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TOMM40 rs2075650 May Represent a New Candidate Gene for Vulnerability to Major Depressive Disorder

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Evidence suggests that depression is a risk factor for dementia; however, the relationship between the two conditions is not fully understood. A novel gene (*TOMM40*) has been consistently associated with Alzheimer's disease (AD), but has received no attention in depression. We conducted a three-level cross-sectional study to investigate the association of the *TOMM40* rs2075650 SNP with depression. We recruited a community sample of 1220 participants (571 controls, 649 lifetime depression) to complete a psychiatric background questionnaire, the Brief Symptom Inventory, and Big Five Inventory at Level-1, 243 (102 controls, 97 remitted, 44 currently depressed) to complete a face-to-face clinical interview and neuropsychological testing at Level-2 and 58 (33 controls, 25 remitted) to complete an emotional face-processing task during fMRI at Level-3. Our results indicated that the *TOMM40* rs2075650 G allele was a significant risk factor for lifetime depression ($p = 0.00006$) and, in depressed subjects, was a significant predictor of low extraversion ($p = 0.009$). Currently depressed risk allele carriers showed subtle executive dysfunction ($p = 0.004$) and decreased positive memory bias ($p = 0.021$) together with reduced activity in the posterior ($p_{(FWE)} = 0.045$) and anterior ($p_{(FWE)} = 0.041$) cingulate during sad face emotion processing. Our results suggest that *TOMM40* rs2075650 may be a risk factor for the development of depression characterized by reduced extraversion, impaired executive function, and decreased positive emotional recall, and reduced top-down cortical control during sad emotion processing.
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INTRODUCTION

There is a near two-fold increased risk of developing dementia, particularly Alzheimer's disease (AD), after a diagnosis of depression (Green *et al*, 2003; Jorm, 2001; Ownby *et al*, 2006; Saczynski *et al*, 2010). This risk may be partially explained by depression forming a dementia prodrome, given the higher risk of dementia in late-life depression compared with earlier onset depression (Barnes *et al*, 2012). However, this cannot explain the greater risk of developing dementia in those who only suffer from depression earlier in their lives (Green *et al*, 2003), suggesting common biology linking the conditions. If true, then genetic factors associated with an increased risk of dementia may also contribute to an increased risk of depression.

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Genetic susceptibility to developing AD is well recognized. Both the apolipoprotein E (*APOE*) gene and the *TOMM40-APOE* locus, tagged by rs2075650 in the translocase of outer mitochondrial membrane 40 (*TOMM40*) gene (see Supplementary Information), have been implicated (Hong *et al*, 2010; Li *et al*, 2008; Schiepers *et al*, 2011). Investigations of depression have also indicated that the *APOE* ε4 risk allele influences both the onset and risk for late-life depression (Butters *et al*, 2003; Yen *et al*, 2007) and has been associated with gray matter reductions (Cherbuin *et al*, 2007), reduced white matter integrity (Heise *et al*, 2011) and cognitive impairment (Greenwood *et al*, 2000) in healthy adults, further suggesting that genetic mechanisms associated with dementia may contribute to the development of mood disorder.

In comparison to *APOE*, the independent role of *TOMM40* in AD and depression has been little studied. In large genome-wide association studies of AD, *TOMM40* rs2075650 (intron 2, chromosome 19q13.32) has been one of the most significantly associated single-nucleotide polymorphisms (SNPs) (Harold *et al*, 2009; Naj *et al*, 2010; Seshadri *et al*, 2010). *TOMM40* encodes a protein on the outer mitochondrial membrane essential for cell

viability, thus variation in this gene could lead to mitochondrial dysfunction (Ferencz *et al*, 2012; Pfanner *et al*, 1997), of which dementia and depression are symptoms (Anglin *et al*, 2012; Fattal *et al*, 2007). *TOMM40* rs2075650 is in linkage disequilibrium (LD) with the *APOE* ε4 rs429358 SNP (Harold *et al*, 2009; Potkin *et al*, 2009). However, evidence of an extended *TOMM40-APOE* haplotype that influences the regional effects and onset age of AD (Bekris *et al*, 2010; Roses, 2010) suggests that *TOMM40* may have *APOE*-independent effects (Carrasquillo and Morgan, 2012). Even in relation to AD the risk associated with *TOMM40* cannot be fully explained by LD, and it has been suggested that other SNPs must contribute (Bekris *et al*, 2012). Despite *TOMM40* rs2075650 being a good candidate for major depressive disorder (MDD), its possible effect on depression-related phenotypes has not yet been investigated.

Pathophysiological similarities between MDD and AD provide candidate intermediate phenotypes that may identify shared genetic factors. Alterations in premorbid measures of personality factors have been demonstrated in both depression (Kendler *et al*, 2006a) and AD (Robins Wahlin and Byrne, 2011). Cognitive deficits are well-reported features of both MDD (Millan *et al*, 2012) and AD (Christensen *et al*, 1997) that share similar structural and functional brain abnormalities in regions such as hippocampus (Arnone *et al*, 2012a; Potkin *et al*, 2009; Shen *et al*, 2010), amygdala (Drevets *et al*, 2008; Shen *et al*, 2010), cingulate (Johnson *et al*, 2011; Pizzagalli, 2011; Ries *et al*, 2009), and dorsolateral prefrontal cortex (Morbelli *et al*, 2012; Pizzagalli, 2011). *TOMM40* itself has also been associated with hippocampal atrophy (Potkin *et al*, 2009; Shen *et al*, 2010) in AD patients and reduced gray matter in the cingulate of healthy controls (Johnson *et al*, 2011). Variations in *TOMM40* may therefore contribute to a biological vulnerability independent of *APOE* that underpins aspects of both AD and MDD.

In this study, we took an exploratory multiple-level hypothesis-testing approach, using intermediate phenotypes, to investigate the role of the minor (G) allele of *TOMM40* rs2075650 in vulnerability to MDD. We tested the association between rs2075650, lifetime depression, and depressive symptoms in a large cohort and assessed whether personality traits are overexpressed in minor allele carriers. We then assessed whether the minor allele was associated with poorer cognitive function than the AA genotype using tests of memory, executive control, and affective bias. Finally, we investigated the effects of this SNP on brain function using a functional magnetic resonance imaging (fMRI) face emotion processing task as a putative neurobiological marker for depression (Juhasz *et al*, 2011), hypothesizing that risk allele carriers would show similar patterns of brain activations to those seen in currently depressed individuals.

MATERIALS AND METHODS

Participants

Participants aged 18–60 years, predominantly from Greater Manchester, were recruited primarily through NHS general practices and the study website. Detailed description of the recruitment methodology has been published previously (Juhasz *et al*, 2009; Juhasz *et al*, 2011). In summary, self-reported diagnostic and demographic data were collected from the Level-1 community sample, where a final cohort of 1220 participants was selected for the current investigation. All included participants were of Caucasian origin, provided DNA, and successfully genotyped for *TOMM40* rs2075650, with no self-reported history of manic or hypomanic episodes, psychotic symptoms, or obsessive-compulsive disorder. From this initial pool, 129 participants completed a face-to-face clinical interview and an additional neuropsychological testing session. This sample was further enhanced with 114 participants recruited through advertisements, providing a total of 243 participants in the Level-2 cohort. Finally, a subset of 58 participants from Level-2 completed an fMRI scan at Level-3. Further details of the recruitment can be found in the Supplementary Information. All participants provided written informed consent, and the study was approved by the local ethics committees and carried out in accordance with the Declaration of Helsinki.

Level-1 Assessment

The Background Questionnaire included in the Level-1 questionnaire booklet has been detailed previously (Juhasz *et al*, 2009; Juhasz *et al*, 2011). Briefly, this questionnaire included items designed to probe personal psychiatric history, allowing for the coding of participants as either healthy controls or those who reported suffering from depression during their lifetime (see Supplementary Information). Self-reported lifetime depression was used to analyze genetic associations. The Brief Symptom Inventory was used to assess current psychiatric symptoms. Personality was measured using the Big Five Inventory (BFI-44) (John *et al*, 1991), a 44-item instrument that assesses traits of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness.

Level-2 Assessment

In addition to the information provided in the Level-1 background questionnaire, clinical diagnoses were established by trained researchers using the Structured Clinical Interview for DSM-IV (SCID-I/NP; First *et al*, 2002). Participants were grouped into controls (no lifetime psychiatric disorders), remitted depressed (past MDD currently in full remission), and currently depressed (current MDD or MDD in partial remission). Current depressive symptoms were measured using the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). Data from the diagnosed participants were used to validate the Level-1 questionnaire (see Juhasz *et al*, 2011).

The neuropsychological assessment included tasks known to be sensitive to depression (Elliott *et al*, 2011; Millan *et al*, 2012). The *n*-back task (Owen *et al*, 2005) was used as a measure of working memory, as previous work has demonstrated that this paradigm is sensitive to deficits in both AD and depression (Harvey *et al*, 2005; Waltz *et al*, 2004). The CANTAB Stockings of Cambridge (SoC; http://www.camcog.com/) task was used as an index of planning and executive function, as previous studies using the SoC have demonstrated executive deficits in depression (Beats

et al, 1996; Elliott *et al*, 1996). Finally, an emotional word memory task, based on the work of Harmer *et al* (2009), was used as a measure sensitive to changes in affective bias and memory performance in depression. See Supplementary Information for details.

Level-3 Assessment

To assess whether changes in affective processing were associated with carrying the rs2075650 risk allele as distinct from current depressive mood, only healthy controls and remitted patients (with a MADRS score of $\leqslant 10$) underwent fMRI scanning.

fMRI Image Acquisition

Participants were scanned using a 1.5 T Philips Intera while performing an emotional face-processing paradigm (Thomas *et al*, 2011). During this task, participants were asked to identify the gender of faces selected from the Ekman and Friesen (1976) stimuli displaying either a neutral expression, happiness, sadness, or fear (see Supplementary Information for details). Data were acquired using a T_2*-weighted gradient echo-planar sequence with a repetition time (TR) of 2.1 s and an echo time (TE) of 40 ms. Each volume consisted of 29 contiguous axial slices (thickness 4.5 mm, inter-slice gap 0.5 mm). Voxel size was $3.5 \times 3.5 \times 5$ mm^3. A T1-weighted structural scan was acquired for preprocessing.

Genotyping

The *TOMM40* rs2075650 SNP was genotyped using the Sequenom MassARRAY technology (Sequenom, San Diego). See Supplementary Information for information on genotyping.

Statistical Analysis

Level-1 genetic association analysis. PLINK v1.07 (http://pngu.mgh.harvard.edu/purcell/plink/) was used for testing Hardy–Weinberg equilibrium and associations of different genetic models (dominant (DOM), recessive (REC) and additive (ADD)), using linear and logistic regression between *TOMM40* rs2075650 and phenotypes of interest (for power calculations, see Supplementary Information). Age and sex were covariates in all the analyses. Main effects of genotype were investigated using lifetime depression and current depression. Personality factors as possible intermediate phenotypes were tested by the main effects of genotype and by the genotype $\times$ depression status (current or lifetime) interaction. The positive false discovery rate (pFDR; *q*-value: http://genomics.princeton.edu/storeylab/qvalue/) was applied simultaneously across all models to maintain an α of 0.05 (Storey and Tibshirani, 2003).

Level-2 neuropsychological behavioral data analysis. The neuropsychological results were analyzed using SPSS 19 (http://www.ibm.com/software/analytics/spss/). Data were appropriately transformed to satisfy parametric assumptions. The 0-back condition of *n*-back was removed as performance was error-free. Age, sex, and current depression medication (as a binary indicator variable) were treated as covariates in all the models. To test the intermediate phenotype role of cognitive and affective domains, a single MANCOVA was performed for each outcome of each task, with the outcome vector comprising a linear combination of the task conditions. The multivariate main effects and interactions (using Pillai's Trace) were used to infer effects of diagnosis, genotype, and diagnosis $\times$ genotype interactions. Significant diagnosis $\times$ genotype interactions were followed-up by assessing each of the individual task conditions as univariate between-subject ANOVA models in order to explore the direction of any interaction effects. *Post-hoc* testing was conducted on the univariate models using pairwise contrasts across the interaction term with the Šidák multiple-comparison correction. Due to the multiplicity inherent in testing multiple non-independent MANCOVA models, the same pFDR correction used in Level-1 was applied simultaneously across main effects and interactions. See Supplementary Information for details.

Level-3 imaging data analysis. The Level-3 imaging data were analyzed using Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/). Image preprocessing has been detailed previously (Thomas *et al*, 2011). At the first level, $\hat{\beta}$ contrast maps of activation change were created by subtracting the neutral condition from each facial emotion of interest (happy, sad, and fear). For the second level analysis, each of the individual $\hat{\beta}$ contrasts created in the first level were used as raw *Y* vector values in the linear model. The model was a standard factorial cell-means design constructed from genotype and diagnosis. Age, sex, and MADRS scores were entered as covariates, with the continuous measures mean-centered. Our initial analysis was also restricted to the sad-neutral contrast as the most reliable biomarker for MDD (Arnone *et al*, 2012b). Exploratory *post-hoc* analyses for happy-neutral and fear-neutral were also conducted.

Based on *a priori* hypotheses, region of interest (ROI) analyses of the areas common to MDD and AD discussed earlier (Arnone *et al*, 2012a; Drevets *et al*, 2008; Johnson *et al*, 2011; Macqueen and Frodl, 2011; Morbelli *et al*, 2012; Pizzagalli, 2011; Potkin *et al*, 2009; Ries *et al*, 2009; Shen *et al*, 2010) were conducted using the PickAtlas toolbox (http://fmri.wfubmc.edu/software/PickAtlas). All regions were included bilaterally in a single mask consisting of Brodmann areas (BA) 46, posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), hippocampus, and amygdala. All results are reported at a ROI-corrected α of $p_{(FWE)} \leqslant 0.05$ using the MNI standard.

RESULTS

Demographic information for all three levels is presented in Table 1. Participants were similar in age and sex across all groups, with more females than males as expected. The distribution of the AA genotype and the G allele carriers (GA/GG) within each diagnostic group is also presented. *TOMM40* rs2075650 SNP was in HWE in all levels and in all subgroups.

Level-1

Lifetime depression was significantly more frequent in G allele carriers in both additive and dominant models (Table 2). No relationship was shown for the recessive model. All further testing was conducted using a dominant model where GA and GG participants were collapsed into a single group due to the rarity (2% of the sample) of the GG genotype. For the remainder of the paper, our use of the G allele should be read as synonymous with GA and GG combined. G allele carriers did not have significantly greater current depression scores than non-carriers. Scores on the BFI-44-derived personality traits were not significantly affected by genotype. However, in those who suffered from current or past depression the possession of the risk G allele enhanced the low extraversion trait (significant genotype × lifetime depression/current depression scores interaction). There were no statistically significant interactions affecting other personality traits. A *post-hoc* analysis demonstrated that the association of lifetime depression and G allele carrier status was independent of any reported drug or alcohol use problems.

Table 1 Demographic, Diagnostic, and rs2075650 Genotypic Information for Participants at Each Experimental Level

	Level-1		Level-2			Level-3	
	Controls	Lifetime depression	Controls	Remitted MDD	P. remitted and current	Controls	Remitted MDD
N	571	649	102	97	44	33	25
Age	33.23 (10.06)	34.83 (10.24)	30.06 (10.10)	34.48 (10.69)	39.82 (10.60)	31.42 (9.68)	32.80 (10.21)
Gender							
Female	60.2%	77.3%	57%	80%	70.5%	68%	76%
BFI-44							
Neuroticism	2.78 (0.77)	3.76 (0.74)	–	–	–	–	–
Extraversion	3.33 (0.87)	2.96 (0.88)	–	–	–	–	–
Conscientiousness	3.78 (0.64)	3.56 (0.77)	–	–	–	–	–
Openness	3.65 (0.58)	3.61 (0.67)	–	–	–	–	–
Agreeableness	3.86 (0.58)	3.71 (0.66)	–	–	–	–	–
BSI							
BSI-DEP	0.53 (0.62)	1.41 (1.03)	0.26 (0.42)	0.54 (0.59)	2.17 (0.93)	0.27 (0.51)	0.46 (0.57)
	–	–	–	–	–	–	–
Drug/alcohol abuse	0.7%	11.7%	–	–	–	–	–
Financial stability							
Very comfortable	10%	7.3%	7.8%	5.2%	4.5%	9.1%	12%
Quite comfortable	55.5%	40.3%	56.9%	60.8%	29.5%	57.6%	56%
Getting by	26.2%	36%	29.4%	29.9%	41%	24.2%	32%
Difficult	7.4%	13.4%	5.9%	4.1%	13.6%	9.1%	0%
Very difficult	0.9%	3%	0%	0%	11.4%	0%	0%
Depression history							
0 episodes	100%	0%	100%	0%	0%	100%	0%
1 episode	0%	26%	0%	50%	11%	0%	48%
>1 episodes	0%	74%	0%	50%	89%	0%	52%
	–	–	–	–	–	–	–
MADRS	–	–	1.26 (1.80)	3.54 (3.23)	21.86 (7.31)	1.00 (1.54)	2.76 (2.79)
Genotype							
AA	76%	67%	74%	74%	57%	70%	72%
GA/GG	24%	33%	26%	26%	43%	30%	28%
HWE *p*	0.71	0.10	0.69	0.41	0.42	1.00	0.48

Abbreviations: BSI-DEP, Brief Symptom Inventory depression subscale; FFI, Five Factor Inventory; HWE, Hardy–-Weinberg equilibrium; MADRS, Montgomery–Åsberg Depression Rating Scale.
Values are given as mean (SD). Note that depression history and drug/alcohol abuse are self-reported measures in Level-1.

Table 2 Results from the Level-1 Association Between the Big Five Personality Factors and Genetic Models of the *TOMM40* Alleles

	Main effect of genotype				
	OR	**χ^2**	**Model tested**	***p* uncorrected**	***q* FDR corrected**
Lifetime depression	1.6 (1.3–2.1)	3.877	ADD	0.0001**	0.0008**
	1.7 (1.3–2.3)	4.007	DOM	0.00006**	0.0008**
	1.5 (0.6–3.8)	0.876	REC	0.380	0.584
	β	***t***		***p* uncorrected**	***q* FDR corrected**
Current symptoms	0.096	1.589	DOM	0.112	0.287
FFI personality					
Extraversion	0.011	0.188		0.851	0.741
Neuroticism	0.078	1.381		0.168	0.321
Conscientiousness	0.002	0.050	DOM	0.960	0.775
Openness	−0.023	−0.529		0.597	0.705
Agreeableness	−0.026	−0.616		0.538	0.705
Genotype interaction with current depression score					
Extraversion	−0.183	−3.031		0.002**	0.012*
Neuroticism	0.009	0.164		0.870	0.741
Conscientiousness	−0.096	−1.932	DOM	0.054	0.164
Openness	−0.044	−0.922		0.357	0.584
Agreeableness	−0.025	−0.543		0.588	0.705
Genotype interaction with lifetime depression					
Extraversion	−0.341	−2.963		0.003**	0.012**
Neuroticism	0.143	1.442		0.150	0.321
Conscientiousness	−0.034	−0.355	DOM	0.723	0.739
Openness	−0.040	−0.453		0.651	0.713
Agreeableness	0.017	0.196		0.845	0.741

Abbreviations: CI, confidence intervals; FDR, false discovery rate; FFI, Five Factor Inventory; Genetic models, dominant (DOM); additive (ADD), recessive (REC); OR, odds ratio.
*$p<0.05$; **$p<0.01$.

Level-2

Multivariate main effects, diagnosis × genotype interactions, and corrections for multiple testing (FDR *q*-values) are shown in Table 3. In summary, no significant multivariate main effects or diagnosis × genotype interactions were found for the *n*-back correct moves model or the SoC initial thinking time model. The SoC subsequent thinking time model showed no significant multivariate main effects but did indicate a significant multivariate diagnosis × genotype interaction. Follow-up univariate analysis of the individual task conditions indicated a significant interaction effect in the 2-move-solution condition ($F(2, 202) = 4.515$, $p = 0.012$) with the 4-move condition *p*-value only marginally < 0.1 ($F(2, 202) = 2.599$, $p = 0.077$). However, none of the *post-hoc* contrasts across the interaction term survived correction.

The SoC average number of moves model also showed a significant multivariate diagnosis × genotype interaction with the follow-up univariate between-subject tests indicating significance in the 3-move-solution condition ($F(2, 202) = 5.630$, $p = 0.004$) and in the 4-move-solution condition ($F(2, 202) = 3.844$, $p = 0.023$). Šidák corrected *post-hoc* pairwise comparisons of the interaction term indicated significant differences between G allele carriers with current MDD and all other groups (all $p \leqslant 0.01$) for the 3-move solution condition. This *post-hoc* univariate interaction result is shown in Figure 1.

For the emotional word memory task, a significant multivariate main effect of diagnosis was shown for the number of correctly recalled immediate words and the number of correctly recalled delayed words. There was a significant multivariate diagnosis × genotype interaction for the number of delayed intrusions (not surviving FDR). The follow-up univariate between-subject tests showed a significant interaction for the number of positive intrusions only ($F(2, 225) = 6.143$, $p = 0.003$). Šidák corrected *post-hoc* pairwise contrasts for the interaction term in the positive word condition indicated that G allele carriers with current MDD had fewer positive intrusions on delayed recall than

Table 3 Multivariate Main Effect and Interaction Results from the Level-2 Neuropsychological Test Battery

	Multivariate main effect (Pillai's Trace)	*F*	*df*	*p*-value	FDR *q*-value
n-back (1-back, 2-back, 3-back)					
Number correct	D	1.939	6, 440	0.073	0.230
	G	0.064	3, 219	0.979	0.968
	D × G	0.993	6, 440	0.429	0.625
Stockings of Cambridge (2-, 3-, 4-, 5-moves)					
Initial thinking time (ITT)	D	0.862	8, 400	0.549	0.718
	G	1.175	4, 199	0.323	0.513
	D × G	0.226	8, 400	0.986	0.968
Subsequent thinking time (STT)	D	0.692	8, 400	0.699	0.823
	G	1.296	4, 199	0.273	0.495
	D × G	2.623	8, 400	0.008**	0.047*
Average number of moves	D	1.397	6, 402	0.215	0.440
	G	1.470	3, 200	0.224	0.440
	D × G	3.270	6, 402	0.004**	0.047*
Emotional word memory (positive, negative, neutral)					
Number of correctly recalled immediate words	D	4.033	6, 448	0.001**	0.024*
	G	2.452	3, 223	0.064	0.230
	D × G	1.911	6, 448	0.078	0.230
Number of immediate intrusions	D	0.387	6, 448	0.887	0.968
	G	0.155	3, 223	0.926	0.968
	D × G	0.962	6, 448	0.451	0.625
Number of correctly recalled delayed words	D	3.040	6, 448	0.006**	0.047*
	G	1.673	3, 223	0.174	0.403
	D × G	0.691	6, 448	0.657	0.814
Number of delayed intrusions	D	1.159	6, 448	0.327	0.513
	G	1.808	3, 223	0.146	0.382
	D × G	2.510	6, 448	0.021*	0.099

Abbreviations: D, diagnosis; df, degrees of freedom; D × G, diagnosis and genotype interaction; FDR, false discovery rate; G, genotype.
*$p<0.05$; **$p<0.01$.

AA carriers with current MDD ($p<0.001$), remitted G allele carriers ($p=0.002$), and control G carriers ($p=0.026$). This *post-hoc* univariate interaction result is shown in Figure 2.

Level-3

Analysis of covariance for the sad-neutral contrast indicated a significant ROI-corrected main effect of genotype in the left PCC ($F(1,51)=17.34$, $p_{(FWE)}=0.045$) at $-7\ -46\ 20$ and the left dorsal ACC (*d*ACC; $F(1,51)=17.62$, $p_{(FWE)}=0.041$) at $-4\ 35\ 20$. A corrected follow-up *t*-contrast indicated that greater responses were found for the AA genotype group compared with the G allele group in both regions (PCC: $t(51)=4.20$, $p_{(FWE)}=0.021$; ACC: $t(51)=4.16$, $p_{(FWE)}=0.023$) (Figure 3). No ROI-corrected clusters were found for the main effect of diagnosis. The genotype × diagnosis interaction also indicated no ROI-corrected clusters, suggesting that the effects were due to genotype alone (Figure 4). The cell sizes for the interaction term were: AA genotype + remitted MDD ($n=18$), AA genotype controls ($n=23$), G allele + remitted MDD ($n=7$), and G allele controls ($n=10$). Owing to the rarity of the minor allele, this result is tentative due to the small numbers in each group. Repeating the analysis using the happy-neutral contrast and the fear-neutral contrast revealed no significant ROI-corrected activations for either contrast and no diagnosis × genotype interaction. See Supplementary Information for details of medicated participants and power.

DISCUSSION

Our main finding is an association between the *TOMM40* G allele and a history of depression. Using depression-related intermediate phenotypes, our results indicate that rs2075650 polymorphism does not increase the risk of depression via the expected neuroticism pathway but rather appears to interact with extraversion. This effect was not

found globally at the behavioral level but only appeared within the context of depression, namely the risk allele carriers displayed decreased extraversion if they had lifetime or current depression. The *TOMM40* risk allele also appeared to be associated with cognitive deficits during current depressive episodes, specifically mild executive dysfunction and a decrease in positive memory intrusions, and may therefore act by enhancing cognitive deficits within the most vulnerable group. Our imaging data identified functional differences between the protective and risk allele carriers that did not appear to be influenced by diagnosis. Instead of the predicted increase in activation in ROIs during sad emotion processing, we found a stable decrease of activity in the PCC and a state/medication-dependent deactivation in the *d*ACC.

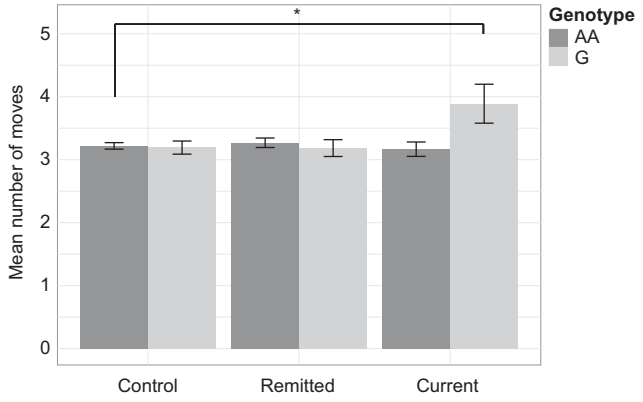

Figure 1 Univariate results from the 3-move-solution condition of the Stockings of Cambridge (SoC) task detailing the direction of interaction for the mean number of moves between the two genotype categories and the three diagnostic groups. Error bars represent SE. *$p \leqslant 0.01$.

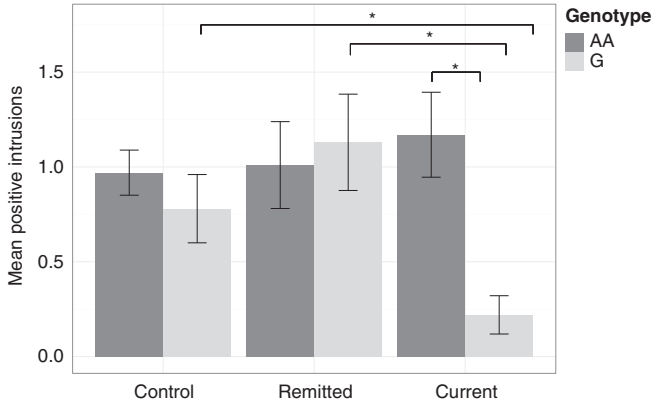

Figure 2 Univariate results for the mean number of intrusive positive words recalled from the delayed word memory task, detailing the direction of the interaction effect between the two genotypes and three diagnostic categories. Error bars represent SE. *$p \leqslant 0.05$.

Decreased Extraversion and Depression

Both extraversion and neuroticism are key personality traits for affective processing (Canli, 2004). In fact, it has been claimed that 50% of the genetic vulnerability to depression is shared with genes that influence the expression of neuroticism (Juhasz *et al*, 2009), whereas extraversion is only weakly linked (Kendler *et al*, 2006b). Our results showed no interaction between *TOMM40* and depression on neuroticism but a significant finding for decreased extraversion. *TOMM40* may therefore act as a particular mediator of the extraversion trait alone, reducing expression in carriers of the risk allele with either a history of, or current, depressive episodes. This is compatible with a number of studies implicating low extraversion as a risk factor for developing depression (Cox *et al*, 2004; Farmer *et al*, 2002; Jylha and Isometsa, 2006; Jylha *et al*, 2009) although the association is not as strong as with neuroticism. It may be that even mildly decreased extraversion is important during depressive episodes (Jylha *et al*, 2009) where it might inhibit recovery. Further study will be needed to clarify this relationship. In addition, given the established relationship between *TOMM40* and AD, it is interesting to note that a decrease in extraversion, as well as increases of neuroticism, have been found to precede and represent risk factors for AD and thus may be markers of early dementia onset (Robins Wahlin and Byrne, 2011).

Executive Dysfunction and a Reduced Positive Memory Bias

Poor performance during the SoC task has been previously demonstrated in depressed patients (Beats *et al*, 1996; Elliott

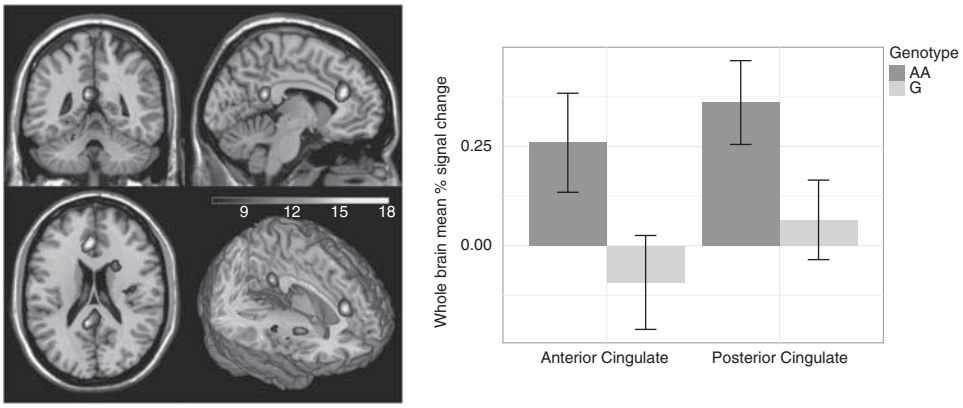

Figure 3 Peak voxel activation for the sad-neutral contrast of the emotional faces task in the AA and GA/GG genotype groups. Columns illustrate whole-brain mean percentage of signal change. Error bars represent 90% confidence intervals.

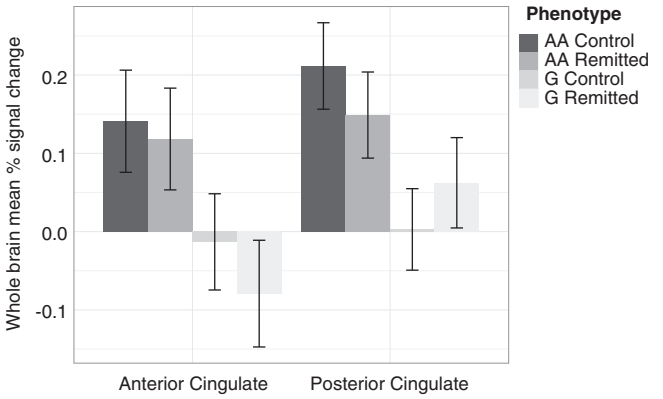

Figure 4 Peak voxel activation for the sad-neutral contrast of the emotional faces illustrating the interaction between diagnosis and rs2075650 genotype. Error bars represent 90% confidence intervals.

et al, 1996), a finding often interpreted as a top-down, executive control deficit (Disner *et al*, 2011). Our finding of some influence of the *TOMM40* risk allele on SoC performance in currently depressed, but not remitted depressed, individuals suggests that there may be a state-dependent effect of the risk allele on executive dysfunction. Although the effect was modest, and therefore caution is needed, it is of interest that impaired cognitive function, in addition to low extraversion, has been associated with poorer treatment outcome in depression (Clark *et al*, 2009), consistent with a potential role for the *TOMM40* risk allele as a marker of worse illness course.

Negative bias is central to cognitive models of depression where positive bias associated with normal processing of affective stimuli is reduced (Elliott *et al*, 2011; Ellwart *et al*, 2003; Harmer *et al*, 2009). In our study, the bias towards the intrusive recall of positive words was seen in all the groups apart from currently depressed individuals carrying the risk allele. The risk allele may therefore play a part in the biasing of the retrieval of affective material from memory (Hamilton and Gotlib, 2008).

Neuronal Differences in Cingulate Activity

Using fMRI during face emotion processing, an imaging marker for depression (Scharinger *et al*, 2010), we found that possession of the risk allele, independent of a history of depression, was associated with altered function of the cingulate cortex during sad emotion processing. Given the finding was in both remitted depressed participants and controls, it appears that the risk allele is associated with a general alteration in affective processing. In depression, both morphological changes (Caetano *et al*, 2006) and dysfunction of the *d*ACC (Fu *et al*, 2004) have been demonstrated and implicated as predictors of treatment response (Fu *et al*, 2008; Pizzagalli *et al*, 2001; Pizzagalli, 2011). Dysfunction of the *d*ACC is consistent with theories of impaired top-down control in depressed individuals (Disner *et al*, 2011). The PCC is associated with affective self-referential processing (Johnson *et al*, 2009; Vogt *et al*, 2006), and abnormal responses in this region have been reported in depressed subjects (Berman *et al*, 2011; Drevets, 2000). One possible interpretation of our results is that the presence of a trait alteration in function in the cingulate cortex, through carrying the risk allele, may interact with those occurring during depression. In particular, the effect in the *d*ACC may contribute to impaired recovery from depression. Of interest also, given the putative link between depression and AD, is that one of the earliest detectable hypo-metabolic neuronal regions in AD is the PCC (Minoshima *et al*, 1997), with the *TOMM40* risk allele known to impact brain regions vulnerable to AD by downstream apoptotic processes (Ferencz *et al*, 2012). These findings suggest that a potential mechanism for depression as a precursor to AD may be via dysfunctional activity within the cingulate.

Limitations

The main limitation of the current study was our focus on a single SNP. Although significant associations were found, it is difficult to know how much of an effect this polymorphism has without further understanding the influence of other mutations within the TOMM40-*APOE* locus. Although the Level-1 cohort was a large sample, the nature of questionnaire data and subsequent response biases means that further replication will be required to support our findings, particularly as the diagnosis of depression was self-reported. In our Level-2 findings, the main effect of emotional word bias did not survive FDR correction, thus this result will need replication. In addition, the sample size for the Level-3 imaging study was modest by genetic standards and as such replication of this result will be required. Also, only remitted depressed and healthy individuals were imaged, and therefore we cannot generalize our findings to a currently depressed state.

Summary

The current study presents evidence of a possible new risk allele for the development of depression. Our results indicate that possession of the *TOMM40* G allele is associated with lifetime risk of depression and with altered neural processing of sad faces shown by fMRI. In addition, current depressive states revealed further genotypic associations with impaired cognitive performance, changes in positively biased affective recall, and a decrease in extraverted personality traits. Extrapolation of these results beyond the current study remains speculative given that this is the first study to investigate the link between depression and *TOMM40* rs2075650. It may be that the risk allele distorts the development of neural systems processing executive function and emotion and that therefore the effects of the *TOMM40* G allele might be expected not only to increase risk of depression but also to prolong illness. This is currently unknown and would be worthy of further investigation. It is intriguing to consider that the same underlying alterations in neural system function may also contribute to vulnerability for the development of dementia, potentially explaining the enhanced risk of AD in individuals who have suffered depression in the past, and the reduced age of onset for AD in these vulnerable populations. Further investigations will be needed in order to fully understand the relationship between *TOMM40*, dementia, and depression.

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Author contributions

GJ and MMF had full access to all the data in the study, performed the statistical analysis, and GJ takes responsibility for the integrity of the data and the accuracy of the data analysis. All other authors contributed to the wording, content, and construction of the final manuscript.

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