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Somatic, positive and negative domains of the Center for Epidemiological Studies Depression (CES-D) scale: a meta-analysis of genome-wide association studies

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Abstract

Background—Major depressive disorder (MDD) is moderately heritable, however genome-wide association studies (GWAS) for MDD, as well as for related continuous outcomes, have not shown consistent results. Attempts to elucidate the genetic basis of MDD may be hindered by heterogeneity in diagnosis. The Center for Epidemiological Studies Depression (CES-D) scale provides a widely used tool for measuring depressive symptoms clustered in four different domains which can be combined together into a total score but also can be analysed as separate symptom domains.

Method—We performed a meta-analysis of GWAS of the CES-D symptom clusters. We recruited 12 cohorts with the 20-or 10-item CES-D scale (32 528 persons).

Results—One single nucleotide polymorphism (SNP), rs713224, located near the brain-expressed melatonin receptor (*MTNR1A*) gene, was associated with the somatic complaints domain of depression symptoms, with borderline genome-wide significance ($p_{\text{discovery}} = 3.82 \times 10^{-8}$). The SNP was analysed in an additional five cohorts comprising the replication sample (6813 persons). However, the association was not consistent among the replication sample ($p_{\text{discovery +replication}} = 1.10 \times 10^{-6}$) with evidence of heterogeneity.

Conclusions—Despite the effort to harmonize the phenotypes across cohorts and participants, our study is still underpowered to detect consistent association for depression, even by means of symptom classification. On the contrary, the SNP-based heritability and co-heritability estimation results suggest that a very minor part of the variation could be captured by GWAS, explaining the reason of sparse findings.

Keywords

Genome-wide association studies; major depressive disorder; meta-analyses

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Supplementary material

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Declaration of Interest

None.

Introduction

Genetic factors play an important role in the susceptibility to depression. A meta-analysis of twin studies on major depressive disorder (MDD) estimated the heritability between 31 and 42% (Sullivan *et al.* 2000). The success of genome-wide association studies (GWAS) aiming to find genes underlying vulnerability for depression, however, has been limited; the most promising findings to date are poorly replicated and explain only a small proportion of this heritability (Muglia *et al.* 2008; Psychiatric GWAS Case Control Consortium *et al.* 2009; Sullivan *et al.* 2009). This may be explained by the polygenic architecture of the trait as well as difficulties in diagnosis. A validated biomarker for depression does not exist and the diagnosis is based solely on symptoms. Such symptoms include depressed mood states, loss of interest in activities, feelings of worthlessness or inappropriate guilt, recurrent thoughts of death, poor concentration, and somatic symptoms such as changes in appetite, sleep patterns, fatigue, and weight gain or loss (American Psychiatric Association, 1994; National Institute for Clinical Excellence, 2003). Depression can manifest with different patterns of symptoms, and such phenotypic heterogeneity may reflect genetic heterogeneity. It is plausible that different genetic pathways are associated with the various symptom clusters, and analyses of more narrowly defined phenotypes may reduce genetic heterogeneity. Indeed, the diverse domains of complaints, which result in variations in presentation of the disease within and between populations, may lead to problems for gene discovery. A focus on outcomes based on depressive symptoms and endophenotypes has been shown to increase power in association studies (Teslovich *et al.* 2010; van der Sluis *et al.* 2013). However, the genetic architecture of these outcomes is also complex and may involve the effects of multiple common variants (Demirkan *et al.* 2011).

Depressive symptoms can be measured by questionnaires, such as the Center for Epidemiological Studies Depression (CES-D) scale, which shows moderate heritability (López-León *et al.* 2010). The CES-D scale measures symptoms clustered in somatic complaints, lack of positive affect, negative affect and interpersonal problems domains, which are usually combined into a single score (Radloff, 1977). The CES-D subscales can also be analysed separately in order to focus on the specific symptom domains. We conducted a meta-analysis of GWAS of specific symptom domains measured by the CES-D scale. The discovery set consisted of 12 cohorts ($n = 32\,528$) and the replication set consisted of five cohorts ($n = 6813$).

Method

Table 1 summarizes the characteristics of the discovery and replication cohorts from the Cohorts for Health and Aging Research in Genetic Epidemiology (CHARGE) Consortium. The main aim of CHARGE is to facilitate GWAS meta-analyses and replication opportunities among multiple large and well-phenotyped longitudinal cohort studies (Psaty *et al.* 2009). The discovery sample consisted of the CHARGE cohorts with eligible 20-item CES-D (CES-D-20) data. These cohorts were the Baltimore Longitudinal Study of Aging (BLSA) (Sutin & Zonderman, 2012), the Dortmund Health Study (Vennemann *et al.* 2008; Pfaffenrath *et al.* 2009), the Erasmus Rucphen Family Study (ERF) (Aulchenko *et al.* 2004; López-León *et al.* 2009), the *National Heart, Lung, and Blood Institute's* Framingham Heart

Study (FHS) (Dawber *et al.* 1951; Feinleib *et al.* 1975; Splansky *et al.* 2007), the Helsinki Birth Cohort Study (HBCS) (Barker *et al.* 2005), European ancestry participants from the Health, Aging and Body Composition study (HEALTH ABC-Eur) (Cesari *et al.* 2003), the Rotterdam Study I-II and III (RS I-II and RS-III) (Hofman *et al.* 2011) and SardiNIA (Pilia *et al.* 2006) and two studies in which the symptoms of depression were measured with the 10-item version of CES-D (CES-D-10): the Atherosclerosis Risk In Communities (ARIC) study (ARIC Investigators, 1989) and the Swedish Twin Registry (STR) study (Rahman *et al.* 2009). FINRISK (Vartiainen *et al.* 2010), the Health and Retirement Study (HRS) (Juster & Suzman, 1995; Weir, 2008), Invechhiare in Chianti (InCHIANTI), and the Memory and Aging Project and Religious Order Study of Rush Alzheimer's Disease Center (RUSH-ROS and RUSH-MAP) (Bennett *et al.* 2005; Bennett, 2006) were used as replication analysis of rs713224 (see online Supplementary text S1 for the study descriptions and online Supplementary text S2 for the items of the CES-D scale). With these sample sizes, we had about 80% power to detect associations that explain about 0.12% of the trait variation in the discovery cohort and replication cohort with a p value of 5×10^{-8} and 0.05, respectively. In the case of multiple measurements the study centers preferred to analyse the measurements that maximize the number in the analysis. This is usually the first measurement as the response declines by years of follow-up. In this case the mean age of the samples refers to the time of measurement date.

GWAS analyses were performed individually by the study centers, according to the same analysis plan; each study excluded dementia cases (Mini-Mental State Examination score < 22), and anti-depressive medication users (except BLSA), since the effect of anti-depressive medication on the scales was not consistent across the studies. There was no restriction on age. Each study center computed the subscales of the CES-D questionnaire that resulted in four separate scores for each individual, measuring different domains of complaints. The reliability coefficients (Cronbach's α) for the somatic complaints (seven items), lack of positive affect (four items) and negative affect (seven items) domains were adequate and ranged from 0.68 to 0.84 whereas for the interpersonal problems domain (two items) those were between 0.45 and 0.63 for the 20-item CES-D scale cohorts. For the 10-item scale, Cronbach's α's for the somatic complaints (three items) ranged from 0.52 to 0.78 and for lack of positive affect (two items) and negative affect (three items) between 0.64 and 0.71. Each study implemented linear regression models, adjusted for age, age-square and sex, under the assumption of an additive genetic model, regressing each subscale on allele dosage and reported the summary statistics. The genotyping and imputation methods for each study are given in online Supplementary Table S1. Additional study site-specific adjustments included linear mixed-effect models to account for familial correlations in the FHS and ERF, and adjustment for the top three Eigen vectors in RUSH-MAP, RUSH-ROS and STR. Prior to meta-analysis, all single nucleotide polymorphism (SNP) IDs were mapped to dbSNP Build 129. Possible measurement and scoring differences across different study centers were checked through extracting the median standard error from the GWAS summary statistics of each study center and plotting it against the square-root of the sample size. Allele frequencies for all SNPs were compared with HapMap frequencies. Stratified Q-Q plots were generated for minor allele frequency (MAF) and imputation quality strata to assess potential sources of inflation. Meta-analyses were performed using the sample size-weighted

method as implemented in METAL software package (Willer *et al.* 2010). Due to poor psychometric properties and differences in the median standard errors across the cohorts we excluded the interpersonal problems domain from further analysis. Furthermore, this domain has been criticized for not being consistent with the current criteria for depression and therefore introducing confounding in the validity of the CESD (Carleton *et al.* 2013). SNPs with a MAF less than 2.5% or an observed:expected variance ratio (imputation quality) less than 0.30 were excluded on a per-study basis. SNPs for which the total sample size was lower than 5000 were removed from further analysis. We did not use genomic control as this method has been shown to be too conservative (Bulik-Sullivan *et al.* 2015). SNP-based heritability was calculated using 1 069 063 markers that were common in the meta-analyses results and linkage disequilibrium (LD) scores were computed using the 1000 Genomes Central EUrope (CEU) reference panel as suggested by the tutorials and provided by the developers of the method.

To test the amount of variance explained by the genetic risk score, we performed a genetic risk score analysis. We excluded one of the cohorts (RS I) ($n = 3709$) from the discovery set and used this cohort as the target sample. The total score for individuals was calculated for each set of SNPs that were defined on the basis of the p values in the discovery set (e.g. $p <$ 0.00001, 0.0001, 0.1, 0.2). Genetic risk scores were calculated by multiplying the Z-score that was obtained in the discovery analyses with the risk alleles per SNP (0, 1, 2). The PLINK toolset was used to calculate the risk scores (Purcell *et al.* 2007). Linear regression analysis was used to test the association of the genetic risk scores with somatic item scores in the target sample.

Results

The inflation factors for the discovery GWAS of the three scales varied between 1.026 and 0.984. We did not observe any genome-wide significant SNPs for any of the scales in the discovery set apart from the top SNP, rs713224, that showed significant association with the somatic complaints scale ($p_{\text{discovery}} = 3.82 \times 10^{-8}$). Q-Q plots and Manhattan plots of this analysis are presented in the online Supplementary Figs S1 and S2. Online Supplementary Table S2 shows the SNPs with $p < 10^{-4}$ from the discovery set of 32 528 persons for the somatic, positive and negative domains. The analysis of rs713224 was further extended to a second stage, which included 6813 persons from five study samples, as shown in Table 1. Study-specific summary results for rs713224 are given in online Supplementary Table S3. The overall analysis yielded a non-significant result ($p_{\text{discovery+replication}} = 1.10 \times 10^{-6}$) in the genome-wide scale. Testing for heterogeneity showed evidence for outliers ($p_{\text{het}} = 0.07$) in the combined analysis, compared with the discovery phase ($p_{\text{het}} = 0.17$).

SNP-based heritability estimates (h^2) were 0.038 (S.E. = 0.01), 0.01 (S.E. = 0.01) and 0.024 (S.E. = 0.01) for the somatic, positive and negative domains, respectively. The somatic and negative domains showed significant co-heritability (genetic correlation: 1.1, S.E. = 0.23, Z-score = 4.6, $p = 4.3 \times 10^{-6}$). The positive domain did not show significant genetic correlation with the negative domain (genetic correlation: 1.5, S.E. = 1.4, Z-score = 1.1, $p =$ 0.27) or with the somatic domain (genetic correlation: 1.5, S.E. = 1.3, Z-score = 1.1; $p =$ 0.27).

In order to search for possible real associations among the subthreshold loci we have performed also a risk score analysis using the discovery set after excluding one of the cohorts as discovery and the RS as the training set. The SNPs with p values less than 10^{-5} explained a significant but very small part of the variance on the somatic items scale ($p = 0.001$, $R^2 = 0.3\%$) (online Supplementary Fig. S4).

Discussion

We conducted a GWAS on specific symptom domains of depression in which we combined the results of 12 population-based studies including 32 528 individuals to find common variants that increase the vulnerability to a particular symptom domain (somatic complaints, lack of positive affect and negative affect). In the discovery set we found evidence for one SNP near the brain-expressed melatonin receptor (*MTNR1A*) gene with respect to the somatic complaints domain only ($p_{\text{discovery}} = 3.82 \times 10^{-8}$). This is in line with an earlier study showing that symptoms of depression linked with physiological functions may show higher heritability compared with symptoms related to negative affect (Jang *et al.* 2004). Rs713224 was further analysed in five separate samples and also in combined meta-analyses of the discovery and replication sets. However, the level of significance of this SNP was attenuated ($p_{\text{discovery+replication}} = 1.10 \times 10^{-6}$). The negative and positive domains did not yield any genome-wide significant SNPs.

Our top SNP, rs713224, is located near the *MTNR1A* gene, which encodes one of the two melatonin receptors expressed in the brain. Melatonin is a circadian and seasonal regulator in many organisms including humans and is secreted in darkness by the pineal gland. Although melatonin is the hormone of the pineal gland, *MTNR1A* is ubiquitously expressed, predominantly in the suprachiasmatic nucleus, hypothalamus and prefrontal cortex. The melatonin receptor pathway is known to be involved in depression (Carman *et al.* 1976; Wetterberg *et al.* 1984; Goldstein, 1985; Bourin & Prica, 2009; Anderson, 2010; Gałecka *et al.* 2011) and its relationship with somatic complaints, and vitality in general, makes it a biologically plausible gene.

However, lack of replication raises the conclusion that our finding for this SNP is likely to be a false positive. Among other reasons, population stratification can result in false-positive findings. To avoid population stratification, only individuals of European descent were included in this study. Including only individuals from population-based studies of European descent also minimized measurement error caused by cultural differences in response to the CES-D (Bernert *et al.* 2009). On the other hand, this does not count for the replication set. Among them, for instance the RUSH sample included more women and older persons and reported very low mean values for the somatic items (Table 1). Difference in age across the study samples can introduce heterogeneity since melatonin and melatonin receptors are shown to decrease by age (Hill *et al.* 2013). An additional sensitivity analysis, excluding the RUSH study, yielded a $p_{\text{discovery+replication}} = 4.96 \times 10^{-7}$ and decreased the heterogeneity ($p_{\text{het}} = 0.08$), but did not exclude it completely. A particular reason of heterogeneity for the melatonin receptor signaling-related outcomes is the interaction with melatonin levels as reviewed extensively before (Pandi-Perumal *et al.* 2008) and therefore the influence on depressive symptoms may be season specific, depending on the calendar time and latitude

that the depression screening took place. However, it was not possible to control for this in the current study.

Although our study is among the largest ones conducted thus far on the common genomic variation in depression with power to detect effects explaining 0.12% of the variation, our study failed to clearly detect and replicate a single loci related to symptoms of depression. Among several reasons, one is that the trait may not be genetically controlled.

The CES-D questionnaire measures depressive symptoms in the past week and the total CES-D scale has been shown to be conserved through life (Radloff, 1977), while this does not rule out the fact that responses to different symptom clusters may differ throughout the lifetime as there is no study to our knowledge that has focused on this. In addition, responses to specific symptom clusters may be population specific due to cultural acceptance or practices. Moreover, age differences across the CHARGE cohorts might have played a role as presentation of depressive symptoms strongly differs by age whereas some genetic variants are hypothesized to interact with age (Simino *et al.* 2014). These would probably introduce phenotypic and genetic heterogeneity. To see if the individual studies were indeed genetically controlled we estimated the SNP-based heritability from the separate GWAS summary statistics collected in this research. The SNP-based heritability estimations in the meta-analysis were surprisingly low (1–4%), indicating the reason for the sparse findings. This is partially due to several reasons sourcing from the genetic architecture of the traits, which are not adequately addressed by the simple association models; such as exclusion of X chromosome, and limiting the analysis only with an additive genetic model which deviates from sufficient power when the MAF < 0.5. Another important reason is that interaction of any genetic determinant with stressful life events, traumas, therapeutic agents, smoking or menopause, which may confer risk to depression (Keers & Uher, 2012), were neglected. We further estimated the co-heritability to see if there are genetic outliers amongst the meta-analysis cohorts. This revealed surprisingly low co-heritability across the contributing cohorts, explaining the lack of successful meta-analysis and replication in our study. The low co-heritability estimations are the indicators of high genetic and phenotypic heterogeneity across the cohorts and are the plausible explanation of insignificant replication in our research. Here it is important to note that the estimates from LD score regression have to be treated with caution because of the small sample size in some individual cohorts.

We also considered the possibility that individual common SNPs explain only a very small proportion of some complex traits, as shown by the polygenic risk score analyses in the current study in which only 0.3% of variance was explained by the most significant SNPs. The risk score for the remaining thresholds did not improve the explained variance, contrary to previous reports (Demirkan *et al.* 2011). Previous studies exploring complex traits (e.g. educational attainment, MDD) revealed similar results (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium *et al.* 2013; Rietveld *et al.* 2013).

The difficulty in finding and replicating GWAS signals for major depression has been a common experience both for depressive symptoms and MDD. A previous study of depressive symptoms of the CHARGE Consortium (Hek *et al.* 2013) on a partially overlapping sample suggested a region on 5q21 in a combined analysis of more than 50 000

persons. A meta-analysis of eight GWAS of MDD status (about 6000 MDD cases and about 7000 controls) yielded only one genome-wide significant finding in the solute carrier family 6 member 15 gene (*SLC6A15*) (Kohli *et al.* 2011), while the recent Psychiatric Genomics Consortium (PGC) mega-analysis (9238 cases and 8039 controls) pointed out one region on 3p21.1 that reached genome-wide significance; however, to our knowledge no replication has been reported so far. A PGC-MDD GWAS also showed an association of rs4478239, located within 800 kB of *MTNR1A*, with recurrent depression ($p = 4.7 \times 10^{-7}$) in a study including 6743 cases and 9519 controls (online Supplementary Fig. S3). However, the proxy for our top SNP in that region (rs2375800) was not associated with MDD. Similarly, we were not able to replicate the two main findings of a recent report by the CONVERGE Consortium (2015) who attributed their success to the recruitment of relatively homogeneous cases with severe illness. For the *LHPP* gene region the proxy SNP rs12258489 yielded insignificant *p* values for negative items (*Z*-score = 1.52, $p = 0.12$), for positive items (*Z*-score = −0.52, $p = 0.59$) and for somatic items (*Z*-score = 1.23, $p = 0.22$). For the sirtuin 1 (*SIRT1*) region, the SNP of interest, rs12415800, did not associate with negative items (*Z*-score = 0.12, $p = 0.89$), positive items (*Z*-score = −0.57, $p = 0.56$) or somatic items scales (*Z*-score = 1.81, $p = 0.07$).

Conclusion

To conclude, our efforts in a large collaboration utilizing phenotypes defined by symptom clustering yielded no genome-wide significant hit except the somatic complaints domain. One SNP, associated with somatic complaints, reached genome-wide significance in the combined sample and suggested the involvement of *MTNR1A* in the melatonin signaling pathway, but was not further replicated. Our results suggest that GWAS for depression in large population-based samples remain underpowered due to phenotypic and genetic heterogeneity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ARIC study

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HEALTH ABC-Eur

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RS

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RUSH-MAP

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North American Brain Expression Consortium (NABEC) brain expression quantitative trait loci (eQTL) data

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Table 1

Study sample characteristics of discovery and replication cohorts

	Somatic items	Negative items	Positive items	Interpersonal items	Age, years	*n*	Women, %
Discovery sample							
BLSA[a]	2.92 (2.81)	1.42 (2.41)	10.31 (2.45)	0.22 (0.65)	71.6 (13.8)	827	45.1
DHS[a]	2.92 (3.18)	1.54 (2.91)	7.03 (3.25)	0.22 (0.72)	52.4 (13.7)	991	52.6
ERF[a]	3.78 (3.76)	2.07 (3.36)	8.43 (3.40)	0.40 (0.89)	55.0 (10.1)	1107	55.2
FHS[a]	1.05 (0.751)	0.61 (0.75)	0.596 (0.739)	0.15 (0.35)	56.1 (10.5)	6636	51.8
HBCS[a]	3.79 (3.31)	2.00 (3.05)	9.22 (2.40)	0.37 (0.79)	63.4 (2.9)	1360	59.4
HEALTH ABC-Eur[a]	1.68 (2.13)	0.93 (1.85)	10.74 (1.82)	0.13 (0.49)	73.8 (2.8)	1520	46.4
RS I[a]	1.52 (2.61)	1.24 (2.65)	10.36 (2.59)	0.09 (0.42)	72.7 (7.2)	3709	58.1
RS II[a]	1.98 (2.78)	1.34 (2.66)	10.19 (2.60)	0.15 (0.53)	64.8 (8.0)	1995	53.3
RS III[a]	2.66 (3.32)	1.17 (2.58)	10.37 (2.41)	0.18 (0.58)	56.0 (5.7)	1917	55.1
SardiNIA[a]	3.27 (2.91)	2.51 (3.08)	4.81 (2.53)	0.48 (0.85)	58.0 (11.4)	2608	58.1
ARIC[b]	2.31 (2.15)	1.19 (1.72)	5.62 (0.95)	0.21 (0.65)	72.7 (5.5)	384	42.1
STR[b]	1.10 (1.60)	0.79 (1.43)	1.22 (1.27)	0.21 (0.58)	57.7 (8.9)	9474	52.7
Replication sample							
FINRISK[b]	1.74 (1.63)	–	–	–	53.1 (13.4)	605	49.7
HRS[b]	1.38 (1.50)	–	–	–	69.3 (5.5)	3753	58.1
InCHIANTI[a]	3.23 (3.18)	–	–	–	66.0 (15.0)	1019	47.0
RUSH-MAP[b]	0.50 (0.80)	–	–	–	80.8 (6.5)	721	71.7
RUSH-ROS[b]	0.57 (0.82)	–	–	–	75.5 (7.2)	715	65.9

Data are given as mean (standard deviation).

n, Number of subjects included; BLSA, Baltimore Longitudinal Study of Aging; DHS, Dortmund Health Study; ERF, Erasmus Rucphen Family Study; FHS, Framingham Heart Study; HBCS, Helsinki Birth Cohort Study; HEALTH ABC-Eur, Health, Aging and Body Composition study (of European ancestors); RS I-II-III, Rotterdam Study first, second and third waves; SardiNIA, SardiNIA study; ARIC, Atherosclerosis Risk in Communities study; STR, Swedish Twin Registry; FINRISK, National FINRISK Study of Finland; HRS, Health and Retirement Study; InCHIANTI, Invechhiare in Chianti; RUSH-MAP, Rush Memory and Aging Project; RUSH-ROS, Rush Religious Orders Study; CES-D, Center for Epidemiological Studies Depression.

[a]20-item CES-D scale.

[b] 10-item CES-D scale.