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Manuscript: 3943 words
Abstract: 236 words
Tables: 4
Figures: 1
Supplemental Tables: 2
Supplemental Figures: 9

Title: Cortical Thickness is not associated with Current Depression in a Clinical Treatment Study

Authors:
Greg Perlman[1]
Elizabeth Bartlett[7]
Christine DeLorenzo[1]
Myrna Weissman[4]
Patrick McGrath[4]
Todd Ogden[4]
Tony Jin[1]
Phil Adams[5]
Madhukar Trivedi[2]
Benji Kurian[2]
Maria Oquendo[4]
Melvin McInnis[3]
Sarah Weyandt[2]
Maurizio Fava[6]
Crystal Cooper[2]
Ashley Malchow[2]
Ramin Parsey[1]

1. Department of Psychiatry, Stony Brook University,
2. Department of Psychiatry, University of Texas Southwestern Medical Center,
3. Department of Psychiatry, University of Michigan,
4. Department of Psychiatry, Columbia University,
5. New York State Psychiatric Institute, New York,
6. Department of Psychiatry, Massachusetts General Hospital,
7. Department of Biomedical Engineering, Stony Brook University,

Corresponding Author:

Greg Perlman
Department of Psychiatry
Putnam Hall, Stony Brook University

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version record. Please cite this article as doi:10.1002/hbm.23664.

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Stony Brook, New York, 11789
Greg.perlman@stonybrookmedicine.edu

Keywords: cortical thickness, MRI, depression, multi-site, adults, biomarker, imaging

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Abstract

Background: Reduced cortical thickness is a candidate biological marker of depression, although findings are inconsistent. This could reflect analytic heterogeneity, such as use of region-wise cortical thickness based on the Freesurfer Desikan-Killiany (DK) atlas or surface-based morphometry (SBM). The Freesurfer Destrieux (DS) atlas (more, smaller regions) has not been utilized in depression studies. This could also reflect differential gender and age effects. Methods: Cortical thickness was collected from 170 currently depressed adults and 52 never-depressed adults. Visually inspected and approved Freesurfer-generated surfaces were used to extract cortical thickness estimates according to the DK atlas (68 regions) and DS atlas (148 regions) for region-wise analysis (216 total regions) and for surface-based morphometry (SBM). Results: Overall, except for small effects in a few regions, the two region-wise approaches generally failed to discriminate depressed adults from non-depressed adults or current episode severity. Differential effects by age and gender were also rare and small in magnitude. Using SBM, depressed adults showed a significantly thicker cluster in the left supramarginal gyrus than non-depressed adults ($p = 0.047$) but there was no associations with current episode severity. Conclusions: Three analytic approaches (i.e., DK atlas, DS atlas, and SBM) converge on the notion that cortical thickness is a relatively weak discriminator of current depression status. Differential age and gender effects do not appear to represent key moderators. Robust associations with demographic factors will likely hinder translation of cortical thickness into a clinically-useful biomarker.

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Introduction

Cortical thickness, a component of gray matter volume and index of cell density and health in the cerebral cortex (Rajkowska et al. 1999), has been reported to be reduced in adults with a lifetime history of major depressive disorder (MDD+) relative to adults without a lifetime history of major depressive disorder (MDD-; Colloby, et al., 2011; Jarnum, et al., 2011; Koolschijn, et al., 2010; Li, et al., 2014; Na, et al., 2016; Schmaal, et al., 2016; Truong, et al., 2013; Tu, et al., 2012; van Eijndhoven, et al., 2013; Wagner, et al., 2012). In addition to helping distinguish subjects with or without MDD for screening or diagnostic purposes, cortical thickness may also represent an etiological factor. For instance, two potent risk factors for MDD -- a history of MDD in first-degree relatives (Ozalay, et al., 2016; Papmeyer, et al., 2015; Peterson and Weissman, 2011) and heightened trait negative affect (Holmes, et al., 2016) -- have also been associated with reduced cortical thickness in certain regions. In addition, reduced cortical thickness was found to precede incidence of depression in a sample of 10-15 year-olds (Foland-Ross, et al., 2015) and in a young adult sample (mean age 21 years-old; (Papmeyer, et al., 2015).

Altogether, cortical thickness could represent an important tool for understanding etiology of depression, inferring latent risk for depression, and guiding clinical care (e.g., risk screening, treatment planning, etc.). Results, however, have been somewhat inconsistent across studies. Depression has not been linked to reduced cortical thickness in any one particular region; rather, each report implicates one or a few frontal, temporal, parietal, and occipital areas (see Table 1). Yet other studies report cortical thinning in some regions AND cortical thickening in other regions (Fallucca, et al., 2011; Peterson, et al., 2009; Tu, et al., 2012). For example, regions found to have cortical thinning in the largest study to date from the ENIGMA workgroup

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(~1900 adult MDD subjects), such as the medial orbitofrontal cortex (Schmaal, et al., 2016), have been previously reported to be thicker in MDD+ compared to MDD- in smaller studies (Qiu, et al., 2014). Furthermore, several other studies reported no difference between MDD+ and MDD- in cortical thickness in any region.

Summarizing the cortical thickness depression literature is difficult in part because of non-uniform approaches to quantifying cortical thickness. As described in Table 1, all studies that conducted region-wise analyses, either *a priori* region of interest (ROIs) or exploratory whole-brain analyses, defined regions according to the Desikan-Killiany (DK) atlas (Desikan, et al., 2006). The DK atlas is a well-studied atlas and is standard in FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), the most utilized software package for analyzing cortical thickness data. To our knowledge, the Freesurfer-based Destrieux (DS) atlas (Destrieux, et al., 2010), which offers smaller and more regions relative to the DK atlas, has not been utilized to study depression. The reason for this absence is unclear, as psychometric properties of the DS atlas are comparable to the DK atlas (Iscan et al., 2015). In any case, ROI analyses assume that depression will be associated with abnormalities that adhere to *a priori* defined regions, which may or may not correspond to underlying pathophysiology. An alternative strategy used by many studies in the literature is surface-based morphometry (SBM), which analyzes whole-brain cortical thickness data unconstrained by *a priori* structure. It is unclear if these approaches converge or diverge in understanding the link between depression and cortical thickness.

The first goal of this study is to compare 170 subjects with current major depressive disorder (MDD+) and 52 never-depressed controls on cortical thickness as measured by these two ROI approaches (DK and DS) and by SBM. This is the first report to our knowledge to utilize these three analytic approaches, providing opportunity to describe converging vs

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diverging links with depression across them. A secondary goal of the current study is to identify potential moderators of the link between depression and cortical thickness. Prior studies in this area utilized case-control comparisons that focused on main effects without exploration of potential moderators. In this report, we consider two demographic moderators (age and gender), which show profound links to depression in epidemiological studies of depression. We also examine a clinical feature of depression, namely current episode severity, as it may track cortical thickness.

In this study, we leveraged data collected as part of the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) project, a multisite study of depression and treatment response (Trivedi, et al., 2016). Data was available for 170 subjects with current major depressive disorder (MDD+) and 52 never-depressed controls (MDD-) assessed at one of four university centers in Massachusetts, Michigan, New York, and Texas. The design of EMBARC is well-suited for investigating the link between cortical thickness and depression based on relatively large sample size for a clinical imaging study, uniform multi-site recording procedures, uniform data processing blind to diagnosis, and thorough clinical characterization of participants using both self-report and diagnostic interviews. Importantly, the imaging protocol and analytic steps utilized by EMBARC, including manual inspection procedures, have been thoroughly described and investigated elsewhere (Iscan, et al., 2015). As described by Iscan *et al.* (2015) in a test-retest study of 40 healthy adults, cortical thickness data that is visually-inspected and manually approved demonstrates higher reliability (ICC = 0.77 for DS; ICC = 0.81 for DK) compared to when this is skipped (ICC = 0.59 for DS; ICC = 0.62 for DK). Because visual inspection is burdensome and time consuming, many studies are unable to implement this processing step. To our knowledge,

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this is the largest study to date that uses identical processing conditions and manual-inspection procedures to compare Freesurfer-derived cortical thickness measurements between depressed and non-depressed cohorts.

Methods and Materials

Details about the ongoing EMBARC study, including ascertainment and randomization, have been reported elsewhere (Trivedi, et al., 2016; Webb et al., 2016; Delaparte et al., 2017; Olvet et al., 2015). All participants were between the ages of 18 and 65 years-old and provided signed consent. Inclusion criteria for MDD+ subjects were to be in a current depressive episode, verified by a semi-structured clinical interview conducted by a trained interviewer, and to have a clinically-significant score of at least 14 on the Quick Inventory of Depressive Symptoms (QIDS-SR; (Rush, et al., 2003)). MDD+ and MDD- subjects were excluded for current pregnancy, lifetime history of psychosis or bipolar disorder, substance dependence within the previous 6 months, substance abuse within the past 2 months, or any factor that would obscure treatment response in the randomization trial (recent treatment for depression involving other medications, somatic treatments, or psychotherapy) or contraindicate use of study medication (i.e., risk of interaction with ongoing medication, clinically significant laboratory results, etc.).

Data Acquisition

Specific details about scanning, processing, and sequence parameters have been published elsewhere (Iscan, et al., 2015). To summarize, T1w images were acquired with 3T MRI scanners at each site. An MPRAGE sequence was used at the University of Texas Southwestern Medical Center (TX: Philips Achieva, 8-channel (ch) head coil), University of Michigan (UM: Philips Ingenia, 15-ch), and Massachusetts General Hospital and Stony Brook

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University (MGH & SBU: Siemens TrioTim, 12-ch), while an IR-FSPGR sequence was used at Columbia University Medical Center (CU: GE Signa HDx, 8-ch). The following MR parameters were consistent across sites: TR (repetition time): 5.9-8.2 ms, TE (echo time): 2.4-4.6 ms, Flip Angle: 8-12°, slice thickness: 1 mm, Field of View: 256×256 mm, voxel dimensions: 1 mm isotropic, acquisition matrix: 256×256 or 256×243, acceleration factor: 2, and 174-78 sagittal slices. Acquisition times ranged from 4.4 to 5.5 minutes.

Processing

Cortical thickness was computed for 34 bilateral Desikan-Killiany (DK) atlas regions (Desikan, et al., 2006) and 74 bilateral Destrieux (DS) atlas regions (Destrieux, et al., 2010) using FreeSurfer 5.3.0's standard, automated cortical reconstruction pipeline (http://surfer.nmr.mgh.harvard.edu/) on a Linux-based computing cluster. The pipeline's subroutines have been described in previous publications (Iscan, et al., 2015); the processing steps include skull-stripping (Segonne, et al., 2004), Talairach transformation, subcortical grey/white matter segmentation (Fischl, et al., 2002), intensity normalization (Sled, et al., 1998), grey/white matter tessellation, topology correction (Fischl, et al., 2001; Segonne, et al., 2007) and intensity gradient based surface deformation to generate grey/white and grey/cerebrospinal fluid surface models (Dale, et al., 1999; Fischl, et al., 2001; Segonne, et al., 2007). The resulting surface models were then inflated and registered to a spherical surface atlas, allowing parcellation of cortical regions of interest (Fischl, et al., 1999a; Fischl, et al., 1999b; Fischl, et al., 2004). Finally, regional cortical thicknesses were computed by taking the mean of the white-pial distance at all vertices within each parcellated region (Fischl and Dale, 2000). The surface models (used to calculate cortical thickness) then underwent an empirical, systematic inspection process (Iscan, et al., 2015) in which a trained technician carefully inspected 2D sections of the

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pial and white surface models overlaid on the T1w image for fidelity to visible tissue class boundaries. Cases where inaccurate tissue delineation persisted for ≥6 consecutive coronal and axial slices were deemed inaccurate and thus disqualified from further analyses. Of 293 eligible cases inspected, 222 (76%) passed inspection. All technicians were blinded to subject diagnoses.

Statistical Analysis

Region-Wise Analysis: The region-wise cortical thickness estimates from the DS and DK atlases were analyzed in R (R Development Core Team, Vienna, Austria. http://www.R-project.org). Bivariate associations were described using Pearson correlations. Group differences (i.e., MDD+ vs MDD-) were tested using hierarchical linear models. First, extraneous factors were modeled as covariates in Step 1: age and age^2 (Salat, et al., 2004; Sowell, et al., 2007), gender (Luders, et al., 2006; Savic and Arver, 2014), education (Kim et al., 2015), and recording site (Iscan, et al., 2015). Then, group status (MDD+ vs MDD-) was added in Step 2 to determine the amount of variance associated with diagnosis over and above Step 1. Next, the interactions for diagnosis by age (Step 3a) and diagnosis by gender (Step 3b) were added to determine the amount of variance accounted for over and above Step 2. Analysis of current depression severity (QIDS score) excluded controls, as well as one depressed case for which QIDS score was not available (n = 169).

In all region-wise analyses, the magnitude of effect (i.e., change in r^2 from Step 1 to Step 2, change in r^2 from Step 2 to Step 3a/3b) and *p*-value level were reported. **Pearson's r were reported for the association between depression severity and cortical thickness in order to convey the direction of the association.** When interpreting the results, we also considered the number of significant effects relative to number of tests. We note that r^2 is easily converted to other effect size metrics for comparison with other studies or use in meta-analysis (See

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Rosenthal, 1994).

SBM Analysis: All SBM analyses were performed in Freesurfer 5.3.0. The approved cortical thickness maps for each subject were first registered to a common spherical atlas (Fischl, et al., 1999b) and smoothed with a 10mm Gaussian kernel. A general linear model (GLM) was used to examine the vertex-wise differences in cortical thickness: (1) between the MDD+ and MDD- groups and (2) associated with QIDS score, controlling for age, age^2, gender, education, and site. Right and left hemispheres were examined separately. A Monte Carlo Null-Z simulation cluster analysis with 10,000 iterations and cluster-forming threshold of $p < 0.001$ was used to correct for multiple comparisons and is explained in detail elsewhere (Wagner, et al., 2012). In short, the family-wise error significance threshold was set at $p < 0.05$ and through a combination of probability and cluster-size thresholding, cluster-wise probability (CWP) *p*-values are obtained for resulting clusters. This CWP result represents the overall alpha significance level for the cluster. The Monte Carlo simulation and clustering is based on the AlphaSim algorithm (Ward, 2000).

Results

Demographics: Table 2 presents the sample characteristics by imaging site. The sites were similar in proportion of MDD+ vs MDD-, course of depression, gender, age, education, QIDS score, and total brain volume. There was a significant site effect for number of discreet episodes of depression reported by MDD+ subjects (log10 transformed due to skew; winsorized to 20 as maximum due to skew). *Post hoc* comparisons revealed that MDD+ subjects at Michigan reported more discrete episodes of depression than MDD+ subjects at Columbia ($p = 0.006$) and Harvard ($p = 0.04$). The MDD+ subjects did not differ by site in lifetime rates of Panic Disorder, Obsessive Compulsive Disorder, Specific Phobia, Social Phobia, Anorexia Nervosa, Bulimia

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Nervosa, or Any Illicit Substance Use Disorder (a composite category that excluded nicotine and alcohol). MDD+ subjects at Michigan were more likely to meet criteria for Post-traumatic Stress Disorder and Alcohol Use Disorder than MDD+ subjects at other sites.

Freesurfer Desikan-Killiany Atlas: Table 2 presents the proportion of variance in cortical thickness accounted for by age, age^2, gender, education, and site. On average, these factors accounted for approximately 23% of individual differences in left hemisphere and right hemisphere cortical thickness. The incremental main effect of depression (Model 2) was weakly related to cortical thickness (all *p-values* > 0.05). The interaction between depression and age (Model 3a; while controlling for main effects) was weakly related to cortical thickness (all *p-values* > 0.05). The interaction between depression and gender (Model 3b; while controlling for main effects) identified 2 significant effects at $p \leq 0.01$ (2.94% of 68 interactions; **see Supplemental Figure 1 and 2**). The largest effect was the left cuneus, which accounted for 2.8% of variance in that region over and above covariates and main effect of depression**. In both cases, greater cortical thickness was observed in depressed males compared to depressed females and less cortical thickness was observed in non-depressed males compared to non-depressed females.**

Among depressed cases only, covariates accounted for approximately 22% of individual differences in left hemisphere and right hemisphere cortical thickness on average (see supplemental table 1). Current depression severity (Model 2) was **negatively** associated with cortical thickness in the right middle temporal gyrus at $p < 0.01$ (1.47% of 68 tests). This effect accounted for 4.28% of variance in that region over and above covariates. The interaction between depression severity and age (Model 3a) was significant in the left bankssts at $p < 0.01$

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(1.47% of 68 interactions**)**, which accounted for 3.53% of variance in that region over covariates and main effect of depression severity **(see Supplemental Figure 3)**. **As shown in Supplemental Figure 3, higher QIDS scores were associated less cortical thickness in this region at older ages.** The interaction between depression severity and gender (Model 3b) was weakly related to cortical thickness (all *p-values* > 0.01).

Freesurfer Destrieux Atlas: Table 3 presents the proportion of variance in cortical thickness accounted for by age, age^2, gender, and site. On average, these factors accounted for approximately 19% (left hemisphere) and 20% (right hemisphere) of individual differences in cortical thickness. The incremental main effect of depression (Model 2) was weakly related to cortical thickness (all *p-values* > 0.01). One interaction between depression and age (Model 3a) identified the left middle occipital gyrus as significant at p < 0.01 (0.06% of 148 interactions**; see Supplemental Figure 4)**. **In this region, cortical thinning with age appears attenuated in currently depressed compared to never depressed adults.** The interaction between depression and gender (Model 3b) identified 4 significant effects at p < 0.01 (2.7% of 148 interactions; (**see Supplemental Figure 5 – Figure 8**). The largest magnitude of effect was in the right temporal transverse sulcus, which accounted for 3.7% of variance in cortical thickness in that region. **As shown in Supplemental Figure 8, never-depressed males exhibit less cortical thickness in this region than never-depressed females, whereas similar cortical thickness was observed between currently depressed males and females.**

Among depressed cases only, covariates accounted for approximately 18% (left hemisphere) and 19% (right hemisphere) of individual differences in cortical thickness. Current depression severity (Model 2) was **negatively** associated with cortical thickness in 4 regions at p < 0.01, the strongest of which was in the right occipital anterior sulcus (5.29% of variance; 2.7%

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of 148 interactions). Depression severity interacted with age (Model 3a) in one region at $p < 0.01$, the left anterior occipital sulcus and accounted for 4.41% of variance in that region (**see Supplemental Figure 9)**. **As shown, higher QIDS scores was associated with less cortical thickness in this region at older ages.** The interaction between depression severity and gender (Model 3b) was weakly related to cortical thickness (all *p-values* > 0.01).

Surface-Based Morphometry: After multiple comparisons correction, vertex-wise whole-brain comparisons of MDD+ to MDD- revealed that the MDD+ group had thicker left supramarginal gyri than the MDD- group, with a cluster size of 177.86 mm^2 and a cluster-wise, corrected *p*-value of 0.047 (see Figure 1). This region is denoted as supramarginal in Freesurfer, although the cluster extends into the inferior parietal region. The analysis of current depression severity (QIDS score) in the MDD+ group did not identify any clusters after multiple comparisons correction.

Discussion

In this report, we examined the association between cortical thickness and major depressive disorder using data from 170 currently-depressed adults and 52 never-depressed adults collected as part of a multi-site study. To our knowledge, this is the first depression study to examine three strategies for assessing cortical thickness and is the largest to employ a previously validated, slice-wise visual-inspection method on every participant's cortical thickness data (Iscan, et al., 2015). This essential step is often impractical due to the burden of staff time required, but improves data quality (i.e., test-retest reliability) relative to fully-automated processing steps without manual approval (Iscan, et al., 2015). Moreover, this is also the first study to our knowledge to compare depressed and non-depressed adults using regions

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defined by the DS atlas. Compared to the DK atlas, the DS atlas offers more, smaller targets, and has also demonstrated strong test-retest reliability (Iscan, et al., 2015). Finally, this is the first cortical thickness depression study to explore differential age and gender effects.

Essentially, our main result is that currently-depressed adults and never-depressed adults exhibited comparable levels of cortical thickness. The DK atlas--which is notable for fewer, larger regions and use in all prior *a priori,* region-based studies of depression--did not discriminate subjects with depression from never-depressed adults in any region. A few effects were observed with the smaller, more regions defined by the DS atlas; however, effect sizes were small and consistent with the false positive rate. The third analytic method, surface-based morphometry, identified a small area of cortical thickening in the left supramarginal gyrus that survived correction for multiple comparisons. Thus, if present in depressed adults, reduced cortical thickness likely reflects a small effect size in affected regions. A similar conclusion was reached in prior reports that utilized the DK atlas to measure cortical thickness (Phillips, et al., 2015; Schmaal, et al., 2016). The currently study extends this conclusion to cortical thickness analyzed using the SBM approach and the DS atlas.

That we identified the left supramarginal gyrus as thicker in depression is intriguing because it replicates two previous SBM studies of depression (Qiu, et al., 2014; Yang, et al., 2015) and contradicts a third (Ozalay, et al., 2016). It is worth noting that the DS and DK atlases each cover this area. Unfortunately, we can only speculate as to why SPM but not region-wise analysis identify this region as tracking increased cortical thickness in depression. The inconsistency of results across methods may reflect that atlases define regions, according to structural boundaries that do not necessarily correspond to indicators of cortical pathophysiology in depression. That is, SPM may be better for detecting cortical thickness effects that do not fit

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neatly into predefined regions. Of note, previous ROI studies using the DK atlas have not always reported results for regions corresponding to the supramarginal gyrus. This "missing data" in the literature significantly hinders efforts to integrate findings in either a qualitative review of the literature or a meta-analysis. Thus, focused hypothesis-testing designs keep the false positive rate low, but also hinder efforts to integrate findings across studies.

Depression is a heterogeneous phenotype subject to wide intra- and inter-variability in course, symptoms, response to treatment, and etiology. This heterogeneity may obscure the link between depression and cortical thickness, at least to the extent that only specific features of depression track cortical thickness. We pursued this question via exploratory age and gender interactions with depression. Overall, these effects provided no more than a few small magnitude effects, and it remains unclear which features of current depression best track cortical thickness. It is important to emphasize that our study examined a cohort that was relatively homogenous for chronic depression, which includes many who reported a single-episode of depression that continued unremitted or with only partial remission for many years, as well as many who report recurrent depression characterized by full inter-episode recovery. Therefore, we cannot rule out the possibility that cortical thickness better tracks depression in other kinds of depressed cohorts. In addition, more powerful within-subject designs may yet reveal that depression is associated with differential rate of change in cortical thickness across adulthood.

That cortical thickness appears no more than weakly related to current depression should inform the design and implementation of future studies. Strategies to combine datasets or results (e.g., meta-analysis), such as that employed by ENIGMA (Schmaal, et al., 2016), may be more effective than single studies in confirming the presence of subtle thinning in specific regions. Second, cortical thickness appears highly sensitive to several extraneous sources of

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variances. In this study, the combined effects of age, age^2, sex, education, and site differences accounted for nearly a fifth of the total individual differences in cortical thickness. This is much larger than estimates of the effect of depression on cortical thickness. Thus, the strategies by which studies adjust for these factors may have a significant impact on the results. Future research may benefit from establishing cortical thickness normative data to enhance compatibility between recording sites and studies and optimally control for these factors.

There are a number of limitations to this study. First, although we examined a large sample of depressed subjects relative to many other studies, larger samples may be needed to detect subtle associations and identify moderators. In particular, inclusion of fewer non-depressed adults than depressed adults necessarily lowered statistical power to detect group differences. However, larger samples would not be expected to yield larger magnitude associations (Phillips, et al., 2015; Schmaal, et al., 2016). Second, site differences may have masked an association between cortical thickness and depression. However, considerable effort was made to create and apply uniform procedures for sample ascertainment and recording; sites were matched on proportion of cases and controls, gender, mean age, and current depressive severity; and site differences were statistically controlled for in our analyses in order to minimize impact on results. Third, we were unable to conduct exploratory analyses of all candidate moderators of the association between MDD and cortical thickness. This is because the sample was relatively homogenous for long-duration, chronic depression. Future studies of moderators may benefit from examining a more heterogeneous depressed cohort, including remitted cases and recent first-onset cases. The list of potential moderators of the link between cortical thickness and MDD is lengthy, as it includes any trait or disease previously correlated with cortical thickness. This list includes health-related phenotypes, such as diabetes (Ajilore, et al.,

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2010; Franc, et al., 2011) and obesity (Kim, et al., 2015); as well as individual difference traits, such as cognitive ability (Burzynska, et al., 2012; Klein, et al., 2014), religiosity (Miller, et al., 2014), meditation experience (Lazar, et al., 2005), and negative affect (Holmes, et al., 2016). Along these lines, diagnostic comorbidity is a potential moderator of the link between cortical thickness and depression. While comorbidity is common in clinical samples of depressed adults, the current study was not designed to parse unique effects of comorbidity patterns on cortical thickness.

In summary, to our knowledge, this was the second largest study of cortical thickness in depression, the first to examine three separate analytic methods and differential age and gender effects, and the first large study to employ strict quality control procedures during data processing. Although previous reports describe robust associations between major depressive disorder and reduced cortical thickness, the current study finds such an association to be relatively weak at best. Larger sample sizes and more comprehensive searches for moderators may yield more robust effects.

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Table 1 Selected Publications Investigating Cortical Thickness in MDD

Author	Year	Journal	Subjects	Method	Relevant CT Findings in MDDs compared to HCs
Koolschijn	2010	Eur Neuropsychopharmacol	28 elderly MDDs, 38 HCs	SBM	No findings.
Colloby	2011	J Affect Disord	38 late-life MDDs, 30 HCs	Freesurfer Region-wise: DK	No findings.
Han	2014	J Affect Disord	20 1st ep. MDDs, 22 HCs	Freesurfer SBM	No findings.
Lan	2014	Bipolar Disord	56 MDDs, 54 HCs	Freesurfer SBM	No findings.
Phillips	2015	Int J Neuropsychopharmacol	26 treatment-resistant MDDs, 28 HCs	Freesurfer Region-wise: DK	No findings.
Peterson	2009	Proc Natl Acad Sci USA	66 HR children, 65 LR children	Freesurfer SBM	🡻 **right lateral cerebral hemisphere** in HRs vs LRs.
Peterson & Weissman	2011	Annu Rev Med	66 HR children, 65 LR children	Freesurfer SBM	🡻 **cortical mantle over the lateral convexity of the right hemisphere** & the **medial surface of the left hemisphere** in HRs vs LRs.
Tu	2012	Psychiatry Res	36 MDDs, 36 HCs	Freesurfer SBM	🡻 **left anterior insula** & **left lOFC.** 🡻 **left lOFC, par opercularis**, and **caudal** & **rostral middle frontal gyrus** in MDDs with more episodes vs MDDs with less episodes.
Wagner	2012	J Psychiatr Res	15 HR for suicide MDDs, 15 not-HR for suicide MDDs , 30 HCs	Freesurfer SBM	🡻 **left dlPFC, left vlPFC** & **dACC** in HR MDDs vs non-HR MDDs.
Truong	2013	Psychiatry Res	49 MDDs, 64 HCs	SBM	🡻 **left dlPFC**. 🡻 **dlPFC, pre- and postcentral gyrus,** & **lingual gyrus** in early onset MDDs vs HCs.
Li	2014	J Affect Disord	24 MDDs, 24 HCs	Freesurfer SBM	🡻 **dACC** in MDDs vs HCs.
Holmes	2016	J Neurosci	1050 young adults without MDD	Freesurfer SBM	🡻 **left sgACC** & **left rACC** associated with heightened negative affect.

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Holmes	2016	J Neurosci	1050 young adults without MDD	Freesurfer SBM	🡻 **left sgACC** & **left rACC** associated with heightened negative affect.
Liu	2015	Depress Anxiety	30 med-naïve MDDs, 41 HCs	Freesurfer SBM	🡻 **left lOFC** in MDDs vs HCs.
Foland-Ross	2015	J Abnorm Psychol	28 adolescent daughters of mothers with MDD (HRs), 36 adolescent LRs	Freesurfer SBM & Region-wise: DK	🡻 **right fusiform gyrus** in HRs vs LRs.
Na	2016	Sci Rep	65 recurrent MDDs, 65 HCs	Freesurfer SBM	🡻**right mOFC, lingual gyrus, lateral occipital** & 🡻**left lOFC, pars triangularis, lingual gyrus** in MDDs vs HCs.
Schmaal	2016	Mol Psychiatry	1902 adult MDDs, 7658 HC; 213 adolescent MDDs, 294 HCs	Freesurfer Region-wise: DK	🡻**mOFC, fusiform gyrus, rACC, PCC, insula,** & **temporal lobe** in adult MDDs vs HCs**.** 🡻**left middle temporal gyrus, right inferior temporal gyrus,** & **right cACC** in adult MDDs vs HCs. No findings in adolescent MDDs vs adolescent HCs.
Jaworska	2014	Biomed Res Int	36 MDDs, 18 HCs	Freesurfer Region-wise: DK	🡹 **frontal pole** in MDDs vs HCs.

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Qiu	2014	Transl Psychiatry	46 1st ep, med-naïve MDDs, 46 HCs	Freesurfer SBM	↑ **right mOFC, pars opercularis, rostral middle frontal gyrus,** & **supramarginal gyrus** in MDDs vs HCs.
Reynolds	2014	BMC Psychiatry	30 adolescent MDDs, 16 adolescent HCs	Freesurfer Region-wise: DK	↑ **right** & **left rostral middle frontal gyrus** and **left cACC** in adolescent MDDs vs adolescent HCs.
Yang	2015	Psychiatry Res	27 1st-ep MDDs, 27 HCs	Freesurfer SBM	↑ **right OFC** & **left inferior parietal gyrus** in MDDs vs HCs.
Szymkowicz	2016	Int J Geriatr Psychiatry	43 elderly MDDs	Freesurfer SBM & Region-wise: DK	↑ **right isthmus cingulate** & **left precuneus** associated with depressive symptom severity.
Fonseka	2016	BMC Psychiatry	13 young adult MDDs, 14 HCs	Freesurfer Region-wise: DK	↑ **left pars opercularis** in MDDs vs HCs.
van Eijndhoven	2013	Am J Psychiatry	20 med-naïve, 1st ep. MDDs, 31 HCs	Freesurfer SBM	↓ **left mOFC.** ↑ **left & right temporal pole, left cACC** & **left PCC** in MDDs vs HCs.
Fallucca	2011	Arch Gen Psychiatry	24 pediatric MDDs, 24 pediatric OCDs, 30 HCs	Freesurfer SBM	↓ **right pericalcarine, right postcentral, right superior parietal gyrus,** & **left supramarginal gyrus.** ↑ **left & right temporal pole** in pediatric MDDs vs pediatric HCs.

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Foland-Ross	2015	Int J Dev Neurosci	33 adolescents without MDD	Freesurfer Region-wise: DK	CT correctly predicted onset of MDD (accuracy of 70%) in adolescents. **Right mOFC, right precentral, left ACC**, & **bilateral insula** contributed most strongly.
Papmeyer	2015	Biol Psychiatry	111 HR young adults, 93 HCs, 20 HRs developed MDD	Freesurfer Region-wise: DK	↓ **right parahippocampal** & **right fusiform gyrus** in HRs vs HCs. ↓ **parahippocampi** & ↑ **left inferior frontal gyrus** in MDDs vs HRs who did not develop MDD. ↑ **left inferior frontal** & **left precentral gyrus** in MDDs vs HRs who did not develop MDD & vs HCs
Ozalay	2016	Psychiatry Res	24 female MDDs & daughters (HRs), 24 HC females & daughters (LRs)	Freesurfer SBM	↓**right supramarginal gyrus, caudal middle frontal gyrus,** & **lOFC** in female MDDs vs female HCs.**.** ↑**left superior temporal gyrus** in female MDDs vs female HCs. ↓**right inferior parietal gyrus, right superior frontal gyrus,** & **left ventral insula, left superior posterior temporal, temporal pole, fusiform gyrus,** & **dACC** in HRs vs LRs. ↑**right precentral gyrus** in HRs vs LRs.

CT: Cortical Thickness | SBM: Surface-Based Morphometry | MDDs: Persons with major depressive disorder | HCs: Healthy Controls | HRs: Persons at high-risk for MDD | LRs: Persons at low-risk for MDD | DK: Desikan-Killiany Atlas | DS: Destrieux atlas| lOFC, mOFC, OFC: lateral-, medial-, orbitofrontal cortex | dlPFC, vlPFC: dorsolateral-, ventrolateral prefrontal cortex | dACC, cACC, sgACC, rACC: dorsal-, caudal-, subgenual-, rostral anterior cingulate cortex | PCC: posterior cingulate cortex

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Table 2. Descriptive Statistics by Imaging Site

	Columbia		Harvard		Michigan		UTSW		Statistic
	MDD+	MDD-	MDD+	MDD-	MDD+	MDD-	MDD+	MDD-	
	n	n	n	n	n	n	n	n	
Group	44	12	34	17	33	9	59	14	$\chi_{site}(3) = 3.74$, $p = 0.29$
Course									$\chi_{site}(3) = 6.18$, $p = 0.10$
Recurrent	36	--	26	--	32	--	51	--	
Single Episode	8	--	8	--	1	--	8	--	
Gender									$\chi_{site}(3) = 2.59$, $p = 0.47$
M	21	4	16	8	11	3	20	8	
F	23	8	18	9	22	6	39	6	
Education Level									$\chi_{site}(3) = 5.78$, $p = 0.12$
≥16 years	26	7	15	9	14	5	21	8	
< 16 years	16	5	19	8	19	4	38	6	

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Lifetime Psychopathology									
Panic Disorder	9	0	6	0	5	0	7	0	$\chi_{site}(3) = 1.40$, p = 0.71
OCD	0	0	2	0	0	0	4	0	$\chi_{site}(3) = 5.20$, p = 0.16
Specific Phobia	8	0	6	0	11	0	7	0	$\chi_{site}(3) = 6.46$, p = 0.09
Social Phobia	2	0	0	0	4	0	9	0	$\chi_{site}(3) = 4.99$, p = 0.17
PTSD	6	0	1	0	11	0	9	0	$\chi_{site}(3) = 11.97$, p = 0.01
Anorexia	1	0	0	0	0	0	1	0	$\chi_{site}(3) = 1.39$, p = 0.71
Bulimia	0	1	3	0	0	0	1	0	$\chi_{site}(3) = 5.51$, p = 0.14
Alcohol Use Disorder	6	0	2	1	10	0	15	0	$\chi_{site}(3) = 8.78$, p = 0.03
Illicit Use Disorder	5	1	3	0	6	0	12	0	$\chi_{site}(3) = 3.00$, p = 0.39
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	
Number of Episodes[^&]	5.32 (6.23) 1-20	--	6.18 (6.31) 1-20	--	9.36 (6.74) 1-20	--	9.14 (7.60) 1-20	--	$F_{site}(3,166) = 2.85$, p = 0.04, Post Hoc: M >

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									C, M > H
Age	34.45 (10.52) 18-61	36.92 (13.23) 18-64	35.44 (14.69) 18-60	39.24 (18.46) 18-65	34.36 (13.11) 18-58	43.78 (15.19) 23-62	41.37 (11.40) 19-63	32.71 (11.75) 20-57	$F_{site}(3,214) = 0.37$, $p = 0.77$, $F_{DX}(1,214) = 0.69$, $p = 0.41$, $F_{int}(3,214) = 3.30$, $p = 0.02$
Total Brain Volume*	1.15 (0.14) 0.85-1.54	1.14 (0.13) 0.99-1.44)	1.12 (0.10) 0.91-1.41	1.12 (0.11) 0.87-1.29	1.12 (0.12) 0.92-1.43	1.09 (0.15) 0.90-1.28	1.11 (0.11) 0.85-1.39	1.19 (0.16) 0.97-1.54	$F_{site}(3,214) = 1.23$, $p = 0.30$, $F_{DX}(1,214) = 0.24$, $p = 0.62$, $F_{int}(3,214) = 1.82$, $p = 0.14$
Quick Inventory of Depression Symptoms	19.00 (2.98) 14-24	1.50 (1.13) 0-4	17.65 (2.89) 14-27	1.12 (1.05) 0-3	18.67 (3.27) 14-27	2.22 (1.99) 0-6	17.28 (2.43) 14-24	1.14 (1.29) 0-4	$F_{site}(3, 213) = 2.11$, $p = 0.10$, $F_{DX}(1,213) = 1,561$, $p < 0.01$, $F_{int}(3,213) = 0.51$, $p = 0.68$

Note: ^ = For ANOVA, data was log10 +1 transformed due to positive skew; & = Data was windsored to 20 for reporting descriptive statistics. * = 10^5 and millimeters^3 2 participants at Columbia declined to report education.

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Table 3. Effect of Depression on Cortical Thickness derived from DK atlas

	MDD+				MDD-				Model 1: Covariates only		Model 2: Covariates + MDD		Model 3a: Model 2 + MDD x Age		Model 3b: Model 2 + MDD x Gender	
	L		R		L		R		L	R	L	R	L	R	L	R
Region adapted from atlas	Mean	SD	Mean	SD	Mean	SD	Mean	SD	r^2 %		Δr^2 %		Δr^2 %		Δr^2 %	
Bankssts	2.51	0.17	2.60	0.18	2.52	0.18	2.59	0.18	21.06	21.47	0.04	0.02	0.02	0.00	0.27	0.25
Caudal Anterior Cing ulate	2.58	0.26	2.54	0.21	2.64	0.25	2.57	0.29	9.56	10.26	0.29	0.22	0.52	0.07	0.04	1.06
Caudal Middle Frontal	2.54	0.17	2.54	0.16	2.55	0.15	2.52	0.16	25.46	24.2	0.02	0.35	0.00	0.06	0.03	0.80
Cuneus	1.75	0.15	1.78	0.15	1.77	0.12	1.82	0.14	21.43	30.36	0.04	0.09	0.20	0.00	2.83**	1.15
Entorhinal	3.37	0.35	3.47	0.40	3.33	0.30	3.40	0.37	8.36	19.59	0.63	0.75	0.35	0.05	0.86	0.11
Frontal Pole	2.82	0.30	2.78	0.30	2.83	0.33	2.78	0.28	22.25	12.27	0.15	0.02	0.54	0.14	1.53*	0.74
Fusiform	2.72	0.16	2.70	0.18	2.72	0.19	2.72	0.16	28.2	26.23	0.03	0.03	0.35	0.29	0.04	0.04
Inferior Parietal	2.45	0.14	2.47	0.13	2.45	0.15	2.47	0.14	17.67	24.25	0.03	0.03	0.22	0.08	0.44	1.18
Inferior Temporal	2.81	0.17	2.81	0.18	2.82	0.16	2.86	0.16	17.46	16.87	0.01	0.77	0.24	0.01	0.78	0.12
Insula	3.03	0.18	2.99	0.19	3.02	0.17	3.04	0.16	22.51	27.01	0.22	0.51	0.28	0.14	0.53	0.27
Isthmus Cingulate	2.54	0.24	2.47	0.22	2.51	0.21	2.43	0.23	17.86	15.71	0.33	0.23	0.01	0.03	0.15	0.41
Lateral Occipital	2.14	0.14	2.20	0.15	2.13	0.13	2.20	0.15	11.48	8.38	0.24	0.07	0.20	0.03	0.40	0.47
Lateral Orbitofrontal	2.68	0.18	2.65	0.19	2.68	0.18	2.65	0.22	25.91	25.97	0.02	0.01	0.05	0.63	0.20	0.35
Lingual	1.96	0.16	2.01	0.16	1.98	0.15	2.03	0.12	37.13	34.01	0.01	0.00	0.00	0.07	1.41*	2.43**
Medial Orbitofrontal	2.43	0.19	2.42	0.21	2.38	0.18	2.45	0.24	26.44	30.89	0.92	0.44	0.52	0.07	1.27	1.75*
Middle Temporal	2.88	0.16	2.91	0.17	2.89	0.16	2.93	0.17	28.67	24.97	0.10	0.49	0.01	0.32	1.17	1.31
Paracentral	2.30	0.17	2.32	0.19	2.34	0.14	2.32	0.17	26.02	33.72	0.22	0.29	0.07	0.32	0.12	0.16
Parahippocampal	2.77	0.36	2.70	0.30	2.75	0.34	2.70	0.25	10.79	17.52	0.22	0.28	0.05	0.07	1.17	0.62
Pars Opercularis	2.58	0.16	2.59	0.18	2.59	0.17	2.61	0.19	31.82	25.11	0.15	0.21	0.16	0.33	0.32	0.52
Pars Orbitalis	2.77	0.25	2.74	0.24	2.72	0.26	2.75	0.26	30.97	25.4	0.29	0.21	0.26	1.10	0.44	0.04

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Pars Triangularis	2.48	0.18	2.50	0.17	2.47	0.20	2.52	0.20	36.51	30.99	0.00	0.81	0.15	0.10	0.03	0.36
Pericalcarine	1.50	0.16	1.52	0.16	1.51	0.16	1.54	0.14	36.04	34.35	0.33	0.09	0.00	0.00	1.38*	0.63
Postcentral	2.03	0.12	2.02	0.13	2.04	0.13	2.00	0.12	18.53	13.86	0.07	0.94	0.14	0.01	0.38	0.73
Posterior Cingulate	2.52	0.18	2.49	0.17	2.52	0.19	2.49	0.16	27.30	23.20	0.01	0.03	0.17	0.12	0.38	0.43
Precentral	2.51	0.15	2.48	0.14	2.50	0.15	2.49	0.14	32.00	24.94	0.38	0.02	0.65	0.03	0.15	1.01
Precuneus	2.34	0.15	2.36	0.15	2.34	0.14	2.36	0.14	23.26	23.44	0.00	0.08	0.15	0.00	0.37	0.84
Rostral Anterior Cingulate	2.83	0.22	2.81	0.22	2.89	0.25	2.85	0.28	13.69	17.31	1.02	0.45	0.16	1.47	2.14*	0.45
Rostral Middle Frontal	2.38	0.17	2.37	0.16	2.38	0.16	2.36	0.17	34.76	35.68	0.06	0.07	0.40	0.24	0.20	0.27
Superior Frontal	2.73	0.16	2.72	0.16	2.71	0.16	2.71	0.18	36.92	37.9	0.21	0.00	0.01	0.46	0.31	0.20
Superior Parietal	2.14	0.13	2.14	0.14	2.14	0.12	2.15	0.12	16.1	12.91	0.06	0.01	0.20	0.16	0.53	0.08
Superior Temporal	2.79	0.16	2.82	0.18	2.79	0.18	2.83	0.16	26.9	36.09	0.00	0.02	0.89	0.01	1.46*	0.21
Supramarginal	2.55	0.14	2.56	0.15	2.57	0.15	2.56	0.14	24.61	19.55	0.29	0.00	0.09	0.01	0.77	0.11
Temporal Pole	3.68	0.32	3.78	0.33	3.64	0.31	3.73	0.31	4.92	2.60	0.34	0.46	0.01	0.01	1.29	0.39
Transverse Temporal	2.31	0.23	2.35	0.24	2.28	0.21	2.33	0.25	15.46	14.92	0.87	0.33	0.17	0.35	2.07*	1.74*
Mean	2.54	0.19	2.55	0.19	2.54	0.19	2.55	0.19	22.95	22.70	0.23	0.24	0.21	0.20	0.75	0.62

Model 1 presents Total R squared for a model including age, age^2 gender, education, and recording site. Model 2 presents the delta R-squared when adding a group term (MDD+ vs MDD-). Model 3a and 3b present the increment in r^2 from the interaction term. * = $p < .05$, ** = $p < .01$. Cortical thickness is expressed in millimeters.

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Table 4. Effect of Depression on Cortical Thickness derived from DS Atlas

	MDD+				MDD-				Model 1: Covariates only		Model 2 Adds MDD		Model 3a Adds Age x MDD		Model 3b Adds Gender x MDD	
	L		R		L		R		L	R	L	R	L	R	L	R
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	r^2 %		Δr^2 %		Δr^2 %		Δr^2 %	
Ins lg S cent ins	3.20	0.25	3.36	0.29	3.22	0.29	3.31	0.34	11.16	17.70	0.28	0.19	0.03	0.61	0.53	0.19
S Cingul Ant	2.64	0.18	2.61	0.24	2.63	0.20	2.61	0.21	19.34	31.51	0.10	0.14	0.02	0.47	0.44	1.22
S Cingul MidAnt	2.65	0.20	2.70	0.20	2.62	0.21	2.68	0.20	26.58	30.11	0.13	0.15	0.05	0.12	0.24	0.37
S Cingul MidPost	2.53	0.18	2.54	0.17	2.51	0.17	2.55	0.17	34.71	36.12	0.01	0.36	0.21	0.07	0.03	0.34
S frontomargin	2.35	0.21	2.38	0.23	2.36	0.24	2.40	0.24	21.53	22.15	0.00	0.01	0.18	0.17	0.07	0.58
S Occipital Inf	2.41	0.23	2.56	0.19	2.40	0.20	2.55	0.24	6.41	6.88	0.02	0.00	0.02	0.65	0.66	0.14
S Paracentral	2.26	0.18	2.20	0.19	2.22	0.18	2.19	0.19	20.02	25.52	0.05	0.22	0.12	0.40	0.01	0.01
S Subcentral	2.68	0.19	2.72	0.19	2.70	0.18	2.68	0.18	25.40	19.37	0.19	0.71	0.25	0.05	0.19	0.06
S Transv Fronto pol	2.59	0.31	2.55	0.24	2.60	0.22	2.56	0.23	17.60	21.73	0.01	0.00	0.03	0.14	1.09	0.00
Cingul Postdorsal	2.94	0.22	2.89	0.18	2.90	0.21	2.91	0.19	25.07	19.43	0.16	0.51	0.80	0.31	1.88*	1.79*
Cingul Postventral	2.38	0.30	2.71	0.31	2.44	0.31	2.70	0.30	8.69	15.85	0.82	0.01	0.02	0.07	0.01	2.19*
Cuneus	1.71	0.14	1.74	0.14	1.69	0.14	1.71	0.15	24.11	32.74	0.02	0.01	0.37	0.03	1.68*	1.82*
Front Inf Opercular	2.77	0.18	2.79	0.21	2.76	0.18	2.77	0.19	31.47	26.59	0.05	0.13	0.32	0.38	0.24	1.24
Front Inf Orbital	2.76	0.24	2.83	0.24	2.79	0.26	2.77	0.25	11.88	18.56	0.38	0.90	0.04	0.82	0.09	0.10
Front Inf Triangul	2.64	0.22	2.71	0.22	2.67	0.20	2.68	0.20	32.99	22.28	0.08	1.21	0.16	0.10	0.00	0.23
Front Middle	2.63	0.18	2.62	0.19	2.63	0.18	2.64	0.17	34.63	33.64	0.06	0.02	0.01	0.34	0.35	1.06
Front Sup	2.84	0.17	2.83	0.18	2.85	0.18	2.84	0.17	36.76	35.43	0.13	0.05	0.01	0.30	0.64	0.21
Insular Short	3.58	0.22	3.58	0.25	3.60	0.23	3.52	0.22	9.41	14.85	0.52	0.22	0.03	0.01	1.17	1.26
Octemp Lat Fusifor	2.82	0.22	2.83	0.21	2.80	0.20	2.78	0.23	23.99	24.15	0.04	0.24	0.40	0.63	0.01	0.08
Octemp Med Lingual	1.93	0.16	2.04	0.13	1.91	0.17	2.00	0.18	30.73	32.05	0.00	0.21	0.08	0.08	0.95	2.39**
Octemp Med Parahip	3.06	0.27	3.08	0.27	3.10	0.29	3.09	0.30	15.00	16.84	0.84	0.26	0.11	0.15	0.89	0.00
Occipital Middle	2.52	0.18	2.57	0.16	2.52	0.17	2.58	0.17	6.20	7.77	0.03	0.07	3.24**	0.00	0.00	1.38
Occipital Sup	2.06	0.18	2.14	0.17	2.05	0.20	2.14	0.20	8.68	6.66	0.01	0.01	0.00	0.02	1.43	0.06
Orbital	2.80	0.20	2.82	0.24	2.80	0.20	2.80	0.20	35.28	30.70	0.02	0.12	0.01	0.93	0.28	0.08

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Pariet Inf Angular	2.62	0.19	2.67	0.18	2.64	0.19	2.69	0.17	14.81	25.74	0.09	0.04	0.88	0.00	0.03	0.37
Pariet Inf Supramar	2.72	0.17	2.72	0.17	2.72	0.16	2.73	0.18	20.57	22.15	0.04	0.01	0.29	0.59	0.54	0.00
Parietal Sup	2.31	0.13	2.32	0.15	2.31	0.14	2.31	0.15	15.67	11.92	0.14	0.01	0.99	0.59	0.16	0.00
Postcentral	2.13	0.17	2.06	0.17	2.11	0.16	2.11	0.17	13.44	10.11	0.01	2.03*	0.06	0.05	0.35	1.03
Precentral	2.74	0.19	2.72	0.21	2.75	0.18	2.74	0.18	22.01	17.22	0.30	0.65	1.29	0.26	0.23	1.94*
Precuneus	2.47	0.16	2.46	0.17	2.47	0.17	2.45	0.17	17.73	15.55	0.00	0.02	0.07	0.19	0.60	0.31
Rectus	2.55	0.23	2.54	0.31	2.59	0.26	2.50	0.27	40.31	45.00	0.67	0.42	0.22	0.14	0.18	1.44*
Subcallosal	2.68	0.48	2.55	0.42	2.61	0.39	2.49	0.41	8.87	11.05	0.38	0.15	0.37	0.00	0.01	0.00
Temp sup G T Transv	2.36	0.20	2.41	0.27	2.37	0.23	2.41	0.26	11.71	13.88	0.16	0.05	0.09	0.29	1.79*	1.70*
Temp Sup Lateral	3.07	0.19	3.10	0.21	3.08	0.20	3.09	0.20	17.13	28.51	0.11	0.00	0.16	0.19	1.03	0.34
Temp Sup Plan polar	3.46	0.32	3.28	0.23	3.39	0.28	3.26	0.29	10.86	13.26	0.43	0.00	0.05	0.10	2.42*	0.03
Temp Sup Plan tempo	2.56	0.21	2.57	0.19	2.57	0.19	2.58	0.20	10.03	16.55	0.04	0.04	0.65	0.03	3.15**	0.40
Temporal Inf	2.96	0.20	3.00	0.20	2.94	0.21	2.94	0.22	21.09	21.02	0.00	0.79	0.32	0.02	0.25	0.08
Temporal Middle	3.06	0.19	3.10	0.19	3.04	0.18	3.09	0.19	27.58	26.79	0.08	0.22	0.14	0.04	0.57	2.13*
Lat Fis Ant Horizont	2.25	0.32	2.26	0.24	2.24	0.28	2.26	0.23	16.09	16.09	0.27	0.00	0.31	0.14	0.05	0.13
Lat Fis Ant Vertical	2.42	0.28	2.48	0.34	2.37	0.28	2.45	0.31	20.99	17.02	0.49	0.16	0.06	0.00	0.11	0.22
Lat Fispost	2.38	0.18	2.46	0.17	2.37	0.18	2.44	0.18	20.76	24.93	0.05	0.49	0.04	0.42	2.02*	0.17
Pole Occipital	1.89	0.14	1.92	0.17	1.91	0.17	1.93	0.15	14.69	18.35	0.63	0.70	0.00	0.03	0.48	0.52
Pole Temporal	3.31	0.21	3.35	0.23	3.38	0.25	3.39	0.25	8.75	7.35	1.99*	0.94	1.39	0.01	1.65*	0.12
S calcarine	1.78	0.17	1.82	0.14	1.79	0.17	1.82	0.16	40.30	36.53	0.59	0.16	0.01	0.02	1.98**	1.09
S central	1.80	0.17	1.78	0.15	1.81	0.15	1.77	0.16	31.20	27.13	0.74	0.10	1.54*	0.00	0.01	0.22
S Cingul Marginalis	2.19	0.15	2.20	0.17	2.19	0.17	2.20	0.18	19.82	23.37	0.08	0.09	0.07	0.00	0.41	0.09
S Circular Insula Ant	2.80	0.30	2.85	0.31	2.78	0.26	2.84	0.28	14.71	18.54	0.03	0.00	0.01	0.09	0.02	0.50
S Circular Insula Inf	2.76	0.22	2.67	0.18	2.75	0.20	2.70	0.23	22.15	16.98	0.06	0.26	0.68	0.10	0.44	0.62
S Circular Insula Sup	2.56	0.16	2.62	0.21	2.56	0.17	2.60	0.19	33.46	29.08	0.02	0.47	0.00	0.05	0.00	0.16
S Collat Transv Ant	2.72	0.35	2.68	0.27	2.74	0.32	2.67	0.31	9.97	15.47	0.00	0.03	2.73*	0.37	0.82	0.05
S Collat Transv Post	2.06	0.24	2.10	0.27	2.02	0.25	2.08	0.25	13.10	11.28	0.09	0.16	0.67	0.03	0.55	0.03
S Front Inf	2.24	0.17	2.22	0.17	2.23	0.16	2.21	0.16	22.93	22.98	0.54	0.27	0.44	0.24	0.06	0.14
S Front Middle	2.15	0.18	2.16	0.18	2.17	0.20	2.16	0.18	20.44	26.18	0.03	0.31	0.21	0.01	0.06	0.26
S Front Sup	2.38	0.15	2.38	0.15	2.40	0.16	2.38	0.16	20.45	16.33	0.67	0.01	0.00	0.15	0.48	0.07
S Interm Prim Jensen	2.52	0.43	2.24	0.18	2.38	0.35	2.28	0.20	5.48	8.95	2.62*	0.59	1.34	0.96	0.04	0.00

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S Intrapariet P Trans	2.09	0.15	2.10	0.13	2.09	0.14	2.08	0.14	9.05	7.23	0.14	0.57	0.06	0.02	0.59	0.07
S Octemp Lat	2.55	0.22	2.56	0.23	2.51	0.20	2.50	0.20	6.31	12.11	0.76	1.05	0.00	1.03	0.14	0.01
S Octemp Med Lingual	2.40	0.20	2.37	0.18	2.39	0.20	2.35	0.22	31.71	26.58	0.00	0.01	0.00	0.02	0.03	0.33
S OC Middle Lunatus	1.96	0.21	2.04	0.25	1.99	0.19	2.05	0.20	9.69	1.14	0.48	0.04	0.01	0.29	0.03	1.55
S OC Sup Transversal	2.03	0.19	2.05	0.16	2.01	0.16	2.04	0.17	11.01	10.42	0.11	0.00	0.06	0.06	0.40	0.33
S Occipital Ant	2.26	0.16	2.31	0.18	2.27	0.17	2.32	0.19	7.23	10.55	0.05	0.00	0.01	0.05	0.13	0.46
S Orbital H Shaped	2.56	0.27	2.57	0.25	2.61	0.26	2.62	0.26	14.86	28.13	0.32	0.20	0.65	1.01	0.09	0.29
S Orbital Lateral	2.17	0.36	2.16	0.32	2.19	0.32	2.21	0.30	19.62	23.83	0.17	0.03	0.03	0.02	0.23	0.80
S Orbital Med olfact	2.37	0.29	2.23	0.32	2.40	0.33	2.20	0.29	16.18	19.84	0.09	0.57	0.26	0.03	0.00	0.00
S Parieto Occipital	2.13	0.15	2.18	0.18	2.10	0.19	2.15	0.19	15.16	17.47	0.09	0.26	0.10	0.00	1.09	1.34
S Pericallosal	2.31	0.33	2.19	0.28	2.30	0.34	2.18	0.26	11.27	15.24	0.02	0.16	0.55	0.00	0.07	0.13
S Postcentral	2.08	0.13	2.01	0.14	2.06	0.14	2.02	0.15	18.41	11.13	0.28	0.22	0.07	0.00	0.86	0.75
S Precentral Inf Part	2.41	0.16	2.44	0.15	2.43	0.18	2.42	0.17	31.73	21.71	0.14	0.38	0.51	0.96	0.64	0.04
S Precentral Sup Part	2.32	0.15	2.34	0.19	2.34	0.19	2.33	0.21	21.86	28.85	0.26	0.01	0.00	0.17	0.02	0.28
S Suborbital	2.30	0.28	2.40	0.43	2.40	0.31	2.41	0.43	12.55	7.37	1.78*	0.03	0.02	0.04	2.54*	0.26
S Subparietal	2.30	0.20	2.35	0.21	2.34	0.19	2.40	0.19	16.72	22.21	1.06	1.78*	0.24	0.00	0.06	0.34
S Temporal Inf	2.48	0.19	2.55	0.17	2.50	0.18	2.48	0.22	15.06	6.84	0.03	1.83*	0.17	0.49	0.24	0.25
S Temporal Sup	2.45	0.15	2.50	0.15	2.44	0.14	2.48	0.14	29.28	30.38	0.27	0.26	0.00	0.24	0.82	0.19
S Temporal Transverse	2.37	0.36	2.55	0.28	2.43	0.32	2.52	0.32	15.90	12.20	0.70	0.11	0.11	0.22	0.64	3.66**
Mean	2.49	0.21	2.50	0.22	2.49	0.22	2.51	0.21	19.17	19.96	0.30	0.30	0.33	0.22	0.57	0.57

Model 1 presents Total R squared for a model including age, age^2 gender, education, and recording site. Model 2 presents the delta R-squared when adding a group term (MDD+ vs MDD-). Model 3a and 3b present the increment in r^2 from the interaction term. * = $p < .05$, ** = $p < .01$. Cortical thickness is expressed in millimeters.

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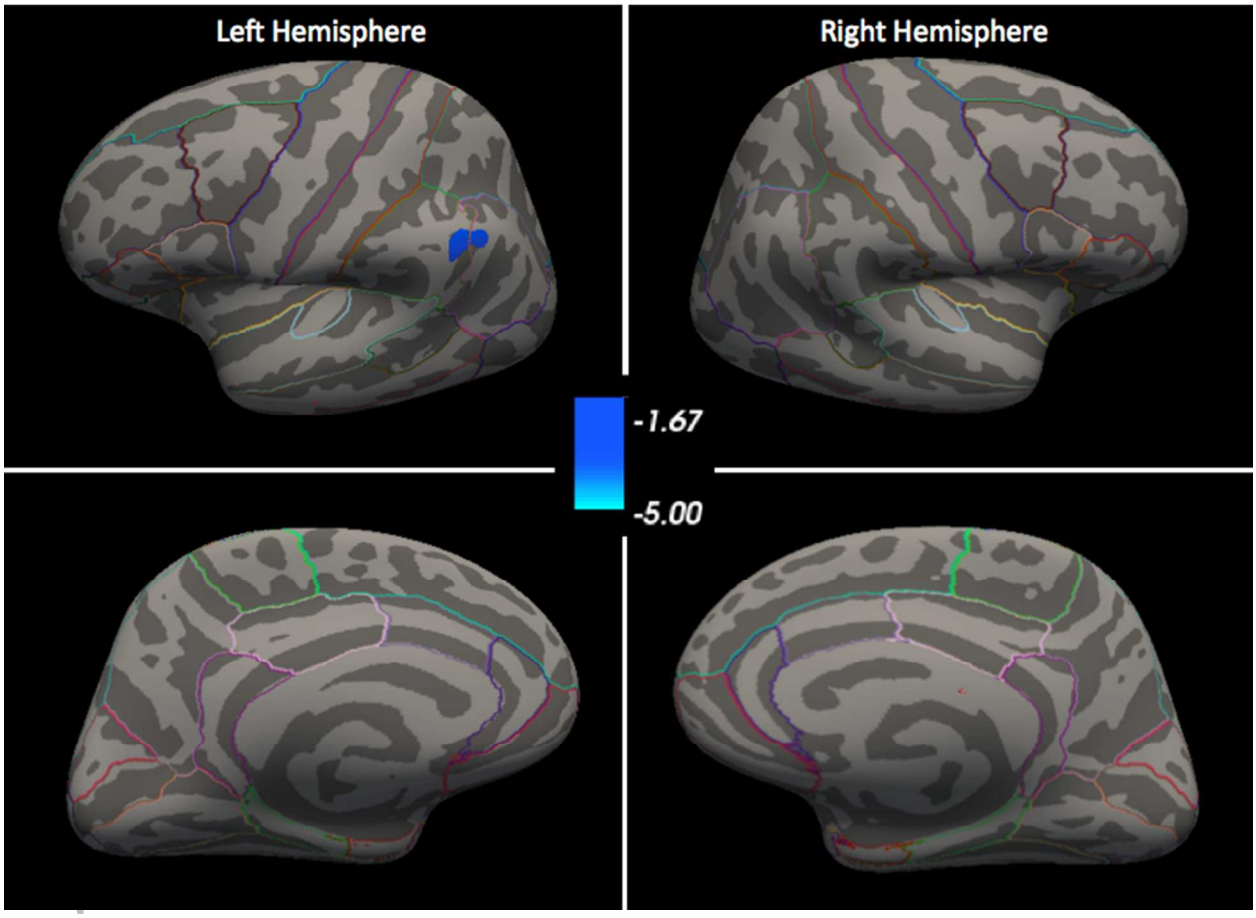

Figure 1. Surface-Based Morphometry comparison of MDD+ to MDD- after multiple comparisons correction. Colorbar represents log(p), multiple comparisons corrected, where blue represents cortical thickening in MDD+ compared to MDD-. All maps thresholded at $p < 0.05$. Outlines of all DK regions are mapped onto the common atlas.

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Supplemental Table 1. DK atlas and QIDS score

	QIDS only		Model 1: Covariates only		Model 2: Adds QIDS		Model 3a: Adds Age x QIDS		Model 3b: Adds Gender X QIDS	
	L	R	L	R	L	R	L	R	L	R
	r		r^2 %		Δ r^2 %		Δ r^2 %		Δ r^2 %	
Bankssts	-0.13	-0.14	19.08	19.89	0.64	0.21	3.53**	0.17	0.03	0.23
Caudal Anterior Cingulate	-0.15	-0.09	16.03	12.51	0.85	0.31	0.12	0.01	0.50	0.79
Caudal Middle Frontal	-0.13	-0.13	23.51	24.26	1.54	1.65	0.33	1.87*	0.54	0.19
Cuneus	-0.02	-0.08	21.50	31.40	0.03	0.41	0.76	0.01	0.01	0.07
Entorhinal	0.12	0.12	14.05	21.62	0.38	0.37	0.31	0.19	0.54	0.00
Frontal Pole	-0.04	0.09	19.42	10.60	0.03	0.74	0.20	3.53*	0.00	1.55
Fusiform	-0.03	-0.01	26.29	24.46	0.19	0.01	0.50	0.12	1.06	0.40
Inferior Parietal	-0.13	-0.11	15.44	20.90	1.11	0.79	0.62	0.08	0.00	0.14
Inferior Temporal	0.02	-0.13	14.43	17.89	0.00	2.94*	0.01	0.01	0.09	0.02
Insula	0.00	-0.05	19.01	27.95	0.06	0.07	0.00	0.09	0.44	0.00
Isthmus Cingulate	-0.05	-0.04	17.45	14.34	0.15	0.15	0.90	0.00	0.12	0.06
Lateral Occipital	-0.06	-0.10	11.88	10.28	0.55	0.58	0.23	0.19	0.38	0.16
Lateral Orbitofrontal	0.01	-0.04	23.90	23.22	0.15	0.66	0.70	0.00	0.03	0.06
Lingual	0.00	-0.01	37.98	35.62	0.01	0.04	0.56	0.57	2.08*	0.56
Medial Orbitofrontal	-0.02	0.05	26.72	28.49	0.15	0.01	0.02	0.54	0.20	0.37
Middle Temporal	-0.12	-0.22**	28.31	21.36	0.56	4.28**	1.23	0.01	0.01	0.06
Paracentral	-0.07	-0.13	29.69	33.13	0.45	1.39	0.11	0.35	0.24	0.61
Parahippocampal	0.02	0.02	10.34	18.53	0.01	0.00	0.58	0.07	2.96*	1.83
Pars Opercularis	-0.10	-0.15	28.41	19.08	0.17	0.90	1.56	0.02	0.49	0.14
Pars Orbitalis	-0.11	-0.04	27.08	17.64	1.33	0.04	1.50	0.29	1.07	0.26
Pars Triangularis	-0.11	-0.08	29.92	26.69	0.56	0.06	0.18	0.04	0.13	0.09
Pericalcarine	0.04	-0.02	38.73	35.87	0.41	0.07	0.63	1.91*	0.17	0.00
Postcentral	-0.09	-0.08	18.05	17.07	0.55	0.84	0.26	0.02	0.00	0.11
Posterior Cingulate	-0.04	-0.14	27.38	23.97	0.05	1.53	0.14	0.04	1.14	0.23
Precentral	-0.18*	-0.14	26.64	24.19	1.44	0.81	0.00	0.01	0.33	0.53

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Precuneus	-0.16*	-0.12	20.08	21.36	1.20	0.56	0.40	0.00	0.07	0.22
Rostral Anterior Cingulate	-0.13	-0.04	15.15	12.14	1.12	0.01	0.07	0.00	0.00	0.40
Rostral Middle Frontal	-0.11	-0.12	32.00	30.45	1.26	1.43	0.21	0.32	0.32	0.71
Superior Frontal	-0.17*	-0.15	32.81	29.75	1.98*	2.00*	1.28	1.03	0.03	0.67
Superior Parietal	-0.16*	-0.07	14.95	11.52	1.42	0.08	0.46	0.01	0.00	0.05
Superior Temporal	-0.14	-0.11	20.20	29.99	0.65	0.26	0.13	0.21	0.06	0.20
Supramarginal	-0.16*	-0.07	21.38	16.79	1.48	0.35	0.19	0.13	0.08	0.08
Temporal Pole	0.03	-0.06	6.77	2.63	0.26	0.50	0.40	1.78	0.49	0.08
Transverse Temporal	-0.09	0.03	16.35	18.84	0.46	0.06	0.00	1.32	0.45	0.05
Mean			22.09	21.60	0.62	0.71	0.53	0.44	0.41	0.32

Model 1 presents Total R squared for a model including age, age^2 gender, education, and imaging site. Model 2 presents the delta R-squared when adding QIDS score. Model 3a and 3b present the increment in r^2 from the interaction term. * = $p < .05$, ** = $p < .01$. Cortical thickness is expressed in millimeters.

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Supplemental Table 2. DS atlas and QIDS score

	QIDS only		Model 1: Covariates only		Model 2: Adds QIDS		Model 3a: Adds Age x QIDS		Model 3b: Adds Gender X QIDS	
	L	R	L	R	L	R	L	R	L	R
	r		r^2 %		Δr^2 %		Δr^2 %		Δr^2 %	
Ins lg S cent ins	-0.11	0.04	11.22	19.46	0.59	0.31	0.19	0.80	2.32*	0.52
S Cingul Ant	-0.10	-0.05	16.31	25.92	1.20	0.19	0.55	0.35	0.90	1.04
S Cingul MidAnt	-0.21**	-0.10	29.12	25.69	3.13**	1.24	0.07	0.67	0.14	0.14
S Cingul MidPost	-0.11	-0.13	33.87	35.89	0.41	0.83	0.30	0.03	0.31	0.21
S frontomargin	-0.09	0.02	20.70	19.55	1.70	0.07	0.00	1.88	1.65	1.49
S Occipital Inf	0.00	-0.07	7.80	10.82	0.01	0.57	0.27	0.05	0.00	0.06
S Paracentral	-0.03	-0.06	23.00	24.78	0.14	0.28	0.18	0.03	0.02	0.21
S Subcentral	-0.12	-0.11	20.78	16.31	0.50	0.30	0.20	0.95	0.10	0.48
S Transv Fronto pol	-0.11	-0.09	18.36	16.92	1.05	0.99	0.04	0.32	0.84	1.75
Cingul Postdorsal	-0.08	-0.04	22.70	20.35	0.28	0.00	0.19	0.51	0.54	0.00
Cingul Postventral	-0.07	-0.04	10.10	20.70	0.61	0.55	0.08	0.01	0.00	0.23
Cuneus	0.01	-0.04	25.73	35.88	0.03	0.21	0.72	0.01	0.35	0.12
Front Inf Opercular	-0.02	-0.14	27.59	21.82	0.09	1.14	2.48*	0.07	0.92	0.00
Front Inf Orbital	-0.01	-0.09	10.88	13.33	0.00	0.80	0.48	2.62*	0.72	2.72*
Front Inf Triangul	-0.16	-0.11	28.17	20.63	1.68	0.86	0.18	0.10	0.16	0.01
Front Middle	-0.07	-0.13	31.57	27.80	0.60	1.32	0.05	0.56	0.15	0.09
Front Sup	-0.16	-0.13	33.20	28.56	1.91*	1.54	1.35	1.19	0.01	0.24
Insular Short	-0.02	-0.09	11.67	17.28	0.05	0.44	0.41	0.29	0.78	0.00
Octemp Lat Fusifor	-0.06	-0.02	22.98	21.73	0.30	0.01	0.14	0.01	1.98*	1.03
Octemp Med Lingual	0.01	0.02	32.66	35.68	0.05	0.05	0.47	0.26	1.87*	0.43
Octemp Med Parahip	0.08	0.01	16.15	20.46	0.19	0.11	0.03	0.82	0.63	0.19
Occipital Middle	-0.11	-0.12	4.35	8.02	1.76	0.85	0.09	0.87	0.34	0.10
Occipital Sup	-0.12	-0.06	10.39	6.56	0.46	0.04	0.07	0.02	0.61	0.11
Orbital	0.01	-0.02	37.07	28.55	0.28	0.47	0.54	0.01	0.19	0.01

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Pariet Inf Angular	-0.11	-0.07	12.06	22.60	0.94	0.16	0.02	0.03	0.06	0.63
Pariet Inf Supramar	-0.14	-0.03	15.92	18.54	1.67	0.24	0.25	0.04	0.11	0.00
Parietal Sup	-0.19*	-0.06	11.04	9.88	2.70*	0.18	0.15	0.03	0.20	0.00
Postcentral	-0.10	-0.12	12.17	13.15	0.89	1.62	0.31	0.11	0.02	0.00
Precentral	-0.15	-0.16*	16.21	14.21	0.67	1.13	0.03	0.61	0.53	0.30
Precuneus	-0.17*	-0.08	15.11	12.94	1.74	0.48	0.07	0.02	0.07	0.50
Rectus	0.05	0.03	40.21	48.11	0.08	0.28	0.62	0.26	0.50	0.01
Subcallosal	0.06	0.05	9.43	12.22	0.17	0.19	0.03	0.69	0.46	0.02
Temp sup G T Transv	-0.08	0.05	12.07	17.85	0.69	0.14	0.01	1.61	0.06	0.12
Temp Sup Lateral	-0.10	-0.03	13.11	21.72	0.28	0.11	0.34	0.10	0.18	0.51
Temp Sup Plan polar	-0.04	-0.09	13.56	12.74	0.00	0.40	0.14	0.03	0.02	0.03
Temp Sup Plan tempo	-0.21**	-0.08	8.03	15.81	2.39*	0.23	0.09	0.95	0.03	0.00
Temporal Inf	-0.03	-0.10	17.98	23.74	0.28	2.49*	0.08	0.15	0.52	0.46
Temporal Middle	-0.13	-0.17*	25.68	25.34	0.89	2.81*	1.91*	0.01	0.43	0.00
Lat Fis Ant Horizont	0.01	-0.04	11.40	15.29	0.24	0.08	0.95	0.40	0.13	0.01
Lat Fis Ant Vertical	-0.17*	-0.02	19.19	11.87	1.01	0.24	0.68	0.02	0.00	0.21
Lat Fispost	-0.17*	-0.07	20.58	24.41	1.41	0.05	0.07	0.21	0.06	0.15
Pole Occipital	-0.02	-0.03	12.50	17.34	0.33	0.01	0.52	2.87*	1.13	0.02
Pole Temporal	0.01	-0.01	14.35	6.82	0.00	0.17	0.29	0.44	0.01	0.29
S calcarine	0.00	-0.03	41.19	34.98	0.15	0.00	0.04	0.93	0.12	0.19
S central	-0.05	-0.01	32.63	30.15	0.12	0.01	0.02	0.02	0.44	0.73
S Cingul Marginalis	-0.09	-0.09	21.28	21.00	0.57	0.33	0.07	0.05	0.02	0.33
S Circular Insula Ant	-0.06	-0.11	13.34	18.12	0.01	0.37	0.19	0.27	0.27	0.73
S Circular Insula Inf	0.03	-0.01	17.74	18.29	0.68	0.05	0.05	0.00	0.27	0.88
S Circular Insula Sup	-0.09	-0.12	27.27	23.71	0.28	0.48	0.17	0.05	0.00	0.04
S Collat Transv Ant	0.15	-0.05	6.34	13.26	1.31	0.47	0.71	0.34	0.05	0.30
S Collat Transv Post	-0.04	-0.15	17.52	9.12	0.00	1.43	0.69	0.02	2.77*	0.00
S Front Inf	-0.16*	-0.13	22.12	18.84	1.71	0.70	0.11	0.14	0.17	0.35
S Front Middle	-0.01	-0.06	17.99	26.37	0.00	0.49	2.16*	0.02	0.81	0.18
S Front Sup	-0.06	-0.15	18.86	15.11	0.22	2.20*	1.06	0.46	0.36	0.01
S Interm Prim Jensen	-0.13	-0.01	9.29	10.18	0.85	0.23	0.01	0.00	0.11	0.00

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S Intrapariet P Trans	-0.14	-0.09	11.06	7.10	0.86	0.38	0.25	0.00	0.01	0.00
S Octemp Lat	-0.09	-0.02	6.84	18.79	0.27	0.00	0.31	0.41	0.01	0.17
S Octemp Med Lingual	-0.03	-0.01	29.24	25.37	0.05	0.00	0.23	0.02	0.22	0.16
S OC Middle Lunatus	0.00	-0.14	12.45	3.56	0.00	1.30	1.08	0.15	0.64	0.95
S OC Sup Transversal	-0.08	-0.09	10.28	10.01	0.12	0.06	0.05	0.28	1.25	0.09
S Occipital Ant	-0.05	-0.23**	6.44	10.70	0.36	5.29**	4.41**	0.11	0.08	0.03
S Orbital H Shaped	-0.06	-0.04	9.45	23.55	0.40	0.19	2.35*	0.44	0.56	0.46
S Orbital Lateral	-0.22**	0.09	15.94	15.66	3.98**	0.30	0.07	0.13	1.38	0.01
S Orbital Med olfact	-0.05	0.02	16.45	22.32	1.01	0.13	0.00	0.21	0.01	0.09
S Parieto Occipital	-0.11	-0.12	16.83	17.01	0.36	0.39	0.23	0.03	0.43	0.25
S Pericallosal	-0.05	-0.09	13.82	13.83	0.00	0.57	0.21	0.03	1.04	0.11
S Postcentral	-0.09	-0.02	19.86	13.06	0.37	0.04	2.16*	0.06	0.03	0.44
S Precentral Inf Part	-0.19*	-0.20*	33.00	23.12	2.06*	2.31*	0.11	1.39	0.37	0.01
S Precentral Sup Part	-0.16*	-0.11	20.74	26.63	2.34*	1.33	0.25	0.37	0.41	0.00
S Suborbital	-0.12	-0.03	15.72	6.88	0.20	0.02	0.35	0.01	0.08	0.02
S Subparietal	-0.09	-0.10	15.29	22.09	0.30	0.47	1.84	0.00	0.27	0.10
S Temporal Inf	0.01	-0.18*	15.58	6.64	0.01	3.76**	0.00	0.23	0.95	0.18
S Temporal Sup	-0.10	-0.18*	27.18	25.99	0.26	1.43	2.32*	0.06	0.03	0.00
S Temporal Transverse	-0.18*	-0.08	15.92	13.14	2.25*	0.40	0.39	0.66	0.03	0.15
Mean			18.44	19.08	0.74	0.67	0.51	0.38	0.45	0.29

Model 1 presents Total R squared for a model including age, age^2 gender, education, and imaging site. Model 2 presents the delta R-squared when adding QIDS score. Model 3a and 3b present the increment in r^2 from the interaction term. * = $p < .05$, ** = $p < .01$. Cortical thickness is expressed in millimeters.

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Supplemental Figure Legends

Figure 1. Gender x Depression diagnosis interaction ($p < 0.01$) in the Left Cuneus defined by the Desikan-Killiany atlas.

Figure 2. Gender x Depression diagnosis interaction ($p < 0.01$) in the Right Lingual defined by the Desikan-Killiany atlas.

Figure 3. Age x Depression severity interaction ($p < 0.01$) in the Left Bankssts defined by the Desikan-Killiany atlas.

Figure 4. Age x Depression diagnosis interaction ($p < 0.01$) in the Left G Occipital Middle defined by the Destrieux atlas.

Figure 5. Gender x Depression diagnosis interaction ($p < 0.01$) in the Left Temp Sup Plan Tempo defined by the Destrieux atlas.

Figure 6. Gender x Depression diagnosis interaction ($p < 0.01$) in the Left S Calcerine defined by the Destrieux atlas.

Figure 7. Gender x Depression diagnosis interaction ($p < 0.01$) in the Right Octemp Med Lingual defined by the Destrieux atlas.

Figure 8. Gender x Depression diagnosis interaction ($p < 0.01$) in the Right S Temporal Transverse defined by the Destrieux atlas.

Figure 9. Age x Depression severity interaction ($p < 0.01$) in the Left S Occipital Ant defined by the Destrieux atlas.

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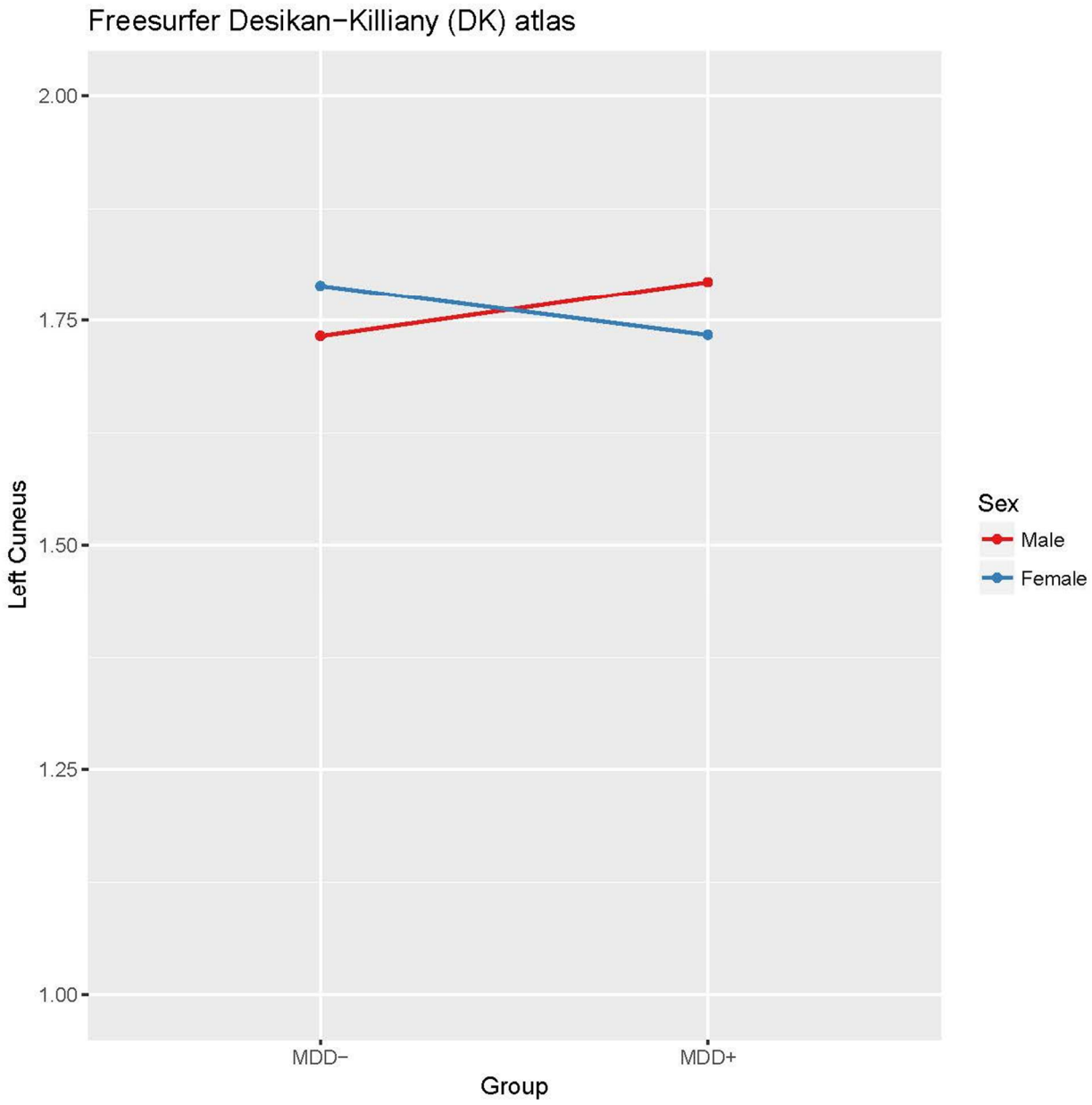

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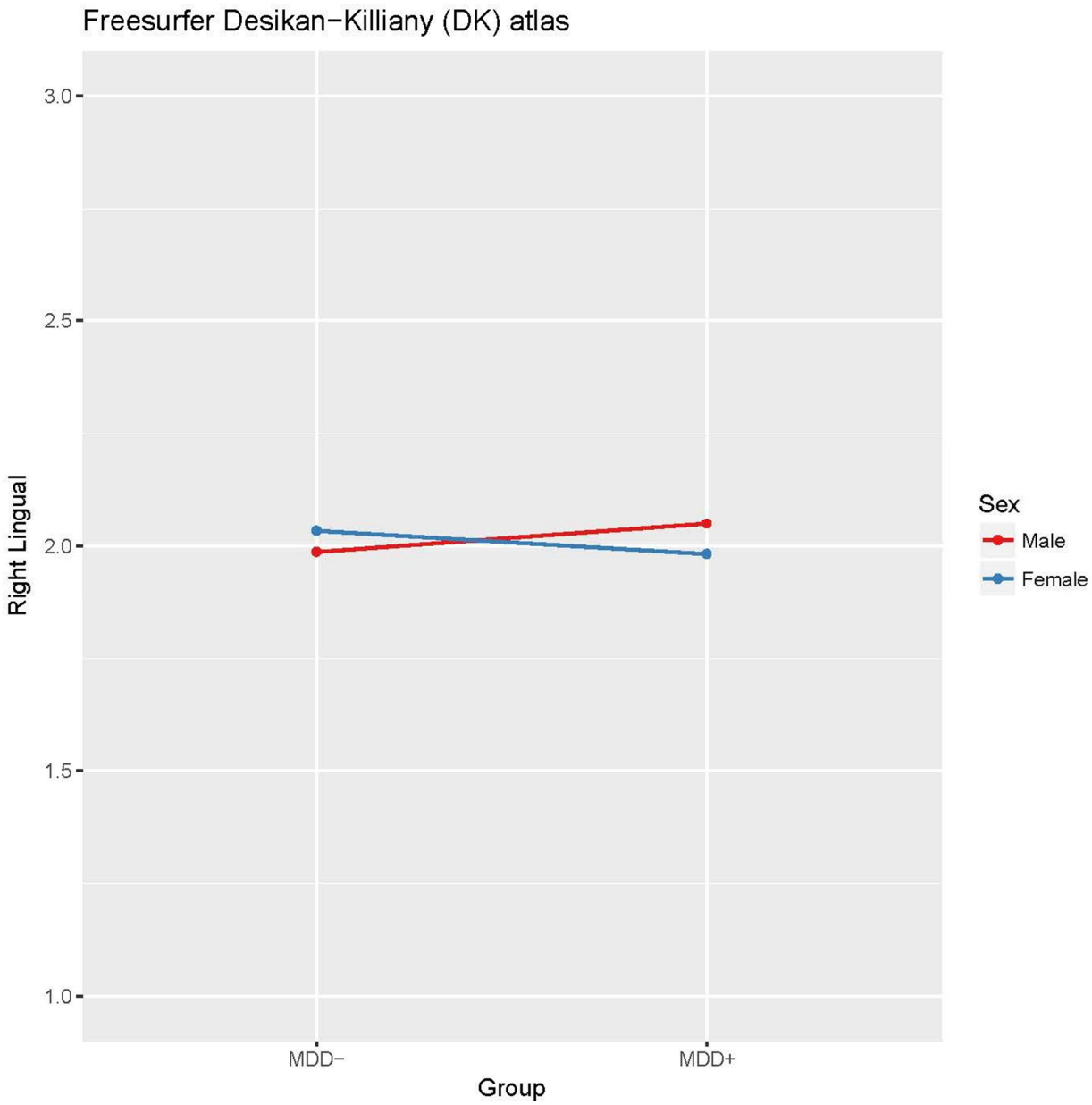

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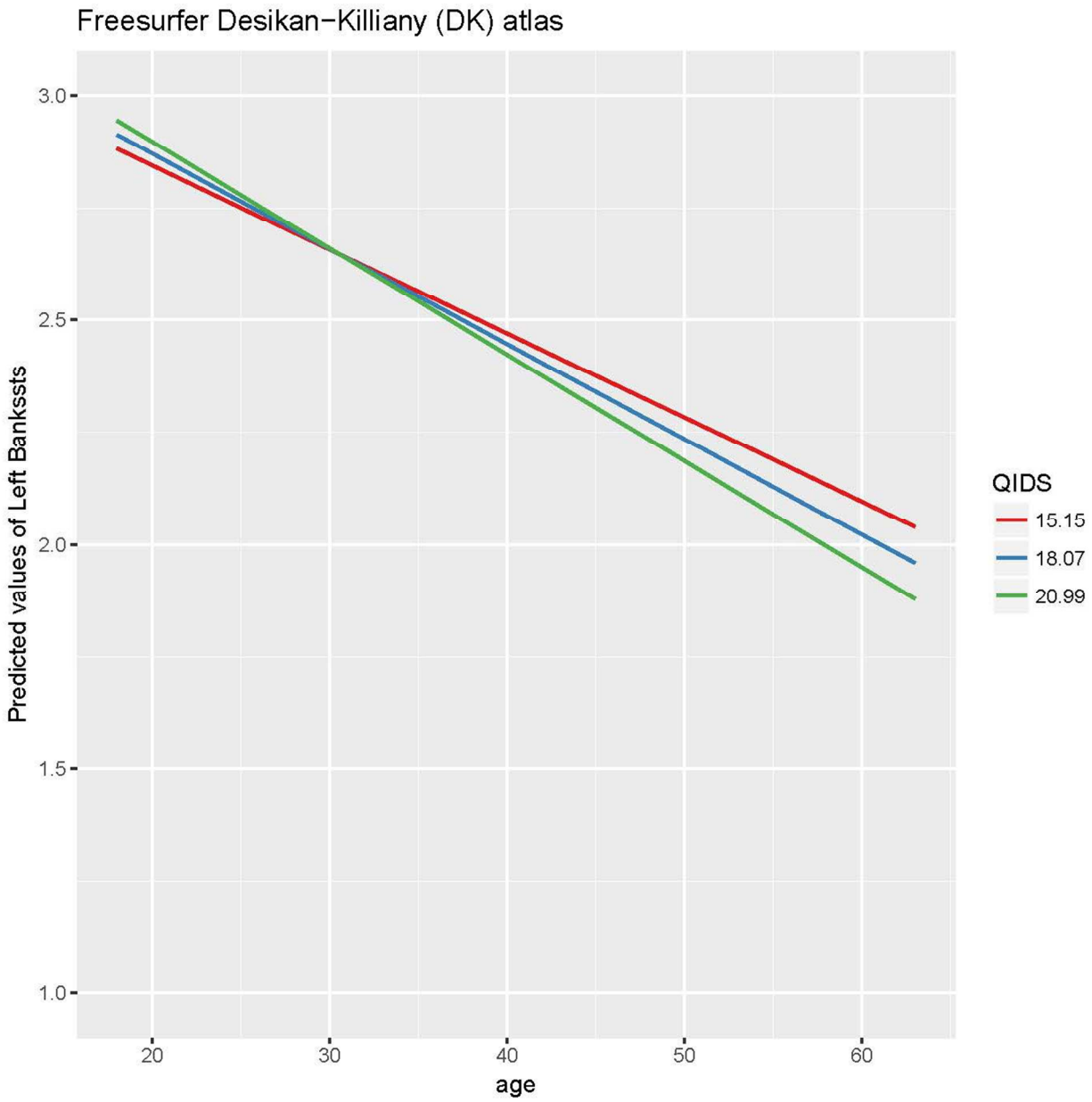

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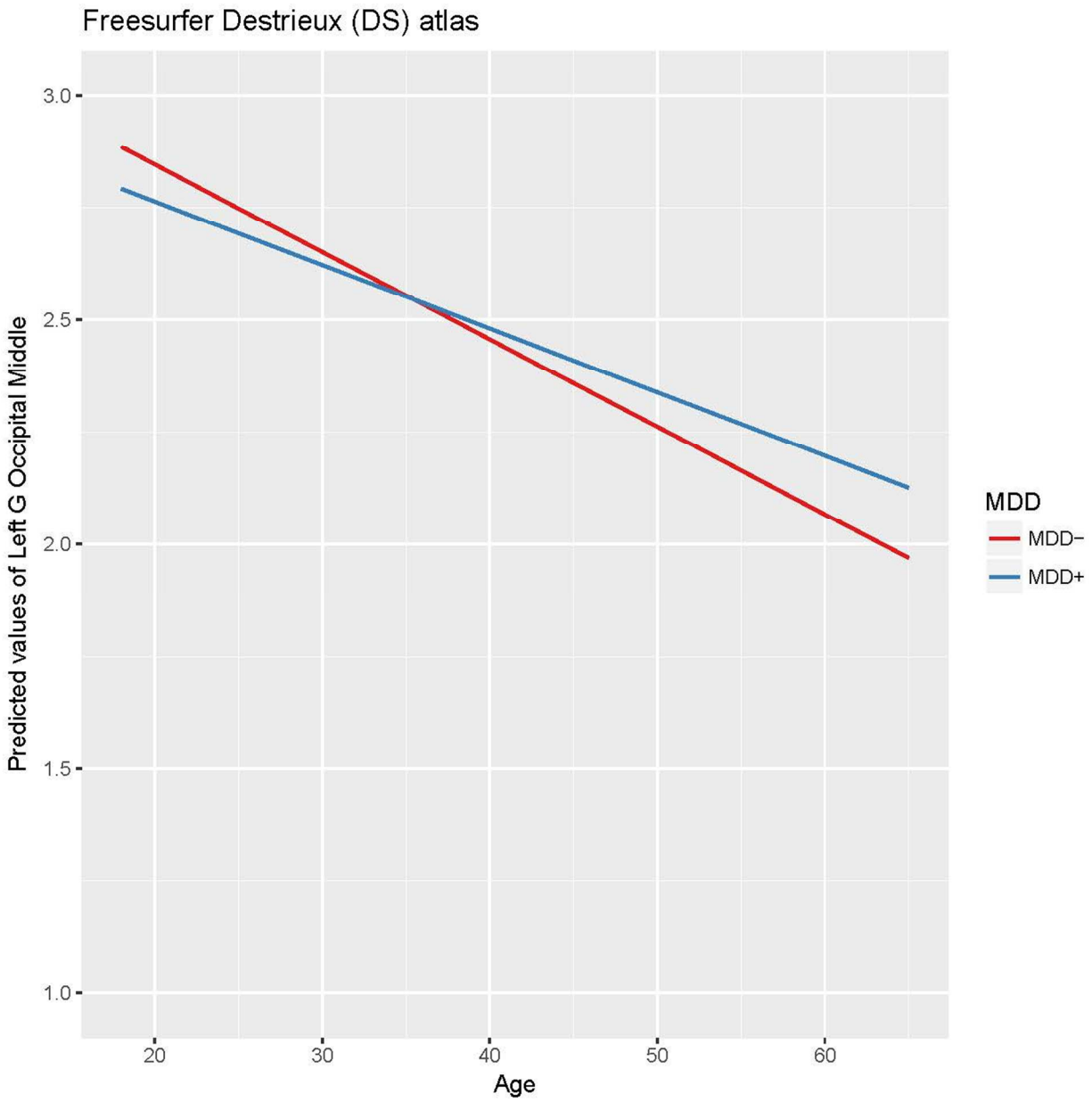

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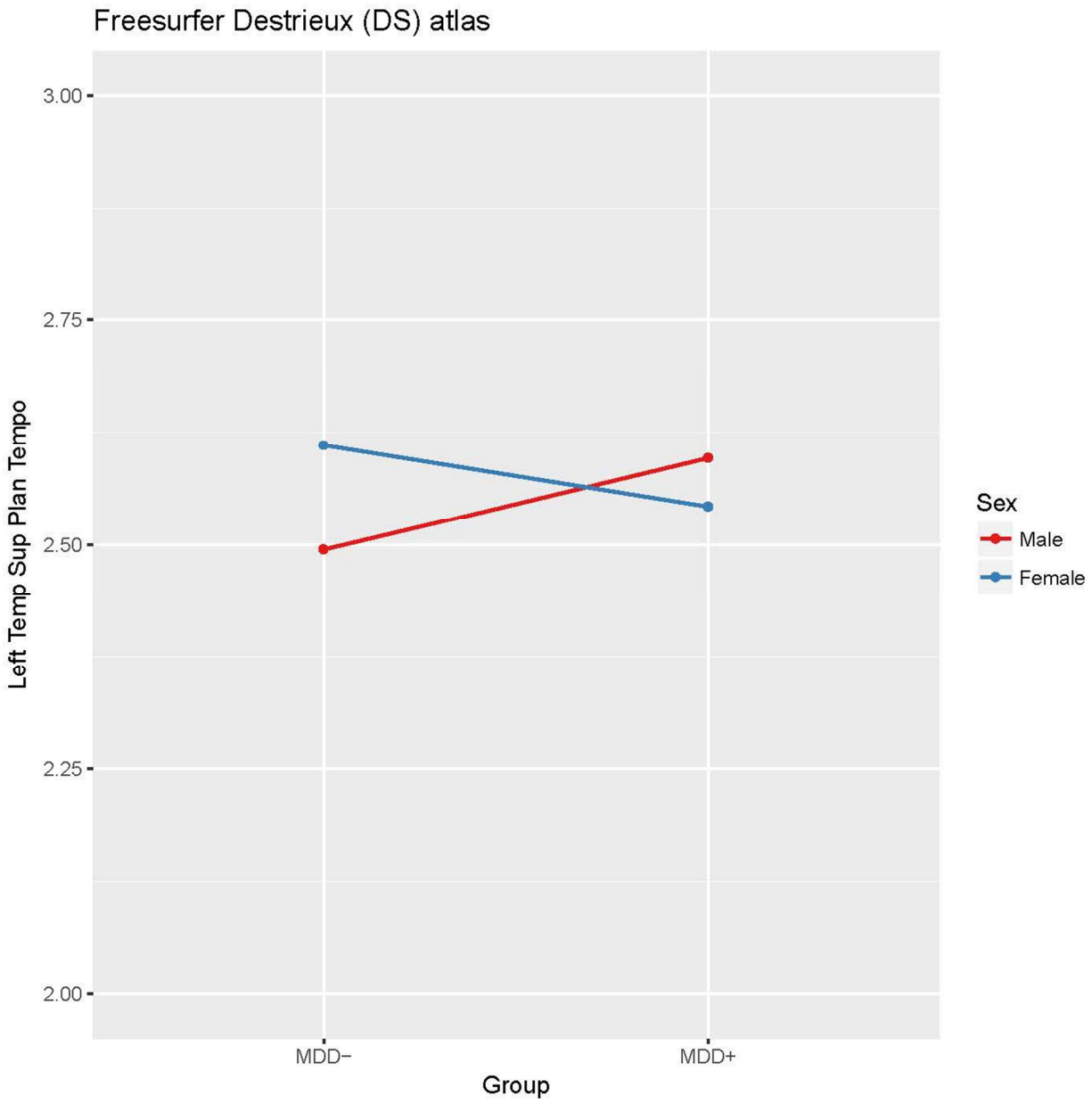

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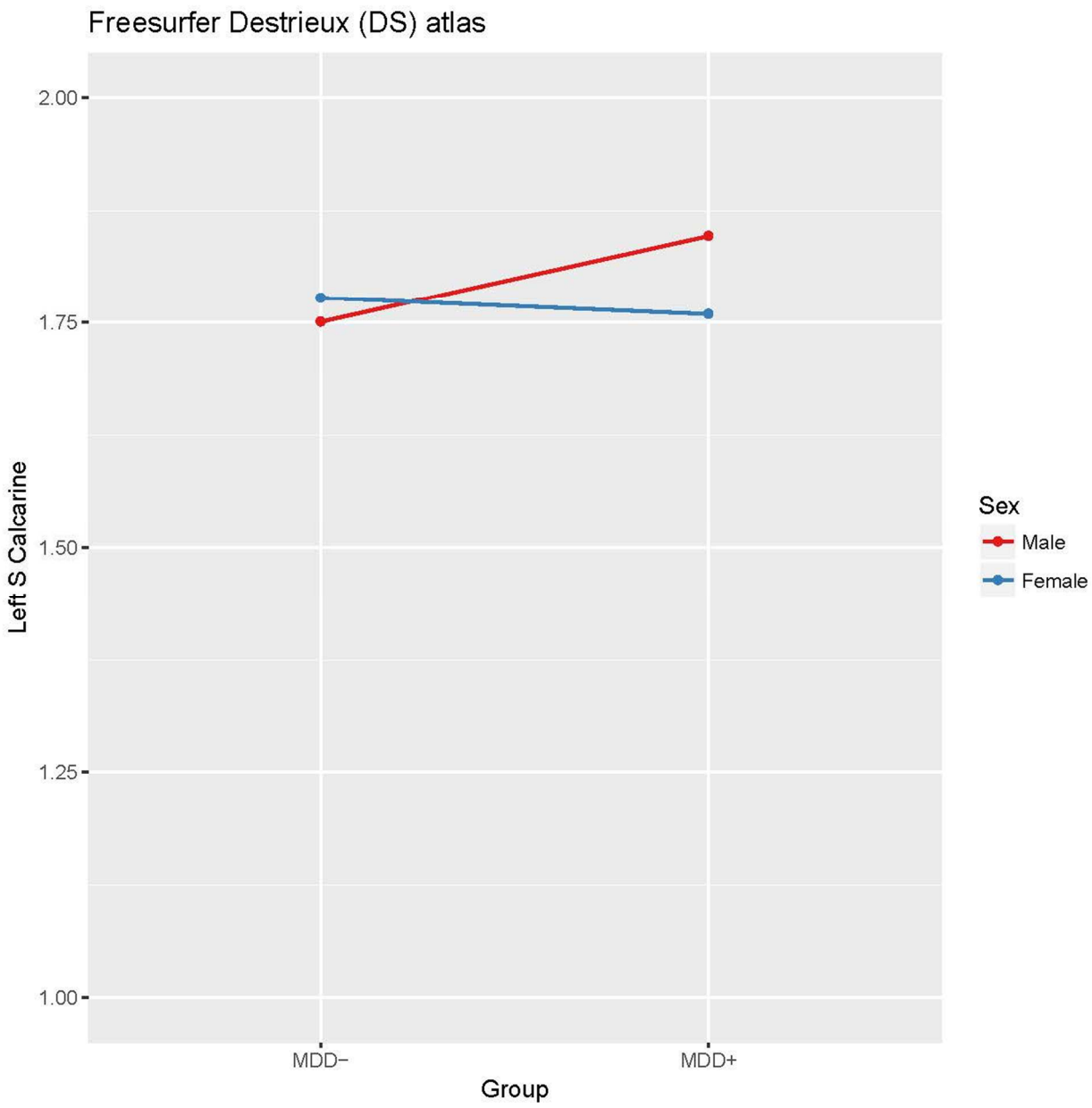

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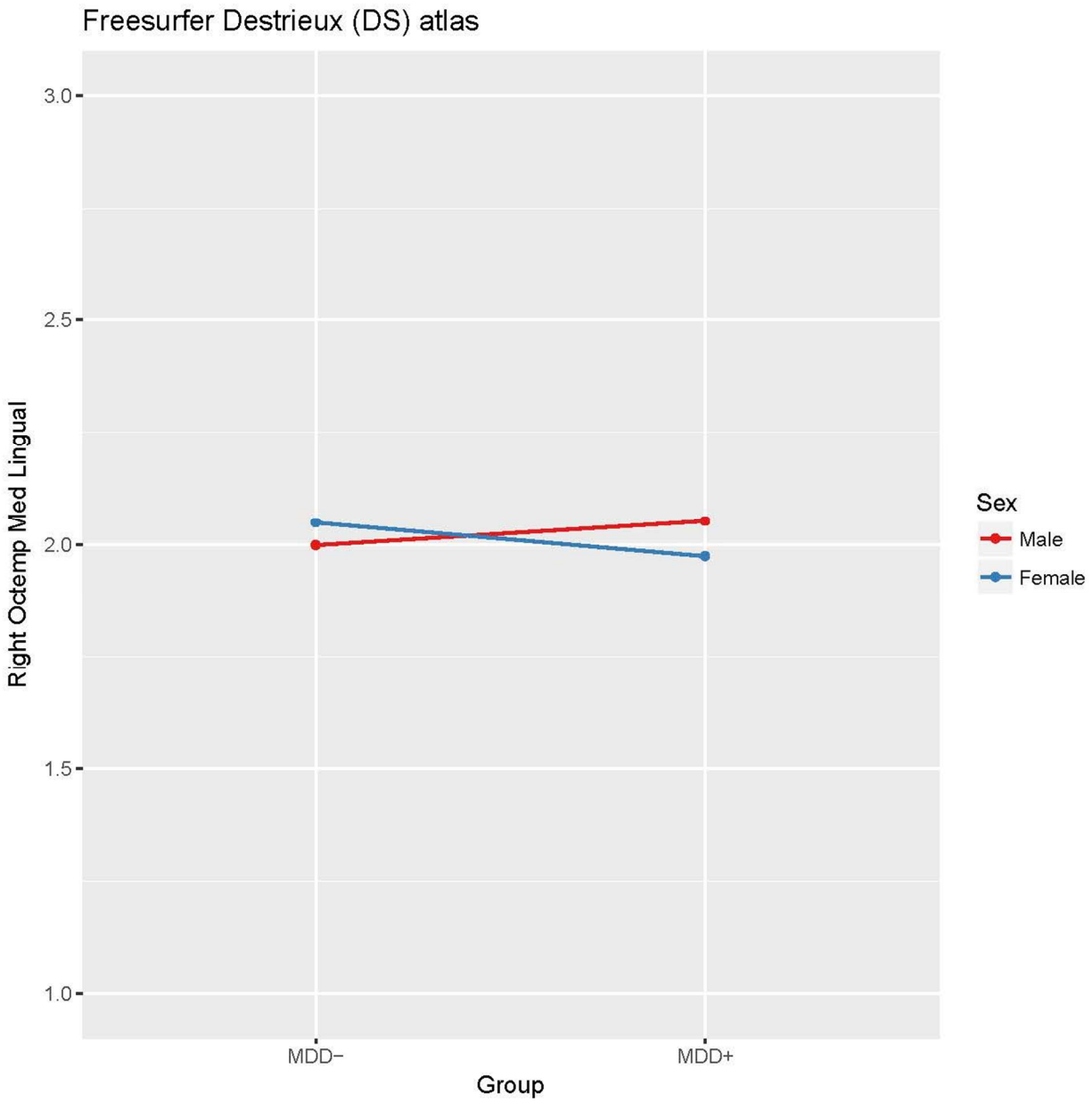

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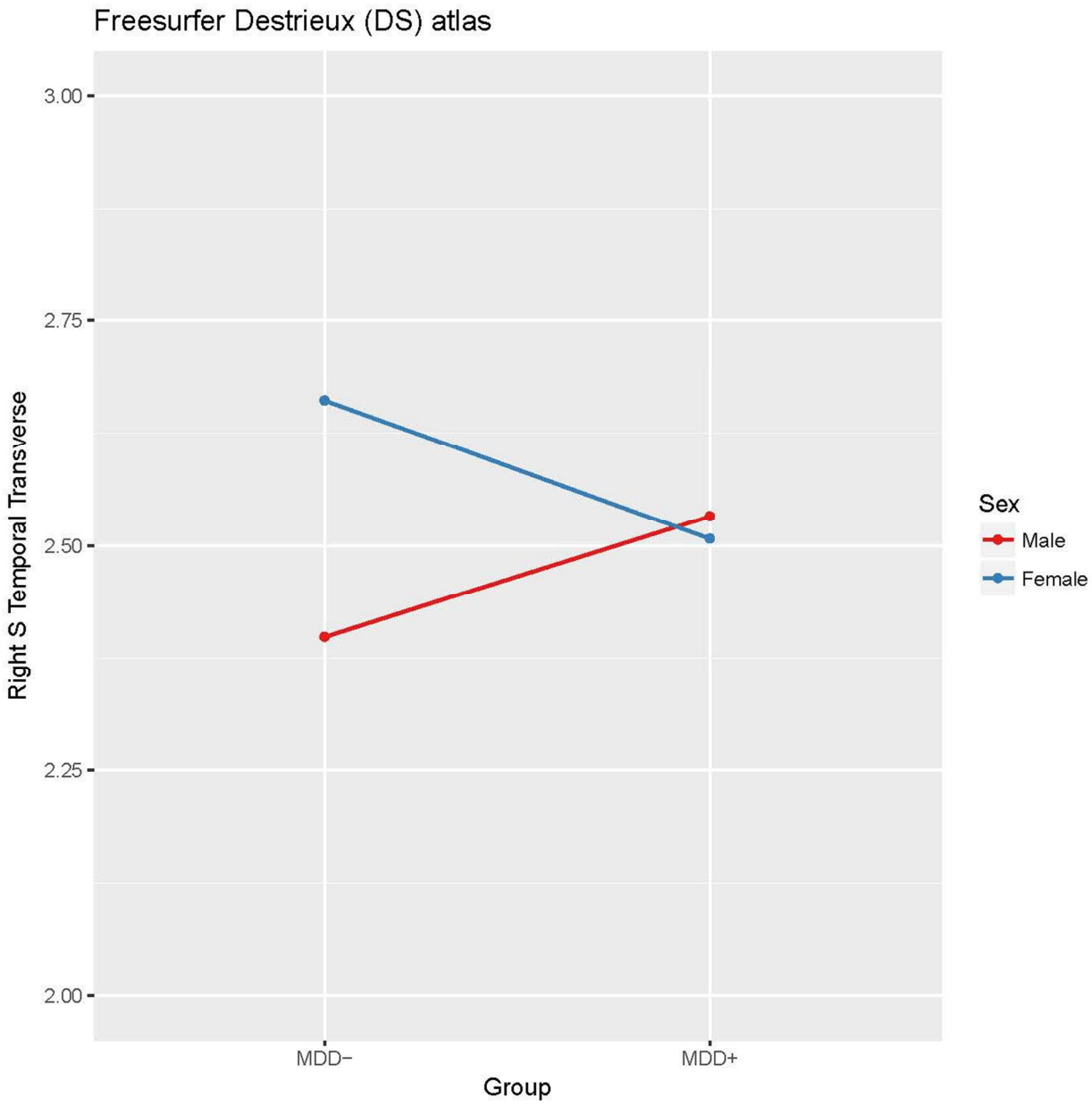

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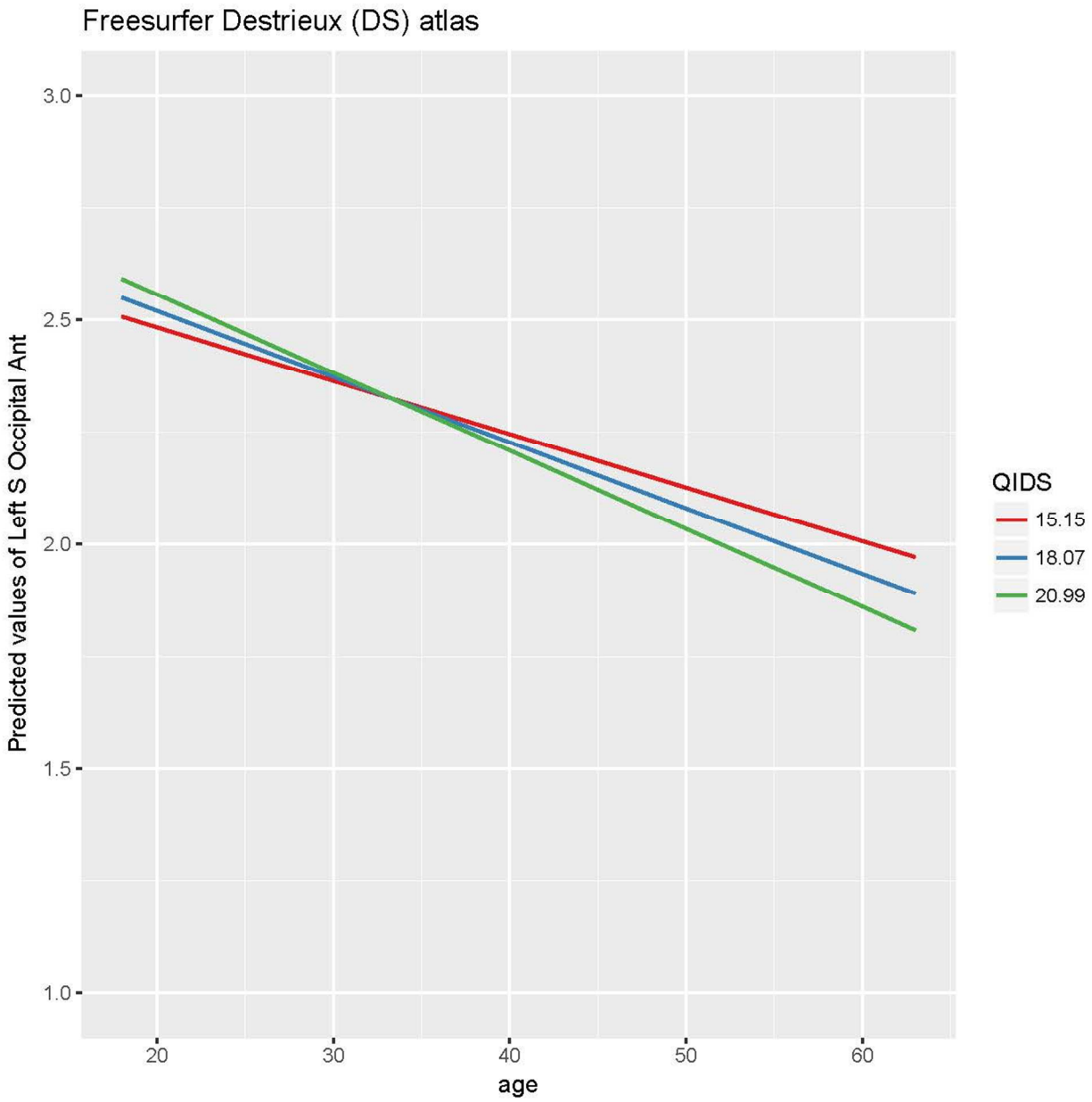

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Acknowledgments

The EMBARC study was supported by the National Institute of Mental Health of the National Institutes of Health under award numbers U01MH092221 (Trivedi, M.H.) and U01MH092250 (McGrath, P.J., Parsey, R.V., Weissman, M.M.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Valeant Pharmaceuticals donated the Wellbutrin XL used in the study. This work was supported by the EMBARC National Coordinating Center at UT Southwestern Medical Center, Madhukar H. Trivedi, M.D., Coordinating PI, and the Data Center at Columbia and Stony Brook Universities. We thank Randy Buckner for providing comments on earlier draft of the manuscript.

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Financial Disclosures

- Dr. Perlman reported no biomedical financial interests or potential conflicts of interest.
- Elizabeth Bartlett reports no biomedical financial interests or potential conflicts of interest.
- Dr. DeLorenzo reports no biomedical financial interests or potential conflicts of interest.
- Dr. Weissman receives royalties from the Oxford University Press, Perseus Press, the American Psychiatric Association Press, and MultiHealth Systems.
- Dr. McGrath has received research support from National Institute of Mental Health, New York State Department of Mental Hygiene, Research Foundation for Mental Hygiene (New York State), Forest Research Laboratories, Sunovion Pharmaceuticals, Naurex Pharmaceuticals (now Allergan).
- Tony Jin reported no biomedical financial interests or potential conflicts of interest.
- Dr. Adams reported no biomedical financial interests or potential conflicts of interest.
- Dr. Trivedi is or has been an advisor/consultant and received fee from Alkermes, AstraZeneca, Cerecor, Eli Lilly & Company, Lundbeck, Naurex, Neuronetics, Otsuka Pharmaceuticals, Pamlab, Pfizer Inc., SHIRE Development and Takeda.
- Dr. Kurian has received grant support from Targacept, Inc.; Pfizer, Inc.; Johnson & Johnson; Evotec; Rexahn; Naurex; and Forest Pharmaceuticals.
- Dr. Fava has received research support from Abbot Laboratories; Alkermes, Inc.; American Cyanamid;Aspect Medical Systems; AstraZeneca; Avanir Pharmaceuticals; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon; Cerecor; Clintara, LLC; Covance; Covidien; Eli Lilly and Company;EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; Ganeden Biotech, Inc.; GlaxoSmithKline; Harvard Clinical Research Institute; Hoffman-LaRoche; Icon Clinical Research; i3 Innovus/Ingenix; Janssen R&D, LLC; Jed Foundation; Johnson & Johnson Pharmaceutical Research & Development; Lichtwer Pharma GmbH; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante; Methylation Sciences Inc; National Alliance for Research on Schizophrenia & Depression (NARSAD); National Center for Complementary and Alternative Medicine (NCCAM); National Institute of Drug Abuse (NIDA); National Institute of Mental Health (NIMH); Neuralstem, Inc.; Novartis AG; Organon Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; Pharmacia-Upjohn; Pharmaceutical Research Associates., Inc.; Pharmavite® LLC;PharmoRx Therapeutics; Photothera; Reckitt Benckiser; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Sanofi-Aventis US LLC; Shire; Solvay Pharmaceuticals, Inc.; Stanley Medical Research Institute (SMRI); Synthelabo; Tal Medical; Wyeth-Ayerst Laboratories; has served on an advisory board or consulted for Abbott Laboratories; Acadia; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Avanir Pharmaceuticals; AXSOME Therapeutics; Bayer AG; Best Practice Project Management, Inc.; Biogen; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-

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- Dr. Ogden reported no biomedical financial interests or potential conflicts of interest.
- Dr. Cooper reported no biomedical financial interests or potential conflicts of interest.
- Dr. Malchow reported no biomedical financial interests or potential conflicts of interest.
- Dr. Weyandt reported no biomedical financial interests or potential conflicts of interest.
- Dr. Oquendo owns stock in Bristol Myers Squibb.
- Dr. McInnis has consulted with Janssen pharmaceuticals in the past 3 years.
- Dr. Parsey reports no biomedical financial interests or potential conflicts of interest.

Accepted Article

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