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Recurrent Major Depression and Right Hippocampal Volume: A Bivariate Linkage and Association Study

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Abstract: Previous work has shown that the hippocampus is smaller in the brains of individuals suffering from major depressive disorder (MDD) than those of healthy controls. Moreover, right hippocampal volume specifically has been found to predict the probability of subsequent depressive episodes. This study explored the utility of right hippocampal volume as an endophenotype of recurrent MDD (rMDD). We observed a significant genetic correlation between the two traits in a large sample of Mexican American individuals from extended pedigrees ($\rho_g = -0.34$, $p = 0.013$). A bivariate linkage scan revealed a significant pleiotropic quantitative trait locus on chromosome 18p11.31-32 (LOD = 3.61). Bivariate association analysis conducted under the linkage peak revealed a variant (rs574972) within an intron of the gene *SMCHD1* meeting the corrected significance level ($\chi^2 = 19.0$, $p = 7.4 \times 10^{-5}$). Univariate association analyses of each phenotype separately revealed that the same variant was significant for right hippocampal volume alone, and also revealed a suggestively significant variant (rs12455524) within the gene *DLGAP1* for rMDD alone. The results implicate right-

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hemisphere hippocampal volume as a possible endophenotype of rMDD, and in so doing highlight a potential gene of interest for rMDD risk. *Hum Brain Mapp 37:191–202, 2016.*

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INTRODUCTION

Major depressive disorder (MDD) is a common, costly, and potentially life-threatening illness [Belmaker and Agam, 2008; Greenberg et al., 2003; Kessler et al., 2003; Sullivan et al., 2000] that is recognized by the World Health Organization as one of the leading causes of disability worldwide [World Health Organization, 2015]. It is heritable [e.g., Kessler et al., 2003; Sullivan et al., 2000], and previous family-based linkage studies have identified quantitative trait loci (QTLs) associated with MDD [Breen et al., 2011; Neff et al., 2009; Pergadia et al., 2011]. However, research has so far struggled to find specific genes that mediate depression risk—the results of many previous candidate-gene studies appear to have been false positives [Bosker et al., 2011; Wray et al., 2012], and genome-wide association (GWA) studies of common genetic variants, including the latest mega-analysis from the Psychiatric Genetics Consortium [Ripke et al., 2013], have been largely unable to identify genes at the level of genome-wide statistical significance [see also Hek et al., 2013; Kohli et al., 2011; Lewis et al., 2010; Muglia et al., 2010; Rietschel et al., 2010; Shi et al., 2011; Shyn et al., 2011; Sullivan et al., 2009; Wray et al., 2012]. Thus, despite substantial research effort, there has been a dearth of substantive molecular genetic findings for MDD (for a critical review, see [Flint and Kendler, 2014]).

Given the slow pace of gene discovery for MDD, alternative approaches may be necessary. One such approach is to consider specific subtypes of MDD, such as recurrent MDD (rMDD). Focusing on subtypes may reduce heterogeneity within the sample of affected cases and thereby improve genetic tractability [Flint and Kendler, 2014]. Indeed, rMDD is generally estimated to be more highly heritable than MDD [e.g., Kendler et al., 2007; Levinson et al., 2007; Shi et al., 2011; Sullivan et al., 2000]. Another approach is to use "endophenotypes," traits that share underlying genetic influences with the illness [Gottesman and Gould, 2003]. Because endophenotypes are typically quantitative, they vary among individuals regardless of whether the illness is expressed phenotypically, making clinically unaffected relatives informative for genetic analysis [Blangero et al., 2003; Glahn et al., 2014]. In some cases, the genetic determinates of the endophenotype may be less complex, and therefore more tractable, than those of the illness itself [but see Iacono et al., 2014].

Several lines of evidence suggest that hippocampal volume is a propitious endophenotype of MDD (for reviews, see [Campbell and Macqueen, 2004; MacQueen and Frodl, 2011]). Perhaps the strongest evidence for a relationship between the two traits comes from meta-analyses of structural imaging studies that have shown that patients with MDD have smaller hippocampal volumes than do healthy controls [Cole et al., 2011; McKinnon et al., 2009; Schmaal et al., 2015; Videbech and Ravnkilde, 2004]. Two of these meta-analyses found that the effect size was larger for MDD and right-hemisphere hippocampal volumes than MDD and left-hemisphere hippocampal volumes [Cole et al., 2011; Videbech and Ravnkilde, 2004], and, via a meta-regression, one study found that right hippocampal volume reduction predicted the probability of recurrent depressive episodes [Videbech and Ravnkilde, 2004]; the latter result suggests a specific link between rMDD and the right hippocampus. Finally, in a previous study from our laboratory, which ranked potential endophenotypes by their standardized genetic co-variances with rMDD, bilateral hippocampal volume was ranked as the third best endophenotype out of 85 neuroanatomical measures [Glahn et al., 2012]. However, since that study only considered bilateral measures, it is not known whether greater specificity would have been achieved by considering right hippocampal volume independently.

In this study, we aimed to investigate the utility of right hippocampal volume as an endophenotype of rMDD in a large sample of Mexican American individuals from extended pedigrees. To this end, we (i) estimated the genetic correlation between rMDD and right hippocampal volume; (ii) identified regions of the genome that were pleiotropically influential on the two traits via univariate and bivariate linkage; and (iii) more finely localized the genetic influences on both traits via univariate and bivariate association analysis. This work forms part of a wider effort to disentangle the molecular influences on depression risk, in order to improve diagnosis and treatment of the disorder.

MATERIALS AND METHODS

Participants

Genetic and clinical diagnostic data (including rMDD diagnoses) were available from a total of 1286 participants from extended Mexican–American pedigrees (809 female; age range: 18–97 years; mean age: 46.15 years; family size range: 1–131; mean family size: 9.72). Neuroanatomical data (including right hippocampal volumes) were available from 893 of these individuals. The sample made up a subset of the cohort from the San Antonio Family Study.

The selection criteria required that participants were of Mexican-American ancestry, were part of a large family, and lived in the San Antonio region [for recruitment details, see Olvera et al., 2011; McKay et al., 2014]. All participants provided written informed consent in accordance with the institutional review board (IRB) at the University of Texas Health Science Center, San Antonio.

Diagnostic Assessment

All participants received the Mini-International Neuropsychiatric Interview (MINI) [Sheehan et al., 1998], a semi-structured interview augmented to include items on lifetime history. Masters- and doctorate-level research staff, with established reliability for diagnosing affective disorders ($\kappa \geq 0.85$), conducted all interviews. All participants with possible psychopathology were discussed in case conferences that included licensed psychologists or psychiatrists. Lifetime consensus diagnoses were determined based on available medical records, the MINI interview, and the interviewer's narrative. Consistent with our previous study [Glahn et al., 2012], rMDD was defined as two or more distinct episodes of depression meeting DSM-IV criteria.

MRI Data Acquisition

All images were acquired on a research-dedicated, Siemens 3 T TIM Treo MR scanner and a high-resolution phase array head coil housed in the Research Imaging Institute, UTHSCSA. Seven high-resolution T1-weighted 3D turbo-flash sequences with an adiabatic inversion contrast pulse were acquired in each subject [TE/TR/TI = 3.04/2100/785 ms, flip angle = 13°, 800 μm isotropic resolution; see Kochunov et al., 2006 for more details].

Image Processing

FreeSurfer [Dale et al., 1999; Fischl et al., 1999] was used to extract hippocampal volumes. These methods have been described previously [Fischl et al., 2002, 2004]. Briefly, Fischl et al. developed a procedure for automatically and accurately labelling each voxel as one of 40 subcortical structures; this procedure is based on modeling the segmentation as a nonstationary anisotropic Markov Random Field. Probabilities were computed separately at each position in an atlas, resulting in maximum a posteriori estimation of each voxel's label in each image. While manual extraction of subcortical volumes is still considered the gold standard, automatic FreeSurfer segmentation has been shown to be reliable enough to reveal differences in hippocampal volume between depressed individuals and healthy controls in previous studies [Tae et al., 2008]. Hippocampal volume was extracted separately for each hemisphere, enabling us to focus specifically on right hippocampal volume.

Data Analysis

Genotyping

The participants were genotyped for approximately 1 million SNPs using Illumina HumanHap550v3, HumanExon510Sv1, Human1Mv1, and Human1M-Duov3 BeadChips, according to the Illumina Infinium protocol (Illumina, San Diego, CA). To ensure harmonization across microarray versions, SNP loci were repeatedly checked for Mendelian errors utilizing SimWalk2 [Sobel et al., 2002], and the most likely incorrect genotypes were blanked and imputed according to Mendelian laws based on available pedigree data using MERLIN [Abecasis et al., 2002], until the genotypes for all high-quality genotyped SNPs were present in all genotyped individuals without any remaining Mendelian inconsistencies. Monomorphic SNPs, SNPs exhibiting low call rates or requiring excessive blanking (i.e., if <95% of the genotypes are retained), SNPs whose minor allele was present in <10 individuals, and SNPs with Hardy–Weinberg Equilibrium (HWE) test statistics of $p \leq 0.0001$ were eliminated from the analyses. Maximum-likelihood techniques, accounting for pedigree structure, were used to estimate allelic frequencies [Boehnke, 1991]. For linkage analyses, multipoint identity-by-descent (IBD) matrices were calculated based on 28,387 SNPs selected from the 1 M GWA panel, as follows. Using genotypes for 345 founders, SNPs on each chromosome were selected to be at least 1 kb apart, MAF ≥5%, and LD within a 100 kb sliding window not exceeding |rho| = 0.15. The resulting selection averaged 7–8 SNPs/centimorgan. For each centimorgan location in the genome, multipoint IBD probability matrices were calculated using a stochastic Markov Chain Monte-Carlo procedure implemented in LOKI [Heath, 1997].

Quantitative genetic analyses

All genetic analyses were performed in SOLAR [Almasy and Blangero, 1998]. SOLAR implements maximum-likelihood variance decomposition to determine the contributions of genes and environmental influences to a trait by modeling the covariance among family members as a function of expected allele sharing given the pedigree. First, to ensure that right-hippocampal volumes were normally distributed, volumes were converted to ranks and the inverse normalization (probit) transformation was applied. Second, univariate variance decomposition was applied to rMDD and transformed right hippocampal volumes, allowing estimation of their heritability indices. Second, bivariate analysis was applied to the two variables, wherein the phenotypic covariance between the traits was decomposed into its genetic and environmental constituents to determine the extent to which they were influenced by shared genetic effects. Age, age squared, sex, and their interactions were included as covariates in these analyses.

Linkage and association analyses

Quantitative trait linkage analysis was performed to localize specific chromosomal locations influencing rMDD and right hippocampal volume [Almasy and Blangero, 1998]. Model parameters were estimated using maximum likelihood. The hypothesis of significant linkage was assessed by comparing the likelihood of a classical additive polygenic model with that of a model allowing for both a polygenic component and a variance component due to linkage at a specific chromosomal location (as evidenced by the location-specific IBD probability matrix). The LOD score, given by the log 10 of the ratio of the likelihoods of the linkage and the polygenic null models, served as the test statistic. Genome-wide thresholds for linkage evidence were computed for this exact pedigree structure and density of markers, using the method by Feingold et al. [1993]: an LOD of 1.69 is required for suggestive significance (likely to happen by chance less than once in a genome-wide scan), and an LOD of 2.90 is required for genome-wide significance.

Initially, univariate linkage scans were performed for rMDD and right hippocampal volume separately over the whole genome. Following the discovery of a potentially pleiotropic region on chromosome 18 (see Results), this chromosome was additionally subjected to a bivariate linkage analysis. For comparison to the univariate results, the resulting LOD scores from the bivariate scan were converted to a single degree-of-freedom (df) equivalent based on the *p*-value for the 2-df test (linkage to both traits versus linkage to neither [Almasy et al., 1997]). To ensure that the bivariate LOD scores were truly driven by both and not one of the traits, we tested the null hypothesis of the absence of pleiotropy (i.e., co-occurrence of linkage is by chance) versus the alternative of complete pleiotropy by comparing the likelihoods of the relevant nested models. To this end, we maximized two models: one where the genetic correlation between linkage peaks was allowed to vary freely; and a null model where this correlation was constrained to be zero. The likelihoods of these two models were then compared, the difference between them being distributed as 1-df χ^2 distribution. This method has been established as powerful approach for detecting pleiotropic effects [Williams et al., 1999].

The genomic region meeting bivariate genome-wide significance for linkage (see Results) was investigated in greater detail using association analysis of the single-nucleotide polymorphisms (SNPs) encapsulated by the linkage peak. The peak was defined as spanning in either direction from the locus with the maximum LOD score until the locus-specific LOD dropped below the maximum minus 1. Statistical significance levels were established according to the effective number of tested SNPs given the structure of linkage disequilibrium (LD) within the region. To this end, the pairwise genotypic correlations were calculated in an effort to establish the effective number of independent tests carried out during association analysis. This method, developed by Moskvina and Schmidt [2008], is considered to be conservative. A corrected *p*-value was obtained from a Bonferroni correction based on the total number of independent tests. Age, age squared, sex, and their interactions were included as covariates in all linkage and association analyses.

RESULTS

Both rMDD (h^2 = 0.47; standard error = 0.12; $p = 9.0 \times 10^{-6}$) and right hippocampal volume (h^2 = 0.66; standard error = 0.07; $p = 7.0 \times 10^{-26}$) were highly heritable, and there was a statistically significant genetic correlation between them ($\rho_g = -0.34$; standard error = 0.14; $p = 0.013$), indicating overlap between the genetic influences on the two traits.

Univariate linkage analysis for rMDD did not reveal genome-wide significant QTLs, but there was a suggestively significant QTL on chromosome 4 (LOD score = 2.62 at 35 cM). The second strongest QTL was on chromosome 18 (LOD score = 1.54 at 10 cM). Univariate linkage analysis for right hippocampal volume revealed significant QTLs on chromosome 13 (LOD score = 3.42 at 53 cM) and chromosome 18 (LOD score = 2.96, 9 cM), and a suggestively significant QTL on chromosome 4 (LOD score = 2.01 at 122 cM).

Given the potential overlap in the univariate linkage analyses on chromosome 18, this chromosome alone was subjected to bivariate linkage. This analysis revealed a genome-wide significant bivariate QTL (1-df-equivalent LOD score = 3.61 at 9 cM). The bivariate linkage signal was stronger than either univariate signal (see Fig. 1, top panel), suggesting that the locus mediates both rMDD risk and right hippocampal volume. The test for pleiotropy versus coincident linkage confirmed the presence of pleiotropy for the two traits at this locus ($\chi^2 = 5.43$, $p = 0.010$).

Univariate and bivariate association analyses were conducted for rMDD and right hippocampal volume under the linkage peak on chromosome 18 (defined as 6–12 cM). There were 794 SNPs in this region in total, and 521.6 effective SNPs after taking into account LD structure [Moskvina and Schmidt, 2008], necessitating a Bonferroni-corrected α of $p = 9.58 \times 10^{-5}$. For the univariate rMDD association analysis, the top-ranked SNP was rs12455524 within the gene *DLGAP1* (see Fig. 1, bottom panels; Table I). The association reached the level of suggestive significance ($\chi^2 = 14.73$, $p = 0.0001$; see Fig. 1, top panel). For the univariate hippocampus association analysis, the top-ranked SNP was rs574972 within *SMCHD1*, which met the criterion for peak-wide significance ($\chi^2 = 17.7$, $p = 2.6 \times 10^{-5}$; Fig. 1, middle and bottom panels). The same SNP was also peak-wide significant in the bivariate association analysis ($\chi^2 = 18.8$, $p = 8.1 \times 10^{-5}$; see Table II).

When the SNP rs574972 was included as a covariate in the bivariate linkage analysis of rMDD and right hippocampal volume at 9 cM, the LOD score was reduced

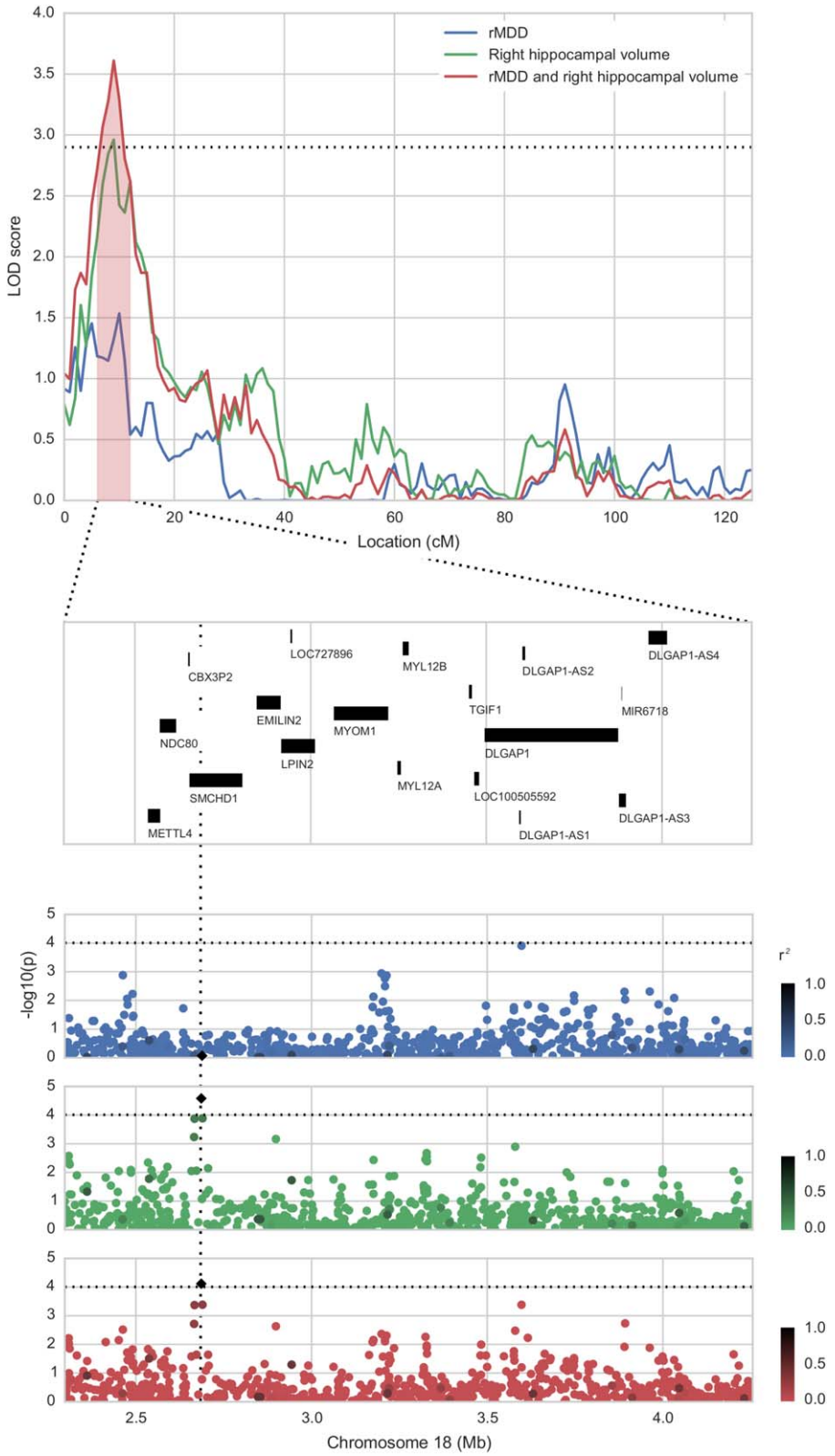

Figure 1.

Results of the univariate and bivariate linkage and association analyses. Top panel: Chromosome 18 multipoint plot for univariate and bivariate linkage analyses. The horizontal dotted line represents the threshold LOD score for genome-wide significant linkage. Middle panel: genes under the linkage peak. Bottom panels: QTL-specific univariate and bivariate association analyses for the QTL region under the linkage peak. The top-ranked variant rs574972 is indicated by a diamond symbol. Symbol color represents each variant's linkage disequilibrium (r^2) with rs574972. The horizontal dotted line represents the threshold for peak-wide significant association.

TABLE I. Estimates for the top five variants within the two QTL-specific univariate association analyses (rMDD alone and right hippocampal volume alone)

Trait	SNP	χ^2	p	β	MAF	HWE p
Right hippocampal volume	rs574972	17.664792	0.000026	0.316781	0.07	0.065
	rs8094926	14.646644	0.00013	0.297751	0.07	0.039
	rs648105	14.590576	0.000134	0.297188	0.07	0.065
	rs622289	11.825838	0.000584	0.266033	0.07	0.062
	rs6506038	11.53497	0.000683	−0.19521	0.18	0.928
rMDD	rs12455524	14.733226	0.000124	0.421027	0.12	0.202
	rs1815955	10.584736	0.00114	0.317768	0.14	0.306
	rs7235479	10.315824	0.001319	−0.2587	0.18	0.320
	rs976655	10.260248	0.001359	0.272171	0.19	0.914
	rs9966747	9.83018	0.001717	0.310365	0.14	0.180

SNP = single-nucleotide polymorphism; MAF = minor allele frequency; HWE p = Hardy–Weinberg equilibrium p value.

compared to linkage without the covariate (2.78), and was no longer significant. This test of linkage conditional on association provides further support for the association between rs574972, rMDD, and right hippocampal volume.

Since this study focused specifically on the utility of right hippocampal volume as an endophenotype of rMDD, we restricted our whole-genome linkage analyses to these two traits. However, it was worth investigating whether left or bilateral hippocampal volumes were also good endophenotypes of rMDD. We found that right, left, and bilateral hippocampal volumes were similarly heritable (left $h^2 = 0.69$, standard error = 0.07, $p = 6.5 \times 10^{-26}$; bilateral $h^2 = 0.70$, standard error = 0.07, $p = 3.16 \times 10^{-26}$). Moreover, each hippocampal trait had a significant genetic correlation with rMDD (left $\rho_g = -0.39$, standard error = 0.14, $p = 0.006$; bilateral $\rho_g = -0.37$, standard error = 0.13, $p = 0.006$). We therefore performed univariate linkage analyses for left and bilateral hippocampal volumes, as well as the corresponding bivariate analyses with rMDD, over our significant linkage peak on chromosome 18 at 9 cM. For left hippocampal volume, neither the univariate linkage peak for left hippocampal volume at 9 cM nor the bivariate linkage peak at the same location reached the threshold for genome-wide statistical significance (univariate LOD = 1.15; bivariate LOD = 2.01). The same was true of bilateral hippocampal volume (univariate LOD = 1.87; bivariate LOD = 2.65). These results suggest that although right, left, and bilateral hippocampal volumes were genetically similar, greater specificity was achieved by considering right hippocampal volume specifically.

The possible confounding influence of overall intracranial volume was investigated using univariate and trivariate linkages. Univariate linkage revealed little evidence of genetic influence on intracranial volume on chromosome 18 at 9 cM (LOD score = 0.53). Moreover, in a trivariate linkage model of rMDD, right hippocampal volume and intracranial volume, the linkage peak remained significant (1-df equivalent LOD score = 3.01), and the pleiotropy test supported pleiotropy between rMDD and right hippocampal volume ($\chi^2 = 15.87$, $p = 3.39 \times 10^{-5}$). Thus, our main results were not readily explicable by a mediating influence of intracranial volume.

DISCUSSION

The main findings of this study were as follows: (i) we observed a significant genetic correlation between rMDD and right hippocampal volume in a large sample of Mexican-Americans from extended pedigrees; (ii) bivariate linkage analysis revealed a QTL on chromosome 18 that pleiotropically influenced both traits; and (iii) association analysis under the linkage peak implicated *SMCHD1* as influencing right hippocampal volume. The bivariate association between the top variant within *SMCHD1*, rMDD, and right hippocampal volume was also significant, but likely driven by the relationship between *SMCHD1* and

TABLE II. Estimates for the top five variants from the QTL-specific bivariate association analysis

SNP	χ^2	p	β (rMDD)	β (right hippocampus)	MAF	HWE P
rs574972	18.84723	0.000081	−0.01439	0.325537	0.07	0.065
rs8094926	15.585198	0.000413	0.000432	0.306349	0.07	0.039
rs12455524	15.577936	0.000414	0.407959	−0.066439	0.12	0.202
rs648105	15.529434	0.000424	0.000029	0.30582	0.07	0.065
rs3910708	12.593764	0.001842	0.438748	−0.219293	0.05	0.90

SNP = single-nucleotide polymorphism; MAF = minor allele frequency; HWE p = Hardy–Weinberg equilibrium p value.

right hippocampal volume. Within the same region, there was also a suggestively significant association between the top variant within *DLGAP1* and rMDD alone.

Previous work has established a relationship between depression and the hippocampus, with many studies implicating stress as a mediating factor in this relationship [MacQueen and Frodl, 2011; Campbell and Macqueen, 2004]. The hippocampus is a part of the cortical network that regulates mood and response to stress, providing modulation to the hypothalamic–pituitary–adrenal axis [Jacobson and Sapolsky, 1991]. Excessive exposure to stress or glucocorticoids (the adrenal steroid hormones secreted in response to stress) causes deleterious changes to both the structure and function of the hippocampus in nonhuman animals [for a review, see Sapolsky, 2003]. Moreover, some human studies have reported that individuals who experienced traumatic events in early life had smaller hippocampal volumes than those who did not experience trauma [Bremner et al., 1997; Teicher et al., 2002; Vythilingam et al., 2002; cf. Gilbertson et al., 2002]. Although the existence of a relationship between stress, MDD, and the hippocampus is no longer under much doubt, the nature of the relationship is not yet understood. For example, it could be that hippocampal volume reductions are circumstantial to MDD, caused by the same environmental stressors that trigger the illness. Another possibility, however, is that changes in hippocampal volume reflect a mechanism through which life adversity is transduced into MDD risk [Campbell and Macqueen, 2004; MacQueen and Frodl, 2011]. The findings of this study provide tentative support for the latter hypothesis, insofar as that our results could be explained in terms of an underlying biological mechanism that causes pathology in an individual's ability to deal with stress, leading to both smaller right hippocampal volumes and an increased likelihood of exhibiting rMDD. However, since our data are not longitudinal, we cannot determine whether hippocampal volumes were mediated due to prolonged stress, or were smaller prior to prolonged stress, in depressed individuals.

The gene *SMCHD1* (structural maintenance of chromosomes hinge domain containing 1) has an established role in maintaining X inactivation, the dosage compensation mechanism by which the transcription of X-linked genes is equalized across males and females, which *SMCHD1* maintains via hypermethylation of CpG islands (a process by which a gene is silenced) on the inactive X chromosome [Blewitt et al., 2008]. It is likely that *SMCHD1* also has epigenetic functions beyond X inactivation [Mould et al., 2013]. For example, *SMCHD1* acts upon the gene *FSHD2* in such a way that leads to mutations in chromatin regulatory proteins, which in turn reduces epigenetic repression and increases expression of the deleterious gene *DUX4*, which causes facioscapulohumeral muscular dystrophy [Jones et al., 2015; Lemmers et al., 2012; Sacconi et al., 2013; Winston et al., 2015]. This illness may be unrelated to rMDD, but there is limited evidence to suggest that depression may present as a feature of muscular dystrophy [Sabharwal, 2014]. Moreover, wnt/β-catenin signaling suppresses the expression of *SMCHD1* downstream target *DUX4* [Block et al., 2013]. Not only is wnt/β-catenin signaling heavily implicated in neurological and psychiatric disorders [Freyberg et al., 2010; MacDonald et al., 2009], but there is some evidence to suggest that it plays a major role in affective disorders [Gould et al., 2006; Sani et al., 2012; Wada, 2009]. Research in mice has implicated the wnt antagonist Dickkopf-1 as being involved in hippocampal damage due to chronic stress, where reduced wnt pathway activity was associated with neuronal loss and dendritic atrophy [Matrisciano et al., 2011]. Mice administered intracerebroventricularly with GSK-3 inhibitors, where GSK-3 phosphorylates β-catenin, showed antidepressant effects and concomitant increased β-catenin expression in the hippocampus [Kaidanovich-Beilin et al., 2004]. Taken together with these previous findings, our results suggest that *SMCHD1* and its downstream signaling events make a plausible and interesting candidate gene for depression risk.

The top-ranked variant for rMDD alone fell within an intron of *DLGAP1*. The DLGAP gene family has an established role in the etiologies of several psychiatric illnesses—*DLGAP3* has been associated with Tourette's Syndrome and obsessive compulsive disorder [Boardman et al., 2011; Crane et al., 2011; Welch et al., 2007; Zuchner et al., 2009]; *DLGAP2* has been associated with autism [Pinto et al., 2010]; and *DLGAP1*, *DLGAP2*, and *DLGAP3* have all been associated with psychosis [Li et al., 2013a,b,]. Given the genetic overlap between psychiatric illnesses, it is unsurprising that a single gene family has been implicated across multiple diagnoses [Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013]. This study adds to this literature by further implicating the DLGAP gene family in rMDD.

DLGAP genes play a crucial role in the recruitment and stabilization of synaptic junctions, as well as the regulation of neurotransmission [Takeuchi et al., 1997]. Genes in this family encode isoforms of the postsynaptic density 95 (PSD95]-associated SAPAP proteins, and *DLGAP1* in particular encodes SAPAP1 [Cho et al., 1992; Yao et al., 2003]. Postsynaptic densities are clusters of specialized proteins attached to the postsynaptic membrane which play key roles in the regulation of synaptic adhesion, transmitter receptor clustering, and modulation of receptor sensitivity [Kennedy, 1993]. PSD-95 is concentrated at *N*-methyl-D-aspartate (NMDA)-type glutamate receptors [Kornau et al., 1995]. In the hippocampus, the activation of NMDA receptors contributes to the induction of long-term potentiation [Ehrlich and Malinow, 2004; Malinow et al., 1989]. Given the above discussion of the relationship between *SMCHD1*, wnt signaling, and long-term potentiation in the hippocampus, it seems our top-ranked genes converge on complementary molecular mechanisms of learning and memory.

Recently, large-scale GWA studies have identified multiple common genetic variants on chromosome 12 influencing hippocampal volumes in unrelated individuals [Bis et al., 2012; Hibar et al., 2015; Stein et al., 2012]. These variants appear to be associated with hippocampal volumes specifically, rather than global cortical or subcortical volumes. In this study, we did not observe linkage for right hippocampal volume on chromosome 12. One possible reason for this is that hippocampal volume may be subject to polygenic effects throughout the genome. Another possibility is that our approach may highlight sources of genetic variation (i.e., rare variants) that are distinct from those highlighted using GWA (i.e., common variants). The use of extended pedigrees as here improves the chances of detecting association with rare variants because Mendelian transmissions from parents to offspring maximize the chances that multiple copies of rare variants exist in the pedigree.

In this study, we propose that the complex genetic architecture of depression may become more tractable if we search for genetic loci that jointly influence depression risk and depression endophenotypes. This idea relies on the assumption that a small number of the genes that increase depression risk also influence specific endophenotypes, and that constraining analyses to these common genetic factors profitably focuses the search. This study exploited the evidence for pleiotropy between rMDD and right hippocampal volume to identify a region on chromosome 18 that contains a number of potential genes of interest for depression. This work expands upon our previous study, which established bilateral hippocampal volume as a putative endophenotype for rMDD [Glahn et al., 2012], by examining the right hippocampus specifically and by providing a novel QTL. In general, our findings support the endophenotype approach, and highlight a possible way forward in delineating depression genes.

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