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Research paper

Genetic architecture of *DCC* and influence on psychological, psychiatric and cardiometabolic traits in multiple ancestry groups in UK Biobank

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ABSTRACT

Background: People with severe mental illness have a higher risk of cardiometabolic disease than the general population. Traditionally attributed to sociodemographic, behavioural factors and medication effects, recent genetic studies have provided evidence of shared biological mechanisms underlying mental illness and cardiometabolic disease. We aimed to determine whether signals in the *DCC* locus, implicated in psychiatric and cardiometabolic traits, were shared or distinct.

Methods: In UK Biobank, we systematically assessed genetic variation in the *DCC* locus for association with metabolic, cardiovascular and psychiatric-related traits in unrelated "white British" participants ($N = 402,837$). Logistic or linear regression were applied assuming an additive genetic model and adjusting for age, sex, genotyping chip and population structure. Bonferroni correction for the number of independent variants was applied. Conditional analyses (including lead variants as covariates) and trans-ancestry analyses were used to investigate linkage disequilibrium between signals.

Results: Significant associations were observed between *DCC* variants and smoking, anhedonia, body mass index (BMI), neuroticism and mood instability. Conditional analyses and linkage disequilibrium structure suggested signals for smoking and BMI were distinct from each other and the mood traits, whilst individual mood traits were inter-related in a complex manner.

Limitations: Restricting analyses in non-"white British" individuals to the phenotypes significant in the "white British" sample is not ideal, but the smaller samples sizes restricted the phenotypes possible to analyse.

Conclusions: Genetic variation in the *DCC* locus had distinct effects on BMI, smoking and mood traits, and therefore is unlikely to contribute to shared mechanisms underpinning mental and cardiometabolic traits.

1. Introduction

A link is well-established between mental health traits (MHTs) and cardiometabolic traits (CMTs) in epidemiological studies, with the presence of severe mental disorders resulting in a reduction in life expectancy of 15 years in women and 20 years in men (Wahlbeck et al., 2011), with a large proportion of deaths being attributed to CMT (Joukamaa et al., 2001). Indeed, individuals with serious mental illness have estimated 3.6 times higher likelihood of developing a cardiometabolic disease (Ilyas et al., 2017). Though this association is clear, there exists very little knowledge about the mechanisms. Key contributors to this association may be lifestyle factors such as exercise, diet and drug use (Chaddha et al., 2016) with additional links being drawn between the use of treatments for psychosis and increased body mass index (BMI) (Baptista, 1999). However, contemporary genetic studies suggest shared biological mechanisms underlying this association (Amare et al., 2017; Furtjes et al., 2021; Hagenaars et al., 2020; Hubel et al., 2019; Kan et al., 2016; Milaneschi et al., 2017; So et al., 2019; Wong et al., 2019). A number of loci have been identified wherein genetic variation is pleiotropic for both cardiometabolic and mental health associations (Amare

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et al., 2017), with many more loci implicated in both MHT and CMT.

Deleted in Colorectal Carcinoma (DCC) is a transmembrane receptor, which transmits signals involved in axonal development. Genetic variation in this locus has been implicated (through genome-wide association studies, GWAS) in significant number of phenotypes relevant to MHT and CMT including brain volume (Hibar et al., 2015), depression (Torres-Berrio et al., 2017), neuroticism (Li et al., 2020), BMI (Sakaue et al., 2021) and glucose homeostasis (Palmer et al., 2015).. Obesity (BMI), glucose dysregulation (such as type 2 diabetes) and cardiovascular disease are tightly interlinked, and all show increased risk and prevalence in severe mental illness. Therefore it is possible that the *DCC* locus might contribute to a mechanism shared by MHT and CMT. To date there has been no assessment of whether the reported associations overlap (one signal influencing multiple traits) or are distinct (signals for each trait are independent). Whilst summary statistics are available for many traits analysed in GWAS, differences in study recruitment, analytic design and differences in linkage disequilibrium (LD) between populations hinder cross-trait comparisons. The UK Biobank (UKB), with phenotypic and genetic data being available on CMTs and MHTs for ~0.5 M participants, provides new opportunities for detailed cross-trait analyses at specific loci. Specifically, large samples sizes with consistent genetic data handling and phenotyping of CMT and MHT enables consistent covariate selection and statistical modelling. Similar candidate loci studies have provided advances in understanding the link between CMT and MHT by demonstrating a plausible mechanism (for *CADM2*(Morris et al., 2019) and *PCSK9(*Hay et al., *2022)*) or providing no evidence for a role (for ASTN2 (Burt et al., 2021) and the contactin gene family (Morris et al., 2020)).

We set out to systematically investigate the *DCC* locus: for association with a wide range of psychological, psychiatric and cardiometabolic traits; to describe the genetic architecture underlying these associations and to explore mechanisms by which variants might have their effects.

2. Materials and methods

2.1. Study description

UK Biobank recruited ~500,000 individuals at 22 centres across the UK, between 2006 and 2010, and has been described in detail elsewhere (Bycroft et al., 2018; Matthews and Sudlow, 2015; Swanson and The, 2012). Blood was sampled and stored for genetic analysis. Participants underwent a physical examination and completed extensive questionnaires on lifestyle, personal and family history of disease. Baseline questionnaire data provided information on current smoking (data field #20116, current smokers *vs* former/non-smokers), risk-taking behaviour (#2040, "do you consider yourself to be someone who takes risks?"), mood instability (#1920, "does your mood often go up and down?") and anhedonia (#2060, "over the past two weeks, how often have you had little interest or pleasure in doing things?"). Controls were those who responded "not at all", with other responses being considered cases. Neuroticism (#20127) was assessed using the Eysenck Personality Questionnaire (Revised Short Form) which consisted of 12 yes/no (coded 0/1) questions (including #1920), which were summed, BMI was calculated from baseline height and weight measurements (#21001). Waist:hip ratio adjusted for BMI (WHRadjBMI) was calculated in a sex- and ancestry-specific manner from recorded waist (#48), hip (#49) and BMI (#21001) measurements as per Shungin et al. (Shungin et al., 2015) WHRadjBMI values for men and women were analysed together by ancestry group. Systolic and diastolic blood pressure were recorded (average of two measurements) and adjusted for effects of anti-hypertensive medication where appropriate (as per Ehret et al., SBP + 15 mmHg and DBP + 10 mmHg if using anti-hypertensive medication, (Ehret et al., 2016)). Probable type 2 diabetes (T2D) was defined as per Eastwood et al. (Eastwood et al., 2016). Ischemic heart disease (IHD, heart attack/angina) and stroke were assessed from self-report of a diagnosis (#6510). Venous thromboembolism was self-reported (deep-vein thrombosis and/or pulmonary embolism, #6152). A subset of UK Biobank participants completed an online mental health questionnaire (6–10 years after baseline) (Davis et al., 2020), enabling assessment of

Table 1
Cohort description by ancestry group.

	"White British"	European	Mixed	South Asian	African-Caribbean
N	402,837	50,514	10,450	7727	7645
N Men	185,216 (46.0)	22,148 (43.9)	5980 (57.2)	3566 (46.2)	4359 (57.0)
Age (years)	56.9 (8.0)	55.6 (8.1)	52.0 (8.1)	53.0 (8.5)	52.0 (8.1)
BMI (kg/m^2)	27.4 (4.8)	27.2 (4.9)	27.0 (4.9)	27.3 (4.5)	29.5 (5.4)
WHR	0.87 (0.09)	0.87 (0.09)	0.87 (0.08)	0.90 (0.09)	0.87 (0.08)
SBP	138 (19)	135 (18)	133 (19)	135 (19)	138 (19)
DBP	82 (10)	81 (10)	82 (11)	82 (10)	85 (11)
SBP[a]	141 (21)	138 (21)	136 (21)	139 (21)	143 (22)
DBP[a]	84 (11)	83 (11)	84 (12)	85 (12)	88 (12)
Current smoking	40,622 (10.1)	6598 (13.1)	1437 (13.8)	687 (9.0)	952 (12.6)
Hypertension	205,849 (53.6)	22,789 (47.4)	4523 (44.7)	3833 (51.0)	4322 (57.4)
Anti-hypertensive medication	83,951 (21.0)	9235 (18.4)	2048 (20.2)	2082 (27.9)	2341 (31.0)
Lipid-lowering medication	70,184 (20.6)	8044 (18.7)	1807 (20.7)	2050 (31.9)	1212 (21.1)
IHD	18,384 (6.1)	2136 (5.5)	414 (5.2)	575 (10.2)	264 (5.4)
Stroke	6151 (2.1)	708 (1.9)	94 (1.24)	128 (2.5)	118 (2.5)
VTE	10,444 (3.7)	1239 (3.5)	189 (2.8)	131 (2.4)	185 (3.6)
T2D	17,420 (4.0)	2121 (4.2)	865 (8.3)	1289 (16.7)	812 (10.6)
Anhedonia	78,882 (19.6)	11,257 (22.3)	3339 (32.0)	2814 (36.4)	2389 (31.3)
Mood instability	178,003 (45.2)	22,091 (45.0)	4757 (48.7)	3779 (53.2)	3725 (52.2)
neuroticism score	1.65 (5.90)	1.39 (6.11)	−0.28 (6.79)	−0.73 (7.07)	−0.25 (6.44)
Risk-taking	98,439 (24.4)	16,241 (32.2)	3706 (35.5)	2688 (34.8)	2986 (39.1)
Mental Health questionnaire	109,788 (27.3)	13,985 (27.7)	1872 (17.9)	845 (10.9)	910 (11.9)
GAD[b]	9097 (10.1)	1282 (11.5)	167 (10.9)	74 (10.4)	54 (6.7)
BD[b]	1873 (1.5)	324 (2.0)	51 (2.3)	25 (2.4)	24 (2.2)
MDD[b]	30,879 (28.1)	4186 (29.9)	539 (28.8)	196 (23.2)	203 (22.3)

Where: continuous variables are presented as mean (standard deviation) and binary variables are presented as N (%). IHD, ischemic heart disease; VTE, venous thromboembolism; T2D, type 2 diabetes; GAD, Generalised anxiety disorder; BD, bipolar disorder; MDD, major depressive disorder.

[a] Adjusted for anti-hypertensive medication.

[b] Of those completing the Mental Health Questionnaire.

Table 2
Lead SNPs identified in the white British sample (discovery or conditional analyses).

			BMI	(N = 390493)	Smoking	(N = 395132)	GAD	(N = 82055)	MDD	(N = 100081)	Mood instability	(N = 381457)	Neuroticism score	(N = 317318)	Anhedonia	(N = 356576)
SNP	A1	EAF	BETA (SE)	P	OR (95 %CI)	P	OR (95 %CI)	P	OR (95 %CI)	P	OR (95 %CI)	P	BETA (SE)	P	OR (95 %CI)	P
			−0.084		0.99		1.04		1.01		1.00				0.99	
rs5824977[a]	T	0.14	**(0.015)**	**4.87E−08**	(0.98–1.00)	0.0921	(0.99–1.09)	0.0875	(0.98–1.04)	0.6264	(0.99–1.01)	0.9249	0.006 (0.012)	0.5769	(0.97–1.01)	0.2234
			−0.076		0.98		0.98		0.97		0.97		−0.039		0.96	
rs7230034[b]	T	0.11	**(0.017)**	**4.84E−06**	(0.97–1.00)	0.0308	(0.93–1.03)	0.4371	(0.95–1.00)	0.0926	(0.96–0.99)	0.0003	(0.013)	0.0016	(0.94–0.97)	4.06E−07
			0.022		**1.02**		1.00		1.01		1.00		−0.006		1.00	
rs12608052[a]	C	0.48	(0.011)	0.0349	**(1.01–1.03)**	**1.02E−06**	(0.97–1.03)	0.9623	(0.99–1.03)	0.3395	(0.99–1.01)	0.9442	(0.008)	0.4803	(0.99–1.01)	0.6226
			0.017		1.00		**1.08**		1.04		1.03				1.04	
18:50678953[a]	GA	0.44	(0.011)	0.1017	(0.99–1.01)	0.4049	**(1.05–1.11)**	**1.79E−06**	(1.02–1.06)	1.99E−05	(1.02–1.03)	1.40E−07	0.043 (0.008)	8.01E−08	(1.03–1.06)	4.10E−14
			0.019		1.00		**1.08**		1.04		1.03				1.05	
rs7229097[c]	G	0.44	(0.011)	0.0775	(0.99–1.01)	0.4003	**(1.05–1.11)**	**2.34E−06**	(1.02–1.06)	2.14E−05	(1.02–1.03)	9.85E−08	0.045 (0.008)	2.37E−08	(1.03–1.06)	2.02E−14
			0.027		1.01		1.07		**1.05**		1.02				1.05	
rs62098013[a]	A	0.36	(0.011)	0.0142	(1.00–1.02)	0.2766	(1.04–1.11)	1.82E−05	**(1.03–1.07)**	**3.13E−06**	(1.01–1.03)	6.33E−06	0.034 (0.008)	4.01E−05	(1.03–1.05)	1.39E−13
			0.034		1.00		1.07		1.04		**1.03**				1.05	
rs17411061[a]	T	0.42	(0.011)	0.0017	(0.99–1.01)	0.3753	(1.03–1.10)	0.0001	(1.02–1.07)	1.34E−05	**(1.02–1.04)**	**9.26E−12**	0.048 (0.008)	3.58E−09	(1.04–1.07)	4.96E−20
			−0.007		0.99		1.01		1.02		**1.02**				1.01	
rs8096647[b]	T	0.42	(0.011)	0.4885	(0.98–1.00)	0.0539	(0.98–1.04)	0.5295	(1.00–1.04)	0.0335	**(1.01–1.03)**	**1.05E−06**	0.040 (0.008)	5.72E−07	(1.00–1.02)	0.0304
			−0.031		0.99		0.94		0.96		0.97		**−0.059**		0.95	
rs8099145[a]	T	0.49	(0.011)	0.0057	(0.98–1.00)	0.2609	(0.91–0.97)	0.0002	(0.94–0.98)	0.0002	(0.96–0.98)	1.05E−10	**(0.008)**	**1.42E−12**	(0.94–0.96)	5.70E−18
			0.011		1.02		0.98		0.97		0.97		**−0.055**		0.98	
rs28698732[b]	A	0.17	(0.014)	0.4497	(1.00–1.03)	0.0200	(0.94–1.02)	0.3833	(0.95–1.00)	0.0202	(0.96–0.99)	2.91E−05	**(0.011)**	**1.81E−07**	(0.96–0.99)	0.0022
			0.033		1.00		1.07		1.04		1.03				**1.06**	
rs11660938[a]	T	0.42	(0.011)	0.0021	(0.99–1.01)	0.4281	(1.03–1.10)	8.12E−05	(1.02–1.06)	2.39E−05	(1.02–1.04)	1.71E−11	0.048 (0.008)	2.12E−09	**(1.04–1.07)**	**1.74E−20**

Where: N, minimum sample number; A1, effect allele; EAF, effect allele frequency; OR, odds ratio; L95, lower 95 % confidence interval; U95, upper 95 % confidence interval; a, lead SNP; b, secondary signal identified through conditional analyses; c, proxy for lead. Bold indicates significant at P<1E−6. highlighted indicates significant at P<5E−8.

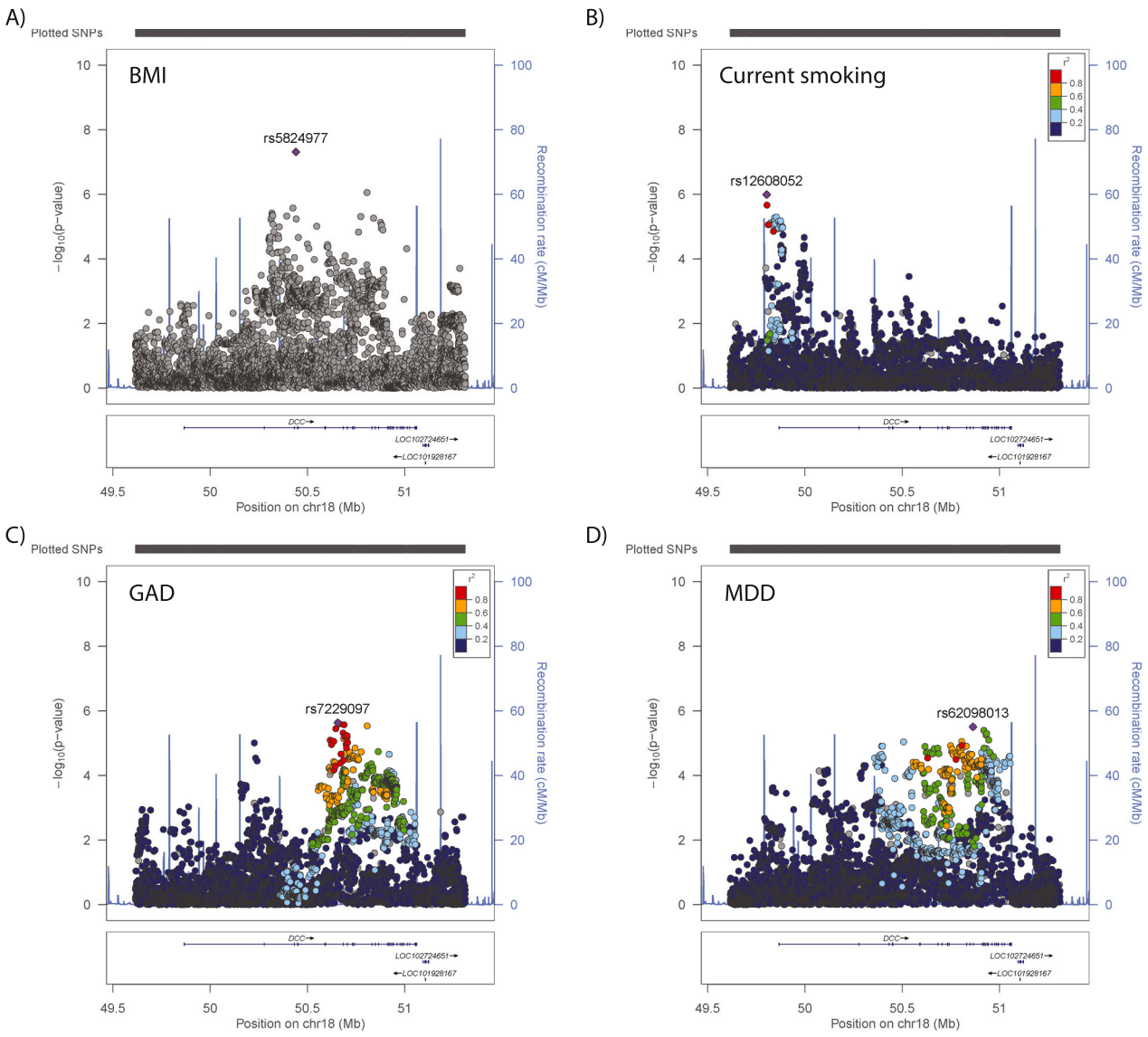

Fig. 1. Regional plots of white British ancestry analyses of A) BMI, B) current smoking, C) GAD, D) MDD, E) mood instability, F) neuroticism score, G) anhedonia. Of note, the lead SNP for GAD, 18:50678953_GA_G is not present in the Locuszoom reference panel so rs7229097 is plotted instead. Colours represent LD with the lead SNP, whilst grey indicates lack of LD information. The yellow horizontal line indicates threshold for significance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

probable lifetime generalised anxiety disorder (GAD), bipolar disorder (BD) and major depressive disorder (MDD) (Davis et al., 2018). Participants responding "don't know" or "prefer not to say" to any question were excluded from analyses (<5 %). Ancestry groups were broadly defined, based on self-reported data, per Eastwood et al. (Eastwood et al., 2016) (see Supplemental methods).

This work was approved under the generic ethical approval for UK Biobank studies granted by the NHS National Research Ethics Service (approval letter dated 29 June 2021, Ref 21/NW/0157). This project used data from UK Biobank applications 6553 (PI. RJS).

2.2. Genetic data

Extracted DNA was genotyped using the Affymetrix UK BiLEVE Axiom or UK Biobank Axiom platforms, (Bycroft et al., 2018), and imputed to the 1000 Genomes and Haplotype Reference Consortium reference panels (Bycroft et al., 2018). Standard genetic quality control of pre and post-imputation data was conducted by the central UK Biobank team. Genetic data was used to verify an individual's categorisation in the "white British" ancestry subset (Bycroft et al., 2018).

2.3. SNP selection

The *DCC* locus was defined as the coding region of *DCC* ± 400 kb (UCSC genome browser (https://genome-euro.ucsc.edu/cgi-bin/hgGateway?redirect=manual&source=genome.ucsc.edu), build 37). Genetic variants in this region were filtered for minor allele frequency > 1 %, broad ancestry groups (Supplemental methods) as defined by Eastwood et al. (Eastwood et al., 2016).

2.4. Genetic analyses

Genetic analyses were conducted separately in the broad ancestry groups (Supplemental methods) as defined by Eastwood et al. (Eastwood et al., 2016) Individuals of self-reported "white British" ancestry make up the majority of the cohort. Therefore, genetic analyses were initially

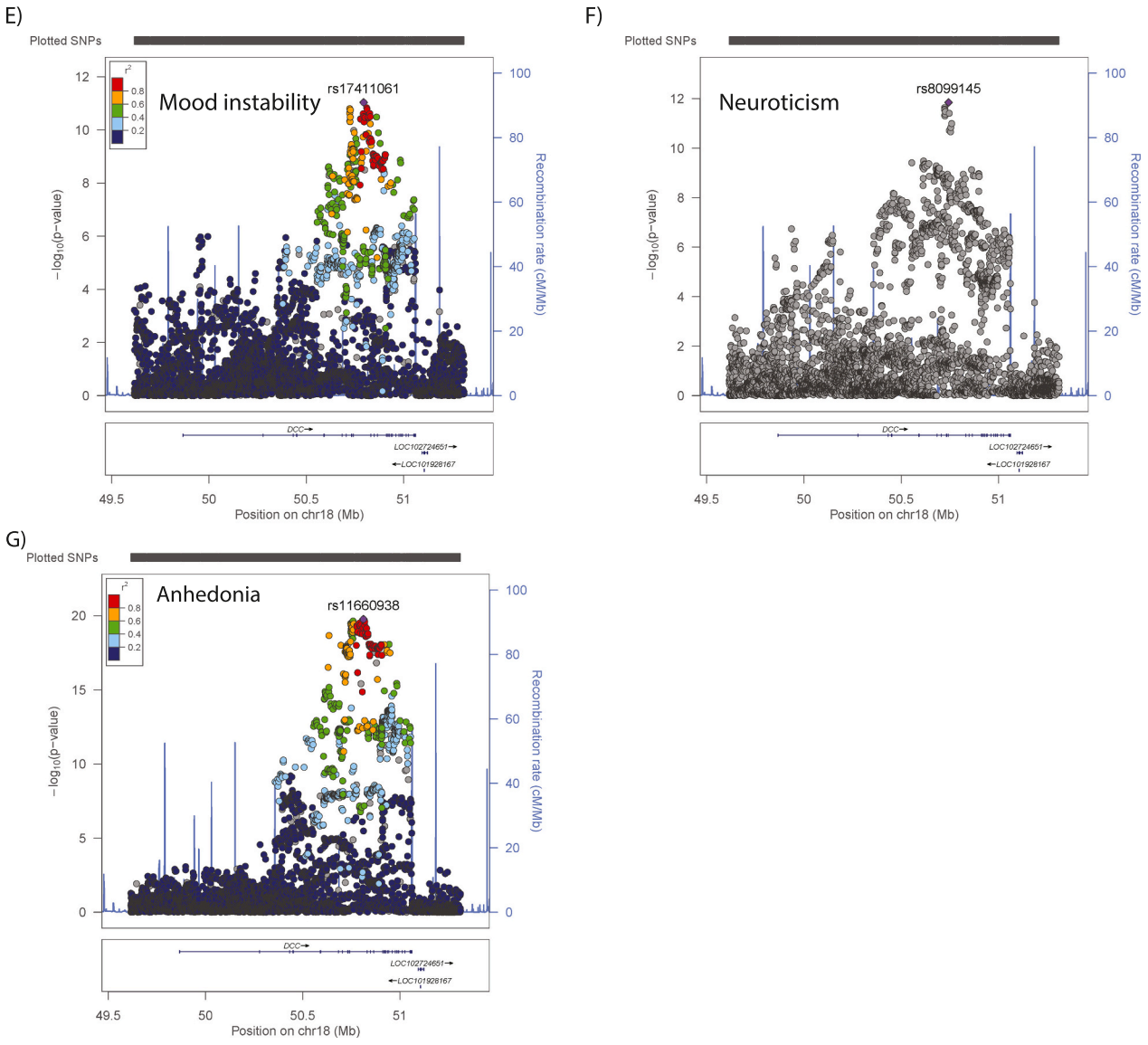

Fig. 1. (*continued*).

restricted to unrelated individuals of self-reported "white British" ancestry. Subsequently, analyses of were conducted in the additional broadly-defined ancestry groups (Supplemental methods, as per Eastwood (Eastwood et al., 2016)): white (non-British) European, South Asian, African-Caribbean and mixed ancestry groups (Eastwood et al., 2016).

For the primary analyses in "white British" individuals, genetic analyses of 7161 variants in the *DCC* locus were conducted using Plink 1.07 (Purcell et al., 2007), assuming an additive genetic model. For continuous and binary variables, linear and logistic regression were applied, respectively. All models were adjusted for age, sex, genotyping chip and population structure (eight genetic principal components (genetic ancestry)), except WHRadjBMI. Analyses of IHD and Stroke were further adjusted for current smoking, anti-hypertensive and lipid-lowering medication. The covariates above were incorporated into the calculation of WHRadjBMI, which was performed separately by sex and ancestry group, therefore no covariates were used for genetic analyses of WHRadjBMI. Sensitivity analyses are described in the Supplemental methods.

Secondary analyses in European, South Asian, African-Caribbean and mixed ancestry groups included 7,123, 7,720, 10,439 and 8,689 variants respectively. All models were adjusted for age, sex, genotyping chip and population structure (eight genetic principal components (genetic ancestry)).

The standard threshold for significance in a GWAS is $P < 5 \times 10^{-8}$ (Bonferroni correction for 1 million tests). As this study is focusing on the *DCC* locus only, and because of prior evidence implicating the *DCC* locus in MHT and CMT, this threshold would be unnecessarily conservative. Therefore, Bonferroni correction for multiple testing was applied, with adjustment for the number of independent variants in the *DCC* locus for the "white British" ancestry sample. This was calculated using Plink 1.07 (Purcell et al., 2007) and the pairwise independence test (using default settings, see Supplemental methods). For the "white British" ancestry sample, of 7161 SNPs in the *DCC* locus 1419 were independent thus significance was set at $p < 3.52 \times 10^{-5}$ (0.05/1419). Whilst it is likely that the number of independent variants would vary between the ancestry groups due to differing LD structures, the same significance threshold was used for all ancestry groups.

2.5. Meta-analyses

To assess trans-ethnic consistency, inverse variance weighted (based

Table 3
Results from the trans-ancestry meta-analysis.

				BMI					Neuroticism				
SNP	A1	EAF	EAFse	Beta	Se	P	Direction	Isq	Beta	Se	P	Direction	Isq
rs5824977	T	0.15	0.03	−0.082	0.014	**5.64E−09**	−−−−+	0	0.012	0.011	0.2652	++++−	0
rs7230285	A	0.50	0.04	0.026	0.010	0.0069	++−++	0	0.051	0.007	**6.73E−12**	+−+++	60
rs1943107	A	0.87	0.05	0.026	0.015	0.0729	+++−+	0	0.064	0.011	**6.39E−09**	+++++	0
rs4456576	C	0.59	0.04	−0.032	0.010	0.0016	−−+−−	0	−0.039	0.008	3.60E−07	−+−−−	63
rs62097985	T	0.41	0.04	0.035	0.010	0.0006	+++++	0	0.044	0.008	6.01E−09	+−+++	71
rs12608052	T	0.51	0.03	−0.019	0.010	0.0474	−−+++	0	0.008	0.007	0.2919	+++−+	0

Where: A1, effect allele; A2, non effect allele; EAF, effect allele frequency; EAFse, se of EAF across the ancestry groups; direction, each symbol indicates direction of the effect alleles effect: white British, European, mixed, south Asian and Africa-Caribbean ancestry groups; Isq, Isq measure of heterogeneity; N = 470,017–477,479.

on Beta and se) meta-analyses of ancestry-specific results for each phenotype, including all variants analysed for each ancestry, was conducted using METAL (Willer et al., 2010) (see Supplemental methods). Odd ratios (OR) were converted to beta coefficients for this analysis, as METAL is capable of handling quantitative but not binary phenotypes. Population stratification was controlled for in the ancestry-specific analyses, not in the meta-analyses. The significance threshold remained at $p < 5.37 \times 10^{-5}$.

2.6. Genetic architecture of DCC

The genetic architecture of significant SNPs within the locus was assessed using Haploview (Barrett et al., 2005) to visualise linkage disequilibrium (LD) blocks, separately for each ancestry group. In addition, conditional analyses (including lead SNPs as covariates) were employed to assess the number of conditionally-independent or secondary signals for each significant trait (trait1 ~ age, sex, population structure, genotyping chip and lead SNP for trait1) and whether signals for each trait were distinct (trait1 ~ age, sex, population structure, genotyping chip and lead SNP for trait2).

2.7. Follow-up analyses

The Variant Effect Predictor (VEP)(McLaren et al., 2016) was used to assess the predicted impact of all variants meeting the threshold for statistical significance (in any analyses). Observed genotype-specific effects of expression quantitative trait loci (eQTLs) were identified in two ways: firstly, lead variants and those with potential functional effects (identified using VEP), and any SNPs in high LD (r2 > 0.75 in Europeans), were assessed for effects on expression of *DCC* or other nearby gene using the LDEXpress (https://ldlink.nci.nih.gov/?tab=ldexpress); secondly, all eQTLs for *DCC* were identified using the GTEx resource (Consortium GT, 2013) and compared to the genetic association analyses. Co-localisation of genetic associations with phenotypes and with gene expression was conducted using R and the coloc v5.1.0 package (Giambartolomei et al., 2014). Genetic variants nominally associated ($p < 0.05$) with a phenotype and/or gene expression were included. This method uses summary statistics for two traits (here, genetic associations with phenotypes in UKB and genetic associations with gene expression in GTEx) Bayesian methods to assess the probabilities of five hypotheses: neither trait is associated (H0), only one trait is associated (H1,H2), both traits associated but different causal variants (H3), both traits associated with same causal variant (H4) (Giambartolomei et al., 2014). Default priors were used (Giambartolomei et al., 2014).

2.8. Comparison with literature

The GWAS catalogue (https://www.ebi.ac.uk/gwas, 20,210,210) was used to identify variants in the *DCC* locus previously reported to be associated with a behavioural, cardiometabolic or psychiatric trait. Where possible, previously reported associations were compared to those observed here.

3. Results

The characteristics of the cohort, by ancestry group, are presented in Table 1.

Individual trait analyses in "white British" ancestry individuals.

The significant associations between the *DCC* locus and phenotypes analysed are summarised in Table 2 and Fig. 1.

Significant associations were identified for BMI (42 SNPs, lead rs5824977, Table 1, Fig. 1A), Smoking (31 SNPs, rs12608052, Table 1, Fig. 1B), GAD (42 SNPs, 18:50678953-GA (proxy rs7229097), Table 1, Fig. 1C), MDD (86 SNPs, rs62098013, Table 1, Fig. 1D), mood instability (883 SNPs, rs17411061, Table 1, Fig. 1E), neuroticism score (1005 SNPs, rs8099145, Table 1, Fig. 1F) and anhedonia (1228 SNPs, rs11660938, Table 1, Fig. 1G). All associations demonstrated effect sizes in line with those normally observed for complex traits (ie. fairly small). The regional plots for most of these traits are suggestive of multiple signals, therefore conditional analyses were conducted. No significant associations were identified for risk-taking behaviour, BD, SBP, DBP, ISH, stroke, VTE, T2D or WHRadjBMI.

Secondary (or conditionally-independent) signals were defined as variants passing the threshold for significant associations and the Beta or OR being minimally reduced (a difference of ≤0.05) when including the lead variant as a covariate. Smoking, GAD, MDD and anhedonia demonstrated no significant secondary signals. For BMI (Supplementary Fig. S1A) a second, conditionally-independent signal was identified (rs7230034-T, $Beta_{discovery}$–0.076 (0.017) ≥ $Beta_{conditional}$ − 0.072 (0.017), Table 1, Supplementary Fig. S1B, Supplementary Table S1). Further conditional analyses including both primary and secondary lead SNPs (rs5824977 and rs7230034) rendered the locus non-significant (Supplementary Fig. S1C, Supplementary Table S1). Mood instability (Supplementary Fig. S1D) demonstrated a second, conditionally-independent signal (rs8096647-T, 1.02 (1.01–1.03) ≥ 1.02 (1.01–1.03), Table 1, Supplementary Fig. S1E, Supplementary Table S2). Further conditioning on both signals removed the signal (Supplementary Fig. S1F). For neuroticism score (Supplementary Fig. S1G), a second, conditionally-independent signal was identified (rs28698732-A, −0.055 (0.011) ≥ −0.060 (0.011), Supplementary Fig. S1H, Supplementary Table S3). Further conditioning on both signals removed the signal (Supplementary Fig. S1I, Supplementary Table S3).

Given that GAD, MDD, mood instability, neuroticism score and anhedonia are positively related phenotypes, it was reassuring that the same effect direction was observed for all of their lead SNPs across all traits (Table 2).

Sensitivity analyses demonstrated that significant associations with MDD were not being driven by inclusion of individuals with GAD (Supplementary Table S4) and associations with GAD were not driven by inclusion of individuals with MDD (Supplementary Table S5), GAD and

Anhedonia					Mood Instability					Current smoking				
Beta	Se	P	Direction	Isq	Beta	Se	P	Direction	Isq	Beta	Se	P	Direction	Isq
−0.005	0.008	0.4816	−−−−−	0	0.000	0.006	0.9668	−+−−−	0	−0.006	0.006	0.3437	−−−++	0
0.018	0.005	0.0007	+−−++	1.3	0.012	0.004	0.0045	+++−+	0	0.001	0.004	0.8458	++−−−	0
0.010	0.008	0.2180	+−−−+	0	0.013	0.006	0.0485	+++++	0	0.002	0.007	0.7442	++−++	0
−0.020	0.005	0.0001	−+−−−	0	−0.010	0.004	0.0255	−+−+−	0	−0.002	0.005	0.6102	−−−−+	0
0.019	0.005	0.0003	+−+++	0	0.013	0.004	0.0032	+++−+	0	0.002	0.005	0.6155	++−+−	0
0.002	0.005	0.7664	++−−+	0	0.001	0.004	0.8445	+++−+	0	−0.010	0.004	0.0251	−−−+−	0

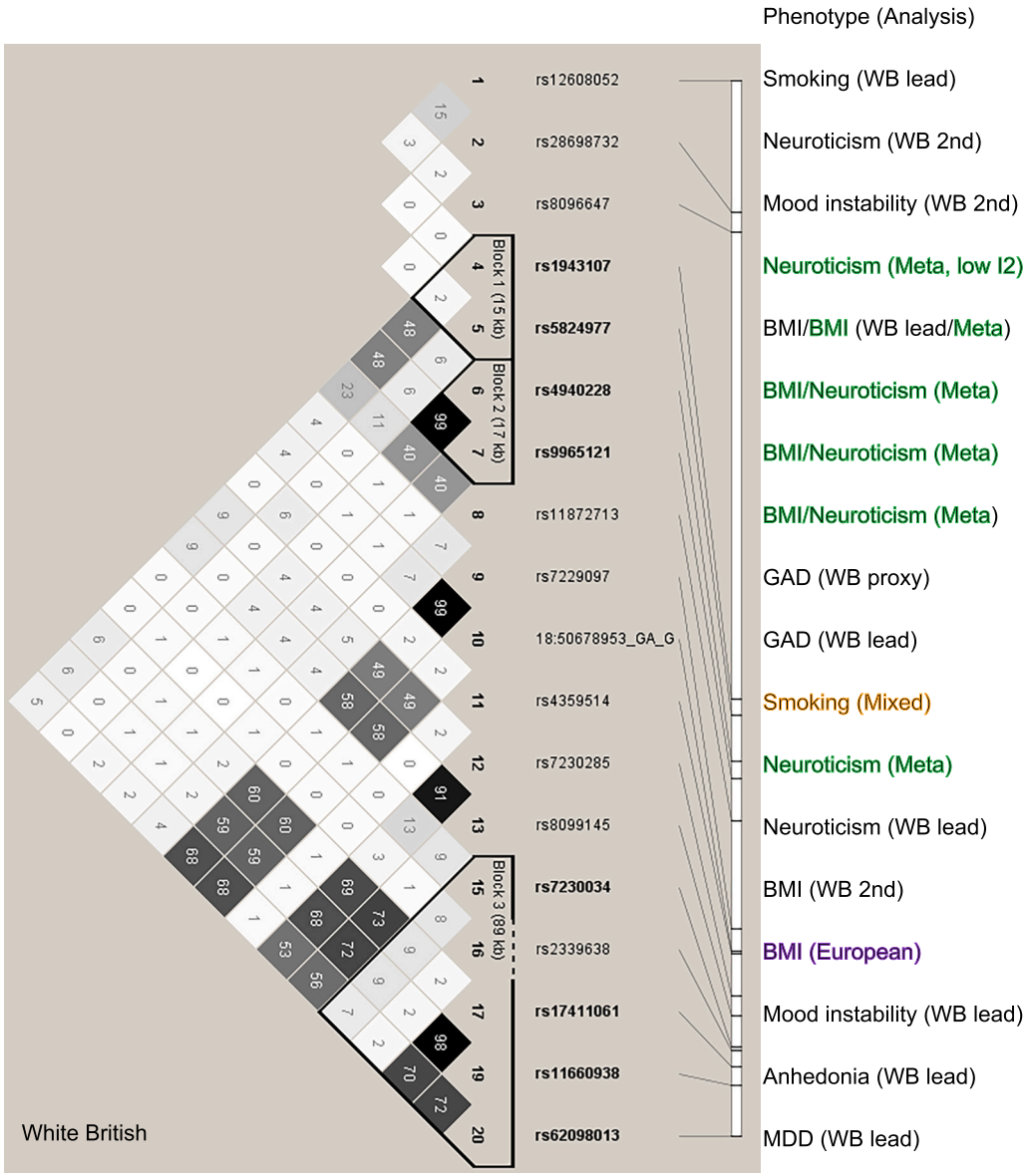

Fig. 2. Linkage disequilibrium of associated SNPs and the respective phenotypes and analyses. The plot gives the LD between SNPs in a random selection of 10,000 unrelated white British ancestry individuals. Colours and values of LD are given as R2.

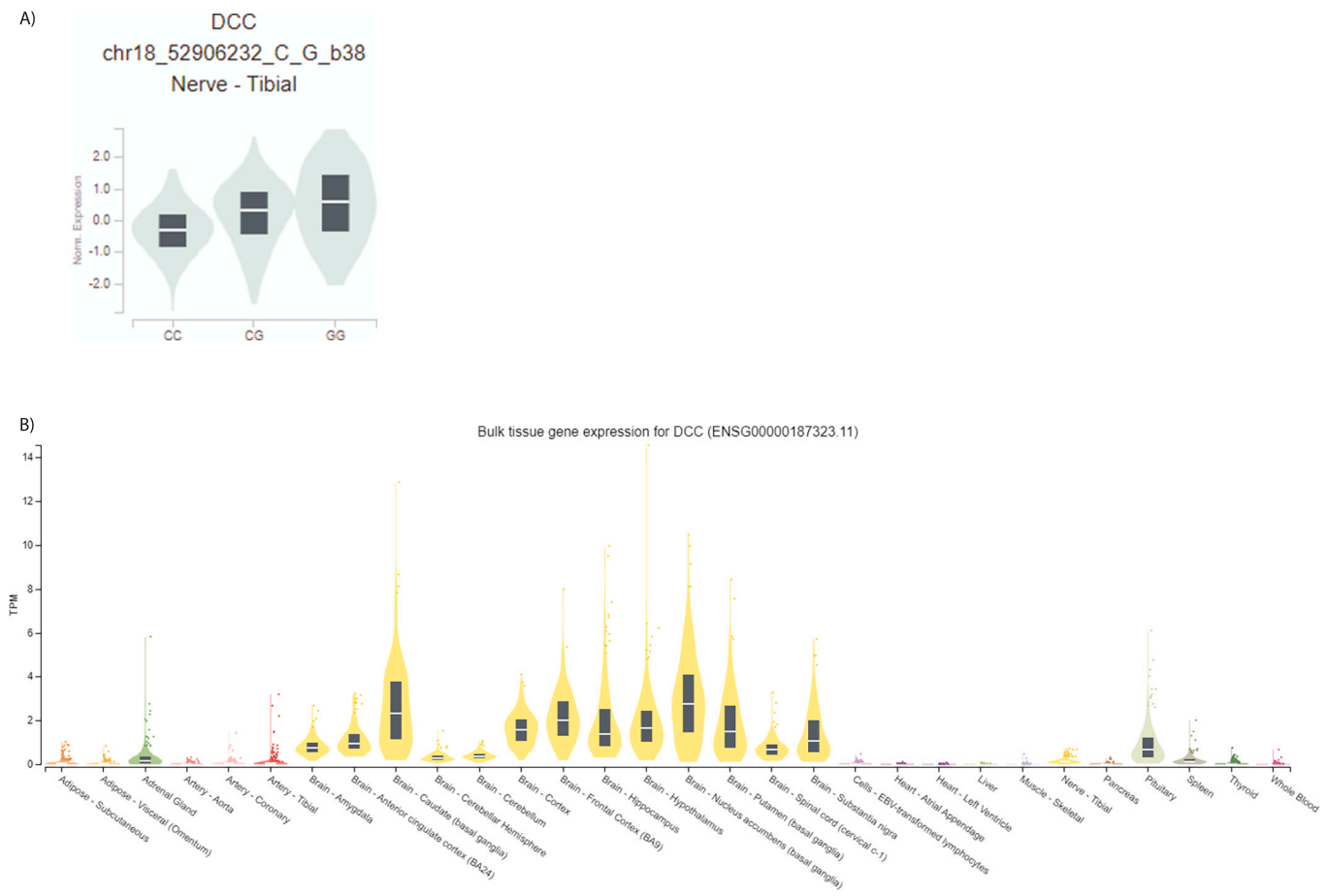

Fig. 3. mRNA expression of *DCC*, A) according to rs2229080 (chr18_52906232_C_G_b38) genotype (measured in 532 individuals within the GTEx dataset) and B) in the main tissues of relevance for MHT and CMT in the GTEx database.

MDD are highly comorbid, so overlapping samples are inevitable, however these analyses suggest that the associations with GAD and MDD are not solely driven by inclusion in both analyses of a co-morbid GAD-MDD subsample. For associations with mood instability (Supplementary Table S6), neuroticism score (Supplementary Table S7) or anhedonia (Supplementary Table S8), effect sizes were comparable, although in some cases associations were no longer significant (which is likely due to the reduced sample size in the sensitivity analyses). Therefore, associations between the *DCC* locus and mood-related traits are not being driven by individuals with mental illness. Inclusion of anti-depressant medication (7.5 % of the population) or hypertension (53.6 % of the population) as covariates in the models had little or no effect on the significant associations (Supplementary Tables S9–S13).

3.1. Cross-trait analyses in "white British" ancestry individuals

To determine whether the signals for MHTs and CMTs overlapped or were distinct, conditional analyses including the lead SNP from the other traits were undertaken.

For BMI, including the other traits lead signals had a negligible effect on the association (Supplementary Fig. S2, Beta range − 0.081—0.086). Similarly, the signal for smoking was unchanged after adjustment for the lead SNPs of the other traits (Supplementary Fig. S3, OR range 0.97–0.98).

For GAD, adjustment for BMI or smoking lead SNPs had no effect on the association (Supplementary Fig. S4A-C, OR 1.08). In contrast, the associations of *DCC* genetic variants with GAD were non-significant after adjustment for MDD, mood instability, neuroticism score or anhedonia lead SNPs (Supplementary Fig. S4D-G, ORs 1.08–1.09). The associations with MDD demonstrated the same null effect when adjusting for the BMI or smoking signal (Supplementary Fig. S5A-C, OR 0.99) and non-significant associations after adjustment for psychiatric-related traits (Supplementary Fig. S5D-G, ORs 0.98–0.99).

For mood instability, again the signal was conditionally-independent from that of BMI or smoking (Supplementary Fig. S6A-C, OR 1.03). Adjustment for GAD or MDD reduced but did not remove the association (Supplementary Fig. S6D-E, ORs 1.03–1.05), whereas adjustment for neuroticism score or anhedonia rendered the associations non-significant (Supplementary Fig. S6F-G, ORs 1.03–1.06). Associations with neuroticism score were unaffected by adjustment for BMI or smoking (Supplementary Fig. S7A-C Beta −0.058). Adjustment for GAD or MDD reduced the significance of the associations (Supplementary Fig. S7D-E, Betas −0.051 to −0.062), whereas adjustment for neuroticism score or anhedonia rendered the associations non-significant (Supplementary Fig. S7F-G, Betas −0.037 to −0.038). Associations with anhedonia were unchanged by conditioning on the BMI or smoking lead SNPs (Supplementary Fig. S8A-C, OR 1.05). Adjustment for GAD and MDD reduced but did not remove the association (Supplementary Fig. S8D-E, ORs 1.05–1.06), whereas adjustment for mood instability or neuroticism score rendered the associations non-significant (Supplementary Fig. S8F-G, OR 1.04 for both).

These results indicated that the BMI and smoking loci were distinct from each other and from the mood traits, but that the signals for mood traits were interrelated.

Associations in European, South Asian, African-Caribbean and Mixed ancestry individuals.

Secondary analyses were conducted in European, South Asian, African Caribbean and mixed ancestry groups. Sample sizes for these

ancestry groups were much smaller than the "white British" ancestry subset, in particular for self-reported GAD or MDD where there was insufficient power for analyses. Therefore, trans-ancestry analyses and meta-analyses focused on baseline BMI, smoking, mood instability, neuroticism score and anhedonia. In European ancestry samples, a significant association was identified for BMI (rs2339638, Supplementary Fig. S9A, Supplementary Table S14). In the mixed ancestry sample, an association was observed for anhedonia (four SNPs, rs7232267, Supplementary Fig. S9B, Supplementary Table S14). No significant associations were observed in the African-Caribbean or south Asian samples. As these were the smallest samples (N < 10,000), this is perhaps unsurprising.

3.2. Meta-analyses across multiple ancestry groups

To investigate whether genetic effects of the *DCC* locus on BMI, smoking, mood instability, neuroticism score and anhedonia were consistent across ancestry groups, meta-analyses were conducted (irrespective of significance in the individual ancestry groups). For BMI, 115 SNPs reached significance (Table 3 and Supplementary Fig. S10A), with 74 % having low heterogeneity (I2 < 25, Supplementary Fig. S10B). 1029 SNPs were significant in the meta-analysis of neuroticism score (Supplementary Fig. S10C), 23 % of which had low heterogeneity (Supplementary Fig. S10D) and 67 % had low or moderate heterogeneity (I2 < 50). Whilst the majority of these variants were associated exclusively with BMI or neuroticism, there was one variant, rs11872713 (Supplementary Table S15), significantly associated with both traits with low heterogeneity (I2 = 0) for BMI but moderate heterogeneity (I2 = 44) for neuroticism. The allele associated with reduced BMI was also associated with reduced neuroticism. No significant associations were observed in the meta-analyses of smoking, mood instability or anhedonia.

3.3. Linkage disequilibrium analyses

Linkage disequilibrium analyses (Fig. 2 and Supplementary Fig. S11) confirmed that the "white British" lead SNPs for BMI and smoking were rarely coinherited with each other (maximum LD r2 = 0.13) or the signals for mood-related traits. Two observations stood out regarding the mood-related traits in "white British" ancestry samples (Fig. 2): firstly, a handful of SNPs constituted a single signal that influenced MDD, anhedonia, mood instability and GAD and neuroticism (unsurprising given the phenotypic relationships between these traits); secondly, for neuroticism and mood instability, there were additional conditionally-independent signals which were distinct from the lead mood traits signal and each other.

The signal for BMI in Europeans had minimal LD with the other lead SNPs (max r2 = 0.09).

In the trans-ancestry meta-analysis, the BMI lead SNP (rs5824977) was the same as that for the "white British" analysis, which was unsurprising given the predominance of the "white British" sample. However, it appeared that the signal was consistent across ancestry groups, as demonstrated by heterogeneity Isq = 0 (Table 3). This was in contrast with the meta-analysis of neuroticism, where the lead SNP in the meta-analysis (rs7230285) was in high LD with that for the "white British" analysis (r2 = 0.91), but high heterogeneity (Isq = 60 %), which suggests ancestry group differences. That there were SNPs with low heterogeneity (rs1943107, Isq = 0) indicates that there were some genetic effects that were consistent across ancestry groups, as well as ancestry-specific effects.

The SNP (rs11872713) with effects on both neuroticism and BMI in the meta-analysis demonstrates varying degrees of LD with the (low heterogeneity) meta-analysis neuroticism signal, with low LD in African-Caribbean (r2 = 0.13), "white British" (r2 = 0.23) and European (r2 = 0.25) ancestry groups or moderate LD in south Asian (r2 = 0.28) or mixed (r2 = 0.37) ancestry groups. How this should be interpreted is unclear.

3.4. Predicted functional effects

Of 1497 unique SNPs significant in any analysis, only rs2229080 (associated with anhedonia in the "white British" analysis, G allele, OR = 0.98) was predicted to have a functional effect by VEP, with the G allele resulting in a missense transcript that was tolerated or benign (according to SIFT and PolyPhen respectively).

3.5. Gene expression by tissue

Considering global tissue expression patterns, outside of the testis, *DCC* was predominantly expressed in the brain tissue using GTEx (Fig. 3A), with little expression in the main metabolic tissues. This combined with SNP effects on neuroticism score and BMI could suggest that effects on BMI are subsequent to those on neuroticism.

3.6. Observed genotype-specific gene expression patterns

None of the lead SNPs, or high-LD proxies from single ancestry analyses or meta-analyses (Table 3, Supplementary Table S15) demonstrated genotype-specific gene expression patterns.

Considering genotype-specific gene expression of the *DCC* gene in GTEx, of 1334 identified eqtls (Supplementary Table S16) 0.18 % were in cerebellum, 0.026 % in hippocampus (together 0.44 % in brain tissues), 63 % were identified in nerve tissue and the strongest 395 effects were detected in nerve tissue. Sixty-five SNPs with eqtlss also had significant association with MDD, mood instability, anhedonia or neuroticism score (Supplementary Table S16). Of 5 eqtls identified in brain tissues (cerebellum and hippocampus), none overlapped with the significant associations. It is worth noting that most eQTLS were observed in nerve cells, but not the brain. However, it should be noted that the brain consists of a complex mixture of cell types, including nerve cells, and the effect of genetic variants on gene expression in nerve cells might be masked by null effects in the other cell types. Where eqtls were observed in both the adrenal gland and nerve tissue, the same allele had the opposite effects on mRNA levels of *DCC* (positive in one, negative in the other). The allele associated with increased risk of anhedonia (and consistent effect on one or more of mood instability, neuroticism score and/or MDD) was consistently associated with reduced *DCC* mRNA levels in nerve tissue.

Rs2229080 (chr18_52906232_C_G_b38) demonstrated genotype-specific gene expression (eQTL) in the GTEx dataset, in nerve tissue for *DCC* (G allele associated with higher *DCC* mRNA levels, Fig. 3A) and *LINC01917*, the latter of which is a long non-coding RNA of unknown function with little expression outside of the testis. It is worth noting that rs2229080-G was the minor allele in European and African ancestry but not in south Asian ancestry (in both UK Biobank and dbSNP (https://www.ncbi.nlm.nih.gov/snp/rs2229080)).

3.7. Co-localisation analyses

We used co-localisation to investigate whether genetic variants associated with phenotypes might be acting through expression of *DCC*. These analyses (Supplementary Table S17) provided no evidence for co-localisation of any phenotype with *DCC* expression in the cerebellum, evidence that genetic variants associated with anhedonia, current smoking, mood instability and neuroticism score colocalised with *DCC* eqtls in tibial nerve tissue but that the causal variants were different and evidence of shared causal variants as well as co-localisation for DCC eqtls in adrenal glands and anhedonia and GAD.

3.8. Comparison with literature

The *DCC* locus has previously been implicated (through GWAS) in

many traits including behavioural, psychiatric and cardiometabolic diseases (Supplementary Table S18). The effect directions from our study were compared to those published where there was sufficient information and loosely comparable traits (Supplementary Table S19). Further detail is provided in the Supplemental results.

4. Discussion

Here we present a systematic assessment of genetic variation in the *DCC* locus for impact on a wide range of MHT and CMT. In a very large sample of self-reported "white British" ancestry individuals, we identified significantly associated signals for current smoking, BMI, anhedonia, neuroticism, mood instability, MDD and GAD. Additional analyses demonstrated that: BMI and mood traits had multiple conditionally-independent signals; BMI, smoking and mood traits constituted distinct signals; some of the BMI and mood trait signals appeared to be relevant across ancestry groups.

The *DCC* (deleted in colorectal cancer) locus has been implicated in many mood-related and psychiatric traits, therefore most functional analyses of *DCC* have investigated neuronal development or tumour progression. Evidence for metabolic traits is restricted to family studies which have described *DCC* variants in idiopathic hypogonadotropic hypogonadism (Zhang et al., 2021), which includes changes in both mood and weight. In mice, homozygous knockout of *dcc* is neonatal lethal, whilst heterozygous knockout has no impact on growth, metabolic, cardiovascular or neurological systems (https://www.mousephenotype.org/data/genes/MGI:94869#phenotypes-section). These results do not confirm our findings, however it is possible that mood traits such as anhedonia, mood instability and neuroticism might require a stressor in addition to genetic predisposition for presentation. In addition, if increased BMI is secondary to mood traits, it might not be evident in a mouse model under controlled feeding conditions.

Regulation of BMI is complex and BMI can be considered a behavioural trait (through food preferences, feeding and exercise patterns). The results presented here suggest that BMI could be secondary to mood traits, given lack of evidence for direct effects of *DCC* or neighbouring genes in metabolic tissues, and a lack of colocalised associations with *DCC* eqtls. Considering our finding that there was a *DCC* signal shared by a number of mood-related traits as well as additional conditionally-independent signals (which may be trait- and ancestry-specific), alongside the BMI and smoking signals, suggests that haplotype analyses of this region in diverse ancestries and with a wide range of phenotypes is required to better understand the complexity of this locus.

Further considering BMI, Couvy-Duchesne et al. (Couvy-Duchesne et al., 2020) demonstrated that relationships between brain size measures and depression were rendered null when adjusting for BMI (using mainly the same data as was included in this study). Genetic variation in this locus has been associated (Hibar et al., 2015) with the same regions as were analysed by Couvy-Duschesne *et al*, suggesting that this locus could act through effects on brain size.

Rare variation in *DCC* was investigated by Backman *et al* using whole exome sequencing (in UKB), for traits including those investigated here, but no associations were identified (Backman et al., 2021). Strict multiple testing correction could mean some true associations might not have been reported by Backman et al. However, it appears that current evidence provides more support for influence of common than rare genetic variation in the *DCC* locus on complex MHT and CMT.

Our previous efforts to explore the role of candidate loci for the link between CMT and MHT have provided clear conclusions (Morris et al., 2019; Hay et al., 2022; Burt et al., 2021; Morris et al., 2020). However, including data from diverse ancestry groups here increases the complexity of the results but is required to fully understand the regulation of complex traits, and to advance the field by considering consistency and implications for the entire global population.

4.1. Limitations

UKB is not truly representative of the general population (skewed towards lower deprivation than average) (Keyes and Westreich, 2019), however this is unlikely to invalidate our findings. As UKB represents the healthy end of the health to disease spectrum, the range of phenotypes (for example BMI or blood pressure measurements) is smaller than for the general population. Similarly, as severe mental or physical illness is likely to be a barrier to participation in the UKB, the cases here are less ill/less different from the controls than if severe cases were included. Thus, these results might be an under-estimate of true effects. We acknowledge that these results might not be generalisable outside of the UK population. Selecting phenotypes for secondary analyses in additional ancestry groups, based on results from the "white British" ancestry subset is a further limitation, however restricted power in the smaller ancestry groups could render such analyses uninformative due to low N. Including genetic data for non-European ancestry individuals imputed to reference panels that perform better for European individuals is not ideal. These limitations mean that whilst what we present is likely true, is does not represent a complete picture of the genetic architecture of the *DCC* locus in non-European individuals. Furthermore, we cannot exclude the possibility that genetic variants are correlated with or interact with covariates in an ancestry-dependent manner.

5. Conclusions

This study demonstrates distinct signals within the *DCC* locus influencing BMI, smoking and mood-related traits, with some traits having trans-ancestry and ancestry-specific signals. Future assessment of the *DCC* locus should consider multiple signals, for example using haplotype or polygenic scores analyses. We cannot exclude *DCC* contributing to shared biological mechanisms underlying MHT and CMT, but current evidence is more suggestive of effects on BMI being secondary to those for mood-related traits.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.07.052.

CRediT authorship contribution statement

RJS conceived the study. LF and RJS conducted analyses, interpreted results and drafted the manuscript. BC, NG and JW managed the data and/or provided coding. All authors contributed to critical review of the manuscript and have approved the final version for publication.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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