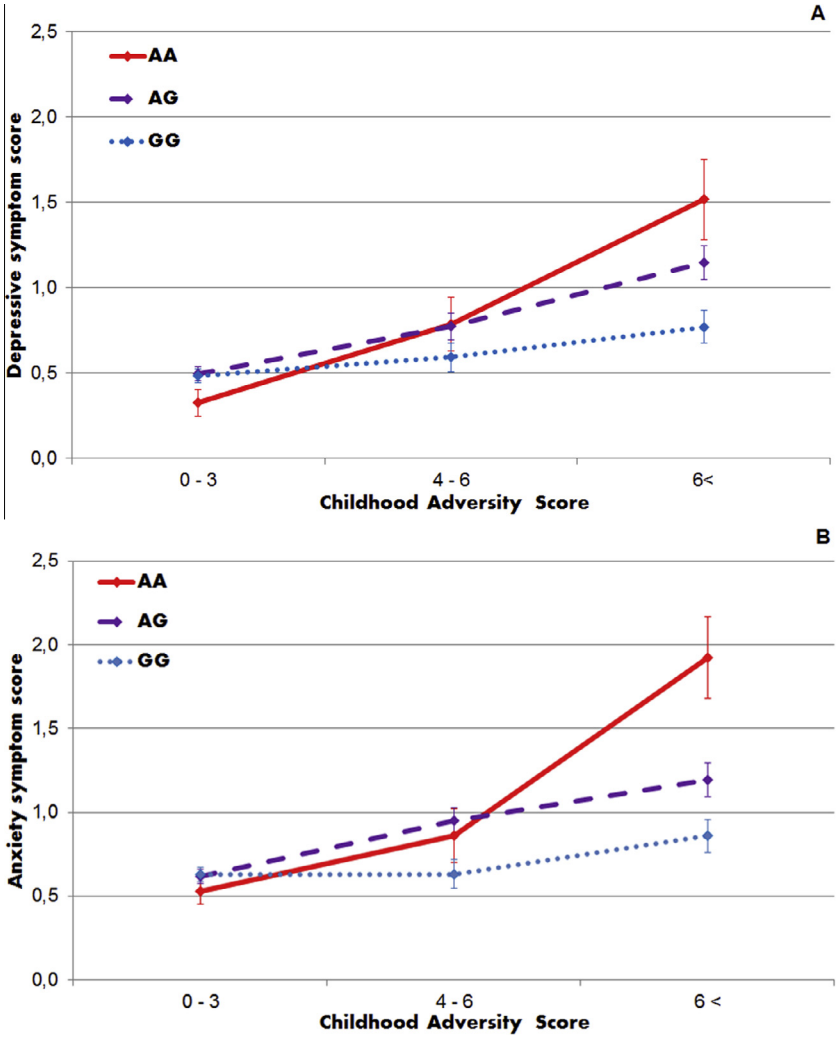

Fig. 2. The effect of interactions between SNP rs16944 and Childhood Adversity, on Depression (A) and Anxiety (B) symptom scores.
Homozygote and heterozygote A allele carriers of the SNP rs16944 showed increased depressive and anxiety symptom scores measured by the Brief Symptom Inventory (BSI) depending on the exposure of Childhood Adversity (CHA). In the case of depressive symptoms, the AA genotype was protective in those who had low (0–3) CHA scores which suggest a qualitative interaction. The vertical axis represents the weighted dimension score of BSI depressive and anxiety symptom scores respectively, from the different groups of subjects, sorted by the exposure to CHA, which was measured by the shortened version of Childhood Trauma Questionnaire (Juhasz et al., 2011). The solid, dotted and dashed lines indicate the carriers of various genotypes of SNP rs16944.

Fig. 3. The effect of interactions between SNP rs1143643 and Recent negative Life Events, on Depressive symptom score.
Among those people who had self-reported negative life events in the previous year, rs1143643 minor A allele carriers had lower depressive symptom scores than non-carriers, representing a protective effect. The figure demonstrates the significant dominant heritability model; GG represents GG genotype carriers of the rs1143643 polymorphism, while the homozygote and heterozygote A allele carriers were collapsed into one group and called AA_AG. The vertical axis represents the achieved weighted dimension score of the Brief Symptom Inventory's depressive symptoms. On the horizontal axis, the Recent negative Life Events (RLE) score is shown, measured by the Threatening Life Events questionnaire (Brugha et al., 1985), summarising the stressful events that had happened in the previous year.

In summary, post hoc analysis found that rs16944 AA genotype has weak protective effect in both CHA and RLE low scoring subjects against depressive symptoms but not against anxiety symptoms. Rs1143643 showed no effect on mood disorder phenotypes regardless of which life stress factor was excluded.

3.6. SNP × SNP interaction and haplotype analysis

During the post hoc testing, we performed SNP × SNP interaction testing. However, we could not identify any significant effects on depressive ($p = 0.684$) or anxiety ($p = 0.722$) symptom scores. These results further emphasised that the effect of SNPs within the *IL1B* gene are dependent on the impact of life stress.

Indeed, haplotype association analysis to test the effects of all possible haplotypes interacting with life events, demonstrated a highly significant haplotype interaction of the GA haplotype (rs1143643 and rs16944 respectively) with CHA, conferring risk for higher depressive ($p = 1.65 \times 10^{-6}$) and anxiety ($p = 2.51 \times 10^{-7}$) symptom scores. Three additional significant haplotype interactions were also found with CHA. However, no association was found of haplotypic main effects or interactions with RLE. Table 4

3.7. Replication of the main significant results after random splitting the population sample

We also re-ran the analysis on two randomly generated subgroups of our population sample, in order to replicate our main findings which survived Bonferroni correction. The power for finding gene-environment interactions with both CHA and RLE reduced from 86% to 58% for rs16944, and from 83% to 58% for rs1143643, as determined by the Quanto program using the same setting as described earlier. The interaction of re16944 with CHA was found to influence both depressive and anxiety symptom scores in both subgroups, with the exception of the recessive heritability model in sub-group 1 (Depressive symptoms: Group 1: ADD $p = 1.61 \times 10^{-2}$ $\beta = 0.044$. DOM $p = 2.22 \times 10^{-2}$ $\beta = 0.051$. REC $p = 0.366$ $\beta = 0.041$. Group 2: ADD $p = 3.31 \times 10^{-4}$ $\beta = 0.056$. DOM $p = 2.59 \times 10^{-3}$ $\beta = 0.061$. REC $p = 5.33 \times 10^{-3}$ $\beta = 0.097$ Anxiety symptoms: Group 1: ADD $p = 1.15 \times 10^{-2}$ $\beta = 0.047$. DOM $p = 1.46 \times 10^{-2}$ $\beta = 0.056$. REC $p = 0.317$ $\beta = 0.047$. Group 2: ADD $p = 6.61 \times 10^{-5}$ $\beta = 0.064$. DOM $p = 2.59 \times 10^{-3}$ $\beta = 0.063$. REC $p = 2.46 \times 10^{-4}$ $\beta = 0.132$). For the interaction of RLE with rs1143643, using dominant heritability model, significant effect on depressive symptom was detected only in sub-group 2 (Group 1: DOM $p = 0.069$ $\beta = -0.095$; Group 2: DOM $p = 6.90 \times 10^{-3}$ $\beta = -0.133$). However, in both groups the direction of effect was protective, similar to the main analysis. This suggests that the lack of sufficient significance levels in the first sub-group might be the result of the reduced statistical power.

3.8. Bayesian relevance analysis of IL1B SNPs in various Childhood Adversity and Recent Life Events exposure groups

Bayesian relevance analysis was carried out in each of the CHA and RLE exposure groups separately. Results indicated that

Table 3
The effects of SNPs rs16944 and rs1143643 on depressive and anxiety symptom scores in the low-scored groups to Childhood Adversity (CHA) and Recent negative Life Events (RLE).

Low-scored groups to childhood adversity (CHA)									
Depressive symptom score	ADD			DOM			REC		
	β	SEM	p value	β	SEM	p value	β	SEM	p value
rs16944	−0.050	0.034	0.134	−0.024	0.045	0.600	−0.168	0.071	0.019
rs1143643	−0.016	0.029	0.581	−0.021	0.042	0.612	−0.022	0.057	0.706
Anxiety symptom score	ADD			DOM			REC		
	β	SEM	p value	β	SEM	p value	β	SEM	p value
rs16944	−0.037	0.037	0.313	−0.03	0.05	0.542	−0.092	0.078	0.238
rs1143643	−0.014	0.035	0.682	−0.018	0.050	0.725	−0.021	0.068	0.753
Low-scored groups to recent negative life events (RLE)									
Depressive symptom score	ADD			DOM			REC		
	β	SEM	p value	β	SEM	p value	β	SEM	p value
rs16944	−0.045	0.037	0.218	−0.011	0.049	0.822	−0.184	0.079	0.021
rs1143643	0.008	0.033	0.808	0.047	0.047	0.315	−0.060	0.065	0.357
Anxiety symptom score	ADD			DOM			REC		
	β	SEM	p value	β	SEM	p value	β	SEM	p value
rs16944	−0.011	0.038	0.776	0.007	0.051	0.892	−0.07	0.083	0.4
rs1143643	−0.005	0.036	0.880	−0.006	0.050	0.908	−0.009	0.070	0.895

Depressive and anxiety symptom scores were measured by Brief Symptom Inventory. SEM – Standard error of mean; ADD, DOM, REC – additive, dominant and recessive heritability models.

Table 4
The effect of the interaction, between *IL1B* haplotypes and Childhood Adversity and Recent negative Life Events, on depressive and anxiety symptom scores.

		HT1: AA −1.25%			HT2: GA −32.61%			HT3: AG −36.42%			HT4: GG −29.72%		
		β	SEM	*p* value	*β*	SEM	*p* value	*β*	SEM	*p* value	*β*	SEM	*p* value
Depressive symptom score	Main effect	−0.210	0.159	0.188	0.011	0.037	0.771	−0.008	0.037	0.824	0.009	0.038	0.805
	CHA interaction	−0.099	0.06	0.096	0.06	0.012	$\mathbf{1.65 \times 10^{-6}}$	−0.019	0.013	0.132	−0.036	0.012	**0.003**
	RLE interaction	−0.087	0.129	0.501	0.055	0.031	0.073	−0.06	0.031	0.052	0.008	0.03	0.801
Anxiety symptom score	Main effect	−0.3	0.161	0.062	0.057	0.038	0.131	−0.016	0.038	0.662	−0.025	0.038	0.52
	CHA interaction	−0.082	0.061	0.181	0.066	0.013	$\mathbf{2.51 \times 10^{-7}}$	−0.029	0.013	**0.024**	−0.032	0.013	**0.011**
	RLE interaction	−0.027	0.13	0.836	0.055	0.031	0.076	−0.014	0.031	0.646	−0.04	0.03	0.183

The first and second letter in the haplotypes indicates the allele of rs1143643 and rs16944 respectively. CHA: Childhood Adversity score. RLE: Recent negative Life Events score. Depressive and anxiety symptom scores were measured by Brief Symptom Inventory. SEM – Standard error of mean.

rs16944 was only relevant with respect to depressive symptoms in the highest scoring CHA group with a moderately high posterior probability (0.48), whereas in the low (0.03) and medium (0.07) scoring groups it was non-relevant (Table 5). In the case of anxiety symptoms, a similar phenomenon could be observed; SNP rs16944 had a moderately high posterior probability for strong relevance in the highest scoring CHA group (0.50), contrary to the low posterior probability of medium (0.10) and low (0.01) scoring groups. Furthermore, rs1143643 had a similar trend with respect to depressive symptoms with the posterior probability of strong relevance given the highest scoring RLE group was considerably greater (0.85) than the low (0.04) and medium (0.12) groups. In contrast, rs1143643 was non-relevant with respect to anxiety symptoms for all RLE groups. In summary, the relevance of the polymorphisms for both symptom scores was consequently higher in the more exposed groups compared to the less exposed ones.

4. Discussion

Our study demonstrated that two polymorphisms of the *IL1B* gene interacted in different ways with Childhood Adversity (CHA) and Recent negative Life Events (RLE) affecting depressive and anxiety symptoms. Rs16944, which is a functional SNP in the promoter region, showed multiple-testing corrected significant interactions with CHA, with the A allele increasing both depressive and anxiety symptom scores, with stronger effect on anxiety, while RLE interactions could not met the Bonferroni corrected threshold. The rs16944-CHA interaction was also replicated when we randomly split our cohort into two sub-groups, in the additive and dominant heritability models. In contrast to this effect rs1143643, which is an intronic SNP at the 3′ end of the gene, showed interaction with RLE with the minor A allele exerting protective effect against depressive but not against anxiety symptoms at a Bonferroni corrected significance level. However, this RLE interaction of rs1143643 was only partially replicated in the randomly split sub-groups. The results of Bayesian relevance analysis also confirmed the interaction between rs16944 and CHA with respect to both depression and anxiety, and also the interaction between rs1143643 and RLE with respect to depression. In addition, Bayesian relevance analysis and the negative SNP × SNP interaction results reinforced the view that the inclusion of environmental factors is crucial for association analyses related to depression phenotypes. Haplotype association analysis, to investigate the effect of the whole *IL1B* gene, demonstrated a highly significant interaction between the GA haplotype and CHA, which elevated both depressive and anxiety symptom scores, and also survived the correction for multiple testing. Regarding haplotype interaction with RLE, only weak trends were observable. These data suggest a strong, long-lasting effect of CHA on the function of the *IL1B* gene, while a much weaker moderating effect of RLE could not be ruled out and warrants further investigations.

Table 5
Posterior probability of strong relevance for rs16944 and rs1143643 with respect to depressive and anxiety symptom scores in various Childhood Adversity (CHA) and Recent negative Life Events (RLE) exposure groups.

SNP	Target	Childhood Adversity		
		Low	Medium	Severe
rs16944	Depression	0.03	0.07	0.48
	Anxiety	0.01	0.1	0.5
rs1143643	Depression	0.01	0.09	0.35
	Anxiety	0.01	0.05	0.52
SNP	Target	Recent life events		
		Low	Medium	Severe
rs16944	Depression	0.05	0.39	0.52
	Anxiety	0.02	0.05	0.16
rs1143643	Depression	0.04	0.12	0.85
	Anxiety	0.03	0.04	0.16

4.1. Rs16944

Our results implicate a bidirectional relationship between life stress and rs16944 polymorphism. A synergic relationship between high stress exposure and the minor A allele (causing vulnerability to more severe depressive and anxiety symptoms) has been identified, while in the low-exposed groups a weak protective function of the A allele was found.

Our results are in line with previous studies that found higher risk of depression in carriers of the higher synthesizing A allele, in schizophrenic (Rosa et al., 2004), Alzheimer (McCulley et al., 2004) and breast cancer patients (Kim et al., 2013). We suggest that the apparent contradiction between our results and earlier studies that found the A allele protective against recurrent major depression (Borkowska et al., 2011) or non-remission in antidepressant therapy (Baune et al., 2010; Yu et al., 2003), was due to the different stress exposure of the examined subject groups, since our post hoc analysis on both of the low-exposed subgroups (CHA or RLE) showed the protective effect described by the three studies above.

Previous studies have demonstrated that risk genes of depression are frequently associated with advantageous immunological and behavioural responses to infection (Raison and Miller, 2013). Thus the protective effect of the A allele in the non-stressed subjects may be explained by better pathogen host defence and thus better quality of life, while the excessive up-regulation of IL-1β production during life stress may interfere with normal brain function and thus create maladaptive behaviour (Dowlati et al., 2010).

The observed interaction in our study was stronger with CHA than RLE suggesting that rs16944 is likely to exert its effect in early brain development, resulting in vulnerability to depression throughout life (Borsini et al., 2015; Semple et al., 2013). Moreover

we demonstrated that both anxiety and depression phenotypes were affected by the life-stress interaction of rs16944, but the protective effect in the low-exposed groups was found in depression phenotypes only, suggesting different roles of cytokines in the development of depression and anxiety (Roy-Byrne et al., 2008).

4.2. Rs1143643

Rs1143643 showed Bonferroni corrected significant interaction with RLE, but only nominally significant interactions with CHA – opposite to the findings for rs16944. In addition, the RLE interaction only influenced depressive symptoms (not anxiety symptoms) providing further support that different underlying mechanisms might occur in depression compared with anxiety (Pollack, 2005). In line with our results, Baune et al. found that the minor A allele of the SNP has been associated with better outcome during antidepressant therapy, namely it protected against non-remission (Baune et al., 2010). According to the National Institute of Environmental Health Sciences (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm), this intronic SNP has no evident functional activity, although HAPMAP states that it is 869 bp from, and in linkage with, rs1071676 which has been associated with different allelic expression of the *IL1B* gene (Serre et al., 2008). As rs1143643 is near to the 3′ end of the *IL1B* gene, it may also affect the stability of the transcripted mRNA which is one of the main mechanisms in adaptation to stress (Guhaniyogi and Brewer, 2001). The stronger interaction with RLE compared to CHA suggests that this SNP, or the 3′ end genetic region in linkage with it, has a role in the adaptation to recent stressors (Dhabhar, 2014). However the results of haplotype analysis suggest that – at gene level – the effect of CHA could be more important, and the potential moderating effect of RLE on the *IL1B* gene function has a smaller effect size which was not sufficiently robust in our study due to limited power.

4.3. Effects of IL-1β in the central nervous system

IL-1β has been proposed to possess a central role in the cross-talk between the immune system and the central nervous system (Baganz and Blakely, 2013). IL-1β modulates tryptophan metabolism by enhancing the activity of the indolamine-2.3-dyoxigenase (IDO) enzyme, and thus indirectly causes lower tryptophan availability for serotonin production; IDO also activates the kynurenine pathway which produces potentially neurotoxic metabolites (Dantzer et al., 2011). IL-1β has a regulatory role in HPA axis activity, thus contributing to depression-induced cortisol-resistance (Maes et al., 1993). Consistently, higher IL-1β activity in the brain can also influence neural plasticity through microglial activation (Miller et al., 2009), while kynurenine and the HPA axis also greatly influence neural plasticity promoting depression-specific changes in the neural network (Rothwell and Luheshi, 2000). Moreover, proinflammatory cytokines, such as IL-1β, have been suggested to play an important role in the internalization of social-environmental stress (including childhood trauma and life stress in adulthood) (Slavich and Irwin, 2014).

4.4. Strength and limitations

Our study is the first that systematically investigated different parts of the *IL1B* gene in interaction with early and recent life stressors on mood disorder related symptoms; for example, this is the first time that the anxiogenic effect of rs16944's life stress interactions has been demonstrated. Also the main results were confirmed by two entirely different statistical methods – linear regression analysis and Bayesian relevance analysis. However, our study has some limitations. First, our analysis was limited to only two polymorphisms based on previous articles (Baune et al., 2010; Borkowska et al., 2011; Yu et al., 2003). Second, our population sample was relatively small and consists mostly of female subjects. Third, we used childhood adversity and recent negative life events as known environmental risk factors but other aspects of interactions such as comorbid diseases or social support were not included in our analysis. Fourth, the risk factors and phenotypes were self-reported by questionnaires, which might bias our variables. Fifth, after the random splitting of our population sample we could not replicate some of our findings in the two pseudo-independent subgroups, possibly because of the reduced statistical power. And finally, some of our results did not survive correction for multiple testing, so further replication studies are required to confirm these findings.

4.5. Conclusions

Our study is the first to provide evidence for the interaction of rs16944 and rs1143643 polymorphisms of the *IL1B* gene with different environmental stress factors. Therefore we suggest that further investigations of the *IL1B* gene should also include, in the analysis, various stress factors (e.g. comorbid disorders, socioeconomic disadvantages, or psychosocial stresses) in order to obtain a consistent effect of the polymorphisms on mood disorder phenotypes. Also organizing the polymorphisms effect by environmental vulnerability can provide us with a better understanding of the role of the *IL1B* gene in pathomechanisms of mood spectrum disorders. Furthermore, analyses carried out in the most exposed groups show much stronger genetic effects as described earlier with other genetic variants also (Juhasz et al., 2015, 2014).

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Conflict of interest

The authors did not declare any conflicting interests.

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References

Alheim, K., Bartfai, T., 1998. The interleukin-1 system: receptors, ligands, and ICE in the brain and their involvement in the fever response. Ann. N. Y. Acad. Sci. 840, 51–58.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed..

Anisman, H., Hayley, S., 2012. Inflammatory factors contribute to depression and its comorbid conditions. Sci. Signal. 5, pe45.

Antal, P., Millinghoffer, A., Hullám, G., Szalai, C., Falus, A., 2008. A bayesian view of challenges in feature selection: feature aggregation, multiple targets,

redundancy and interaction. In: Saeys, Yvan, Liu, Huan, Inza, Iñaki, Wehenkel, Louis, Van de Peer, Yves (Eds.), JMLR Workshop and Conference Proceedings. Antwerpen, Belgium, pp. 74–89.
Antal, P., Millinghoffer, A., Hullam, G., Hajos, G., Sarkozy, P., Szalai, C.A.F., 2014. Bayesian, Systems-based, Multilevel Analysis of Biomarkers of Complex Phenotypes: From Interpretation to Decisions. Oxford University Press, pp. 318–360.
Baganz, N.L., Blakely, R.D., 2013. A dialogue between the immune system and brain, spoken in the language of serotonin. ACS Chem. Neurosci. 4, 48–63.
Baune, B.T., Dannlowski, U., Domschke, K., Janssen, D.G., Jordan, M.A., Ohrmann, P., Bauer, J., Biros, E., Arolt, V., Kugel, H., Baxter, A.G., Suslow, T., 2010. The interleukin 1 beta (IL1B) gene is associated with failure to achieve remission and impaired emotion processing in major depression. Biol. Psychiatry 67, 543–549.
Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., Ruggiero, J., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am. J. Psychiatry 151, 1132–1136.
Borkowska, P., Kucia, K., Rzeznicczek, S., Paul-Samojedny, M., Kowalczyk, M., Owczarek, A., Suchanek, R., Medrala, T., Kowalski, J., 2011. Interleukin-1beta promoter (-31T/C and -511C/T) polymorphisms in major recurrent depression. J. Mol. Neurosci. 44, 12–16.
Borsini, A., Zunszain, P.A., Thuret, S., Pariante, C.M., 2015. The role of inflammatory cytokines as key modulators of neurogenesis. Trends Neurosci. 38, 145–157.
Brugha, T., Bebbington, P., Tennant, C., Hurry, J., 1985. The list of threatening experiences: a subset of 12 life event categories with considerable long-term contextual threat. Psychol. Med. 15, 189–194.
Capuron, L., Miller, A.H., 2011. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol. Ther. 130, 226–238.
Cohen-Woods, S., Craig, I.W., McGuffin, P., 2013. The current state of play on the molecular genetics of depression. Psychol. Med. 43, 673–687.
Converge-consortium, 2015. Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature 523, 588–591.
Dantzer, R., O'Connor, J.C., Lawson, M.A., Kelley, K.W., 2011. Inflammation-associated depression: from serotonin to kynurenine. Psychoneuroendocrinology 36, 426–436.
del Rey, A., Apkarian, A.V., Martina, M., Besedovsky, H.O., 2012. Chronic neuropathic pain-like behavior and brain-borne IL-1beta. Ann. N. Y. Acad. Sci. 1262, 101–107.
Derogatis, L.R., Melisaratos, N., 1983. The Brief Symptom Inventory: an introductory report. Psychol. Med. 13, 595–605.
Dhabhar, F.S., 2014. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol. Res. 58, 193–210.
Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctôt, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.
Freeman, B., Smith, N., Curtis, C., Huckett, L., Mill, J., Craig, I.W., 2003. DNA from buccal swabs recruited by mail: evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. Behav. Genet. 33, 67–72.
Giles, J.A., Greenhalgh, A.D., Davies, C.L., Denes, A., Shaw, T., Coutts, G., Rothwell, N.J., McColl, B.W., Allan, S.M., 2014. Requirement for interleukin-1 to drive brain inflammation reveals tissue-specific mechanisms of innate immunity. Eur. J. Immunol.
Girotti, M., Donegan, J.J., Morilak, D.A., 2011. Chronic intermittent cold stress sensitizes neuro-immune reactivity in the rat brain. Psychoneuroendocrinology 36, 1164–1174.
Guhaniyogi, J., Brewer, G., 2001. Regulation of mRNA stability in mammalian cells. Gene 265, 11–23.
Hall, S.K., Perregaux, D.G., Gabel, C.A., Woodworth, T., Durham, L.K., Huizinga, T.W., Breedveld, F.C., Seymour, A.B., 2004. Correlation of polymorphic variation in the promoter region of the interleukin-1 beta gene with secretion of interleukin-1 beta protein. Arthritis Rheum. 50, 1976–1983.
Hartwell, K.J., Moran-Santa Maria, M.M., Twal, W.O., Shaftman, S., DeSantis, S.M., McRae-Clark, A.L., Brady, K.T., 2013. Association of elevated cytokines with childhood adversity in a sample of healthy adults. J. Psychiatr. Res. 47, 604–610.
Hoeting, J.D., Raftery, A.E., Volinsky, C.T., 1999. Bayesian model averaging: a tutorial. Stat. Sci. 14, 382–417.
Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71, 171–186.
Hullam, G., Antal, P., 2013. The effect of parameter priors on Bayesian relevance and effect size measures. Period. Polytech. Electr. Eng. Comput. Sci. 2, 35–48.
Hullam, G., Juhasz, G., Bagdy, G., Antal, P., 2012. Beyond structural equation modeling: model properties and effect size from a Bayesian viewpoint. An example of complex phenotype-genotype associations in depression. Neuropsychopharmacol. Hung. 14, 273–284.
Juhasz, G., Chase, D., Pegg, E., Downey, D., Toth, Z.G., Stones, K., Platt, H., Mekli, K., Payton, A., Elliott, R., Anderson, I.M., Deakin, J.F., 2009. CNR1 gene is associated with high neuroticism and low agreeableness and interacts with recent negative life events to predict current depressive symptoms. Neuropsychopharmacology 34, 2019–2027.
Juhasz, G., Dunham, J.S., McKie, S., Thomas, E., Downey, D., Chase, D., Lloyd-Williams, K., Toth, Z.G., Platt, H., Mekli, K., Payton, A., Elliott, R., Williams, S.R., Anderson, I.M., Deakin, J.F., 2011. The CREB1-BDNF-NTRK2 pathway in depression: multiple gene-cognition-environment interactions. Biol. Psychiatry 69, 762–771.
Juhasz, G., Hullam, G., Eszlari, N., Gonda, X., Antal, P., Anderson, I.M., Hokfelt, T.G., Deakin, J.F., Bagdy, G., 2014. Brain galanin system genes interact with life stresses in depression-related phenotypes. Proc. Natl. Acad. Sci. U.S.A. 111, E1666–E1673.
Juhasz, G., Gonda, X., Hullam, G., Eszlari, N., Kovacs, D., Lazary, J., Pap, D., Petschner, P., Elliott, R., Deakin, J.F., Anderson, I.M., Antal, P., Lesch, K.P., Bagdy, G., 2015. Variability in the effect of 5-HTTLPR on depression in a large European population: the role of age, symptom profile, type and intensity of life stressors. PLoS ONE 10 e0116316.
Kendler, K.S., Prescott, C.A., 1999. A population-based twin study of lifetime major depression in men and women. Arch. Gen. Psychiatry 56, 39–44.
Kim, J.M., Stewart, R., Kim, S.Y., Kang, H.J., Jang, J.E., Kim, S.W., Shin, I.S., Park, M.H., Yoon, J.H., Park, S.W., Kim, Y.H., Yoon, J.S., 2013. A one year longitudinal study of cytokine genes and depression in breast cancer. J. Affect. Disord. 148, 57–65.
Lawson, M.A., McCusker, R.H., Kelley, K.W., 2013. Interleukin-1 beta converting enzyme is necessary for development of depression-like behavior following intracerebroventricular administration of lipopolysaccharide to mice. J. Neuroinflammation 10, 54.
Laye, S., Liege, S., Li, K.S., Moze, E., Neveu, P.J., 2001. Physiological significance of the interleukin 1 receptor accessory protein. NeuroImmunoModulation 9, 225–230.
Lazary, J., Lazary, A., Gonda, X., Benko, A., Molnar, E., Juhasz, G., Bagdy, G., 2008. New evidence for the association of the serotonin transporter gene (SLC6A4) haplotypes, threatening life events, and depressive phenotype. Biol. Psychiatry 64, 498–504.
Ma, X., Wang, R., Zhao, X., Zhang, C., Sun, J., Li, J., Zhang, L., Shao, T., Ruan, L., Chen, L., Xu, Y., Pan, J., 2013. Antidepressant-like effect of flaxseed secoisolariciresinol diglycoside in ovariectomized mice subjected to unpredictable chronic stress. Metab. Brain Dis. 28, 77–84.
Madigan, D., Andersson, S., Perlman, M., Volinsky, C.T., 1996. Bayesian model averaging and model selection for Markov equivalence classes of acyclic digraphs. Commun. Stat. Theory Methods 25, 2493–2519.
Maes, M., Bosmans, E., Meltzer, H.Y., Scharpe, S., Suy, E., 1993. Interleukin-1 beta: a putative mediator of HPA axis hyperactivity in major depression? Am. J. Psychiatry 150, 1189–1193.
McCulley, M.C., Day, I.N., Holmes, C., 2004. Association between interleukin 1-beta promoter (-511) polymorphism and depressive symptoms in Alzheimer's disease. Am. J. Med. Genet. B Neuropsychiatr. Genet. 124B, 50–53.
Michel, M., Schmidt, M.J., Mirnics, K., 2012. Immune system gene dysregulation in autism and schizophrenia. Dev. Neurobiol. 72, 1277–1287.
Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.
Pascoe, M.C., Crewther, S.G., Carey, L.M., Crewther, D.P., 2011. Inflammation and depression: why poststroke depression may be the norm and not the exception. Int. J. Stroke 6, 128–135.
Plomin, R., Haworth, C.M., Davis, O.S., 2009. Common disorders are quantitative traits. Nat. Rev. Genet. 10, 872–878.
Pollack, M.H., 2005. Comorbid anxiety and depression. J. Clin. Psychiatry 66 (Suppl. 8), 22–29.
Raison, C.L., Miller, A.H., 2013. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol. Psychiatry 18, 15–37.
Rosa, A., Peralta, V., Papiol, S., Cuesta, M.J., Serrano, F., Martinez-Larrea, A., Fananas, L., 2004. Interleukin-1beta (IL-1beta) gene and increased risk for the depressive symptom-dimension in schizophrenia spectrum disorders. Am. J. Med. Genet. B Neuropsychiatr. Genet. 124B, 10–14.
Rothwell, N.J., Luheshi, G.N., 2000. Interleukin 1 in the brain: biology, pathology and therapeutic target. Trends Neurosci. 23, 618–625.
Roy-Byrne, P.P., Davidson, K.W., Kessler, R.C., Asmundson, G.J., Goodwin, R.D., Kubzansky, L., Lydiard, R.B., Massie, M.J., Katon, W., Laden, S.K., Stein, M.B., 2008. Anxiety disorders and comorbid medical illness. Gen. Hosp. Psychiatry 30, 208–225.
Scott, K.M., Bruffaerts, R., Tsang, A., Ormel, J., Alonso, J., Angermeyer, M.C., Benjet, C., Bromet, E., de Girolamo, G., de Graaf, R., Gasquet, I., Gureje, O., Haro, J.M., He, Y., Kessler, R.C., Levinson, D., Mneimneh, Z.N., Oakley Browne, M.A., Posada-Villa, J., Stein, D.J., Takeshima, T., Von Korff, M., 2007. Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. J. Affect. Disord. 103, 113–120.
Semple, B.D., Blomgren, K., Gimlin, K., Ferriero, D.M., Noble-Haeusslein, L.J., 2013. Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species. Prog. Neurobiol. 106–107, 1–16.
Serre, D., Gurd, S., Ge, B., Sladek, R., Sinnett, D., Harmsen, E., Bibikova, M., Chudin, E., Barker, D.L., Dickinson, T., Fan, J.B., Hudson, T.J., 2008. Differential allelic expression in the human genome: a robust approach to identify genetic and epigenetic cis-acting mechanisms regulating gene expression. PLoS Genet. 4 e1000006.
Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol. Bull. 140, 774–815.
Stephens, M., Balding, D.J., 2009. Bayesian statistical methods for genetic association studies. Nat. Rev. Genet. 10, 681–690.
Wohleb, E.S., Patterson, J.M., Sharma, V., Quan, N., Godbout, J.P., Sheridan, J.F., 2014. Knockdown of interleukin-1 receptor type-1 on endothelial cells attenuated stress-induced neuroinflammation and prevented anxiety-like behavior. J. Neurosci. 34, 2583–2591.
Yu, Y.W., Chen, T.J., Hong, C.J., Chen, H.M., Tsai, S.J., 2003. Association study of the interleukin-1 beta (C-511T) genetic polymorphism with major depressive disorder, associated symptomatology, and antidepressant response. Neuropsychopharmacology 28, 1182–1185.