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The Role of Educational Attainment and Brain Morphology in Major Depressive Disorder: Findings From the ENIGMA Major Depressive Disorder Consortium

Sarah Whittle[1], Divyangana Rakesh[1], Lianne Schmaal[2], Dick J. Veltman[3, 4], Paul M. Thompson[5], Aditya Singh[6], Ali Saffet Gonul[7], Andre Aleman[8], Aslıhan Uyar Demir[7], Axel Krug[9], Benson Mwangi[10], Bernd Krämer[11], Bernhard T. Baune[12, 13], Dan J. Stein[14], Dominik Grotegerd[15], Edith Pomarol-Clotet[16, 17], Elena Rodríguez-Cano[18], Elisa Melloni[19], Francesco Benedetti[19, 20], Frederike Stein[21], Hans J. Grabe[22, 23], Henry Völzke[24], Ian H. Gotlib[25], Igor Nenadić[26], Jair C. Soares[10], Jonathan Repple[15], Kang Sim[27], Katharina Brosch[26], Katharina Wittfeld[22, 23], Klaus Berger[28], Marco Hermesdorf[28], Maria J. Portella[17, 29], Matthew D. Sacchet[30], Mon-Ju Wu[10], Nils Opel[15], Nynke A. Groenewold[31], Oliver Gruber[11], Paola Fuentes-Claramonte[16, 17], Raymond Salvador[16, 17], Roberto Goya-Maldonado[6], Salvador Sarró[16, 17], Sara Poletti[19, 20], Susanne L. Meinert[15, 32], Tilo Kircher[21], Udo Dannlowski[15], and Elena Pozzi[1, 2]

[1] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health
[2] Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia
[3] Department of Psychiatry, Amsterdam UMC, Amsterdam Neuroscience, VU University
[4] Amsterdam Neuroscience, VU University Medical Center
[5] Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, University of Southern California
[6] Laboratory of Systems Neuroscience and Imaging in Psychiatry, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen
[7] SoCAT Lab, Department of Psychiatry, School of Medicine, Ege University
[8] Cognitive Neuroscience Center, University Medical Center Groningen, University of Groningen
[9] Department of Psychiatry, Philipps-University Marburg, Germany, Department of Psychiatry and Psychotherapy, University of Bonn
[10] Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences of McGovern Medical School, The University of Texas Health Science Center at Houston
[11] Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University
[12] Department of Psychiatry, University of Münster
[13] Department of Psychiatry, The University of Melbourne

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Sarah Whittle https://orcid.org/0000-0003-3145-1528
Divyangana Rakesh https://orcid.org/0000-0002-8529-2086
Lianne Schmaal https://orcid.org/0000-0001-9822-048X
Dick J. Veltman https://orcid.org/0000-0001-8971-4250
Paul M. Thompson https://orcid.org/0000-0002-4720-8867
Aditya Singh https://orcid.org/0000-0002-0539-7129
Ali Saffet Gonul https://orcid.org/0000-0003-3522-1359
Aslıhan Uyar Demir https://orcid.org/0000-0002-0856-4260
Axel Krug https://orcid.org/0000-0002-0564-2497
Benson Mwangi https://orcid.org/0000-0002-1717-4395
Bernd Krämer https://orcid.org/0000-0002-1145-9103
Bernhard T. Baune https://orcid.org/0000-0001-6548-426X
Dan J. Stein https://orcid.org/0000-0001-7218-7810
Dominik Grotegerd https://orcid.org/0000-0001-8718-0128
Edith Pomarol-Clotet https://orcid.org/0000-0002-8159-8563
Elisa Melloni https://orcid.org/0000-0002-6742-8373
Francesco Benedetti https://orcid.org/0000-0003-4949-856X
Frederike Stein https://orcid.org/0000-0002-5052-6022
Hans J. Grabe https://orcid.org/0000-0003-3684-4208
Henry Völzke https://orcid.org/0000-0001-7003-399X
Ian H. Gotlib https://orcid.org/0000-0002-3622-3199
Igor Nenadić https://orcid.org/0000-0002-0749-7473
Jair C. Soares https://orcid.org/0000-0002-5466-5628
Jonathan Repple https://orcid.org/0000-0003-1379-9491
Kang Sim https://orcid.org/0000-0003-3209-9626
Katharina Brosch https://orcid.org/0000-0002-0526-8095
Katharina Wittfeld https://orcid.org/0000-0003-4383-5043
Klaus Berger https://orcid.org/0000-0001-8966-3684
Marco Hermesdorf https://orcid.org/0000-0003-3541-7212
Maria J. Portella https://orcid.org/0000-0002-2007-9516
Mon-Ju Wu https://orcid.org/0000-0002-0540-8027
Nils Opel https://orcid.org/0000-0003-4749-3298
Nynke A. Groenewold https://orcid.org/0000-0002-0865-8427
Paola Fuentes-Claramonte https://orcid.org/0000-0002-1428-7976
Raymond Salvador https://orcid.org/0000-0001-5557-1562
Salvador Sarró https://orcid.org/0000-0003-1835-2189
Sara Poletti https://orcid.org/0000-0001-9594-0246

[14] SAMRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town
[15] Institute for Translational Psychiatry, University of Münster
[16] FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain
[17] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain
[18] Benito Menni CASM, Barcelona, Spain
[19] Psychiatry and Clinical Psychobiology, Division of Neuroscience, IRCCS Scientific Institute Ospedale San Raffaele
[20] Department of Psychiatry, Vita-Salute San Raffaele University
[21] Department of Psychiatry, Philipps-University Marburg, Germany
[22] Department of Psychiatry and Psychotherapy, University Medicine Greifswald
[23] German Center for Neurodegenerative Diseases DZNE Rostock, Greifswald, Germany
[24] Institute for Community Medicine, University Medicine Greifswald
[25] Department of Psychology, Stanford University
[26] Department of Psychiatry and Psychotherapy, Philipps-University Marburg
[27] West Region, Institute of Mental Health, Singapore
[28] Institute of Epidemiology and Social Medicine, University of Münster
[29] Institute of Biomedical Research Sant Pau, Barcelona, Catalonia, Spain
[30] Center for Depression, Anxiety, and Stress Research, McLean Hospital, Harvard Medical School
[31] Department of Psychiatry and Neuroscience Institute, University of Cape Town
[32] Institute for Translational Neuroscience, University of Münster

Brain structural abnormalities and low educational attainment are consistently associated with major depressive disorder (MDD), yet there has been little research investigating the complex interaction of these factors. Brain structural alterations may represent a vulnerability or differential susceptibility marker, and in the context of low educational attainment, predict MDD. We tested this moderation model in a large multisite sample of 1958 adults with MDD and 2921 controls (aged 18 to 86) from the ENIGMA MDD working group. Using generalized linear mixed models and within-sample split-half replication, we tested whether brain structure interacted with educational attainment to predict MDD status. Analyses revealed that cortical thickness in a number of occipital, parietal, and frontal regions significantly interacted with education to predict MDD. For the majority of regions, models suggested a differential susceptibility effect, whereby thicker cortex was more likely to predict MDD in individuals with low educational attainment, but *less* likely to predict MDD in individuals with high educational attainment. Findings suggest that greater thickness of brain regions subserving visuomotor and social–cognitive functions confers susceptibility to MDD, dependent on level of educational attainment. Longitudinal work, however, is ultimately needed to establish whether cortical thickness represents a preexisting susceptibility marker.

Tilo Kircher https://orcid.org/0000-0002-2514-2625
Udo Dannlowski https://orcid.org/0000-0002-0623-3759
Elena Pozzi https://orcid.org/0000-0001-8360-5571

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Sarah Whittle and Divyangana Rakesh are equal first authors.

Correspondence concerning this article should be addressed to Sarah Whittle, Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, 161 Barry Street, Carlton, Victoria 3053, Australia. Email: swhittle@unimelb.edu.au

General Scientific Summary
Findings from this study provide support for a complex interplay of biological and environmental factors being important in predicting major depressive disorder. Findings suggest that alterations in brain structure may not predict depression in all individuals; rather, such alterations may only predict depression in the context of adverse environmental experiences. Conversely, these same alterations may protect against depression in the context of positive environmental experiences.

Keywords: socioeconomic status, diathesis-stress, differential susceptibility, brain structure, depression

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Studies consistently find that individuals with Major Depressive Disorder (MDD) compared to healthy controls, are more likely to have lower socioeconomic status (SES). Level of education, in particular, is consistently associated with MDD, and is thought to influence its development, potentially more so than other indices of SES (e.g., income; Miech & Shanahan, 2000; Zimmerman & Katon, 2005). The potential mechanisms linking low education with MDD are many, and may include lack of knowledge of and access to resources/treatment options for depressive symptoms (Miech & Shanahan, 2000; Zimmerman & Katon, 2005), increased exposure to life stressors, including chaotic households and violence (Evans, 2004), reduced executive function (Lövdén et al., 2020) leading to difficulties regulating behavior and emotion (Letkiewicz et al., 2014), and reduced social support (Ten Kate et al., 2017).

However, not all individuals with low levels of education develop MDD. Rather, it is likely that low educational attainment, and the inherent related alterations to daily functioning, is one factor that interacts with other factors to confer risk. Indeed, etiological models of MDD suggest that accumulation of risk factors (i.e., cumulative risk) likely best explain the development of MDD (Epkins & Heckler, 2011). These models commonly implicate biological risk factors (e.g., diathesis-stress model [Monroe & Simons, 1991]), with genetic factors commonly investigated (Colodro-Conde et al., 2018; Mullins et al., 2016). There is some evidence, for example, for genetic predisposition to be more strongly related to depression in the context of low educational attainment (Amin et al., 2019). However, investigation of other biological factors has been less common.

Structural brain alterations are commonly seen in MDD, with reduced hippocampal volume and prefrontal structure being one of the most robust findings to date (Schmaal et al., 2016). There is also evidence that some of these structural alterations may in part preexist depression onset and represent a vulnerability factor (MacMaster et al., 2008; Toenders et al., 2019). Importantly, recent work suggests that alterations in brain structure may increase risk for MDD in the context of other risk factors such as environmental adversity (Guyer, 2020). Most relevant studies have investigated adolescent samples, and family-based environmental adversity has been a focus. For example, work by the authors (Whittle et al., 2011) found that adolescents with larger hippocampi were more sensitive to the depressogenic effects of aggressive parenting. More recently, Schriber et al. (2017) reported that adolescents with relatively large hippocampal volumes demonstrated increased vulnerability to low levels of family connectedness and high levels of community crime exposure in the prediction of depression. Only one study to our knowledge has investigated interactions between brain structure and other risk factors in the prediction of depression in adults (Frodl et al., 2010). In a sample of adults with MDD, the authors found that in those with smaller prefrontal cortex and smaller hippocampal white matter, emotional neglect was associated with increased risk for longer cumulative illness duration.

Of note, while alterations in brain structure may confer risk, they may also reflect a 'susceptibility' marker (Guyer, 2020). As per the 'differential susceptibility' theory (Ellis et al., 2011), patterns of brain structure may render individuals more or less "sensitive" to both risk and protective factors leading to worse *or* better outcomes, respectively. As such, the same structural alteration may be associated with high risk for depression if one is exposed to other risk factors *or* may be associated with *lower* risk for depression if one is not exposed to such risk factors (or instead is exposed to protective factors). Indeed, there is some evidence for brain structural susceptibility factors in the context of mental health. In an adolescent sample, we previously found relatively reduced thinning of frontal regions to be associated with higher well-being in the context of positive home environments, and lower well-being in the context of aversive home environments (Deane et al., 2020). Whether brain structural alterations in adult MDD reflect vulnerability or susceptibility markers in the context of educational attainment has not been tested.

Despite the established separate links between MDD and a) educational attainment and b) structural brain alterations, little work has been done to understand how these two factors interact to influence MDD. Indeed, measures of SES, such as level of education are invariably included as nuisance covariates in models of MDD-related structural abnormalities rather than as variables of interest. The aim of this study was to establish, in a large multisite sample, whether educational attainment interacted with cortical and subcortical structure to predict MDD. Based on existing adult literature, we hypothesized that hippocampal volume, and prefrontal thickness and surface area would interact with educational attainment to predict MDD, such that smaller structures would be associated with increased probability of MDD status in the context of relatively low educational attainment, but potentially decreased probability of MDD in the context of high educational attainment. In exploratory analyses, we investigated whether a) age and sex moderated findings, and b) findings held for first-episode versus recurrent, and early- versus late-onset MDD status. Finally, given alternate possible associations between education, brain and MDD —in particular, low education may exacerbate brain structural abnormalities in MDD (i.e., education may interact with MDD status to predict brain structure) – we tested this model in exploratory analyses.

Materials and Methods

Participants

Participants were adults from 16 data sets collected around the world, as part of the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium (MDD Working Group). See Supplementary Tables S1, S2 and S3 for the geographic locations, diagnostic tools used to confirm MDD status, and demographic characteristics of the different samples, respectively. All participating sites obtained approval from local institutional review boards, and all study participants provided written informed consent. In total, the combined data set contained 2069 individuals with MDD and 3116 control participants after local quality control at each study site, and 1858 individuals with MDD and 2921 control participants after exclusions based on missing data (see below). The mean age of participants across data sets was higher for individuals with MDD than for control participants, and a greater proportion of individuals with MDD were female (see Table 1).

Education

Education was operationalized as the total number of years of education completed (school + university/vocational training). Years of education was used rather than categories in line with other international research (Stamler et al., 2003), and because education systems differ markedly across countries. The mean number of years of education was lower for individuals with MDD (see Table 1).

MRI Acquisition and Data Preparation

Structural T1-weighted brain MRI (MRI) scans were acquired at each study site. Images were acquired at different field strengths (1.5 Tesla or 3 Tesla) and with various acquisition parameters, as indicated in Table S1. All sites then applied harmonized processing and quality control protocols developed by the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols). The data used in this study were from the left and right volumes of eight bilateral subcortical structures (including lateral ventricles) and thickness and surface area measures for each of 34 bilateral cortical regions, as calculated using FreeSurfer (Version 5.1 or 5.3) software (Dale et al., 1999). Cortical regions were defined using the Desikan-Killiany atlas (Desikan et al., 2006). Given no hypotheses of lateralized effects, measures of left and right structures were averaged. In addition, intracranial volume was obtained. Parcellation of cortical and subcortical gray matter regions were visually inspected and statistically evaluated for outliers at each site following the standardized ENIGMA protocol, which resulted in the exclusion of some regions for some participants. Centrally, individuals with more than four excluded regions for the eight subcortical volumes were excluded from the analysis of subcortical regions as having possibly unreliable subcortical data. Similarly, individuals with more than eight excluded regions out of 34 regional cortical thickness measures were excluded from the analysis of cortical thickness, and likewise for surface area measures. Based on this criteria, 211 individuals with MDD and 195 healthy controls were excluded from analyses.

Table 1
Demographic Information for the Full Sample

Characteristic	MDD	Control
N	1,858	2,921
Female	65%	55%[b]
Age (years, *M* ± *SD*/range)	44.74 ± 12.44/ 18−86	43.61 ± 15.67/ 18–84[a]
Education (years, *M* ± *SD*/ range)	13.41 ± 2.9/0−26	13.99 ± 2.83/0–25[b]
AD use	894	
First-episode MDD	752	
Recurrent MDD	1,059	
Late onset (>age 33[c])	826	
Early onset (≤age 33)	902	

Note. AD = antidepressant use; MDD = major depressive disorder.
[a] $p < .01$. [b] $p < .001$. [c] Participants were split into early and late onset MDD based on a median split of age of onset.

Statistical Methods

To ensure that findings were robust, the final sample was randomly split into 2390 discovery and 2389 replication cases using the *cvpartition* function in MATLAB with 50% of the data in the discovery set and 50% in the holdout replication set. The discovery and replication samples did not show differences in demographic data (including age, sex, site, and education; $p > .5$). We examined whether brain structure moderated the association between education and diagnosis in both the discovery and replication samples using generalized linear mixed models (GLMM; using lmer::glmer) in R Version 4.2. Separate models were fitted for each brain region. Predictors included years of education, brain region and their interaction. The outcome variable was diagnosis (a binary variable). We covaried for age and sex (and intracranial volume for subcortical and surface area variables). Site was modeled as a random effect. Values of brain morphological measures and education were winsorized (5th–95th percentile [Liao et al., 2016]) and centred for all analyses. To assess for significance of effects we used a false discovery rate (FDR) of $p < .05$ applied within volume (n = 8), thickness ($n = 34$), and surface area ($n = 34$) variables in discovery and replication samples. Only variables that survived FDR correction in both the discovery and replication analyses were considered significant. Further analyses investigated whether age and sex moderated associations.

In order to test for differential susceptibility effects, we utilized the approach by Widaman et al. (2012), whereby a reparameterized regression model is estimtated that makes the crossover point of the interaction one of the parameters to be estimated. The point estimate of the crossover point is accompanied by a standard error, so that an interval estimate can be calculated. The reparameterized model allows model fit under differential-susceptibility and alternate model (e.g., diathesis–stress) conditions to be statistically contrasted, with the better fitting model offered as the optimal representation of the data. Here, Bayesian.

Information Criterion (Schwarz, 1978) was used to select the best fitting model for each significant interaction effect. GxE_interaction_test from the LEGIT package (Jolicoeur-Martineau et al., 2020) in R was used to implement the Widaman modeling. An alternate approach to determining differential susceptibility (Roisman et al., 2012) was also implemented, with results reported in online supplementary material.

Sensitivity Analyses

We ran a number of sensitivity analyses to see if effects were robust to the influence of various confounds, a) including all predictor by covariate interactions as covariates, b) including antidepressant use (vs nonuse) as a covariate, c) excluding individuals $<$ 25 years and $>$ 65 years (given for those $<$ 25, maximum educational attainment might not have been reached, and for those $>$ 65, decline in cognitive function may confound associations), d) including total mean thickness as a covariate in cortical thickness models, and e) excluding outlier sites (see Supplementary Information).

Exploratory Analyses

We conducted exploratory analyses (across the whole sample) to investigate whether previously significant relationships differed as a function of MDD status (first-episode vs recurrent MDD), and age of onset (early vs late, based on a median split). These relationships were also examined using a similar GLMM approach, while replacing the binary diagnosis dependent variable with binary variables for four different comparisons—controls vs first-episode MDD, controls vs recurrent MDD, controls vs early onset, controls vs late onset). We controlled for multiple comparisons using FDR ($p < .05$) within each model. Finally, to test an alternate model, whereby education may interact with MDD to influence brain structure, we examined whether years of education moderated the association between diagnosis and brain structure in the full sample using GLMM. Separate models were run for each brain variable, covariates were included as per our main models, and FDR of $p < .05$ was used to correct for multiple comparisons.

Results

Cortical Thickness Moderates the Relationship Between Education and MDD Status

In the discovery sample, cortical thickness of 23 brain regions was found to moderate the association between years of education and diagnosis (MDD vs control; $p_{FDR} < .05$; Figure 1A; Table S5). A similar relationship was obtained for the cortical thickness of 13 brain regions in the replication sample ($p_{FDR} < .05$; Figure 1B, Table S6), all of which overlapped with the discovery sample (Figure 1C). See Table 2 for model output (based on the full sample, see Table S4 for output for all regions). Surface area of cortical regions and volume of subcortical regions did not significantly moderate the association between education and diagnosis in the discovery sample. Sex and age were not found to moderate any associations.

For all regions, with the exception of the pericalcarine cortex, thicker cortex appeared to function as a differential susceptibility marker, whereby thicker cortex was associated with a higher probability of MDD in the context of low levels of education, but was associated with a lower probability of MDD in the context of higher levels of education (see Figure 2 and Table S7 for output from the Widaman approach modeling). For the pericalcarine region, thicker cortex was associated with a higher probability of MDD in the context of low educational attainment (consistent with a cumulative risk or diathesis-stress effect). Across models, the main effect of education was significant, with lower educational attainment associated with a higher probability of MDD. Note that with the alternate classification approach, fewer models were classified as differential susceptibility (see Table S8).

For the 13 implicated regions, the main effect of cortical thickness was only significant for the pars opercularis and pericalcarine regions ($p_{FDR} < .05$, corrected across 34 regions), where thinner and thicker cortex, respectively, was associated with a higher probability of MDD. As such, for the majority of implicated regions, *thicker* cortex was only associated with MDD in interaction with educational attainment. MDD was associated with *thinner* cortex of a number of other regions in the cingulate, insula, temporal and frontal cortices, consistent with prior work (28).

All moderation findings remained significant a) after covarying for antidepressant use, b) after controlling for total mean thickness, and c) after excluding participants from one outlier site. After controlling for predictor-covariate interactions, effects for all regions except the superior parietal cortex remained significant. After restricting the sample to those aged $>$ 25 years and $<$ 65 years, effects for the majority of regions (10/13) remained significant; effects for pericalcarine, pars triangularis and inferior parietal regions were no longer significant.

Controls Versus First-Episode and Recurrent MDD

Analyses revealed similar effects for first-episode and recurrent MDD (a subset of relationships have been illustrated in S1, see Table S9/10 for model output). For first-episode MDD, the cortical thickness of all 13 regions moderated the relationship between years of education and diagnosis ($p_{FDR} < .05$). For recurrent MDD, the cortical thickness of 9/13 regions moderated the association between educational attainment and diagnosis ($p_{FDR} < .05$).

Early Versus Late-Onset MDD

We found that similar effects existed for early and late-onset MDD, with stronger and more effects observed for late-onset MDD (a subset of relationships have been illustrated in Figure S2, see Table S11/12 for model output). The cortical thickness of all 13 regions moderated the relationship between years of education and late-onset diagnosis ($p_{FDR} < .05$). On the other hand, thickness of 9/13 regions moderated the relationship between education and early-onset diagnosis ($p_{FDR} > .05$).

Alternate Model

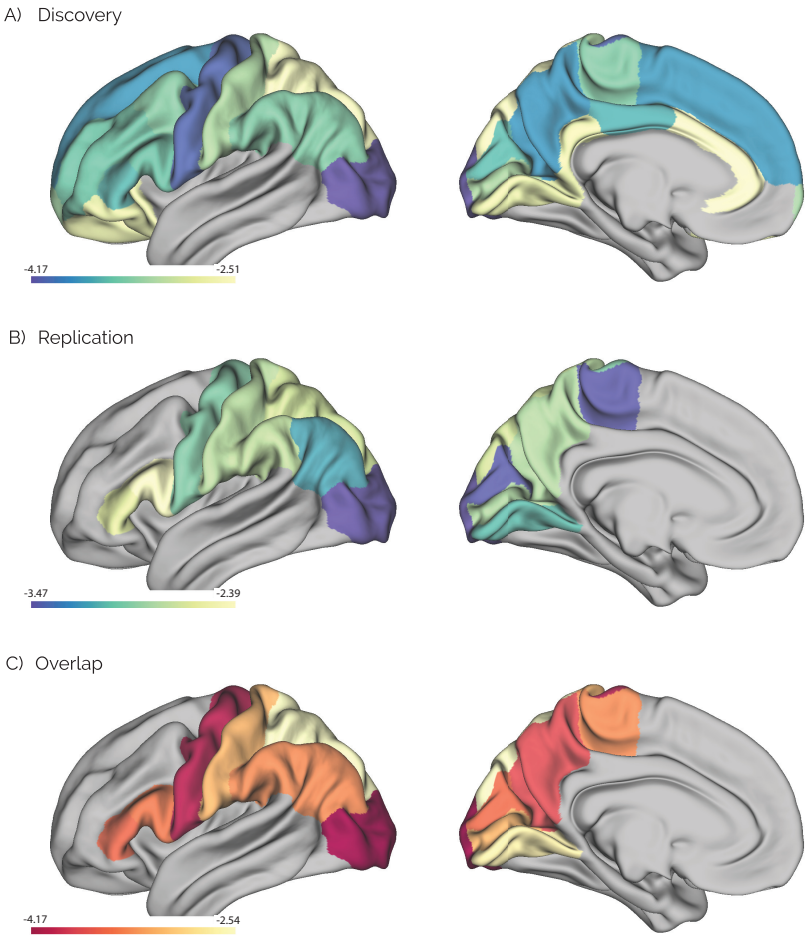
Analyses testing the moderating role of educational attainment in the association between MDD status and volume of subcortical regions/thickness and surface area of cortical regions revealed no significant effects ($p_{FDR} > .05$).

Discussion

In a large sample of adults with MDD, and consistent with hypotheses, we found that brain structure interacted with educational attainment to predict MDD status. However, inconsistent with hypotheses, *thicker* (rather than thinner) cortex of a number of parietal, occipital, and frontal regions was associated with MDD status,

Figure 1

Cortical Renderings of Z Values From Significant GLM Models for Cortical Thickness in the Discovery Sample (A), Replication Sample (B), and the Overlap (C)



Note. Z values from the discovery sample have been used in (C). A different color scheme has been used in (C) to highlight the overlap between (A) and (B), while the direction of the relationship was the same (i.e., negative Z values). Effect sizes (Cohen's *d*) are reported in Table 2. See the online article for the color version of this figure.

dependent on level of educational attainment. These findings point to the importance of brain structural alterations and education as two interacting factors influencing MDD. Most effects were consistent with differential susceptibility; that is, structural alterations indicating a vulnerability in the context of low educational attainment but also protective in the context of high educational attainment.

While some of the regions implicated were prefrontal (i.e., inferior frontal gyrus) as hypothesized, the majority were in posterior frontal, and parietal and occipital regions, including lateral occipital cortex, and pre-, post-, and paracentral gyri. Additionally, that thicker (rather than thinner) cortex was associated with MDD (dependent on level of educational attainment) was inconsistent with hypotheses. Reductions in cortical thickness are typically reported in MDD, particularly in frontal and temporal regions (Schmaal et al., 2017). Indeed, this was the case in the current sample, where there were main effects of thinner cortex in patients with MDD. Notably, the regions interacting with education to predict MDD for the most part were not in these frontal and temporal regions. As such, thicker cortex in the parietal, occipital and inferior frontal regions seen here might be uniquely associated with sensitivity to depression in the context of varying levels of education. There are some reports of thicker cortex in MDD (Li et al., 2020; Suh et al., 2019), and it has been suggested that thicker cortex, particularly in first-episode MDD, may represent an initial compensatory response to depression (Qiu et al., 2014). In line with differential susceptibility theory, however, we interpret our findings to suggest that thicker cortex in specific parietal and occipital regions may represent a preexisting factor that contributes to MDD onset specifically in the context of low educational attainment.

For the majority of implicated regions, effects supported an interpretation of differential susceptibility. Those with thicker cortex in these regions were more likely to have MDD in the context of lower educational attainment, but *less* likely to have MDD if they had higher educational attainment. Implicated regions, including occipital and parietal regions, preand postcentral gyri, and inferior frontal gyrus, appear to map onto the visuomotor integration system,

Table 2
Education and Brain Morphology Predicting MDD Status (MDD = 1, Control = 0)

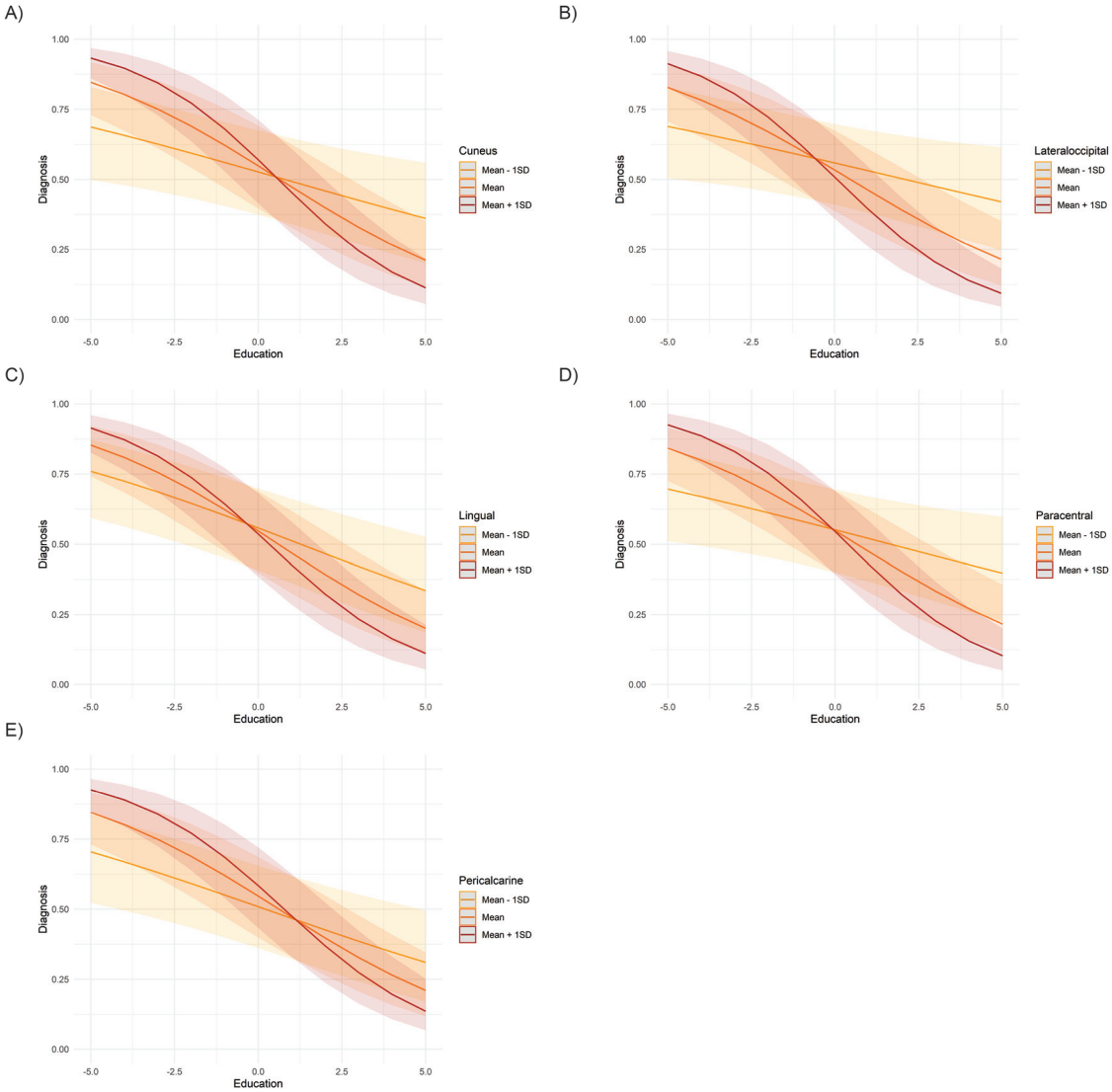
Brain region/variable	*B*	*SE*	*df*	Z	P	Cohen's *d*
Cuneus						
Cuneus × Education	−0.199	0.041	4,709	−4.81	1.53E-06	0.070
Education	−0.312	0.039	4,709	−8.04	8.99E-16	0.117
Cuneus	0.104	0.055	4,709	1.88	0.059878	0.027
Inferiorparietal						
Inferiorparietal × Education	−0.202	0.045	4,719	−4.50	6.74E-06	0.066
Education	−0.307	0.039	4,719	−7.94	1.97E-15	0.116
Inferiorparietal	−0.095	0.058	4,719	−1.64	0.100301	0.024
Lateraloccipital						
Lateraloccipital × Education	−0.219	0.041	4,743	−5.29	1.26E-07	0.077
Education	−0.292	0.039	4,743	−7.56	4.05E-14	0.110
Lateraloccipital	−0.097	0.060	4,743	−1.62	0.105453	0.024
Lingual						
Lingual × Education	−0.170	0.043	4,720	−3.98	6.75E-05	0.058
Education	−0.317	0.039	4,720	−8.20	2.39E-16	0.119
Lingual	−0.041	0.052	4,720	−0.79	0.428176	0.012
Paracentral						
Paracentral × Education	−0.200	0.043	4,755	−4.68	2.80E-06	0.068
Education	−0.302	0.038	4,755	−7.86	3.96E-15	0.114
Paracentral	0.003	0.068	4,755	0.05	0.959551	0.001
Parsopercularis						
Parsopercularis × Education	−0.177	0.044	4,757	−4.01	5.95E-05	0.058
Education	−0.313	0.039	4,757	−8.12	4.61E-16	0.118
Parsopercularis	−0.193	0.056	4,757	−3.47	0.00,053	0.050
Parstriangularis						
Parstriangularis × Education	−0.172	0.041	4,746	−4.15	3.31E-05	0.060
Education	−0.314	0.039	4,746	−8.15	3.56E-16	0.118
Parstriangularis	−0.086	0.052	4,746	−1.65	0.098484	0.024
Pericalcerine						
Pericalcarine × Education	−0.167	0.040	4,684	−4.19	2.83E-05	0.061
Education	−0.310	0.039	4,684	−7.98	1.50E-15	0.117
Pericalcarine	0.155	0.057	4,684	2.71	0.00,683	0.040
Postcentral						
Postcentral × Education	−0.169	0.041	4,702	−4.08	4.47E-05	0.060
Education	−0.305	0.039	4,702	−7.89	2.96E-15	0.115
Postcentral	0.032	0.059	4,702	0.55	0.580816	0.008
Precentral						
Precentral × Education	−0.206	0.043	4,727	−4.83	1.36E-06	0.070
Education	−0.306	0.039	4,727	−7.94	1.99E-15	0.116
Precentral	−0.083	0.069	4,727	−1.19	0.232159	0.017
Precuneus						
Precuneus × Education	−0.206	0.045	4,752	−4.56	5.16E-06	0.066
Education	−0.312	0.039	4,752	−8.10	5.70E-16	0.117
Precuneus	−0.080	0.056	4,752	−1.43	0.151473	0.021
Superiorparietal						
Superiorparietal × Education	−0.148	0.042	4,744	−3.53	0.000419	0.051
Education	−0.311	0.039	4,744	−8.08	6.33E-16	0.117
Superiorparietal	0.034	0.053	4,744	0.66	0.512266	0.010
Supramarginal						
Supramarginal × Education	−0.184	0.044	4,634	−4.15	3.31E-05	0.061
Education	−0.308	0.039	4,634	−7.90	2.88E-15	0.116
Supramarginal	−0.083	0.061	4,634	−1.36	0.172926	0.020

Note. MDD = major depressive disorder. Statistics are presented for the full sample; statistics for covariates have not been included.

responsible for moment-to-moment processing of sensorial inputs and production of motor responses, for appropriate adjustment to the environment (Bueichekú et al., 2020). Thicker cortex in the regions comprising this system may lead to alterations in its functioning and increased sensitivity to stimuli in the environment (Jagiellowicz et al., 2011; Martins et al., 2021). Given that those with lower educational attainment are more likely to encounter threatening stimuli in their environment (Evans, 2004), increased sensitivity to such stimuli may in turn contribute to the onset of MDD. Conversely, given that those with high educational attainment have increased exposure to positive environments (e.g., social support), increased neural sensitivity to such positive stimuli may reduce risk for MDD (Belleau et al., 2021). This interpretation is speculative, however, and it is unclear why these regions, but not those hypothesized, were implicated. In particular, the structure of frontal cortical regions, and the amygdala and hippocampus, have been suggested to confer susceptibility to the environment due to their roles in emotional reactivity, regulation and learning/memory (Deane et al., 2020; Schriber et al., 2017). However, it is of note that the existing studies have used region of interest approaches (Deane et al., 2020; Schriber et al.,

Figure 2

Logit Plots for the Relationship Between Years of Education and Diagnosis (MDD Versus Control), at Mean ±1 SD of Cortical Thickness for Selected Brain Regions Showing Differential Susceptibility Effects (A–D), and Pericalcarine Region (E), Which Shows a Vulnerability Effect



Note. See the online article for the color version of this figure.

2017; Whittle et al., 2011), or only investigated regions where there were main effects of MDD (Frodl et al., 2010), potentially failing to detect significant effects outside of hypothesized regions. More recent work has suggested that the brain regions underlying differential susceptibility are likely to be more widespread, including networks important for attention set shifting (Homberg & Jagiellowicz, 2022). Further work is needed to understand how structure and function across primary and association cortices confers susceptibility to different environments in the prediction of MDD.

Given the cross-sectional study design, we cannot be certain that thicker cortex in the implicated regions represents a preexisting susceptibility factor. However, interaction effects were present even in first-episode MDD, lending some support to this interpretation. In addition, it is of note that for many of these regions implicated, thickness has been shown to be highly heritable (Winkler et al., 2010). It is thus possible that thicker cortex in these regions is genetically driven and confers susceptibility to environments and other factors associated with educational attainment, and ultimately, risk of/protection from MDD. Of note was that effects were particularly prominent for those with later-onset MDD. These individuals may have experienced a greater number or longer duration of negative and positive environments associated with low and high educational attainment, respectively (i.e., longer time between educational attainment and MDD onset/lack of onset), which suggests that thicker cortex may confer particular susceptibility for MDD in the context of extended or cumulative environmental exposure. Again, this interpretation is highly speculative.

While this study is the largest to elucidate the complex role of educational attainment and neuroanatomy in MDD, it has a

number of limitations. First, the assumption of differential susceptibility theory is that the susceptibility marker preexists MDD onset. While longitudinal studies that capture pre and post MDD-onset are best suited to test these theories, our findings in a large sample represent a solid basis for future longitudinal work. Further, we found no support for an interactive effect of MDD and low education in predicting structural alterations. However, it is possible that thicker cortex in the regions implicated partially resulted from low educational attainment and/or MDD onset. Second, an assumption underlying the tested models is that brain structure confers vulnerability or susceptibility to negative and positive environments associated with educational attainment. Although there is work consistently supporting the link between educational attainment and exposure to such environments (Evans, 2004), this was not explicitly tested in this study. Further, there are a number of variables related to educational attainment that may better account for the findings (or may help to interpret them), such as income, IQ, or trauma. Future work is needed to more comprehensively understand the findings presented here.

In summary, in a large multisite sample of adults with MDD, we found support for thicker cortex across occipital, parietal and frontal regions conferring susceptibility to MDD in the context of educational attainment. Although longitudinal work is ultimately needed to establish whether these structural alterations represent preexisting markers, results may indicate that alterations in visuomotor and related social–cognitive functions render individuals sensitive to environments and experiences commonly associated with educational attainment, and in turn risk of, or protection from the development of MDD.

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