Supplemental Information
Bekhbat et al., PSYCHOMOTOR SLOWING IN DEPRESSION: GENE PATHWAYS

Supplemental Methods

Major depression (MD) cohort: Participant exclusion/inclusion criteria

Eighty-eight participants (age 21-65) with a primary diagnosis of major depressive disorder (MDD), or bipolar disorder-current episode depressed (n=5), as determined by Structured Clinical Interview for Diagnostic and Statistical Manual-IV-TR (SCID-IV) were enrolled from 2011 to 2014. Subjects were excluded for a number of medical conditions that might confound study interpretation as confirmed by medical history, laboratory testing, electrocardiogram and physical exam. Patients were excluded for uncontrolled cardiovascular, endocrinologic, hematologic, hepatic, renal, or neurologic disease, autoimmune conditions (i.e. rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, lupus), chronic infection (i.e. HIV, hepatitis B or C), history of liver abnormalities, or evidence of infection within one month of screening that required antibiotic or antiviral therapy. Participants were also excluded for a history of cancer, pregnancy or lactation; a history of schizophrenia (determined by SCID-IV); active psychotic symptoms of any type; substance abuse and/or dependence within the past six months (determined by SCID-IV); an active eating disorder; obsessive compulsive disorder; active suicidal ideation determined by a score of 3 or higher on item #3 of the 17-item HAM-D; and/or a score of less than 28 on the Mini-Mental State Examination. Patients with anxiety disorders were not excluded as long as MD was the primary diagnosis. Subjects were free of all psychotropic medications (e.g. antidepressants, mood stabilizers, antipsychotics, stimulants, sedative hypnotics and benzodiazepines) for at least 4 weeks (8 weeks for fluoxetine) prior to study participation. Patients were also free of medications known to affect the immune system including nonsteroidal or steroidal anti-inflammatory medications, statins or angiotensin 2 receptor inhibitors, and were tested for drugs of abuse at screening and on the day of neurocognitive testing and blood sampling. Medications for other medical conditions were allowed as dictated by the patients’ treating physicians. Participants with evidence of active infections were excluded until medically stable. No subjects were removed from their psychotropic medications for the purposes of this study. Subjects were recruited from a parent study on phenotyping depressed patients with increased inflammation (ClinicalTrials.gov NCT01426997), and psychomotor speed and protein inflammatory markers in these patients have been described previously. All procedures were approved a priori by the Institutional Review Board of Emory University. All participants provided written informed consent.

TRD cohort: Participant exclusion/inclusion criteria

Peripheral blood plasma and RNA samples were collected during a randomized, double-blind trial of infliximab versus placebo in treatment resistant MDD (TRD) patients, defined as patients with MD or bipolar disorder who were depressed and non-responsive to antidepressant treatment as determined by a score ≥2 on the Massachusetts General Hospital Staging (MGH-S) method in the current episode. Fifty-seven participants (age 25-60) with a primary diagnosis of MD, or bipolar disorder-current episode depressed (n=6), as determined by Structured Clinical Interview for Diagnostic and Statistical Manual-IV-TR (SCID-IV) were enrolled. Participants were recruited via local television, radio, and newspaper advertisements and included males and females aged 25-60 years who were on a consistent antidepressant regimen or off antidepressant therapy for at least 4 weeks prior to baseline. To balance the number of male and female participants and to equalize levels of inflammation across groups, treatment assignment was stratified by sex and CRP (≥2mg/L versus <2mg/L). To be enrolled, subjects had to exhibit moderate severity of depression as determined at screening by a score ≥14 on the 16 item Quick Inventory of Depressive Symptomatology Self Report. Antidepressant
regimens were required to remain stable throughout the study and could include conventional antidepressant medications, mood stabilizers, antipsychotic medication, stimulants, and benzodiazepines. Exclusion criteria included any autoimmune disorder (confirmed by laboratory testing); history of tuberculosis (confirmed by chest X-ray, skin, and/or blood testing) or high risk of tuberculosis exposure; hepatitis B or C or human immunodeficiency virus infection (confirmed by laboratory testing); evidence of active fungal infection; history of recurrent viral or bacterial infections; history of cancer excluding basal cell or squamous cell carcinoma of the skin (fully excised with no recurrence); unstable cardiovascular, endocrinologic, hematologic, hepatic, renal, or neurologic disease (determined by medical history, physical examination and laboratory testing); history of schizophrenia (determined by Structured Clinical Interview [SCID] for DSM-IV); active psychotic symptoms of any type; substance abuse/dependence within the past 6 months (determined by SCID); active suicidal ideation determined by a score ≥3 on item #3 on the 17-item Hamilton Depression Rating Scale (HAM-D-17) and/or a score <28 on the Mini-Mental State Exam. All subjects provided written informed consent to the study, and all study procedures were approved by the Emory University Institutional Review Board. The study is registered in ClinicalTrials.gov, Identifier: NCT00463580. Demographic and clinical variables between the infliximab and placebo groups were well-matched with no significant differences.

**Behavioral Assessments and Psychomotor Composite Factor**

To limit variability in sleep-wake patterns, subjects were admitted to the hospital the day prior to blood sampling and neurocognitive assessments. All subjects slept in a single-room with lights out at 11:00 pm and a wake-up time of 7:30 am. Psychomotor slowing was assessed in the afternoon of the same day of blood sampling between 3:00 pm and 6:00 pm using objective measures of psychomotor speed on standardized neurocognitive tasks that have been well-established by the work of our group and others. A single composite factor reflecting psychomotor performance was derived by principal component analysis of measurements of pure motor and psychomotor processing speed, as described previously and below. Tasks included 1) the Reaction Time Task of the Cambridge Neuropsychological Test Automated Battery (CANTAB), involving simple and five-choice reaction time segments and providing distinctions between movement latencies and reaction time measured in milliseconds; 2) the Finger Tapping Test (FTT), a task of pure motor function that requires patients to tap with the index finger of the dominant hand as fast as possible for 10 second intervals resulting in a mean number of taps per 10 seconds; 3) the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale that measures psychomotor processing speed in which patients are presented with numbers and a corresponding blank box and are instructed to fill in as many boxes in 90 seconds with a matching symbol (available in a legend) yielding a measure of the numbers of boxes successfully completed within 90 seconds; and 4) Trail Making Test Part A (Trails A), a task where subjects are instructed to draw a line between non-adjacent numbers in consecutive order yielding the mean number of seconds required to complete the task.

To create a single-factor, composite score of psychomotor performance, natural log-transformed scores on all tasks of psychomotor speed were entered into a principal component analysis (PCA) with no rotation. Factors were determined by Eigen values >1, and only individual variable contributions of >0.3 qualified for loading a component. Individual loadings were examined to ensure that psychomotor variables contributed to the composite factor in a consistent direction. The resulting Bartlett factor scores were subsequently used to test for associations with gene expression in linear models including clinical covariates as described below.

**Measurement of CRP and IL-6**
To control for circadian variations in immune biomarkers, blood was drawn between 8 and 10am the morning of neurocognitive testing through an indwelling catheter after participants had at least 30 minutes of rest. Samples were obtained in chilled EDTA-coated tubes and immediately spun at 1000g for 15 minutes at 4°C. Plasma was collected and stored at -80°C for later batched analysis of the inflammatory cytokine interleukin (IL)-6 and high-sensitivity (hs-)CRP which have been found to associate with composite psychomotor scores and moderate antidepressant response to infliximab, in MD and TRD respectively\(^1,2\), and both of which have been shown to be elevated in patients with depression\(^12,13\).

The immunoturbidimetric method was used to measure hs-CRP concentrations with a Beckman AU480 chemistry analyzer and Ultra WR CRP kit (Sekisui Diagnostics). Concentrations of IL-6 were assessed in duplicate using either high-sensitivity multiplex bead-based assays (R&D Systems; primary MD cohort) or high-sensitivity Quantikine ELISA (R&D systems; secondary TRD cohort) and analyzed on a MAGPIX CCD imager (Luminex) as previously described\(^1,14,15\). The high-sensitivity IL-6 assays on the multiplex and Quantikine ELISA platform from R&D are highly correlated (r=0.99) across a wide range of IL-6 concentrations\(^14,16\). Both had mean intra- and inter-assay coefficients of variation (CV) reliably <10\%,\(^1,4,14,15,17\), and assay detection limits for IL-6 were 0.2 pg/ml and 0.04 pg/ml for the multiplex and Quantikine assays, respectively. Consistent with previous analyses, IL-6 values were natural log transformed to achieve normality for use in correlation analysis with MD co-expression modules (see WGCNA methods below).

**Transcript Origin Analysis (TOA)**

A log transformed cell-type diagnosticity score was derived to quantify the extent of which each gene transcript was predominately expressed by the major leukocyte subtypes (monocyte, plasmacytoid dendritic cell, CD4+ T cell, CD8+ T cell, B cell, NK cell). Reference data on basal expression of all named human genes in distinct leukocyte subsets come from the publicly available Human Gene Atlas (Gene Expression Omnibus [GEO] series GSE1133; http://www.ncbi.nlm.nih.gov/projects/geo/query/acc.cgi?acc=GSE1133). Transcripts found to be associated with psychomotor slowing were tested for enrichment relative to the null hypothesis (genome-wide) average scores using one sample z-tests\(^18\).

**Weighted Gene Co-Expression Network Analysis (WGCNA)**

Weighted Gene Correlated Network Analysis (WGCNA)\(^19,20\) was used to identify co-expressed gene clusters associated with psychomotor slowing in patients with depression. WGCNA is an unsupervised hierarchical clustering method to construct a gene co-expression network and identify clusters (i.e. “modules”) of highly correlated genes. First, a co-expression network is constructed by calculating an adjacency matrix where each element reflects the strength of gene-gene pairwise correlations. A key feature of WGCNA is that, by raising pairwise correlation coefficients to a power (\(\beta\), “soft-thresholding power”), it emphasizes strong correlations while down-weighing weaker ones, thus leading to more cohesive co-expression patterns. The \(\beta\) power is selected while taking into account the sample size to empirically achieve “scale-free network topology”, a core feature of true biological networks. Secondly, following network construction, genes are clustered into modules using average linkage hierarchical clustering, and modules of genes that share similar expression and patterns of connectivity are detected using a dynamic tree-cutting algorithm. The gene expression profile within each module is then summarized by its first principal component (referred to as module eigengene [ME]), which can be subsequently tested for association with biological or clinical traits such as psychomotor variables or plasma inflammatory markers. Functional characterization of genes comprising modules of interest can be made via pathway enrichment analyses. Furthermore, the degree of connectivity between genes within a module can be measured via an intramodular connectivity...
analysis (function “intramodularConnectivity”), and the most highly-connected “hub” genes can be identified. Details of WGCNA are provided below for each patient cohort:

Primary MD cohort: To control for the potential confounding effects of clinical covariates on gene expression outside of their influence on inflammation, co-expression networks were created based on covariate-adjusted gene expression data. Gene expression data were adjusted for age, sex, race, BMI, and education using the “empBayes” function in WGCNA, while retaining the influence of baseline CRP. Of note, sensitivity analyses using unadjusted gene expression data for network construction yielded highly similar co-expression modules (see Module Preservation Analysis below), and these modules in the primary MD cohort similarly correlated with psychomotor slowing (see below). A soft-thresholding power of 6 was selected to achieve approximately scale-free network topology. For network construction, we employed bi-weight mid-correlation using the signed hybrid method, in which only positive correlation coefficients are considered, thus yielding more interpretable co-expression relationships. Modules of co-expressed genes were detected by hierarchical clustering based on a minimum module size of 30 genes, and a dissimilarity threshold for merging modules (mergeCutHeight) of 0.25. Modules associated with the composite motor factor (p<0.05) were assessed for functional enrichment of biological pathways using clusterProfiler as described in the manuscript.

Module preservation analysis: To assess whether modules generated from the primary MD network of covariate-adjusted gene data (“reference set”) were preserved in modules identified from unadjusted data (“test set”), we used the “modulePreservation” function in WGCNA to calculate a permutation-based preservation statistics (Zsummary values) with n=200 permutations of the data. As Zsummary scores reflect whether the connectivity pattern of genes is similar between the reference and test sets, Zsummary values below 2 indicate no evidence of preservation, 2-10 suggest weak preservation, and above 10 suggest strong preservation. In addition to Zsummary statistics which is based on permutation and thus may be influenced by module size, we also reported median rank, a metric of observed preservation which does not depend on module size, to confirm relative preservation of multiple modules that varied in size. The association between MEs of strongly preserved modules of interest (Modules Green and Red based on primary analysis shown in Fig 2) and composite motor factor was then assessed in linear models with or without controlling for clinical covariates (age, sex, race, BMI, and education).

Secondary TRD cohort: As we have shown that baseline CRP levels moderated the antidepressant response to infliximab in this TRD cohort, we conducted separate WGCNA analyses within patients who had high CRP (>5 mg/l) and those who had low CRP (≤5 mg/l). Within each CRP category, a gene network was constructed to examine whether changes in gene expression following infliximab were associated with improvement in psychomotor performance. Given our interest in changes in gene expression following a single infusion of infliximab or placebo, we used as input log2 differential expression data (Week 2 post-infusion - Baseline gene expression) which have been empBayes-adjusted for the same clinical covariates as the primary cohort, while retaining the influence of change in CRP (Week 2 - Baseline). Networks were constructed identically as above, except a soft-thresholding power of 8 was determined to achieve approximately scale-free network topology. Co-expression modules (representing genes co-regulated by treatment) were detected identically as in the primary cohort.

Statistical analysis

Demographic and clinical variables were characterized using descriptive statistics. Normality was assessed using the Shapiro test. Chi-square tests, linear models and Kruskal-Wallis rank tests were used to compare categorical, normal and non-normal continuous variables, respectively, between cohorts. To determine whether infliximab improved
psychomotor speed in TRD, changes in individual psychomotor variables were modeled as a function of treatment (infliximab or placebo) and baseline plasma CRP levels (>5 or ≤5 mg/l) and their interaction, using linear regression with or without covariates (age, sex, race, BMI, and education). Analyses were conducted in R and IBM SPSS Statistics 27.0 (New York, NY, USA).

Supplemental Results

Linear models TOA: Transcripts associated with psychomotor slowing were enriched for genes originating from inflammatory immune cells

Transcript origin analysis (TOA) showed that transcripts linearly associated with psychomotor slowing (n=403) in the primary MD cohort were predominantly expressed by plasmacytoid dendritic cells (pDCs) (z=5.19, p=1.04E-07) and natural killer cells (NKs) (z=3.38, p=0.00036). Similarly, in the secondary TRD cohort transcripts linearly associated with psychomotor slowing (n=266) were predominantly expressed by pDCs (z=2.03, p=0.02) and marginally by NKs (z=1.54, p=0.06).

MD gene co-expression modules are strongly preserved between covariate-adjusted and unadjusted networks

Preservation analysis indicated that all 13 modules constructed from empBayes-adjusted MD data were preserved in the unadjusted MD data (Fig S2). The Z_summary values ranged from 14 (“purple” module) to 68 (“brown” module), demonstrating that all modules were strongly preserved between covariate-adjusted and unadjusted networks. Examination of median ranks of preserved modules further confirmed that modules with higher Z_summary values also exhibited lower median rank (and stronger observed preservation statistics). Furthermore, ME for Module Green equivalent identified from unadjusted MD data was significantly associated with composite psychomotor factor scores (p=0.018), a relationship which remained significant after controlling for age, sex, race, BMI, and education (p=0.005). Similarly, while ME for Module Red equivalent identified from unadjusted MD data was not significantly associated with composite psychomotor scores (p=0.089), this relationship became significant after controlling for covariates (p=0.023).

Infliximab improved reaction speed in TRD patients with high inflammation

None of the seven psychomotor variables were impacted by treatment or were related to baseline CRP (all p>0.26). However, there was a significant Treatment*CRP interaction with regards to change in simple reaction time (SRT) (F(1,41)=6.432, p=0.015) and choice reaction time (CRT) (F(1,41)=9.64, p=0.003). Posthoc tests revealed that infliximab led to improvements in SRT (p=0.033) and CRT (p=0.039) selectively in TRD patients with CRP>5mg/l. These effects persisted when controlling for covariates (p=0.047 and p=0.017).

WGCNA: Gene modules co-regulated by infliximab among TRD patients with low inflammation in association with changes in psychomotor speed are related to immune and mitochondrial function

Among TRD patients with CRP≤5 mg/l (n=30), change in gene expression following a single infusion of infliximab or placebo (Week 2 - baseline) clustered into 17 differential co-expression modules, each arbitrarily assigned a color name. ME of one module, green (“MEgreen”, unrelated to MD Module Green shown in Fig 2), was associated with both infliximab treatment and change in SRT. MEgreen was positively associated with infliximab (r=0.42, p=0.02), indicating that infliximab stimulated the expression of Module Green’s constituent genes. Interestingly, however, larger values of MEgreen corresponded to poorer change in SRT at Week 8 (Week 8 - Baseline; r=0.49, p=0.006). Pathway analysis revealed
significant enrichment of pathways related to oxidative phosphorylation, mitochondrial complex assembly, as well as Th1, Th2, and Th17 cell differentiation (all $p<0.05$ and $q<0.1$). A complete list of genes in the low inflammation green module and enriched pathways is shown in Table S6A-C.

**Potential impact of leukocyte proportion:**
Analysis of complete blood count (CBC) with differential indicated that proportions of white blood cell (WBC) subsets including neutrophils, lymphocytes, monocytes, eosinophils, and basophils were not significantly associated with composite psychomotor scores in the MD cohort while adjusting for covariates (all $p>0.14$). To check for the possibility that percentage of cell types present in whole blood impacts the relationship between the composite motor factor and gene modules created from WGCNA, we performed sensitivity analyses by controlling for WBC subtype percentage in robust biweight mid-correlations associating the composite motor factor with module eigengene, consistent with methods implemented in WGCNA. Specifically, we first created models only for the association between each ME and Motor Factor, then models for the same association adjusted for percentage of each cell type. The associations between Motor Factor with MEred and MEgreen each remained significant after adjusting for WBC cell type proportions (Table S7).

**Sensitivity analysis: Accounting for the use of diabetes medication**
In the MD cohort, one patient was taking diabetes medication. Excluding this patient from linear model analyses (n=87 patients) yielded 428 gene probes significantly associated with the composite psychomotor factor (98.5% of the 403 probes identified from the primary analysis were in common). WGCNA analysis excluding this patient yielded 13 gene co-expression modules consistent with the primary analysis. Modules Red and Green remained significantly associated with the composite psychomotor factor ($r=0.28$, $p=0.008$ and $r=0.24$, $p=0.03$ respectively).

In the TRD cohort, nine patients were taking diabetes medication out of n=57 patients who were studied at baseline. Linear model analyses additionally controlling for diabetes medication revealed n=282 probes significantly associated with the composite psychomotor factor (81.9% of the 266 probes identified from the primary analysis were in common). Of the n=50 patients included in the longitudinal analysis via WGCNA, eight were taking diabetes medication (four patients each in the high and low inflammation groups). Additionally adjusting for diabetes medication yielded 20 gene co-expression modules among patients with high inflammation. Consistent with the primary analysis, MEblue remained significantly associated with both Treatment ($r=-0.5$, $p=0.024$) and change in CRT (Week8 - Baseline) ($r=0.49$, $p=0.029$). No module was significantly associated with both Treatment and change in SRT. Among patients with low inflammation, 17 gene co-expression modules were identified. Consistent with the primary analysis, MEgreen remained significantly associated with both Treatment ($r= 0.47$, $p=0.009$) and change in SRT (Week8 - Baseline) ($r=0.47$, $p=0.009$).
Fig S1. Cluster dendrogram for co-expression modules from the primary MD cohort.
Fig S2. The median rank and $Z_{\text{summary}}$ statistics of module preservation between the covariate-adjusted and unadjusted MD networks.
Table S7. Association between MD co-expression modules and psychomotor slowing with and without controlling for proportions of white blood cell (WBC) subsets.

| Association       | Correlation coefficient | p-value | Covariate       | Partial correlation coefficient | p-value |
|-------------------|-------------------------|---------|-----------------|---------------------------------|---------|
|                   | (No WBC covariates)     |         |                 | (Covariate-adjusted)            |         |
| MotorFactor ~ MEgreen | 0.229                  | 0.032   | % Granulocytes  | 0.231                           | 0.03    |
|                   |                         |         | % Lymphocytes   | 0.231                           | 0.03    |
|                   |                         |         | % Monocytes     | 0.314                           | 0.003   |
|                   |                         |         | % Eosinophils   | 0.233                           | 0.029   |
|                   |                         |         | % Basophils     | 0.214                           | 0.045   |
| MotorFactor ~ MEred | 0.282                  | 0.008   | % Granulocytes  | 0.275                           | 0.009   |
|                   |                         |         | % Lymphocytes   | 0.294                           | 0.005   |
|                   |                         |         | % Monocytes     | 0.289                           | 0.006   |
|                   |                         |         | % Eosinophils   | 0.278                           | 0.009   |
|                   |                         |         | % Basophils     | 0.249                           | 0.02    |

Abbreviations: MD, major depression; MotorFactor, composite psychomotor factor; ME, module eigengene.
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