Neuro-transcriptomic signatures for mood disorder morbidity and suicide mortality

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ABSTRACT

Suicidal behaviors are strongly linked with mood disorders, but the specific neurobiological and functional gene-expression correlates for this linkage remain elusive. We therefore tested the hypothesis that a convergent neuroanatomical and gene-expression signature will underlie mood disorder associated psychiatric morbidity and related suicide mortality. To do so, first, we applied an anatomical likelihood estimation (ALE) MRI meta-analysis across 72 voxel-based morphometry (VBM) studies including 2387 (living) participants that identified a selectively reduced anterior insula cortex gray matter volume (GMV) as a potential neuroanatomical signature for mood disorder. This neuroanatomical signature was then specifically used to guide *postmortem* RNA-Sequencing studies of 100 independent donor brains with a life-time history of major depressive disorder (N=30), bipolar disorder (N=37) and non-affected controls (N=33) using a sample from the National Institute of Mental Health Brain collection core. In this latter study, factor analysis first identified a higher-order factor representing number of Axis-1 diagnoses (i.e. morbidity) and suicide-completion (i.e. suicide-mortality). Using this higher-order factor as a contrast variable, differential gene-expression changes were examined in high psychiatric morbidity and related suicide mortality *versus* low psychiatric morbidity and related suicide mortality in mood disorder cohorts and controls. We identified in immune, inflammasome, neurodevelopmental, and transcriptional pathways and a weighted gene co-activation network analysis identified co-activated gene modules for psychiatric morbidity and suicide-mortality outcomes. These results provide a functional gene-expression link between mood disorder associated psychiatric disease morbidity and suicide-mortality.

Keywords: mood disorders, major depression, bipolar disorder, suicide, gene expression, anterior insula

INTRODUCTION

Major depressive disorder and bipolar disorder – here together referred to as mood disorders, are the third leading cause of the global disease burden (Collins et al. 2011; Murray et al. 2012). Mood disorders account for the majority of completed suicides (Waern et al. 2002; Marangell et al. 2006) and they were linked to ~47,000 suicides in the United States in 2017 alone (American Foundation for Suicide Prevention, 2019). However, the convergent neurobiological basis for mood symptoms/syndromes and suicide is unknown, limiting advances in developing novel interventions.

Neuroimaging studies have identified reduction in gray matter volume (GMV) in the anterior insular cortex and anterior cingulate cortex (ACC) in association with diagnosis of psychiatric disorder in general (Goodkind et al. 2015), and the regional GMV volume reductions in these anterior insula and ACC network have been especially implicated in mood disorder diagnoses in particular (Wise et al. 2017). Neurobiological integrity of the right anterior insular cortex is shown to (a) predict mood diagnostic severity (Hatton et al. 2012), (b) modulate subjective responses to distress, pain, and psychosocial adversity (Wager et al. 2013; Eisenberger 2015), (c) regulate affective interoception (Craig 2009; Slavich et al. 2010), (d) associate with stress-related inflammatory markers (Khalsa et al. 2018), and (e) predict psycho- and pharmaco-therapeutic efficacy in mood disorders (McGrath et al. 2013). Anterior insula cortex-ACC functional connectivity during affective processing differentiated mood disorder suicide-attempters from non-attempters (Pan et al. 2013). Furthermore, abnormalities in anterior insula GMV and synaptic abnormalities are linked to suicidal-behavior in mood disorder (Wagner et al. 2012; Mathew et al. 2013). Anterior insula response to stress is shown to impact hypothalamic-pituitary-adrenal (HPA) axis-driven inflammatory responses (Khalsa et al. 2013), which may

serve to exacerbate mood disorder associated psychiatric morbidity and suicidal-behavior (Oquendo et al. 2014; Wohleb et al. 2016). Although a preponderance of evidence supports abnormal anterior insula integrity in psychosocial distress (Schneidman 1998; Mee et al. 2011; Wager et al. 2013) and mood/comorbid psychiatric symptoms, an underlying functional genetic contribution in terms of functional gene-expression changes for these abnormalities remains largely unknown.

The lack of a well-defined relationship between aberrant brain structure and function with underlying molecular changes within this brain region is an impediment to understanding pathophysiology. Moreover, evidence for shared genetic mechanisms underlying psychiatric diagnoses (Brainstorm consortium, Anttila et al. 2018) is not well-integrated with brain imaging correlates of psychiatric disease-morbidity and specific behaviors, in this case, suicide. In the present study, MRI meta-analysis was used to test the hypothesis that *1*) reduced anterior insula volume will be the most prominent neuroanatomical signature for mood disorder diagnoses. We confirmed this hypothesis with our meta-analytic findings and then used this anatomical hallmark to guide dissection of *postmortem* brain tissue for analyses of molecular/gene-expression signatures that could pave the way for precision profiling of gene functions underlying mood symptoms across diagnoses in clinically-relevant brain sub-regions. This approach enabled us to further test the hypothesis that *2*) gene-expression signatures for psychiatric disease morbidity and related suicide-mortality will share similar molecular profiles in the voxel-based morphometry (VBM) meta-analysis defined-postmortem anterior insula of mood disorder individuals, thereby providing a neurobiological framework for characterizing convergent neural-and-gene expression signatures for behavioral brain diseases.

METHODS

PARTICIPANTS

The imaging meta-analysis provided a consolidation of the current mood disorder VBM work by quantitatively integrating all the published results of volumetric comparisons of interest between controls and mood disorder participants, or correlations of volumetric measures with mood disorder symptom-specific measures that amounted to 72 previously published studies (i.e. unique volumetric comparisons or experiments) of differences in GMV measures between individuals with major depression or bipolar disorder versus healthy subjects. After selecting only publications with more than 20 subjects per comparison samples, data were included from 26 publications consisting of 43 experiments examining major depressive disorder<controls whole-brain GMV changes (demographics in **Table 1A**); and 21 publications of 29 experiments examining bipolar disorder<controls (**Table 1A**) together involving 2387 imaging participants in the meta-analysis.

The 47 studies included in our meta-analysis, as well as relevant studies that ended up not being included based on the above-mentioned inclusion criterion, are listed in supplementary Table S2. While 3 of the 72 studies/experiments included in the meta-analysis assessed suicidal behavior in relation to volumetric changes in mood disorder, suicidal phenotypes was not a specific selection criteria for study inclusion as there were very few studies in the BrainMap database that specifically assessed the relationship between suicidal phenotypes and brain volume. In study 2, RNA samples were extracted from the ALE-defined anterior insular cortex sub-region (in study 1) *postmortem* tissue of 100 donors from NIMH brain bank (**Table 1B**).

DESIGN

Based on the principle that neural structure subserves functional control of complex behavioral repertoires (Koechlin 2016), we localized the structural brain signature for mood disorders across samples and methods in study 1. Experiments of GMV changes associated with mood disorder diagnoses in defined stereotaxic space were included for analysis of localized GMV changes across studies in major depressive disorder, bipolar disorder, and major depressive disorder and bipolar disorder versus controls using the well-established ALE algorithm (Eickhoff et al. 2009). This signature guided localized anatomical-dissection of *postmortem* tissue for whole-transcriptome characterization of differential gene-expression and weighted gene co-expression network analysis (WGCNA).

NEUROIMAGING VBM META-ANALYSIS

Here, models the spatial uncertainty associated with each reported location of significant between-group differences in GMV changes (Eickhoff et al., 2009; 2012) and performed ALE assessment of GMV changes in (i) major depressive disorder<controls, (ii) bipolar disorder<controls, and (iii) mood disorders in general (i.e., pooled across major depressive disorder and bipolar disorder) versus controls.

BRAIN DISSECTION and RNA-EXTRACTION

The NIMH Human Brain Collection Core (HBCC) provided the *Postmortem* samples for which informed consents are acquired according to NIH IRB guidelines. Clinical characterization, neuropathology screening, and toxicology analyses followed previous protocols (Martin et al. 2006). For blocks of brain tissue that were dissected using a cutting-mold, the anterior insula in

pre-existing slabs numbered as 3, 4, and (depending on brain size) slab 5 were dissected systematically dissected with the aid of visualization of several (about ~16) electronic images of anatomical slices and related regional anatomical landmarks of the anterior insula meta-analytic GMV images (see sample images in **Fig 1A** and **Fig 1B**). For blocks of brain tissue that were dissected using free hand, the sections were removed from slabs containing the right anterior insula encompassing the identified reduced volume in the completed meta-analysis by specifically starting at the anatomical landmark where the caudate and putamen are approximately equal in size and extending to the most anterior portion of the insula (see **Fig 1C** showing a sample section before and after anterior insula dissection). All dissected tissues were pulverized and 50mg were aliquoted and used for standardized total RNA extraction and only samples with RNA integrity numbers (RIN) which is a measure of RNA postmortem RNA quality were included in the study (see Table 1B for average RIN values per group).

Illumina-Sequencing, Read-Mapping and Gene-Quantification:

Total RNA was extracted and only samples with RNA integrity numbers > 5 were used. Ribosomal RNA was depleted using RiboMinus Eukaryote kit from Life Technologies (Foster City, CA, USA) for RNA-Seq and confirmed using an Agilent Technologies' Bioanalyzer (Santa Clara, CA, USA). The 100 samples were processed using TruSeq RNA Library Prep Kit v2 and sequenced on the Illumina HiSeq 4000 at the Genome Sequencing and Analysis Facility (GSAF) at the University of Texas, Austin, USA. Paired-end libraries with average insert sizes of 200bp were obtained using NEBNext Ultra II Directions Library Prep kit from New England BioLabs and mRNA selection was done used the Poly(A) purist kit from Thermofisher. 30 million paired-end reads per sample (150 base pairs in length) were generated by sequencing every sample on 4

lanes of the sequencer. Sequenced reads were assessed for quality with Fastqc (Andrews 2010). The reads were pseudo-aligned to the human reference transcriptome (GRCh38- gencode) using kallisto (Kallisto, 2019), and gene-level abundances were obtained. The abundances were normalized using DESeq2, and transformed with variance stabilizing transformation (a transformation to yield counts that are approximately homoscedastic, having a constant variance regardless the mean expression value). Principal Component Analysis was performed using 25% of the highest variance genes in order to look at the underlying structure of the data and to identify the largest sources of variance.

STATISTICAL ANALYSIS

VBM Meta-analysis

Convergence across the findings reported in previous VBM studies was assessed using ALE, which in brief consists of first modelling the spatial uncertainty associated with each reported location for significant between-group differences (Eickhoff et al. 2009; Turkeltaub et al. 2012), computing the convergence across experiments by the union of the ensuing probabilistic model relative to a null-distribution reflecting a random spatial association between the findings of different experiments (Eickhoff et al. 2012) and finally statistical inference for a whole-brain corrected significance level of $p<0.001$ using threshold free cluster enhancement (Smith & Nichols 2009). We performed ALE separately focusing on GMV changes in (i) major depressive disorder, (ii) bipolar disorder, and (iii) mood disorders in general (i.e., pooled across major depressive disorder and bipolar disorder) relative to healthy controls.

Postmortem variable factor-analysis :

The *postmortem* variables included *mood disorder-diagnoses; # of lifetime-Axis-I diagnostic-*

occurrences (Axis-I-load); # of *lifetime-Axis-III diagnoses; manner of death* (natural, suicides/homicides/accidents) and *cause of death* from medical examiner reports*; demographics* (race, age at death, sex, years of education, number of children/fecundity, and marital records); *technical variables* (brain-weight, postmortem-index, pH, and RIN)*;* and *toxicology* (blood alcohol/blood narcotics levels). We applied Principal Axis Factoring (Oblimin Rotation with Kaizer Normalization) (Costello & Osborne 2005) to identify higher-order factors explaining the differences in *postmortem* variables and included those variables with communalities of ≥ 0.5.

Differential Expression Analysis:

Because *mood disorder-diagnoses, Axis I diagnostic-load (i.e. total number of psychiatric diagnoses),* and *manner of death* (together comprising the factor we refer to here as the *psychiatric morbidity and mortality component*) predominantly explains variability in (i) psychiatric disease morbidity (data on any Axis-III/medical morbidity like cardiovascular disorders or cancer have not been accounted for in our analysis) and (ii) suicide mortality (i.e. mortality or completion of suicide that can be directly linked to lifetime mood disorder symptoms), we binned samples into two groups of low versus high psychiatric disease morbidity and suicide-mortality for profiling gene-expression in the anterior insula cortex. Specifically, differential gene-expression between samples differing in psychiatric morbidity and suicide-mortality status was assessed based on the negative binomial distribution for modeled gene counts using DESeq2 (Anders 7 Huber 2010). RIN scores were included in the DESeq2 design matrix as a covariate to control for its potentially confounding effects.

We first defined low versus high scores of psychiatric morbidity using the *psychiatric morbidity and suicide-mortality* scores derived from the factor analytic scores into ≤ 0.82 for low

versus ≥ 0.82 for high scores using a split-half method of dividing the maximum score across groups by 2 (i.e. 1.64/2). We then compared *1*) high versus low *psychiatric morbidity and suicide-mortality* scores across major depressed and control groups (i.e. major depressed with high scores versus major depressed and all controls with low scores); *2*) high versus low *psychiatric morbidity and suicide-mortality* scores across bipolar and control groups (i.e. bipolar with high scores versus bipolar and all controls with low scores); *3*) high versus low *psychiatric morbidity and suicide-mortality* scores across all groups (i.e. bipolar and major depressed with high scores versus bipolar, major depressed and all controls with low scores).

To assess the relationship between suicide mortality and mood disorders specifically, we binned our groups into *1*) low (non-suicidal deaths across all samples to include normal controls who were by definition all non-suicide deaths) versus *2*) high (suicide-completion across major depression and bipolar samples) to assess the presence of specific gene-expression patterns associated with suicide-mortality across our total postmortem population. This analysis was performed separately across ***a***) major depressive disorder suicides vs. major depressive disorder non-suicides & controls, ***b***) bipolar disorder suicides vs. bipolar disorder non-suicides and controls, and ***c***) combined mood disorder, i.e. major depressive disorder and bipolar disorder suicides vs. major depressive disorder and bipolar disorder non-suicides alone in line with a similar approach previously reported by Pantazatos SP et al. 2017). Controls were omitted in the last comparison (i.e. comparison *c*) to identify genes specifically linked to severity of suicide in persons diagnosed with psychiatric disorders. Only genes with corrected p-value (after benjamini-hochberg multiple testing correction) ≤ 0.1 and absolute fold changes ≥1.5 are reported as significantly differentially expressed. Pathways and gene-ontology (GO) terms

enriched in these genes were identified using Enrichr (Chen et al. 2013; Kuleshov et al. 2016).

Weighted Gene Co-expression Network Analysis (WGCNA): Scale-free co-expression networks were constructed with gene-abundances using the WGCNA package in R (Langfelder & Horvath 2008). WGCNA provides a global perspective and allows identification of co-expressed gene-modules. It avoids relying on arbitrary-cutoffs involved in selecting differentially-expressed genes and instead identifies a group of genes that are changing in the same direction and magnitude, even if these changes are smaller in magnitude. WGCNA thereby identifies genes that are potentially co-regulated or belong to the same functional pathway, using a dynamic tree-cutting algorithm based on hierarchical clustering (i.e. minimum module size=30). To identify co-expressed gene modules of interest, we incorporated covariate information and selected those co-expressed gene modules correlating significantly with *diagnostic, and suicide-linked variables*. Driver genes (i.e. genes within co-expressed gene modules whose singular expression patterns are similar to the overall expression profile of the entire co-expressed modules) within these modules were used to identify pathobiological functions associated with each module.

RESULTS

Identification of a Mood Disorder Neuroanatomical Signature in Living Brains

The study 1 VBM meta-analysis (N=2387) revealed reduced GMV in the right anterior insular cortex in mood disorders ($p<0.0001$ corrected) (**Fig 1A**) consistent across both major depressive disorder and bipolar disorder, since major depressive disorder and bipolar disorder groups did not differ significantly (**Fig 1A**). The localized reduced anterior insular neuroanatomical-

signature for mood disorders was manually segmented in ITKSNAP (http://www.itksnap.org/pmwiki/pmwiki.php) (**Fig 1B**) and the segmented volume guided *postmortem* dissection of tissue used in RNA-seq characterization of gene-expression (**Fig 1C**).

Postmortem **Group Differences and Factor Analysis**

Demographic variables did not differ among groups, except for *race*: major depressive disorder and bipolar disorder groups had more Caucasian donors whereas healthy subjects had more African American donors ($p<0.0001$, $F=12$). Covarying for race in subsequent ANOVAs, *Axis-I-load* ($p<0.0001$, $F=30$) (**Fig 2A**) and *suicide-completion* ($p<0.0001$; $F=39.7$) were higher in major depressive disorder and bipolar disorder donors than controls (**Fig 2B**). Using Bonferroni correction, *post-hoc* pairwise-comparisons of the original postmortem variable yielded group-differences in *Axis-I-load* in major depressive disorder>controls ($p<0.0001$); bipolar disorder>controls ($p<0.0001$); and bipolar disorder>major depressive disorder ($p = 0.004$); while *suicide-completion* differed in major depressive disorder>controls ($p<0.0001$) and in bipolar disorder>controls ($p<0.0001$), but not between major depressive disorder and bipolar disorder. Linear regression analysis showed that *Axis-I-load* predicted suicide-completion ($B=.195$, $t=5.2$, $p<0.0001$, $d=1.408$), but not age at death.

Post-hoc multiple comparisons of the high-order factor-analytic variables yielded group-differences in *psychiatric morbidity and suicide-mortality*: using Bonferroni correction, *psychiatric morbidity and suicide-mortality* was highest in bipolar disorder>controls ($p<0.0001$, **Fig 2C**); bipolar disorder>major depressive disorder ($p<0.0001$, **Fig 2C**), and major depressive disorder>controls ($p<0.0001$, **Fig 2C)**. Linear regression revealed that *psychiatric morbidity and suicide-mortality* negatively predicted (a) RIN-scores ($B=-2.1$, $t=-3.3$, $p=0.001$) across groups;

(b) fecundity (B=-3.17, t=-2, p=0.041, *d*=1.79) across groups; and (c) age at death (B=-8.7, t=-.27, p=0.025, *d*=2.1) only across major depressive disorder and bipolar disorder. These findings prescribed our subsequent analytical focus on *psychiatric morbidity and suicide-mortality*.

Differential-Expression & WGCNA Identified Enriched *Postmortem* Anterior Insula Gene-Expression Signatures

Differential gene-expression analyses assessed transcriptomic profiles associating with variability in *psychiatric morbidity and suicide-mortality*. We binned mood disorder associated *psychiatric morbidity and suicide-mortality* scores into ≤ 0.82 for low versus ≥ 0.82 for high scores using a split-half method of dividing the maximum score across groups by 2 (i.e. 1.64/2) and found differentially-expressed immune and inflammatory-pathways, toll-like receptor-signaling, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kb-signaling), chemokine-signaling, and cytokine-cytokine receptor interactive-pathway genes (**Fig 3A-D**, and **Table SA-1A-F**).

Specifically, within major depressive disorder and controls (i.e. major depressive disorder cases scoring high on *psychiatric morbidity* and suicide-mortality versus low scores and controls), we found 9 under-expressed inflammatory cytokine and AKT-signaling (*CCL3* & *CCL4*); innate immunity/antigen recognition and elimination of bound antigens (*IGHV2-5* and *IGHV2-70*); mRNA splicing and enzyme-binding (*HSPA6*); cellular development and homeostasis (*HSPA7*, *PCSK5*, & *SERPINH1*) genes; and 1 mitochondrially encoded cytochrome-C-oxidase lncRNA-pseudogene (*MTCO1P12*); and an over-expressed lncRNA-pseudogene (*MTCO2P12*) (**Fig 3A-D, Table SA-1A**).

Similar differential gene-expression analysis in bipolar disorder individuals with higher *psychiatric morbidity and suicide-mortality* scores versus those with lower scores and controls was associated with 4 under-expressed innate immunity (*IGHV2-70*); neuroprotection, neurodevelopment and CNS-diseases including major depressive disorder (*CXCL11*, *RP11-7461.1*, & *SELE*) pathway genes (**Fig 3A-D, Table SA-1B**). Analysis of high *psychiatric morbidity and suicide-mortality* scores in combined major depressive disorder and bipolar disorder versus low scores and controls yielded 10 under-expressed inflammatory cytokine and AKT-signaling (*CCL4*); innate immunity (*IGHV2-70* & *IGKV2-28*); cell-neurodevelopment and CNS diseases (*CXCL11*, *SELE*, *PCSK5*, & *HSPA7*); and transcriptional regulatory-RNA (*MIR5190*); but also 2 over-expressed innate immunity (RP11-566K19.8) pathway genes; and a lncRNA-pseudogene (*MTCO2P12*) (**Fig 3A-D, Table SA-1C**).

We then examined gene-expression profiles related to suicide *post-hoc* by binning scores ≥1 for completed-suicides in major depressive disorder and 0 for non-suicides in major depressive disorder and controls (i.e. comparing gene-expression in major depressive disorder suicides versus major depressive disorder non-suicide and controls), and found 3 over-expressed WNT-signaling (*FZD8*); transcriptional regulation of adaptive responses to oxygen tension/hypoxia, DNA-binding transcriptional activity/co-activation (*HIF3A*); and dioxygenase activity (*PHYHD*) pathway genes (**Table SA-1D**). Binning suicide completion in bipolar disorder-suicides versus non-suicidal bipolar disorder and controls, we found 5 under-expressed innate immunity (*IGHV2-5*, *IGHV2-70*, I*GHV3-7*, *IGHV4-39*, & *IGHV3-15*); and CNS-disease (*SORD2P*) pathway genes (**Table SA-1E**).

Assessing gene-expression profiles associated with suicide-completion in the pooled major depressive disorder and bipolar disorder completed-suicides versus major depressive

disorder and bipolar disorder non-suicidal deaths yielded 21 under-expressed innate immune and inflammatory-cytokine (*CRISPLD1*, *CHI3L1*, *P2RY6*, & *SECTM1*); protein-protein interaction regulatory (*MT1A*, *HILPDA*, *HELZ2*, *FOSB*, *FAM198A*, *SOCS3*, & *TPST1*); neurodegeneration (*RP11-155G14.6*, *SLC39A14*, & *SERPINA3*); cellular-neurodevelopmental and transcriptional (*LIMK2*, *SFN*, & *EDN3*) pathway genes (**Table SA-1F**); as well as uncharacterized genes/pseudogenes (*MTND2P28*, *BAALC-AS1*, *RP11.420L9.5*, & *RP11.435J9.2*). We also found 5 over-expressed inflammatory (*RP11.1100L3.8*); intracellular protein transport (*TBC1D3E*); cell fate and apoptosis regulation (*GZMA*); and transcriptional, embryonic/forebrain cell development and defect (*CTD-2207O23.3*, & *TDGF1)* pathway genes (**Fig 3D, Table 1A-A-F**).

WGCNA characterized the potential co-regulated gene-modules involved in mood disorder *morbidity and suicide-mortality*. After correcting for covariates and filtering out low-mean genes, we found 2 dominant co-expression modules (coded as **blue** and **black Figs. 4-5; Fig SA1A-B**) strongly associating with *psychiatric morbidity* and suicide-mortality variables. Using the 30 most highly connected (i.e. hub genes) in these two modules, the blue module showed enrichment in infection, addiction and cell signaling pathways, among others. The black module is enriched in major depression, dopaminergic synapse, metabolism and addiction pathways.

DISCUSSION

Using a neuroimaging meta-analysis to refine a structurally reduced anterior insula region of interest in major depression and bipolar disorder, we identified a *postmortem* across-diagnostic mood disorder linked psychiatric morbidity and suicide-mortality associated gene-expression signature within this neuroimaging meta-analysis identified reduced anterior insular cortical gray

matter signature. Given this anterior insula sub-region's documented role in regulating affective and physical pain/distress, general bodily homeostatic and interoceptive salience, our convergent structural neurobiological and functional gene-expression findings of (a) a reduced right anterior insula cortical gray matter signature in living mood disorder patients, coupled with (b) a preponderance of under-expressed, but also albeit to a lesser extent, over-expressed gene-expression signatures within the identified anterior insula-locale in mood disorder *postmortem* brains, identified an anatomically-precise functional gene-expression basis for mood pathologies.

In light of the right anterior insula's role in sensing emotional/physical pain associated with social isolation and disconnection (Eisenberg 2015), these results provides a potential gene-regulatory windows into the neuropathological ramifications for increased mood disorder associated psychiatric morbidity (O'Connor & Nock 2014; Nock et al. 2018), which could compound suicidal outcomes (Nock et al. 2018). The right anterior insula's role in coding affective salience and psychological pain (Schneidman 1998), and the possible collective modulatory impact of these states on maladaptive impulses such as the urge to escape unbearable misery via suicide, provides a putative anatomical framework for mood disorder associated psychiatric morbidity and suicide-mortality (Schneidman 1998; Craig 2009; Slavich et al. 2010; Mee et al. 2011; Hatton et al. 2012; McGrath et al. 2013; Wager et al. 2013; Eisenberg 2015; Goodkind et al. 2015; Koechlin 2016; Wise et al. 2017; Khalsa et al. 2018). The identified association between mood and associated psychiatric morbidity and suicide-mortality scores with fecundity, and with predominant under-expressed gene-expressive functions suggests an evolutionary significance of the current results. For instance, genetic abnormalities governing aberrant anterior insula-mediated social deficits (Jabbi et al. 2012) and severe mood disorders could attenuate reproductive prowess (Mullins et al. 2017).

Within the identified reduced anterior insula signature, our differential gene-expression analyses identified predominant down-regulations in innate immune functions, inflammation pathways, and AKT-signaling related to mood-associated psychiatric morbidity and suicidal-mortality. Further differential-expressions involving cellular-homeostatic, neurodevelopmental, and transcriptional pathways in the anterior insula cortex were found to be associated with psychiatric morbidity and suicidal-mortality in less directionally-specific (i.e. up/down-regulatory) patterns. While the cellular-origins of our findings of predominantly downregulated immune-related and neurodevelopmental gene-expression changes cannot be specified with our bulk tissue RNA-seq methods, astrocyte-derived cytokine functions have been documented to induce synapse engulfment/elimination and thereby influence synaptic pruning (Vianchtien et al. 2018; Bennett & Molofsky 2019). Furthermore, immune pathway mediation of mood dysfunctions and related psychiatric diagnoses are proposed to be likely multifaceted as part of the brain's immune-related response repertoire such as toll-like receptor signaling, can be influenced by both ***a***) pathogen-associated molecular patterns (Kawai & Akira 2007) and ***b***) danger-associated molecular patterns (Klune et al. 2008; Piccinini et al. 2010). This perspective on the multifaceted nature of brain immune signaling in relation to behavioral dysfunctions like mood disorders deserves further analysis especially in light of *1*) the strong link between endogenous danger-associated immune/inflammatory cellular functions in promoting homeostasis (Klune et al. 2008) and *2*) the potential impacts of environmental stress experiences on endogenous cellular stress as well as inflammatory responses (Slavich et al. 2010).

Existing findings of both over-expressed immune-related signals (Pandey GN 2017), and our current imaging-guided anterior insula postmortem findings that clearly replicated previous results of predominantly under-expressed immune/inflammatory function (e.g. chemokine ligand

2 CCL4) and genes/pseudogenes implicated in regulatory cellular functions (e.g. a serpin peptidase inhibitor & HSPA7) in postmortem dorsolateral prefrontal cortex BA9 brains of mood disorder individuals with and without suicide completion (Pantazatos et al. 2017) needs to be better contextualized. For instance whether these differences in the directionality of regulatory patterns of gene-expression findings (i.e. over-expressed versus under-expressed immune expressive genes) in mood disorder postmortem studies is somewhat related to methodological differences in in terms of targeted micro-RNA assays versus whole transcriptome sequencing approaches, or differences in sample sizes, sample selection criteria, or qualitative postmortem material differences between studies, needs to be examined more carefully.

Together, our current findings are consistent with data on the role of immune dysfunctions in CNS diseases (Oquendo et al. 2014; Wohleb et al. 2016; Pantazatos et al. 2017; Butovsky et al. 2018), and inflammasome functional prediction of major depressive disorder treatment outcomes (Syed et al. 2018). The results further lend credence to the hypothesis that neurodevelopmental and transcription-factor genes are critical mediators of complex adaptive brain functions (Changeaux et al. 2017); especially within the context of the anterior insula's integration of affective and physiological feeling states (Craig 2009; Slavich et al. 2010; Kurth et al. 2010; Eisenberg 2015; Khalsa et al. 2018) 'including homeostatic maintenances in sickness and health' (Craig 2009; Khalsa et al. 2018), that are likely not entirely independent of both pathogen-associated molecular patterns (Kawai & Akira 2007) and danger-associated molecular patterns (Klune et al. 2008; Piccinini et al. 2010) known to induce brain immune signaling.

At the systems level, the toll-like receptor (TLR) pathway genes found to be under-expressed here are documented to recognize conserved motifs in microorganisms (Akira 2003) and stimulation of TLRs are shown to mediate acute-immune defense and cytokine

production/release (Perkins 2007). Second, our identified under-expressed NF-κB pathway genes are implicated in controlling DNA transcription, cytokine production and cell survival (Meffert et al. 2003), and are essential for cellular-immune response to infection, stress-related shocks (Van Amerongen et al. 2009), and synaptic plasticity and memory (Meffert et al. 2003; Van Amerongen et al. 2009). Third, the identified under-expressed chemokine-signaling pathways govern critical spatiotemporal cell-positioning during developmental coordination and translational guidance of cell-locomotion and migration (Turner et al. 2014). Fourth, the identified under-expressed cytokines are implicated in cell-specific innate and adaptive inflammatory host defenses, cellular-development, cell-death, angiogenesis, and maintenance of cellular homeostasis (Syed et al. 2018). Conversely, the Wnt-β-catenin signaling pathway found to be over-expressed in major depressive disorder suicides is an evolutionarily conserved inter-cellular communication system that mediates stem cell renewal, cell-proliferation and differentiation during embryogenesis and adulthood (Meffert et al. 2003). Moreover, our WGCNA results showing co-activated gene modules for *a*) lifetime mood disorder-diagnoses, *b*) lifetime Axis-I diagnoses, and *c*) suicide-completion status and the lethality of the committed suicide methods in (i) immune, (ii) major depression diagnosis, and (iii) dopaminergic-pathways, suggest that multi-genic influences may be impacting mood disorder disease burden and suicides. Taken together, our observations of convergent under-expressed TLRs, NF-κB, chemokine, and cytokine-cytokine interactive pathways transcriptomic signatures for psychiatric morbidity and suicide-mortality; and suicide-mortality-specific over-expressed Wnt signaling pathway, suggests possible dysregulatory mechanisms for aberrant cellular processes very early in development. These processes may negatively shape adaptive immune, inflammasome and chemokine-cytokine responses to adverse socio-emotional and environmental distress, with a

prolonged experience of these adverse circumstances likely leading to compromised anterior insula anatomical and physiological integrity, and associated maladaptive rupture in regulatory mood states.

Unlike cardiovascular disease and cancer research, where pathobiological measures are causally linked to disease morbidity and end-point mortality, the causal neurobiological root causes of mental illnesses are unknown, limiting measurable biological predictability of suicidal-mortality. Our findings of convergent structural neurobiologically defined functional gene-expression signatures for mood disorder associated psychiatric morbidity and suicide-mortality across major depressive disorder and bipolar disorder supports shared heritable neurogenetic pathologies underlying comorbid neuropsychiatric symptoms
(Anttila et al. 2018; Gandal et al. 2018). While the cell-type specific aberrations and their relationship with differential gene expression profiles needs to be studied to better understand the molecular mechanisms underlying abnormal neuroanatomical signatures for mood symptoms, especially in-terms of diagnostic specificity between major depressive disorder and bipolar disorder, our results represent a step towards developing brain region-specific functional gene-expression blueprints for therapeutic targeting of broad/specified molecular pathways. Furthermore, the effects of medication on gross neuroanatomical measures and gene-expression profiles also needs to be assessed in future studies. In sum, our findings bridging convergent neuroanatomical and gene-expression signatures for measures of the degree of comorbid psychiatric symptoms in mood disorders and suicides, represents a framework for discoveries of novel biomarkers for brain diseases.

TABLE

Table 1A

	26 publications with 43 experiments (major depressive disorder 'MDD' > Control whole-brain GMV changes)		
	N (% Females)	**Mean Age (years)**	**Age Range (years)**
Major Depressive Disorder	831 (56.6 %)	41 ±13.6	15 – 80
Normal Controls	783 (59.4 %)	39 ±11.9	15 – 80
	21 publications with 29 experiments (bipolar disorder > Control whole-brain GMV changes)		
	N (% Females)	**Mean Age (years)**	**Age Range (years)**
Bipolar Disorder	439 (49.7 %)	31 ±10.9	13 – 46
Normal Controls	331 (54.4 %)	32 ±9	14 – 44

Table 1B

	RNA-seq of anterior insula cortex study sample demographics and *postmortem* quality data			
	N (# of Females)	**Manner of Death (# of Females)**	**Age (in Mean, SD & Range in years)**	**Postmortem Quality Measures: PMI; Ph; RIN (in Mean & Range)**
Major Depressive Disorder	30 (11)	24 Suicides (10 Female Suicides), 6 Natural (1 Female)	47 ±16.8; 13 - 75	PMI (28.86; 15-52.5) Ph (6.47; 5.98-6.77) RIN (6.82; 6-7.9)
Bipolar Disorder	37 (12)	28 Suicides (8 Female suicides), 6 Natural (3 Female), 3 Accidental (1 Female)	43 ±14.78; 18 – 76	PMI (31.05; 15-84.5) Ph (6.37; 6-6.86) RIN (6.96; 6-8.2)
Normal Controls	33 (10)	0 Suicide, 28 Natural (9 Female), 2 Accidental, 3 Homicides (1 Female)	46 ±15; 17 – 74	PMI (30.15; 15-60.5) Ph (6.55; 6.25-6.92) RIN (7.37; 6.3-8.3)

FIGURE LEGENDS

Figure 1. Mood disorder brain structural signature derived sub-regional dissection. A) shows reduced right anterior insula gray matter volume (in living) major depressive disorder<controls, bipolar disorder<controls, and the pooled mood disorder (major depressive disorder and bipolar disorder)<controls. B) shows the anatomical space demarcation of the entire right anterior insula cortex (white region) and the reduced mood disorder signature (red region) and the estimated overlap (red overlapping white) between the reduced region and the anterior insula proper region that was targeted/dissected in the *postmortem* sample. C) *Postmortem* targeted region and the dissected portion, and dissected tissue (in labeled package).

Figure 2. Postmortem psychiatric morbidity & suicide mortality scores. A) Shows the differences in lifetime psychiatric diagnoses on Axis-I across the three groups (i.e., separately in major depressive disorder, bipolar disorder and control groups) with the bipolar disorder group having the highest psychiatric comorbid load relative to major depressive disorder and controls whereas the major depressive disorder group also scored higher than controls. B) Suicide completion shown here to be highest in the mood disorder cohort (major depressive disorder and bipolar disorder) relative to controls. C) Factor loadings reflecting the group differences in psychiatric morbidity and suicide mortality as a higher order variable. Specifically for the results shown in A-C, principal axis factoring yielded three factors together explaining 42.22% of the *postmortem* variance in clinical, biological and technical variables: 17.1% was explained by demographics and health status (i.e. communalities loading on *number of children* (.643), *marital status* (.834), *Axis-III diagnoses* (.635), and *age at death* (.584)); 16.3% was explained by psychiatric morbidity and suicide-mortality (i.e. communalities loading with *mood disorder-diagnosis* (.897), lifetime-A*xis-I-diagnostic-load* (.695), and *suicide-completion* (.670)); and 8.9% was explained by RIN-scores (i.e. communalities loading on *RIN* values (.801)). Error bars in A-D represents 95% confidence intervals.

Figure 3. Differentially-expressed genes associated with mood disorder associated psychiatric morbidity. A) shows Table containing significant differentially-expressed genes in each sample group according to analytic bins. B-D) Kyoto Encyclopedia of Genes and Genome (KEGG) pathways enriched in genes differentially-expressed between low and high suicide-mortality scores. The pathways are ranked by a combined score of p-value and rank based score. B) Bipolar and control samples only; C) major depressive disorder and control samples only; D) major depressive disorder and bipolar samples only.

Figure 4. WGCNA Identified clinical and demographically-associated gene co-expression modules. A). Heatmap showing the relation of the WGCNA identified modules with sample traits. Color scale (red-blue) represents the strength of the correlation between the module and the trait. Correlation values (R^2) followed by corresponding p-values (in parenthesis) are listed within the heatmap. Other modules shown in A have greater negative association with biological covariates (i.e. RIN, sex and race, & technical covariates such as pH). B) Hub Genes from WGCNA Blue Module: Thirty genes with the highest connectivity to other nodes within the blue module were identified as hub genes. Gene-Gene network constructed using the hub genes with the size of nodes scaled by degree and color of nodes scaled by betweenness centrality (darker colors for lower values). C) Enriched KEGG pathways for the 30 hub genes for the blue module. The pathways are ranked by a combined score of p-value and rank based score.

Figure 5. WGCNA Identified clinical and demographically-associated gene-module – Black Module. A) Gene-Gene network constructed using the hub genes with the size of nodes scaled by degree and color of nodes scaled by betweenness centrality (darker colors for lower values. B) Enriched KEGG pathways for the 30 hub genes for the black module. The pathways are ranked by a combined score of p-value and rank based score.

FIGURES

Figure 1

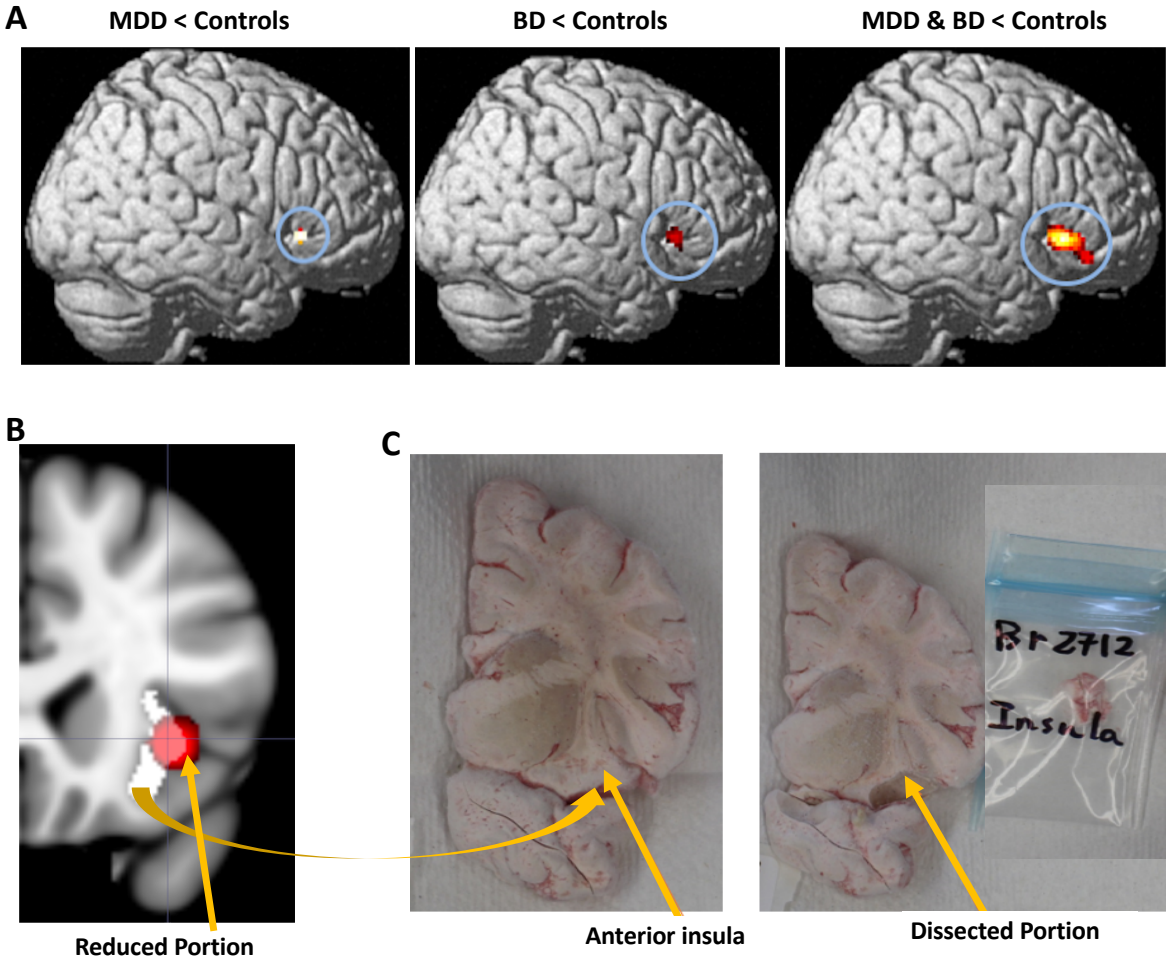


Figure 2

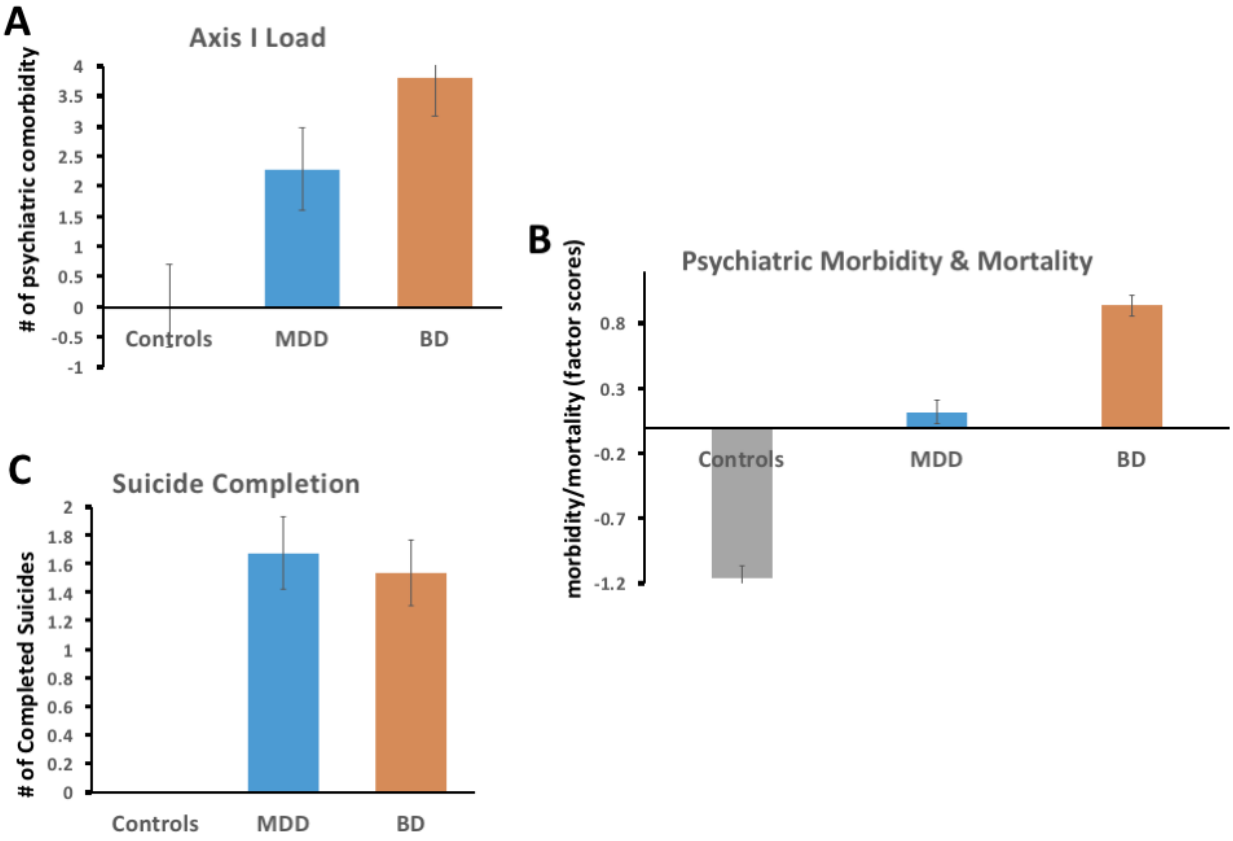

A
Axis I Load
# of psychiatric comorbidity
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
-1
Controls
MDD
BD
B
Psychiatric Morbidity & Mortality
morbidity/mortality (factor scores)
0.8
0.3
-0.2
-0.7
-1.2
Controls
MDD
BD
C
Suicide Completion
# of Completed Suicides
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Controls
MDD
BD

Figure 3

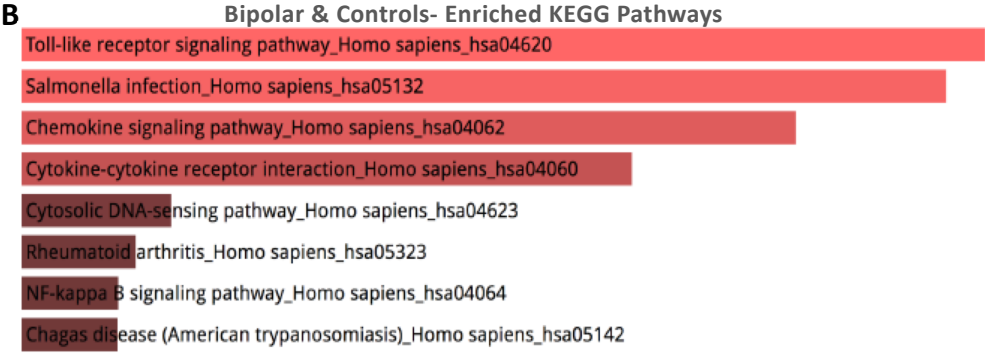
A

Differentially Expressed Genes

Bipolar & Controls	MDD & Controls	MDD & Bipolar
	CCL3	CCL3
	CCL4	CCL4
	HLA-DOB	CCL4L2
CCL4	HSPA6	CXCL11
CXCL11	HSPA7	HSPA7
IGHV2-70	IGHV2-5	IGHV2-70
MTRNR2L12	IGHV2-70	IGKV2-28
RP11-746M1.1	MTCO1P12	MIR5190
SELE	MTCO2P12	MTCO2P12
	PCSK5	PCSK5
	RGS1	RP11-566K19.8
	SERPINH1	SELE

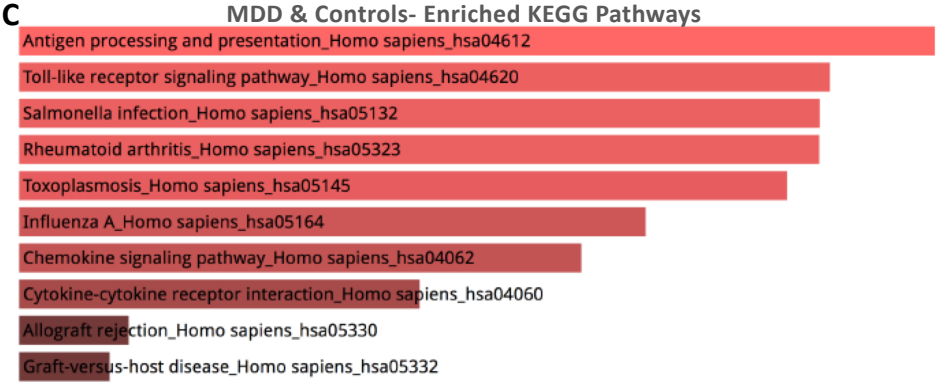
B

Bipolar & Controls- Enriched KEGG Pathways



C

MDD & Controls- Enriched KEGG Pathways



D

Bipolar & MDD- Enriched KEGG Pathways

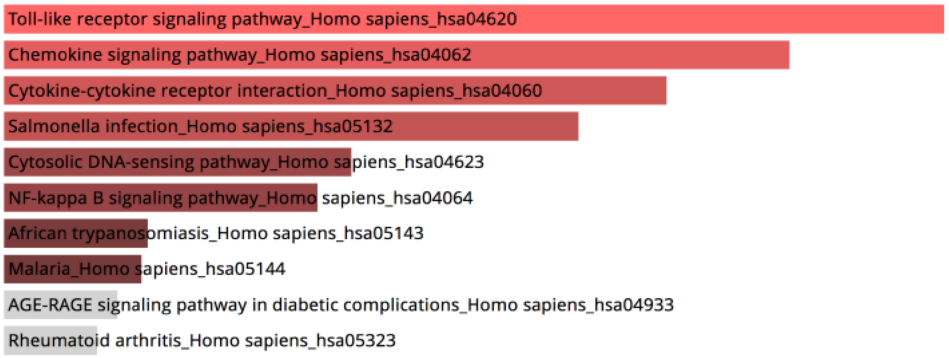
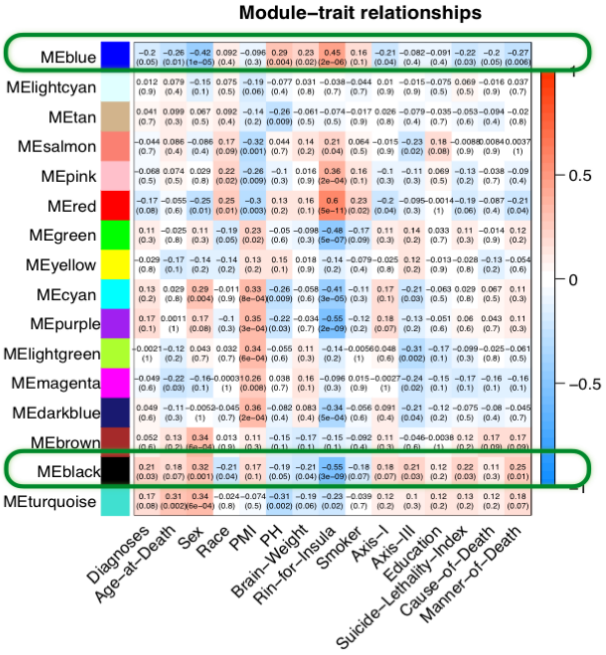
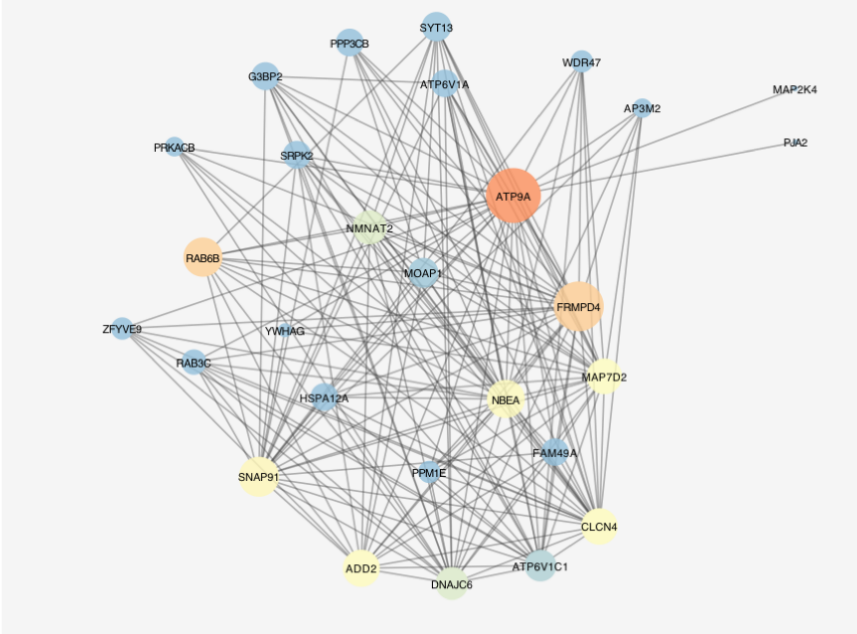


Figure 4

A


Module–trait relationships
MEblue
MElightcyan
MEtan
MEsalmon
MEpink
MEred
MEgreen
MEyellow
MEcyan
MEpurple
MElightgreen
MEmagenta
MEdarkblue
MEbrown
MEblack
MEturquoise
Diagnoses
Age–at–Death
Sex
Race
PMI
PH
Brain–Weight
Rin–for–Insula
Smoker
Axis–I
Axis–III
Education
Suicide–Lethality–Index
Cause–of–Death
Manner–of–Death
1
0.5
0
−0.5
−1

B


CytoscapeInput Edges_Blue Network of top genes
SYT13
PPP3CB
WDR47
G3BP2
ATP6V1A
MAP2K4
AP3M2
PJA2
PRKACB
SRPK2
ATP9A
NMNAT2
RAB6B
MOAP1
FRMPD4
ZFYVE9
YWHAG
RAB3C
MAP7D2
HSPA12A
NBEA
FAM49A
SNAP91
PPM1E
CLCN4
ADD2
ATP6V1C1
DNAJC6

C

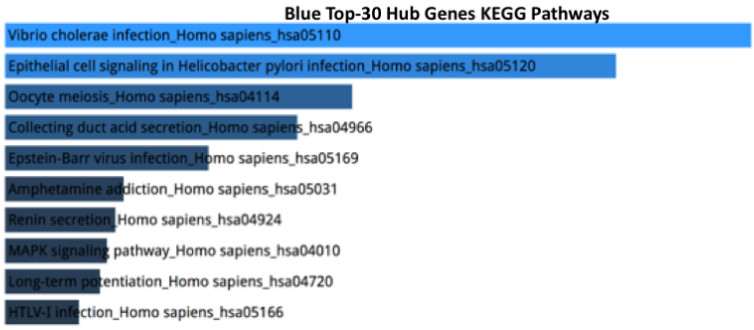
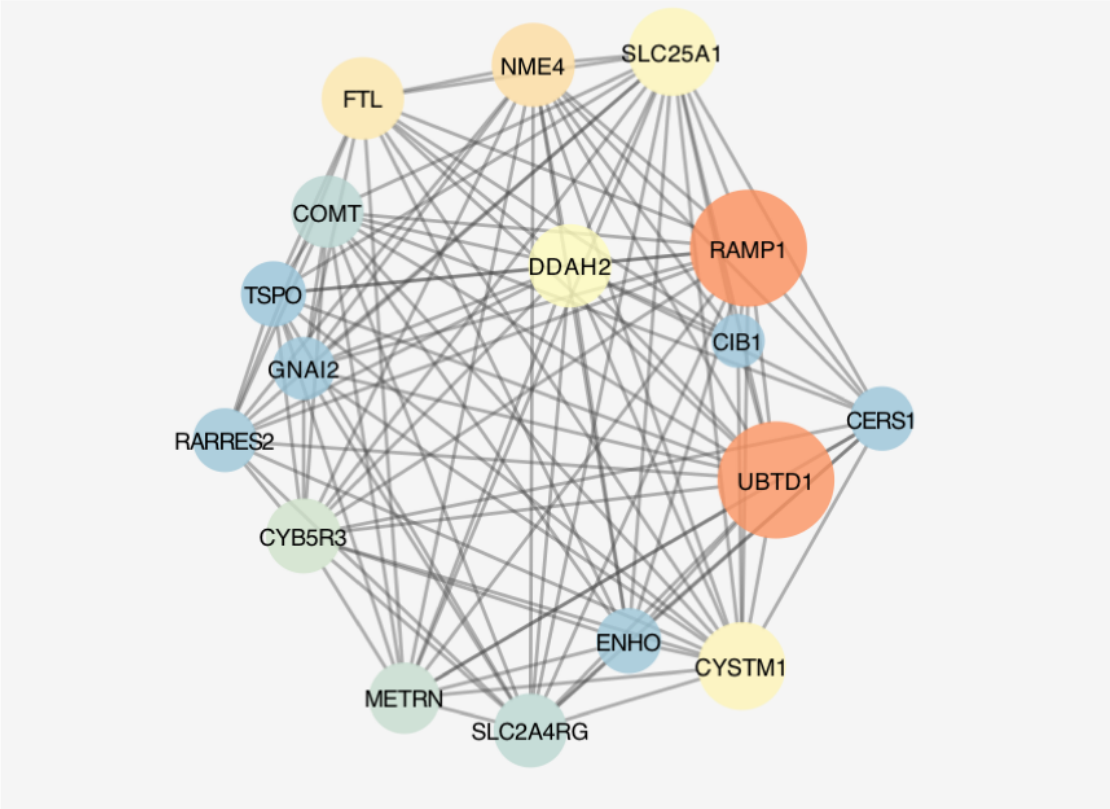

Blue Top-30 Hub Genes KEGG Pathways
Vibrio cholerae infection_Homo sapiens_hsa05110
Epithelial cell signaling in Helicobacter pylori infection_Homo sapiens_hsa05120
Oocyte meiosis_Homo sapiens_hsa04114
Collecting duct acid secretion_Homo sapiens_hsa04966
Epstein-Barr virus infection_Homo sapiens_hsa05169
Amphetamine addiction_Homo sapiens_hsa05031
Renin secretion_Homo sapiens_hsa04924
MAPK signaling pathway_Homo sapiens_hsa04010
Long-term potentiation_Homo sapiens_hsa04720
HTLV-I infection_Homo sapiens_hsa05166

Figure 5

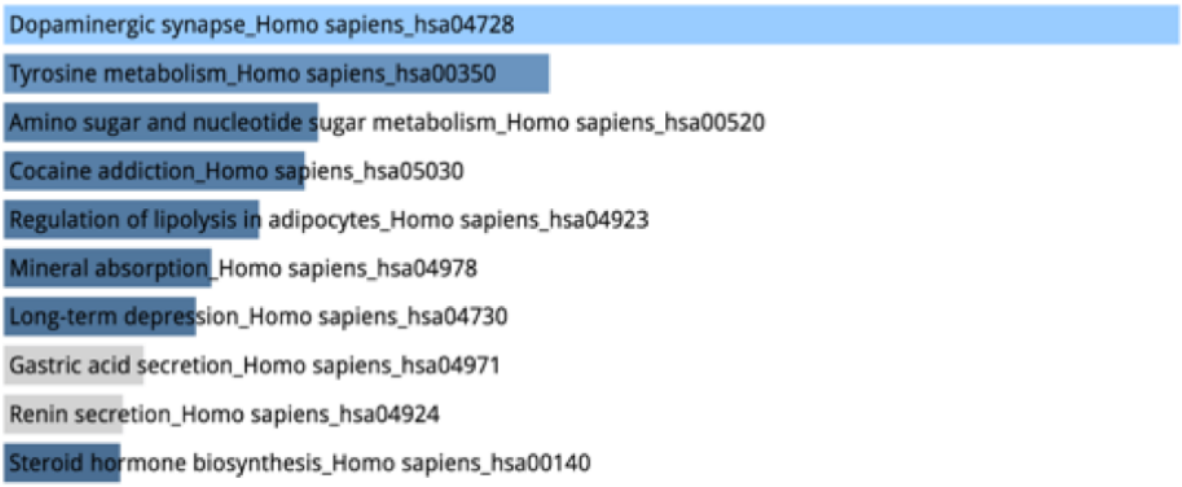
A

CytoscapeInput Edges_Black Network of top genes



B

Black Top-30 Hub Genes KEGG Pathways



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SUPPLEMENTARY APPENDIX
RESULTS

Supplementary Table S1A-F

Table S1A. Unipolar>Controls_Morbidity & Mortality

Ensemble ID	geneName	baseMean	log2FoldChange	lfcSE	stat	Pvalue	p-adj
ENSG00000211937.3	IGHV2-5	1.54151	-29.99940933	3.0220	-9.92672	3.19E-23	2.29E-19
ENSG00000211974.3	IGHV2-70D	1.95591	-29.99979864	3.0219	-9.92719	3.17E-23	2.29E-19
ENSG000001731-10.7	HSPA6	673.590	-5.241638077	0.6850	-7.65093	2.00E-14	9.58E-11
ENSG00000099139.13	PCSK5	13671.7	-4.103060421	0.6586	-6.22923	4.69E-10	1.69E-06
ENSG00000225217.1	HSPA7	97.7743	-3.3412255	0.5590	-5.97696	2.27E-09	5.70E-06
ENSG00000229344.1	MTCO2P12	17.5005	2.732522083	0.4577	5.96989	2.37E-09	5.70E-06
ENSG00000237973.1	MTCO1P12	1258.79	-2.941795623	0.4966	-5.92277	3.17E-09	6.51E-06
ENSG00000277632.1	CCL3	37.4322	-3.036666065	0.5632	-5.39127	7.00E-08	0.000123
ENSG00000275302.1	CCL4	38.2199	-2.34132348	0.4479	-5.22687	1.72E-07	0.000276
ENSG00000149257.13	SERPINH1	482.526	-2.012243118	0.4208	-4.78169	1.74E-06	0.002502

Table S1B. Bipolar>Controls_Morbidity & Mortality

Ensemble ID	geneName	baseMean	log2FoldChange	lfcSE	stat	pvalue	p-adj
ENSG00000263986.1	RP11-746M1.1	3.83145	-29.99995037	1.9423	-15.4452	8.12E-54	1.17E-49
ENSG00000211974.3	IGHV2-70D	1.72236	-29.999916	3.0324	-9.89296	4.47E-23	3.21E-19
ENSG00000007908.15	SELE	77.6309	-2.72156069	0.5046	-5.39263	6.94E-08	0.000332
ENSG00000169248.12	CXCL11	17.7305	-2.299185521	0.5108	-4.50035	6.78E-06	0.024398

Table S1C. Mood disorders_Morbidity & Mortality

Ensemble ID	geneName	baseMean	log2FoldChange	lfcSE	stat	pvalue	p-adj
ENSG00000211974.3	IGHV2-70D	1.20907	-29.9998116	3.0000	-9.99982	1.53E-23	1.10E-19
ENSG00000244116.3	IGKV2-28	1.30879	-29.99972667	2.9970	-10.0091	1.38E-23	1.10E-19
ENSG00000099139.13	PCSK5	8665.69	-3.426020438	0.5002	-6.84925	7.42E-12	3.57E-08
ENSG00000225217.1	HSPA7	74.9022	-2.694207179	0.4222	-6.38072	1.76E-10	6.35E-07
ENSG00000229344.1	MTCO2P12	12.9807	2.10792157	0.3418	6.16707	6.96E-10	2.01E-06
ENSG00000275302.1	CCL4†	32.4254	-1.832816756	0.3476	-5.27251	1.35E-07	0.000323
ENSG00000007908.15	SELE	61.9223	-1.864726877	0.4299	-4.33716	1.44E-05	0.029711
ENSG00000169248.12	CXCL11	16.7270	-1.79350166	0.4176	-4.29451	1.75E-05	0.031534
ENSG00000266146.1	MIR5190	2.23147	-1.486795439	0.3511	-4.23411	2.29E-05	0.033064

ENSG00000273679.1	RP11-566K19.8	3.17546	1.186564333	0.2787	4.25743	2.07E-05	0.033064

Table S1D. Unipolar>Controls_Suicide Completion

Ensemble ID	geneName	baseMean	log2FoldChange	lfcSE	stat	pvalue	p-adj
ENSG00000124440.15	HIF3A	606.769	0.876374135	0.2121	4.13084	3.61E-05	0.03687
ENSG00000177283.6	FZD8	300.131	0.680022637	0.1640	4.14461	3.40E-05	0.03687
ENSG00000175287.18	PHYHD1	256.209	0.74364841	0.1831	4.06058	4.89E-05	0.03995

Table S1E. Bipolar>Controls_Suicide Completion

Ensemble ID	geneName	baseMean	log2FoldChange	lfcSE	stat	pvalue	p-adj
ENSG00000211959.2	IGHV4-39	2.64081	-29.99996573	2.2395	-13.3955	6.42E-41	9.24E-37
ENSG00000211937.3	IGHV2-5	1.44996	-29.99972885	3.0567	-9.81421	9.78E-23	3.10E-19
ENSG00000211938.2	IGHV3-7	1.77501	-29.99939266	3.0593	-9.80581	1.06E-22	3.10E-19
ENSG00000211974.3	IGHV2-70D	1.72236	-29.99984674	3.0598	-9.80429	1.08E-22	3.10E-19
ENSG00000244437.1	IGKV3-15	2.23620	-29.99989291	3.0470	-9.84551	7.16E-23	3.10E-19
ENSG00000259479.6	SORD2P	39.3112	-2.083173445	0.4371	-4.76557	1.88E-06	0.004515

Table S1F. Mood disorders_Suicide Completion

Ensemble ID	geneName	baseMean	log2FoldChange	lfcSE	stat	pvalue	p-adj
ENSG00000278599.5	TBC1D3E	25.4555	23.06765702	1.9640	11.7447	7.51E-32	1.09E-27
ENSG00000247081.7	BAALC-AS1	89.4000	-1.401354659	0.2518	-5.56344	2.64E-08	0.000191
ENSG00000268861.6	CTD-2207O23.3	1.50915	19.18989613	3.5050	5.47485	4.38E-08	0.000211
ENSG00000125740.13	FOSB	549.939	-2.064541269	0.4169	-4.95137	7.37E-07	0.002132
ENSG00000133048.12	CHI3L1	673.770	-1.855486535	0.3734	-4.96791	6.77E-07	0.002132
ENSG00000240758.2	RP11-155G14.6	17.3179	-1.974256698	0.4354	-4.53435	5.78E-06	0.013932
ENSG00000196136.16	SERPINA3	185.211	-3.238714738	0.7324	-4.42186	9.79E-06	0.017695
ENSG00000104635.13	SLC39A14	706.876	-0.896615693	0.2063	-4.34546	1.39E-05	0.020762
ENSG00000175793.11	SFN	19.9333	-2.48987325	0.5739	-4.33841	1.44E-05	0.020762
ENSG00000135245.9	HILPDA	355.391	-1.717122687	0.4045	-4.24469	2.19E-05	0.024359
ENSG00000171631.14	P2RY6	45.6970	-0.836171566	0.1963	-4.25821	2.06E-05	0.024359
ENSG00000274340.1	RP11-435J9.2	8.27136	-1.290148763	0.3070	-4.20161	2.65E-05	0.027386
ENSG00000141574.7	SECTM1	24.3661	-1.631158792	0.3930	-4.1496	3.33E-05	0.028342
ENSG00000182541.17	LIMK2	562.154	-0.687634288	0.1654	-4.15663	3.23E-05	0.028342

ENSG00000259884.1	RP11-1100L3.8	30.1303	1.838831861	0.4425	4.15477	3.26E-05	0.028342
ENSG00000169902.13	TPST1	450.331	-0.587784644	0.1460	-4.02571	5.68E-05	0.041089
ENSG00000241186.8	TDGF1	25.9563	1.061656138	0.2636	4.02732	5.64E-05	0.041089
ENSG00000270504.1	RP11-420L9.5	68.8031	-0.750647171	0.1886	-3.97851	6.93E-05	0.047775
ENSG00000130589.16	HELZ2	172.965	-0.942267286	0.2381	-3.95723	7.58E-05	0.048403
ENSG00000205362.11	MT1A	35.4405	-2.16320041	0.5471	-3.95369	7.70E-05	0.048403
ENSG00000121005.8	CRISPLD1	156.538	-0.70863391	0.1816	-3.90185	9.55E-05	0.049967
ENSG00000124205.15	EDN3	123.582	0.725545274	0.1861	3.89854	9.68E-05	0.049967
ENSG00000144649.8	FAM198A	135.993	-0.742381012	0.1908	-3.89019	0.000101	0.049967
ENSG00000145649.7	GZMA	2.36493	2.726390979	0.6977	3.90723	9.34E-05	0.049967
ENSG00000184557.4	SOCS3	279.865	-2.207043294	0.5651	-3.90489	9.43E-05	0.049967
ENSG00000225630.1	MTND2P28	2528.61	-2.346222019	0.5989	-3.91696	8.97E-05	0.049967

Supplementary Figure 1

WGCNA

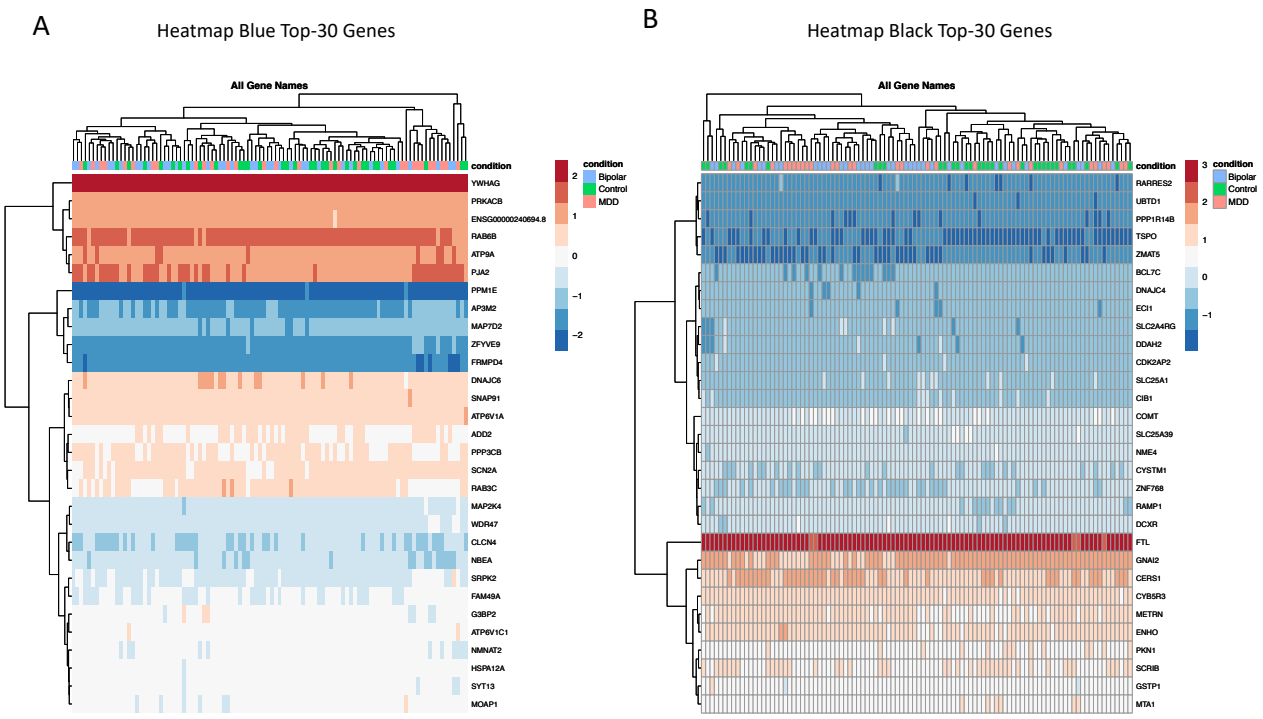

Figure SA1. **WGCNA Identified clinical and demographically-associated gene co-expression modules.** A). Heatmap showing the gene-expression of the 30 hub genes in the Blue module. Dendrograms represent sample and gene clustering by expression. B) Heatmap showing the gene-expression of the 30 hub genes in the Black module.

Supplementary Table S2 (Included publications and Studies/Gray Matter Analysis Contrasts in the Imaging Meta-analysis).

Included	Year	1st Author	Journal	Gray Matter Contrast Analyzed
False	2005	Adler C M	Biol Psychiatry	Bipolar > Healthy Controls
False	2005	Adler C M	Biol Psychiatry	Healthy Controls < Bipolar
False	2005	Adler C M	Biol Psychiatry	First Episode Bipolar < Multi-Episode Bipolar
True	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar & Family History < Healthy Controls
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar with Family History > Healthy Controls
True	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar No Family History < Healthy Controls
True	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar No Family History < Healthy Controls
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar & Psychosis > Healthy Controls
True	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar & Psychosis < Healthy Controls
True	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar without Psychosis < Healthy Controls
True	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar On Lithium < Healthy Controls
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar Not On Lithium > Healthy Controls
True	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar Not On Lithium < Healthy Controls
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar & Family History > Bipolar No FH
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar & Psychosis > Bipolar No Psychosis
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Bipolar On Lithium > Bipolar Not On Lithium
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Gray Matter-Duration of Bipolar Correlation
False	2007	Chen X	The Aust. & New Zealand J. of Psych	Gray Matter-Number of Episodes Correlation
True	2004	Lyoo I K	Biological Psychiatry	Healthy Controls > Bipolar Gray Matter Density

True	2009	Almeida J R	Psychiatry Research NeuroImaging	Bipolar Disorder < Healthy Control
False	2009	Almeida J R	Psychiatry Research NeuroImaging	Male > Female Bipolar
True	2009	Almeida J R	Psychiatry Research NeuroImaging	Healthy Controls > Bipolar
False	2009	Almeida J R	Psychiatry Research NeuroImaging	All Males > Females
False	2009	Almeida J R	Psychiatry Research NeuroImaging	All Females > Males
True	2009	Bergouignan	NeuroImage	Unipolar Depressed < Healthy Controls
True	2010	Peng J	European Journal of Radiology	Unipolar Depressed < Healthy Controls
True	2010	Ha T H	Neuroscience Letters	Bipolar Disorder II < Healthy Controls
True	2010	Ha T H	Neuroscience Letters	Bipolar Disorder I < Healthy Controls
False	2010	Ha T H	Neuroscience Letters	Bipolar Disorder I < Bipolar Disorder II
False	2010	Ha T H	Neuroscience Letters	Onset Age-Gray Matter correlation in Bipolar II
True	2010	Abe O	Psychiatry Research	Unipolar Depressed < Healthy Controls
True	2009	Stanfield A	Bipolar Disorders	Bipolar < Healthy Controls
False	2009	Stanfield A	Bipolar Disorders	Bipolar < Healthy Controls
False	2009	Stanfield A	Bipolar Disorders	Age-GM Density correlation in Healthy Controls and Bipolar Disorder
True	2008	Kim M J	Psychiatry Research	Healthy Controls > Unipolar Depressed
True	2011	Wagner G	NeuroImage	Unipolar Depressed < Healthy Controls
False	2011	Wagner G	NeuroImage	Depressed High Risk Suicide < Healthy Controls
False	2011	Wagner G	NeuroImage	Unipolar Depressed High Risk Suicide < Unipolar Depressed Non-High Risk Suicide
False	2011	Wagner G	NeuroImage	Unipolar Depressed with Suicidal Behavior < Unipolar

				Depressed Non-High Risk Suicide
False	2011	Cui L	Neuroscience Letters	Paranoid-type Schizophrenia < Healthy Controls
False	2011	Cui L	Neuroscience Letters	Paranoid-type Schizophrenia > Healthy Controls
True	2011	Cui L	Neuroscience Letters	Bipolar Mania < Healthy Controls
False	2011	Cui L	Neuroscience Letters	Bipolar Mania > Healthy Controls
True	2009	Arnone D	European Neuropsychopharmacology	Unipolar Depression < Healthy Controls
True	2010	Cheng Y	Neuroscience Letters	Unipolar Depressed < Healthy Controls
True	2010	Cheng Y	Neuroscience Letters	Depression Score-Gray Matter Correlation
True	2008	Frodl T	Archives of General Psychiatry	Unipolar Depressed < Healthy Controls
True	2010	Hwang J	Journal of Ger. Psych and Neurology	Unipolar Depressed < Healthy Controls
False	2010	Hwang J	Journal of Ger. Psych and Neurology	Healthy Controls < Unipolar Depressed
False	2010	Hwang J	Journal of Ger. Psych and Neurology	Unipolar Depressed > Healthy Controls
False	2010	Hwang J	Journal of Ger. Psych and Neurology	Late-Onset Suicidal Depressives < Late-Onset Non-suicidal Depressives
False	2010	Hwang J	Journal of Ger. Psych and Neurology	Suicidal > Non Suicidal
True	2010	Li C T	NeuroImage	Non-Remitting Unipolar Depressed < Remitting Unipolar Depressives
False	2010	Li C T	NeuroImage	Remitting Unipolar Depressed > Non-remitting Unipolar Depressed
False	2010	Li C T	NeuroImage	Non-remitting Unipolar Depressed < Remitting Unipolar Depressed
True	2011	Salvadore G	NeuroImage	Chronic Unipolar Depressed
True	2011	Salvadore G	NeuroImage	Chronic Unipolar Depressed
True	2011	Salvadore G	NeuroImage	Remission Unipolar Depressed

True	2011	Salvadore G	NeuroImage	Chronic Unipolar Depressed
True	2011	Salvadore G	NeuroImage	Chronic Unipolar Depressed
True	2011	Salvadore G	NeuroImage	Remission Unipolar Depressed
True	2011	Soriano-Mas	Biol Psychiatry	Unipolar Depressed
False	2011	Soriano-Mas	Biol Psychiatry	Healthy Controls
False	2011	Soriano-Mas	Biol Psychiatry	Unipolar Depressed-HAM-D Correlation
False	2011	Soriano-Mas	Biol Psychiatry	Unipolar Depressed-Gray Matter Correlation with Days to Remission After Treatment
False	2011	Soriano-Mas	Biol Psychiatry	Old vs. Follow-Up, Gray Matter Volume
False	2011	Soriano-Mas	Biol Psychiatry	Correlation Gray Matter Volume vs. # of Depression Episodes Between Both Scan Points
False	2011	Soriano-Mas	Biol Psychiatry	Correlation White Matter Volume vs. # of Depression Episodes Between Both Scan Points
False	2011	Soriano-Mas	Biol Psychiatry	Gray Matter Volume Decreases, Male Unipolar Depressed
False	2011	Soriano-Mas	Biol Psychiatry	White Matter Volume Decreases, Old Patients
False	2010	van Tol M J	Archives of General Psychiatry	Unipolar Depressed/CDA/ANX
True	2010	van Tol M J	Archives of General Psychiatry	Unipolar Depressed
True	2010	van Tol M J	Archives of General Psychiatry	CDA
False	2010	van Tol M J	Archives of General Psychiatry	ANX
False	2010	van Tol M J	Archives of General Psychiatry	UNIPOLAR DEPRESSED/CDA/ANX
True	2010	van Tol M J	Archives of General Psychiatry	Early vs. Late Onset Unipolar Depressed
False	2010	van Tol M J	Archives of General Psychiatry	ACC Reduction, Unipolar Depressed
False	2010	van Tol M J	Archives of General Psychiatry	ACC Reduction, ANX Group

True	2010	Zou K	Biol Psychiatry	Depression
True	2008	Haldane M	Journal of Psychopharmacology	Bipolar
False	2008	Haldane M	Journal of Psychopharmacology	Bipolar > CS
False	2008	Haldane M	Journal of Psychopharmacology	Negative SCWT Score-Gray Matter Correlation
False	2008	Haldane M	Journal of Psychopharmacology	Negative SCWT Score-Gray Matter Correlation
False	2008	Haldane M	Journal of Psychopharmacology	Negative HSCT Score-Gray Matter Correlation
False	2008	Haldane M	Journal of Psychopharmacology	Negative HSCT Score-Gray Matter Correlation
True	2011	Lee H Y	Journal of Affective Disorders	Healthy Controls > Unipolar Depressed
False	2011	Lee H Y	Journal of Affective Disorders	Depression duration-Gray Matter Correlation
True	2011	Li M	Psychiatry Research Neuro-Imaging	Bipolar Disorder
True	2011	Wang F	Brain	Bipolar Disorder
False	2012	Watson D R	Behavioural Brain Research	Schizophrenia
False	2012	Watson D R	Behavioural Brain Research	Schizophrenia > sCS
False	2012	Watson D R	Behavioural Brain Research	Schizophrenia
False	2012	Watson D R	Behavioural Brain Research	Schizophrenia > sCS
True	2012	Watson D R	Behavioural Brain Research	Bipolar
False	2012	Watson D R	Behavioural Brain Research	Bipolar > bCS
False	2012	Watson D R	Behavioural Brain Research	Bipolar
True	2013	Serra-Blasco	British Journal of Psychiatry	Healthy Controls > Unipolar Depressed
True	2013	Serra-Blasco	British Journal of Psychiatry	Healthy Controls > Unipolar Depressed
True	2013	Serra-Blasco	British Journal of Psychiatry	fUnipolar Depressed > tUnipolar Depressed
True	2012	Shad M U	J. of Child & Adol. Psychopharm.	Healthy Controls > Unipolar Depressed
True	2012	Zhang X	Journal of Affective Disorders	Healthy Controls > CVD
True	2012	Zhang X	Journal of Affective Disorders	Healthy Controls > Unipolar Depressed

False	2012	Zhang X	Journal of Affective Disorders	Unipolar Depressed > CVD
True	2012	Zhang X	Journal of Affective Disorders	Unipolar Depressed > Healthy Controls
False	2012	Zhang X	Journal of Affective Disorders	CES-D(Depr Scale)Score- Gray Matter Correlation
False	2012	Zhang X	Journal of Affective Disorders	Weakest Link CSQ score-Gray Matter Correlation
False	2012	Zhang X	Journal of Affective Disorders	Consequences CSQ score-Gray Matter Correlation
False	2012	Zhang X	Journal of Affective Disorders	Causal Attributions CSQ-Gray Matter Correlation
False	2012	Zhang X	Journal of Affective Disorders	Gray Matter Volume, Main Effect of Group
True	2013	Arnone D	Molecular Psychiatry	Unipolar Depressed < Healthy controls
False	2013	Arnone D	Molecular Psychiatry	Unipolar Depressed < Remitted Unipolar Depressed
False	2013	Arnone D	Molecular Psychiatry	Currently Unipolar Depressed > Healthy controls
False	2013	Arnone D	Molecular Psychiatry	Remitted Unipolar Depressed > Healthy Controls
False	2013	Arnone D	Molecular Psychiatry	Effect of medication in remitted patients
False	2013	Arnone D	Molecular Psychiatry	cUinpolar symptoms-Grey matter Correlation
False	2013	Grieve S M	NeuroImage	Unipolar Depressed > Controls, Cortical thickness
True	2013	Grieve S M	NeuroImage	Healthy Controls > Unipolar Depressed
True	2013	Grieve S M	NeuroImage	Healthy Controls > Unipolar Depressed
True	2014	Stratmann	PLoS One	Healthy Controls > Unipolar Depressed
True	2014	Stratmann	PLoS One	Healthy Controls > Current Unipolar Depressed
False	2014	Stratmann M	PLoS One	Depressed Episodes-Grey Matter Correlation
True	2014	Guo W	Prog. In Neuro-Psychopharm. & Biological Psychiatry	Unipolar Depressed < Healthy Controls

True	2014	Guo W	Prog. In Neuro-Psychopharm. & Biological Psychiatry	1st episode Unipolar Depressed < Healthy Controls
True	2014	Guo W	Prog. In Neuro-Psychopharm. & Biological Psychiatry	Recurrent Unipolar Depressed < Healthy Controls
True	2014	Tang L R	Psychiatry Research NeuroImaging	Healthy Controls > Bipolar I
False	2014	Tang L R	Psychiatry Research NeuroImaging	Healthy Controls < Bipolar I
False	2014	Tang L R	Psychiatry Research NeuroImaging	Brain regions with statistically significant volume differences, both groups
True	2010	Tost H	Journal of Affective Disorders	Healthy Controls > Bipolar
True	2010	Tost H	Journal of Affective Disorders	Healthy Controls > Bipolar
False	2010	Tost H	Journal of Affective Disorders	Healthy Controls > Bipolar
False	2010	Tost H	Journal of Affective Disorders	Bipolar > Healthy Controls
False	2010	Tost H	Journal of Affective Disorders	Bipolar > Healthy Controls
True	2011	Gong Q	NeuroImage	Healthy Controls > Refractory Depression
False	2011	Gong Q	NeuroImage	Refractory Depression > Healthy Controls
True	2011	Gong Q	NeuroImage	Healthy Controls > Non-Refractory Depression
False	2011	Gong Q	NeuroImage	NDD > Healthy Controls
False	2011	Gong Q	NeuroImage	Healthy Controls > RDD
False	2011	Gong Q	NeuroImage	RDD > Healthy Controls
False	2011	Gong Q	NeuroImage	Healthy Controls > NDD
False	2011	Gong Q	NeuroImage	NDD > Healthy Controls
False	2015	Cai Y	Neuroscience Bulletin	Main effect of group, gray matter
True	2015	Cai Y	Neuroscience Bulletin	Bipolar I < Healthy Controls
True	2015	Cai Y	Neuroscience Bulletin	Unipolar Depressed < Healthy Controls
False	2015	Cai Y	Neuroscience Bulletin	Bipolar I < Unipolar Depressed
True	2013	Kim D	Journal of Affective Disorders	Bipolar < Healthy Controls

False	2015	Saricicek A	Journal of Affective Disorders	Group Gray matter differences
False	2015	Saricicek A	Journal of Affective Disorders	Bipolar I > Healthy Controls
True	2015	Saricicek A	Journal of Affective Disorders	Bipolar I < Healthy Controls
False	2015	Saricicek A	Journal of Affective Disorders	Healthy first-degree relatives > Healthy Controls
False	2015	Saricicek A	Journal of Affective Disorders	Healthy first-degree relatives < Healthy Controls
False	2014	Redlich R	Archives of General Psychiatry	Munster Sample
False	2014	Redlich R	Archives of General Psychiatry	Pittsburgh Sample
False	2014	Redlich R	Archives of General Psychiatry	Combined Sample Pittsburgh & Munster Samples
True	2014	Redlich R	Archives of General Psychiatry	Unipolar Depressed < Healthy Controls
True	2014	Redlich R	Archives of General Psychiatry	Bipolar < Healthy Controls
False	2014	Redlich R	Archives of General Psychiatry	Bipolar < Unipolar Depressed Munster Sample
False	2014	Redlich R	Archives of General Psychiatry	Unipolar Depressed < Bipolar Munster Sample
False	2014	Redlich R	Archives of General Psychiatry	Bipolar < Unipolar Depressed Pittsburgh Sample
False	2014	Redlich R	Archives of General Psychiatry	Unipolar Depressed < Bipolar Pittsburgh Sample
False	2014	Redlich R	Archives of General Psychiatry	Bipolar < Unipolar Depressed Combined Sample
False	2014	Redlich R	Archives of General Psychiatry	Unipolar Depressed < Bipolar Combined Sample
False	2014	Redlich R	Archives of General Psychiatry	Effect of medication load + clinical course of illness on gray matter, MD patients vs Bipolar
False	2014	Redlich R	Archives of General Psychiatry	Gray matter volume-Unipolar Depressed illness duration Correlation

False	2014	Redlich R	Archives of General Psychiatry	Gray matter volume-Unipolar Depressed illness duration, Munster sample
False	2014	Redlich R	Archives of General Psychiatry	Gray matter volume-Unipolar Depressed illness duration, Pittsburgh sample
False	2012	Adleman N	Journal of Child Psychology and Psychiatry	Bipolar > Healthy Controls and SMD
False	2012	Adleman N	Journal of Child Psychology and Psychiatry	Bipolar Disorder > SMD
True	2012	Adleman N	Journal of Child Psychology and Psychiatry	Healthy Controls > Bipolar Disorder
False	2012	Adleman N	Journal of Child Psychology and Psychiatry	2 year scan > Initial scan; Bipolar group
True	2016	Alonso-Lana	PLoS ONE	Cognitively preserved patients < Healthy Controls
False	2016	Alonso-Lana	PLoS ONE	Cognitively preserved patients < Healthy Controls
False	2015	Lai C H	Journal of Affective Disorders	Healthy Controls > Panic Disorder
True	2015	Lai C H	Journal of Affective Disorders	Healthy Controls > Unipolar Depressed
False	2015	Lai C H	Journal of Affective Disorders	Panic Disorder > Unipolar Depressed
True	2012	Singh M K	Bipolar Disorders	Bipolar I < Healthy Controls
True	2012	Singh M K	Bipolar Disorders	Bipolar < Healthy Controls