Title: The NCAM1 gene set is linked to depressive symptoms and their brain structural correlates in healthy individuals

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ABSTRACT

Depressive symptoms exist on a continuum, the far end of which is found in depressive disorders. Utilizing the continuous spectrum of depressive symptoms may therefore contribute to the understanding of the biological underpinnings of depression. Gene set enrichment analysis (GSEA) is an important tool for the identification of gene groups linked to complex traits, and was applied in the present study on genome-wide association study (GWAS) data of depression scores and their brain-level structural correlates in healthy young individuals. On symptom level (i.e. depression scores), robust enrichment was identified for two gene sets: NCAM1 Interactions and Collagen Formation. Depression scores were also associated with decrease in fractional anisotropy (FA) –a brain white matter property- within the forceps minor and the left superior temporal longitudinal fasciculus. Within each of these tracts, mean FA value of depression score-associated voxels was used as a phenotype in a subsequent GSEA. The NCAM1 Interactions gene set was significantly enriched in these tracts. By linking the NCAM1 Interactions gene set to depression scores and their structural brain correlates in healthy participants, the current study contributes to the understanding of the molecular underpinnings of depressive symptomatology.

Key words: NCAM1 Interactions, depressive symptoms, MADRS, gene set enrichment analysis, DTI, healthy participants

INTRODUCTION

Depressive symptoms are continuously distributed in the general population, as supported by taxometric studies of large community samples (Hankin et al., 2005; Slade and Andrews, 2005). Depressive disorders are considered to represent the far end of this continuum (Ayuso-Mateos et al., 2010; Kendler and Gardner Jr, 1998; Slade, 2007), and subthreshold depressive symptoms have been associated with the same risk factors as diagnosable depressive episodes worldwide (Ayuso-Mateos et al., 2010). Moreover, higher depressive symptoms have been associated with higher levels of psychosocial dysfunction and increased risk for Major Depressive Disorder (MDD) and substance use disorder in the general adult population (Lewinsohn et al., 2000).

Furthermore, while multiple brain-level structural changes have been implicated in MDD (LeWinn et al., 2014; Ota et al., 2015; Wu et al., 2011; Zuo et al., 2012), microstructural changes within various neuroanatomical tracts have also been associated with subthreshold depressive symptoms (Hayakawa et al., 2013; McIntosh et al., 2013; Sprengelmeyer et al., 2014). Therefore, utilizing the continuous spectrum of depressive symptoms may contribute to the understanding of the biological underpinnings of depression.

Self-reported depressive symptoms are moderately heritable in healthy adults, with heritability estimates of 30-37% (Kendler et al., 1994; Sham et al., 2000), which approximately equals heritability estimates for MDD of 31-42% (Sullivan et al., 2000), rendering them a suitable phenotype for genetic studies.

Gene set enrichment analysis (GSEA) can be used to improve the detection and the explanatory power of the genetic basis of heritable traits (Wang et al., 2010). Importantly, GSEA is particularly suitable for the study of complex traits, which are characterized by small genetic effects of multiple genetic variants that contribute to the trait in question (Lohmueller et al., 2003), as demonstrated by previous studies (Heck et

al., 2014; Heck et al., 2015; Lips et al., 2012; Nurnberger et al., 2014). Specifically, it tests whether multiple genes with modest associations with a given complex trait are enriched in specific biological process. The objective of the current study was to dissect the biological basis of depression scores, measured as a continuous, quantitative phenotype in healthy participants, by applying GSEA to genome-wide association study (GWAS) data. Notably, the NETRIN1 signaling pathway was recently associated with MDD using a similar approach (Zeng et al., 2017). Furthermore, the Synaptic transmission pathway was associated with MDD and several immune-inflammatory pathways with depressive symptoms, respectively, using genome-wide expression data (Elovainio et al., 2015; Hori et al., 2016). Therefore, it was hypothesized that depression scores are related to particular gene sets in the current study. Replication was performed in an independent study, having the identical phenotype. Additionally, diffusion tensor imaging (DTI) data in individuals of the replication study were available. Decreases of fractional anisotropy (FA) have been previously reported in both MDD (LeWinn et al., 2014; Ota et al., 2015; Wu et al., 2011; Zuo et al., 2012) and subthreshold depressive symptoms (McIntosh et al., 2013; Sprengelmeyer et al., 2014). FA is a measure of the directional dependence of diffusion (Basser, 1995) and reflects white matter tracts properties such as fiber density, as well as coherence within a voxel (Beaulieu, 2002). To test the hypothesis of a link between depression scores and FA values in our sample of healthy young adults, we first identified brain structural correlates of the depression scores by associating them with brain-wide FA measurements. To furthermore check if depressive symptoms and brain structural correlates of the depression scores share some genetic background we ran a GSEA for each of the identified brain tracts, by extracting the mean FA values for depression score-associated voxels from the DTI analysis and using these as a phenotype in the subsequent GSEA.

MATERIALS AND METHODS

Studies

Discovery study (Basel_1): This study was conducted with 2099 cognitively healthy young adults from the general population, recruited in Basel, Switzerland, as part of an ongoing behavioral genetics study (data lock May 2015). Sample characteristics are presented in Table 1. Participants were free of medication and of any neurological and psychiatric conditions at the time of the study, as assessed by standard questionnaires. All participants provided written informed consent, prior to participation in the study. Data of the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), consisting of ten items rated on a scale from 1 to 6, were available for $n=1651$ participants. The ratings were summed up to a single depression score (0-60) per participant, ranging from 0 to 46 in this sample, with a mean value ($\pm$ SD) of 8.48 ($\pm$ 6.32). For comparison, mean MADRS score ($\pm$ SD) of 23.4($\pm$ 13.2) has been reported for MDD patients (Muller et al., 2003). Score distributions for our participants are reported in Supplementary Figure 1. The internal consistency was high (Cronbach 's alpha = 0.83), and correlation between the self-reported MADRS and Beck Depression Inventory (Beck et al., 1996) was $r=0.62$, and thus in line with prior reports comparing both instruments in both clinical and healthy samples (Carter et al., 2010; Kjaergaard et al., 2014; Wikberg et al., 2015).

Replication study (Basel_2): This study was conducted with 1523 cognitively healthy young adults from the general population, recruited in Basel, Switzerland, as part of an ongoing imaging genetics study (data lock May 2015). Sample characteristics are presented in Table 1. Participants were free of medication and of any neurological and psychiatric conditions at the time of the study, as assessed by standard questionnaires. All participants provided written informed consent, prior to participation in the study. 1135 participants completed the MADRS in this sample. MADRS scores ranged from 0 to

33 in this sample, with a mean value ($\pm$ SD) of 7.29 ($\pm$ 5.40). Score distributions are reported in Supplementary Figure 2. Furthermore, a magnetic resonance imaging (MRI) scanning session was conducted, including a picture recognition task, followed by an anatomical imaging sequence and a DTI sequence, conducted for 658 of the participants. Sample characteristics and MADRS scores distribution for the DTI subsample are provided in Table 1 and Supplementary Figure 3, respectively. Additional information regarding the scanning procedure is provided in the Supplementary Materials.

We used sex and age-corrected depression scores for all analyses by regressing out the effects of sex and age in both studies.

The ethics committee of the Canton of Basel approved both protocols.

Array-based SNP genotyping

Array-based SNP genotyping was performed as described in the Genome-Wide Human SNP Nsp/Sty 6.0 User Guide (Affymetrix). Briefly, genomic DNA was digested with Nsp I and Sty I restriction enzymes and ligated to an enzyme-specific adaptor. Adaptor-ligated DNA fragments were subjected to polymerase chain reactions (PCR). PCR amplification products were combined and purified using Agencourt Magnetic Beads. The amplified DNA was fragmented, labeled and hybridized onto a Genome- Wide Human SNP 6.0 Array. The hybridized array was washed, stained and scanned. Generation of SNP calls and array quality control (QC) was performed. Contrast QC was chosen as the QC metric, using a default value ≥ 0.4 . All samples passing the QC criteria were genotyped using the Birdseed (v2) algorithm. Mean Call Rate averaged $>98.5\%$. Additional information is provided in the Supplementary Materials.

Brain imaging

Scanning procedure

Scanning was performed on a Siemens Magnetom Verio 3 T whole body MR unit equipped with a twelve-channel head coil. For a detailed description of the scanning procedure please refer to the Supplementary Materials.

DTI: Preprocessing

After visual inspection, 38 participants were excluded due to corrupted T1-weighted images (movement or anatomical abnormalities). Furthermore, two participants were excluded due to excessive movement during the DTI acquisition. Complete datasets (behavior and imaging) were available for N=658 participants. Diffusion-weighted images were analyzed using FSL (4.1.7). Images were co-registered to the reference unweighted volume (b=0) using an affine transformation for correction of head motion and eddy current induced image distortion.

DTI: FA statistical analysis

Voxel-wise statistical analysis of fractional anisotropy (FA) data was conducted using Tract-Based Spatial Statistics (TBSS 1.2) (Smith et al., 2006), part of the FMRIB Software Library (FSL) (Smith et al., 2004). Briefly, individual FA data were non-linearly warped to the standard space FA template (FMRIB58_FA) and projected onto the population mean FA skeleton. These data were used as input for voxel-wise between-subject statistics. GLM analyses, as implemented in the randomize tool (Winkler et al., 2014), were applied in search of negative voxel-wise FA associations with depression scores. Statistical significance was assessed through 5000 permutations and results were considered significant for $p < 0.05$, corrected for multiple comparisons across space using the 'two-dimensional' parameter settings with threshold-free cluster enhancement (Smith and Nichols, 2009), which avoids using an arbitrary threshold for the initial cluster-formation.

Statistical genetics analysis

GWAS

For the input for the GSEA (i.e., association statistics on a genome-wide level), a standard GWAS was performed on autosomal SNPs using the “--assoc” command with asymptotic (Wald test) significance values, as implemented in the PLINK software package (Purcell et al., 2007). SNPs with a genotype call-rate < 0.95, minor allele frequency (maf) < 0.01, or a deviation from Hardy-Weinberg equilibrium (hwe) < 0.0001 were excluded from the analysis.

Genetic Heterogeneity

The genomic control inflation factor indicated no notable admixture in the discovery sample ($\lambda = 1.0017$) and the replication sample ($\lambda = 1.0000$), respectively. Q-Q plots are presented in Supplementary Figure 4 and 5, for the discovery and the replication sample, respectively.

GSEA

GWAS-derived association statistics were entered in a GSEA. More in detail, SNPs were mapped onto genes and genes were assigned to gene sets. Information regarding pre-defined gene sets was obtained from the following databases: Gene Ontology (GO) (<http://geneontology.org/>), Kyoto Encyclopedia of Genes and Genomes (KEGG) (<http://www.genome.jp/kegg/>), BioCarta (<http://www.biocarta.com/>) and Reactome (<http://www.reactome.org/>). GSEA was conducted using the MAGENTA software package (Segrè et al., 2010). Gene boundaries were set to ± 0 kb, thus capturing only SNPs within transcripts, in order to avoid known potential biases introduced by overlapping genes (Sedeno-Cortes and Pavlidis, 2014). Consequently, high-effect SNPs in regulatory regions may be missed. Gene set size was limited to 20 to 200 genes. 1411 gene sets met this criterion and an enrichment p-value was provided for each of them. The enrichment p-value is estimated based on the difference between the observed

number of phenotype-associated genes above a given enrichment cutoff within the gene set and the number of phenotype-associated genes that is expected by chance for a gene set of the same size. In order to correct for multiple testing within a gene set, false discovery rate (FDR) correction with a 75th percentile cutoff was used, which is considered the optimal cutoff for GSEA of complex traits with multiple weak effects (Segrè et al., 2010). The FDR cutoff was computed jointly for all gene-set databases.

Workflow

GSEA for depression scores

Gene sets with $q_{75\%} < 0.05$ were identified for depression scores in the discovery sample. Significantly enriched gene sets in this sample were checked for association with depression scores in the replication sample. In case of significant enrichment, defined as $p < 0.05/N_{(\text{GENE SETS})}$ in the replication sample, the gene set was considered to be within-phenotype replicated.

From tract-based statistics to GSEA

As a next step, DTI analysis was conducted to investigate the neural correlates of depression scores, by applying a GLM in search of voxel-wise FA associations. Age and sex were used as covariates in the analysis. Voxel-wise FA-depression associations derived from the DTI statistical analysis were localized to brain tracts using the JHU White-Matter Tractography Atlas (Hua et al., 2008). The proportion of significant voxels ($p < 0.05$) belonging to each of the specific tracts was calculated. We focused on tracts containing a sizable portion (over 20%) of the overall significant voxels for further analysis. For each participant we extracted an average FA value for the depression score-associated voxels within each of the relevant tracts separately, and used them as phenotypes in a hypothesis-driven GSEA. More specifically, GWAS analysis was run on

the tract-based FA values and GSEA was applied to the genome-wide association data for these traits.

RESULTS

GSEA for depression scores

Significant enrichment of depression score associations was identified on a multiple testing-corrected level for three gene-sets: Collagen Formation (Reactome: REACT_120729), $q_{75\%} = 0.011$; NCAM1 Interactions (Reactome: REACT_18312), $q_{75\%} = 0.021$; Acute Myocardial Infarction (AMI) Pathway (BioCarta: h_amiPathway), $q_{75\%} = 0.034$. Furthermore, enrichments for the Collagen Formation and the NCAM1 Interactions gene set were also significant ($P < 0.01$) in the replication sample (Collagen Formation $P = 9.90 \times 10^{-5}$; NCAM1 Interactions $P = 1.00 \times 10^{-4}$). FDR corrected ($q_{75\%}$) and nominal (p) GSEA values for each of these gene sets are reported in Table 2. Of note, including regions 110kb upstream and 40kb downstream of the gene in the GSEA did not significantly change the results (Supplementary Table 1).

Notably, there is a substantial genetic overlap between these two gene sets ($p = 1.94 \times 10^{-40}$). Furthermore, the NCAM1 Interactions and the Collagen Formation gene set enrichments were due to collagen-related genes, respectively, as shown by a systematic overview of genes contributing to the gene set associations with depression scores i.e. passing the enrichment cutoff in each sample (Table 3).

Of note, the genetic effects of the NCAM1 Interactions and the Collagen Formation gene sets on depression scores were significantly mediated by trait anxiety ($p < 0.001$).

Major depressive disorder (MDD) and anxiety disorders share significant amount of genetic etiology (Kendler et al., 2003) and these results suggest that depression and anxiety may also have overlapping genetic bases at symptom/trait level in healthy participants. For more details regarding this analysis please refer to the Supplementary Information.

The AMI gene set did not exceed the significance threshold in the replication sample ($P = 0.016$). GSEA values of the remaining gene sets that were nominally associated with

depression scores ($p < 0.05$) are provided in Supplementary Table 2A and 2B, for the discovery and the replication sample, respectively.

Of note, no SNP reached genome wide significance ($p < 5 \times 10^{-8}$) in the GWAS analysis of depression scores in the discovery sample and the replication sample, respectively, demonstrating the usefulness of GSEA to detect associations of weaker effects. The GWAS p-values for the best SNP of each gene passing the enrichment cutoff in the GSEA are provided in Supplementary Table 3 and Supplementary Table 4 for the NCAM1 Interactions and the Collagen Formation gene set, respectively.

GSEA for MDD

As a next step, we investigated whether the NCAM1 Interactions and the Collagen Formation gene sets are associated with MDD diagnosis, by applying the GSEA to publically available summary statistics of a large MDD case-control GWAS (<https://www.med.unc.edu/pgc/results-and-downloads>) (Ripke et al., 2013). While we identified nominally significant enrichment for the Collagen Formation gene set in this sample ($P=0.013$), the depression association with the NCAM1 Interactions gene set did not extend to MDD patients ($P=0.13$). Of note, the MDD analysis was conducted using case-control data. However, it has been previously demonstrated that the use of continuous measurements, rather than clinical cut-offs, can substantially improve the power for detection of genetic variants associated with polygenic traits (van der Sluis et al., 2013).

DTI results: FA associations with depression scores

We found whole-brain significant negative associations between FA and depression scores, as illustrated in Figure 1. FA reductions have been associated with subclinical depressive symptoms in two previous studies (Hayakawa et al., 2014; McIntosh et al., 2013).

The JHU White-Matter Tractography Atlas was used for tract identification. The proportion of significant voxels allocated to a particular tract, as well as the proportion of significant voxels among all the voxels within each tract is provided in Table 4. The majority of significantly associated voxels was localized within the forceps minor (FM) (21.86%) and the left superior longitudinal fasciculus (SLF) (34.08%), mainly confined to its temporal part (tSLF) (24.38%). FA decreases within these regions have been previously associated with MDD (LeWinn et al., 2014; Ota et al., 2015; Wu et al., 2011; Zuo et al., 2012).

Hypothesis-driven GSEA of depression score-associated FA within three brain tracts

Average FA values for the voxels significantly associated with depression scores were calculated for the forceps minor, the left SLF and the left tSLF, respectively. To test if there is a shared genetic basis between depression scores and the respective brain tracts, we ran a separate GSEA for each brain tract. The GSEAs showed significant enrichment for the NCAM1 Interactions gene set on a nominal level (FM: $p=0.016$; SLF: $p=0.033$; tSLF: $p=0.007$), and no association with the Collagen Formation gene set (see Table 5). An overview of the remaining significantly enriched gene sets is provided in Supplementary Table 5, Supplementary Table 6 and Supplementary Table 7, for the FM, the left SLF and the left tSLF, respectively.

We further investigated if the enrichment of the NCAM1 Interactions gene set for each DTI phenotype is solely dependent on depression scores. The respective FA values were corrected for depression scores using linear regression analysis, and the GSEA was re-run. Removing the depression-related variance reduced the NCAM1 Interactions FA association for each DTI-derived phenotype (FM: $p=0.14$; SLF: $p=0.080$; tSLF: $p=0.016$), suggesting that these associations may be partly mediated by depression scores.

DISCUSSION

This study identified two gene sets related to self-reported depression scores in healthy participants. By applying a GSEA approach, robust associations were identified for the Collagen Formation and the NCAM1 Interactions gene set, respectively.

As a next step, a DTI analysis was conducted in search of brain structural correlates of depressive symptom scores, resulting in the identification of depression score-associated FA reductions, localized mainly in the forceps minor and the left SLF. Although based on depression score-differences in healthy participants, our findings are in line with previously reported FA decrease in the SLF and corpus callosum in individuals diagnosed with MDD (LeWinn et al., 2014; Ota et al., 2015; Wu et al., 2011; Zuo et al., 2012), bipolar disorder (Saricicek et al., 2016), generalized anxiety disorder (Wang et al., 2016) and autism spectrum disorders (Fitzgerald et al., 2016). Additionally, subclinical depressive symptoms have been associated with widespread FA decrease in healthy female participants, including corpus callosum and the right anterior cingulum (Hayakawa et al., 2014), and FA decrease in the bilateral uncinate fasciculus in healthy individuals over 70 years of age (McIntosh et al., 2013). An FA decrease was also detected in a small fraction of the right uncinate fasciculus in the current study (Table 4).

Moreover, in order to further validate our initial genetic findings, DTI-derived measurements of depression score-associated microstructural properties within the forceps minor and the left (temporal) SLF were subjected to a hypothesis-driven GSEA. The NCAM1 Interactions gene set was significantly associated with each of the three DTI phenotypes, additionally pointing to its possible involvement in depression-relevant biological pathways.

Genes constituting the neural cell adhesion molecule (NCAM1) Interactions gene set are implicated in neural development and synaptic plasticity (Nielsen et al., 2010; Rutishauser, 2008; Walmod et al., 2004) and code for both intracellular components e.g.

subunits of voltage-gated calcium channels, and molecules of the extracellular matrix, most prominently collagen components (coded by 17 out of the 39 genes comprising this gene set), associated with NCAM activity.

Noteworthy, Collagen Formation, a gene set with substantial genetic overlap with NCAM1 Interactions ($p=1.94 \times 10^{-40}$), was also associated with depression scores in this study (Table 2). Ten out of the 17 genes shared by these gene sets contributed to the association with depression scores in the discovery and the replication sample, respectively (Table 3).

NCAM has been investigated in the context of depression, due to its modulatory role in intracellular cascades and brain plasticity (Wainwright and Galea, 2013). NCAM deficits and resulting changes in neural plasticity have been associated with an increase of depression-like behavior and reduced efficacy of common antidepressants in animal models (Aonurm - Helm et al., 2008; Jürgenson et al., 2012; Wainwright et al., 2015). Additionally, genetic variants within or near *NCAM1* have been associated with suicidal behavior (Sokolowski et al., 2016), cannabis use and MDD (Hodgson et al., 2017), as well as other disorders, such as bipolar disorder, (Arai et al., 2004), schizophrenia (Zhang et al., 2014) and autism (Marui et al., 2009). According to the references listed above, one may assume *NCAM1* as a general vulnerability factor for neurodevelopmental and psychiatric disorders. Moreover, collagens have a notable impact on NCAM downstream activity (Monzo et al., 2013). Our genetic association data are inline with these biological observations.

Furthermore, the NCAM1 Interactions gene set was associated with DTI correlates of depression scores. NCAM-derived polysialic acid has been implicated in axonal development, myelination and path finding (Rutishauser, 2008), all of which can impact the microstructural properties of brain tracts and therefore be reflected by the DTI (FA) measurement. Moreover, as regressing out the depression-related variance reduced the association between the NCAM1 Interactions gene set and each DTI-derived

phenotype, the respective associations are likely to be at least partly mediated by depression scores.

By linking the NCAM1 Interactions gene set to depression scores and their structural brain correlates in healthy participants, the current study contributes to the understanding of the molecular underpinnings of depressive symptomatology.

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Table 1 Sample descriptives

Sample	N	N Females (%)	Age range (years)	Age mean
Basel_1	2099	1378 (65.6)	18-35	22.47
Basel_2	1523	939 (61.6)	18-35	22.37
Basel_2: DTI	658	393 (59.73)	18-35	22.36

Table 2 Gene set associations with depression scores in A) Basel_1 and B) Basel_2

Table 2A

Database	Gene Set	p	q _{75%}	Gene set size	Number of observed genes above enrichment cutoff	Difference between number of observed and expected genes above enrichment cutoff
REACTOME	Collagen Formation	1.00×10^{-4}	0.011	53	27	14
REACTOME	NCAM1 Interactions	3.00×10^{-4}	0.021	35	19	10
BIOCARTA	AMI Pathway	6.00×10^{-4}	0.034	15	10	6

p, uncorrected values; q_{75%}, FDR corrected values.

Table 2B

Database	Gene Set	p	q _{75%}	Gene set size	Number of observed genes above enrichment cutoff	Difference between number of observed and expected genes above enrichment cutoff
REACTOME	Collagen Formation	9.90×10^{-5}	0.030	53	26	13
REACTOME	NCAM1 Interactions	1.00×10^{-4}	0.025	35	19	10
BIOCARTA	AMI Pathway	0.016	0.44	15	8	4

p, uncorrected values; q_{75%}, FDR corrected values.

Table 3 Genes contributing to the gene set association with depression scores i.e. passing the enrichment cutoff

Discovery sample: Basel 1		Replication sample: Basel 2	
Collagen Formation	NCAM1 Interactions	Collagen Formation	NCAM1 Interactions
<i>ADAMTS14</i>	<i>CACNA1I</i>	<i>ADAMTS3</i>	<i>CACNA1H</i>
<i>ADAMTS2</i>	<i>CACNB2</i>	<i>COL1A1</i>	<i>CACNA1I</i>
<i>BMP1</i>	<i>CACNB4</i>	<i>COL1A2</i>	<i>CACNA1S</i>
<i>COL1A1</i>	<i>CNTN2</i>	<i>COL3A1</i>	<i>CACNB1</i>
<i>COL1A2</i>	<i>COL1A1</i>	<i>COL4A1</i>	<i>COL1A1</i>
<i>COL2A1</i>	<i>COL1A2</i>	<i>COL4A2</i>	<i>COL1A2</i>
<i>COL4A1</i>	<i>COL2A1</i>	<i>COL4A3</i>	<i>COL3A1</i>
<i>COL4A2</i>	<i>COL4A1</i>	<i>COL5A1</i>	<i>COL4A1</i>
<i>COL4A3</i>	<i>COL4A2</i>	<i>COL6A2</i>	<i>COL4A2</i>
<i>COL4A4</i>	<i>COL4A3</i>	<i>COL6A3</i>	<i>COL4A3</i>
<i>COL5A1</i>	<i>COL4A4</i>	<i>COL8A1</i>	<i>COL5A1</i>
<i>COL5A3</i>	<i>COL5A1</i>	<i>COL9A2</i>	<i>COL6A2</i>
<i>COL6A1</i>	<i>COL6A1</i>	<i>COL11A1</i>	<i>COL6A3</i>
<i>COL6A2</i>	<i>COL6A2</i>	<i>COL13A1</i>	<i>COL9A2</i>
<i>COL8A1</i>	<i>GDNF</i>	<i>COL14A1</i>	<i>GDNF</i>
<i>COL12A1</i>	<i>GFRA2</i>	<i>COL15A1</i>	<i>NCAM1</i>
<i>COL13A1</i>	<i>NRTN</i>	<i>COL19A1</i>	<i>NCAN</i>
<i>COL15A1</i>	<i>ST8SIA2</i>	<i>COL21A1</i>	<i>ST8SIA2</i>
<i>COL22A1</i>	<i>ST8SIA4</i>	<i>COL22A1</i>	<i>ST8SIA4</i>
<i>COL27A1</i>	-	<i>COL23A1</i>	-
<i>COL28A1</i>	-	<i>COL25A1</i>	-
<i>GLT25D2</i>	-	<i>COL27A1</i>	-
<i>LEPREL1</i>	-	<i>COL28A1</i>	-
<i>PPIB</i>	-	<i>LEPREL1</i>	-
<i>SERPINH1</i>	-	<i>PCOLCE2</i>	-
<i>TLL1</i>	-	<i>TLL2</i>	-
<i>TLL2</i>	-	-	-

Genes contributing to the gene set association with depression scores i.e. passing the enrichment cutoff are listed for each sample, for the Collagen Formation gene set and the NCAM1 Interactions gene set, respectively. Overlapping genes between the two gene sets per sample are marked in gray color.

Table 4 Proportion of depression scores-associated voxels per brain tract

Tract name	Overall associated voxels %	Tract's associated voxels %
Anterior_thalamic_radiation_L	5.05	1.68
Anterior_thalamic_radiation_R	0.48	0.18
Cingulum_(cingulate_gyrus)_L	3.28	5.05
Cingulum_(cingulate_gyrus)_R	0	0
Cingulum_(hippocampus)_L	0	0
Cingulum_(hippocampus)_R	0	0
Corticospinal_tract_L	0	0
Corticospinal_tract_R	0	0
Forceps_major	0	0
Forceps_minor	21.86	6.01
Inferior_fronto-occipital_fasciculus_L	0.48	0.13
Inferior_fronto-occipital_fasciculus_R	2.05	0.51
Inferior_longitudinal_fasciculus_L	0	0
Inferior_longitudinal_fasciculus_R	0	0
Superior_longitudinal_fasciculus_L	34.08	10.74
Superior_longitudinal_fasciculus_R	0	0
Superior_longitudinal_fasciculus_(temporal_part)_L	24.38	14.63
Superior_longitudinal_fasciculus_(temporal_part)_R	0	0
Uncinate_fasciculus_L	0	0
Uncinate_fasciculus_R	1.30	1.97

Overall associated voxels %: Proportion (in percent) of all significant voxels belonging to the specific tract; Tract's associated voxels %: the proportion (in percent) of significant voxels, among all the voxels of the particular tract; Abbreviations: L, left; R, right

Table 5 Gene set associations with DTI-derived phenotypes

DTI phenotype	Database	Gene Set	p value	Gene set size	Genes above enrichment cutoff
Forceps Minor	REACTOME	Collagen Formation	0.15	53	14
Forceps Minor	REACTOME	NCAM1 Interactions	0.016	35	12
Left SLF	REACTOME	Collagen Formation	0.093	53	16
Left SLF	REACTOME	NCAM1 Interactions	0.033	35	13
Left tSLF	REACTOME	Collagen Formation	0.093	53	16
Left tSLF	REACTOME	NCAM1 Interactions	0.007	35	15

Figure 1

Association between FA data and depression scores

Associations are presented using color-coded, multiple testing corrected t values within a display range of 0.95:1 (corresponding to $p < 0.05$). The mean FA image of the Basel_2 sample is presented in coronal (upper left), sagittal (upper right) and axial (lower left) view. The mean FA skeleton, overlaid on the mean FA image, is presented in green color. Negative associations are presented in blue color. Abbreviations: FA, Fractional Anisotropy; L, left; R, right.

R

L