#### **∂** Open Access Full Text Article

### ORIGINAL RESEARCH

# Exploration of a genomic expression and pathway analysis approach to neurocognitive performance: preliminary findings

Chad A Bousman<sup>1</sup> Gursharan Chana<sup>2</sup> Stephen J Glatt<sup>3</sup> Sharon D Chandler<sup>1</sup> Todd May<sup>1</sup> James Lohr<sup>1</sup> Ian P Everall<sup>2</sup> William S Kremen<sup>1</sup> Ming T Tsuang<sup>1</sup>

<sup>1</sup>Psychiatry, University of California, San Diego, CA, USA; <sup>2</sup>Psychiatry, University of Melbourne, Melbourne, Victoria, Australia; <sup>3</sup>Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA

Correspondence: Chad A Bousman Center for Behavioral Genomics, Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92039, USA Email cbousman@ucsd.edu. Abstract: Identification of genomic biomarkers for neurocognitive performance could revolutionize screening, diagnosis, staging, and/or prognosis practices for HIV-associated neurocognitive disorders (HAND). This study sought to explore the relationship between blood-based gene expression and neurocognitive performance. 8 healthy adults were recruited. Subjects were non-smokers, reported taking no medications, and were free of any psychiatric disorders. Correlations adjusting for education and ancestry were conducted to generate lists of genes significantly correlated with scores on neurocognitive test from the National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB). Ingenuity pathway analysis was used to identify canonical pathways. For each of the 10 MCCB tests, large effect sizes (r > 0.49) were observed. 65% of the genes and 80% of canonical pathways were unique to 1 of the 10 MCCB tests, albeit none survived a 10% FDR correction. Minimal gene overlap was observed across tests; however, several overlapping canonical pathways were observed. Analysis of the relationship between gene expression alterations and neurocognitive performance may provide the potential for improving our ability to identify genomic markers of HAND as well as provide guidance to physicians and researchers in HIV medicine and other disciplines in their pursuit of viable genomic biomarkers for neurocognitive impairment.

Keywords: gene expression, cognitive, methodology, MATRICS

# Introduction

The examination of genetic attributes of neurocognition (ie, cognitive neurogenetics) to understand and uncover the underlying biological mechanisms of the pathogenesis as well as clinically viable biomarkers for early identification of HIV-associated neurocognitive disorders (HAND) has become an exciting aspect of NeuroAIDS research.<sup>1</sup> Genomic biomarkers for HAND could assist physicians in their determination of whether further neurological investigation would be valuable and/or assist in tailoring pharmacological interventions. In addition, genomic biomarkers have the potential to improve screening, diagnostic, staging and/or prognostic procedures.<sup>2,3</sup> To date, the majority of genetic work related to neurocognitive performance, HAND, and other neurobehavioral disorders has been candidate-gene driven and concerned primarily with testing genotypic associations for neurocognitive performance among a small pool of candidate genes.<sup>1,4</sup> To our knowledge, no study has attempted to examine gene expression and/or pathway associations with neurocognitive performance. This type of analysis may be advantageous in that it could identify novel candidate genes and/or biological pathways from which additional candidate genes could be extracted

submit your manuscript | www.dovepress.com
Dovepress

© 2010 Bousman et al, publisher and licensee Dove Medical Press Ltd. This is an Open Access article which permits unrestricted noncommercial use, provided the original work is properly cited.

Dovepress

and further investigated for their significance. In this study, we sought to explore a blood-based genomic expression and pathway analysis approach to neurocognitive performance among a group of healthy adults rather than those with HAND to avoid confounds related to medication or disease status and to provide preliminary data for a novel method that could be used in future biomarker discovery efforts.

# Methods

### Subjects

Ten healthy volunteers were recruited from the University of California, San Diego Psychopharmacology Research Initiatives Center for Excellence participant network and clinically assessed using the Diagnostic Interview for Genetic Studies (DIGS)<sup>5</sup> as described elsewhere.<sup>6</sup> Participants were free of: (1) substance abuse or dependence in the past year; (2) neurologic problems (eg, stroke); (3) systemic medical illnesses (eg, diabetes, HIV); (4) history of head injury with documented loss of consciousness lasting longer than 10 minutes; (5) pregnancy; (6) physical disabilities; (7) use of prescribed medications; (8) current tobacco use; or (9) a personal or family history of a schizophrenia, bipolar disorder, major depressive disorder, or a cluster-A (schizotypal, schizoid, or paranoid) personality disorder, all of which may affect gene expression. All study procedures were approved by the Institutional Review Board at University of California, San Diego.

## Neurocognitive assessment

Participants were administered the National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB).<sup>7,8</sup> The MCCB contains 10 tests representing 7 domains, takes approximately 60 minutes to administer (for more details on the battery see references 7 and 8), and contains neurocognitive tests within the domains required for diagnosing HAND<sup>9</sup> (Table 1). The MCCB was administered by a trained Master's-level research assistant, on a single occasion, and in the order listed in Table 1.

# Blood collection and processing

Whole blood (10 mL) was collected in the morning after subjects fasted overnight but directly prior (< 30 minutes) to administration of the neurocognitive battery. Blood samples were immediately transferred to an RNase-free laboratory, where all subsequent procedures (ie, stabilization, isolation, storage) took place.<sup>6</sup> Prior to hybridization, two subjects were excluded for low RNA integrity (RIN < 6.0).<sup>10</sup> The remaining eight samples were then transcribed to cDNA and hybridized to GeneChip<sup>®</sup> Human Exon 1.0 ST Arrays (Affymetrix, Inc., Santa Clara, CA, USA) per the "Whole Transcript (WT) Sense Target Labeling Assay" protocol (Affymetrix, 2006) using 1 µg of total RNA from each sample.

# Microarray data analyses

The principal analyses of these data were designed to explore gene expression and pathway correlates among the 10 neurocognitive tests in the battery described above, as well as to potentially demonstrate the utility of a more robust biomarker discovery method for neurocognitive performance. To accomplish this, microarray data were imported into Partek Genomics Suite software (Partek Inc., St Louis, MO, USA)

 Table I National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition In Schizophrenia (MATRICS)

 consensus cognitive battery

- Test	Domain	Test score used
Trail making tost Part A	Speed of information processing	Time to completion
Deleferences of a minimum in SCZ (DACC) such all as dis-	Speed of information processing	
brief assessment of cognition in SCZ (BACS), symbol coding	speed of information processing	Total number correct
Hopkins verbal learning test (HVLT)-revised, immediate recall subtest	Verbal learning	Total number words (all three trials)
Wechsler memory scale (WMS), 3rd ed., spatial span task	Working memory	Sum of raw scores on forward and backward conditions
Letter-number (LN) span test	Working memory	Number of correct trials
Neuropsychological assessment battery, mazes subtest	Reasoning and problem solving	Total raw score
Brief visuospatial memory test (BVMT)-revised	Visual learning	Total recall over three trials
Category fluency test, animal naming	Speed of information processing	Total number of animals named
Mayer-Salovey-Caruso emotional intelligence test	Social cognition	Branch score using general
(MSCEIT), managing emotions subtest		consensus scoring
Continuous performance test (CPT)	Attention/vigilance	Mean d' value across 2-, 3-, and
		4-digit conditions

**Note:** Table adapted with permission from Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res.* 2004;72(1):29–39.<sup>13</sup> **Abbreviation:** SCZ, schizophrenia. using robust multichip average to analyze probe intensities and to determine gene expression correlates of each of the 10 neurocognitive tests (for more detail on data processing, see Glatt et al<sup>6</sup>). Pearson's partial correlations (adjusting for education and ancestry) between raw scores on each of the neurocognitive tests and the mean expression level on a gene-by-gene basis were conducted.

### Pathway analysis

Following correlational analysis of individual gene transcripts, gene lists containing all nominally (P < 0.05) significantly correlated genes for each of the 10 neurocognitive tests were generated. These lists were then imported into Ingenuity Pathway Analysis (IPA) software (Ingenuity Systems®, Redwood City, CA, USA) to associate correlated genes with their representative canonical pathways. Canonical pathways that were most significant to the selected gene lists were identified by querying the IPA library of canonical pathways. The significance of the association between the datasets and the canonical pathways was measured in two ways: (1) using the Fischer's exact test, we calculated the probability that the association between the gene list and the canonical pathway was explained by chance alone; and (2) we calculated a ratio of the number of genes from the gene list that mapped to the pathway divided by the total number of molecules that exist in the canonical pathway. Pathways with a high ratio and a low P-value were interpreted as indicative of potentially good candidates for further exploration.

### Results

### Participant characteristics

Participant characteristics and raw neurocognitive test scores for each of the eight participants are shown in Table 2. Participants ranged in age from 37–53 years (M = 45, sd = 7), were predominantly Caucasian (63%) and male (63%), and had completed between 12 and 17 years (M = 15, sd = 2) of education. Mean raw scores for each neurocognitive test among participants were in the normative range of those reported among healthy subjects recruited to determine norms for the MCCB.<sup>8</sup>

# Gene expression correlates of neurocognitive performance

Correlation analyses identified 6496 of a possible 21,866 genes whose expression was significantly correlated (nominal P < 0.05) with one or more of the MCCB tests. The number of genes significantly correlated with each test ranged from 65 (Mayer-Salovey-Caruso Emotional

Subject	Demog	raphics			Reason and	Verbal	Working r	nemory	Visual	Speed			Attention/	Social
					prob. solv.	learning			learning	of proce	ssing		vigilance	cognition
	Age	Sex	Ethnic	Edu	Mazes	Hopkins	WMS	LN Span	BVMT	Cat	BACS	Trails A	CPT	MSCEIT
SI	49	Σ	CEU	16	61	20	14	16	32	20	37	30	3.05	100
S2	44	Σ	CEU	13	20	30	18	4	25	27	63	17	3.13	103
S3	49	Σ	CEU	17	26	31	18	13	31	31	44	36	3.68	80
S4	53	щ	HISP	4	21	27	12	=	19	24	54	24	2.14	92
S5	52	Σ	CEU	12	23	25	15	4	24	30	60	34	2.04	83
S6	38	Σ	AA	15	6	23	4	16	23	26	53	17	2.78	109
S7	37	щ	Asian	4	22	30	61	17	35	26	75	30	4.24	109
S8	38	щ	CEU	16	17	29	17	17	26	23	76	15	4.15	96
Mean (s.d)	45 (7)	ı	ı	15 (2)	20 (5)	27 (4)	16 (3)	15 (2)	27 (5)	26 (4)	58 (14)	25 (8)	3.151 (0.83)	66 (11)

Neurobehavioral HIV Medicine 2010:2

Intelligence Test: MSCEIT) to 1425 (Hopkins Verbal Learning Test: HVLT) (Table 3). 63% (4116/6496) of these genes were correlated with a single neurocognitive test only. None of the genes was significantly correlated with more than three tests. Interestingly, the letter-number span, animal-naming, and MSCEIT tests showed the most unique gene expression correlates in that the unique proportion (ie, number of genes only significant for the test/total number of significant genes for the test) of correlated genes for these tests was 68%, 85%, and 100%, respectively (Table 3). In contrast, the other tests showed less than 50% (range: 22%-47%) uniqueness and thus shared a greater majority of their gene correlates with other tests in the MCCB. It should be noted that due to the small sample size, the large number of comparisons made, and the consequent severity of the penalty for multiple testing, no individual gene correlate remained significant after correction (ie, 10% FDR). However, correlation coefficients (r) ranged from 0.98 to -0.98 and large effect sizes  $(r > \pm 0.49)^{11}$  were observed for a majority of the nominally significant genes for most of the individual tests and domains (Table 3).

# Canonical pathway correlates of neurocognitive performance

Examination of the top 10 canonical pathways populated by all the correlated genes for each of the 10 MCCB tests (Supplemental Table 1) showed that 80% of pathways were unique to one of the 10 tests. No pathways overlapped with all MCCB tests. Although, NF-kß signaling, N-Glycan degradation, one carbon pooling by folate, and phenylalanine metabolism canonical pathways were the most represented pathways among the MCCB, with each of these pathways mapping onto 3 or more of the 10 tests. Table 4 provides a comprehensive summary of gene and canonical pathway overlap among the tests of the MCCB.

### Discussion

This study sought to explore the relationship between bloodbased gene expression and neurocognitive performance among healthy adults to avoid confounds related to medication or disease status and provide preliminary data for a novel method that could be used in future biomarker discovery efforts in HAND as well as other neurocognitive-related disorders. We found that nominally significant (P < 0.05) neurocognitive performance-associated genes mapped onto several canonical pathways, particularly those involved in cell signaling or metabolism. Among the top 10 pathways across the 10 tests (k = 100), 49% were signaling and 17% were metabolism pathways. It should be noted that these pathways have extensive interactions with a variety of biological processes such as cell growth, proliferation, and apoptosis,<sup>12</sup> so it is not surprising that these pathways are represented in associations with neurocognitive performance. In fact, several studies of HAND have investigated gene polymorphisms in signaling (eg, chemokine and dopamine receptors) and to lesser extent metabolism pathways (eg, dopamine metabolism).1

Fable 3 Gene expression	n correlates, ur	niqueness, and	effects by	MCCB test and domain
-------------------------	------------------	----------------	------------	----------------------

Test/domain	# of sig. correlated	# Unique to	Unique proportion	% of genes
	genes	test/domain		r > 0.49
NAB-mazes	720	349	48.47%	52.22%
Hopkins verbal learning	1,425	667	46.81%	62.53%
WMS-spatial span	1,234	476	38.57%	56.89%
LN Span	929	629	67.71%	61.46%
Working memory domain	633	36	5.69%	51.18%
BVMT	1,225	487	39.76%	66.53%
Animals	1,137	963	84.70%	66.31%
BACS	962	97	10.08%	63.83%
Trails A	533	183	34.33%	48.41%
Speed of information	866	113	13.05%	59.12%
processing domain				
CPT	558	51	9.14%	50.72%
Social cognition	65	65	100.00%	61.54%

Note: r = Pearson's partial correlation coefficient.

Abbreviations: MCCB, National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus cognitive battery; NAB, Neuropsychological Assessment Battery; HVLT, Hopkins Verbal Learning Test; WMS, Wechsler Memory Scale; LN span, letter-number span; BVMT, Brief Visuospatial Memory Test; Cat, category test-animals; BACS, Brief Assessment of Cognition in Schizophrenia; CPT, Continuous Performance Test; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test.

	Reason	Vrb. Irn	Workin	ng memo	ory	Vis. Irn	Processing	speed			Att/vig	Soc.Cog.
	Mazes	Hopkins	WMS	LN	Wrk	BVMT	Category	BACS	Trails	SIP	СРТ	MSCEIT
				span	mem				Α			
Mazes		0	0	267	0	0	142	0	0	0	0	0
Hopkins	0		758	0	0	0	0	0	0	0	0	0
WMS	0	3		0	0	0	0	0	0	0	0	0
LN span	2	I	0		0	0	61	0	0	0	0	0
Wrk mem	2	0	0	0		37	0	175	223	329	380	0
BVMT	I.	I	I	0	0		0	704	0	438	0	0
Category	2	I	0	1	0	2		0	0	0	0	0
BACS	0	I	I	0	0	6	I		0	560	44	0
Trails A	0	0	0	0	4	0	0	0		17	344	0
SIP	0	0	0	0	I	I	0	I	I		122	0
CPT	2	0	0	I	5	0	0	0	3	I		0
MSCEIT	I	0	0	0	I.	0	0	0	0	I	I	

Table 4 Summary of overlapping genes (above diagonal) and canonical pathways (below diagonal) among the MCCB tests and domains

Abbreviations: MCCB, National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus cognitive battery; HVLT, Hopkins Verbal Learning Test; SSpan, Wechsler Memory Scale-spatial span; LN span, letter-number span; BVMT, Brief Visuospatial Memory Test; Cat, category testanimals; BACS, Brief Assessment of Cognition in Schizophrenia; CPT, Continuous Performance Test; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test.

From a gene expression and pathway vantage point, our results also suggest that tests within established neurocognitive domains<sup>13</sup> may be more unique than similar. This was observed for two of the domains (ie, working memory and processing speed) which were represented by more than one test. Whereas, examination of between-domain overlap revealed that several domains had multiple gene expression and pathway correlates in common (eg, visual learning [BVMT] and processing speed [BACS] tests). These findings suggest neurocognitive tests, particularly those in the MCCB, may not hold to their established neurocognitive domain structure<sup>13</sup> when examined from a blood-based genomic perspective. This is particularly relevant to future biomarker discovery efforts in HAND in that the current diagnosis of HAND requires assessment of at least five areas of neurocognitive functioning known to be affected by HIV (eg, executive functioning, episodic memory, speed of information processing, motor skills, attention/working memory, language, and sensoriperception) but does not stipulate the use of any particular neurocognitive tests.9 From a genomic perspective, HAND diagnosed using the current criteria may be very heterogeneous and result in difficulties with biomarker discovery and replication. Thus, if our results are replicated in a larger sample, this ultimately could advocate for restructuring of domains, examination of neurocognitive tests independent of domain membership, or adoption of a specific core group of neurocognitive tests for future genetic research related to biomarker discovery in HAND.

It must be acknowledged that these explanations are both speculative and post hoc. Moreover, there are several areas of overlap in cognitive component processes across tests that do not coincide with gene or pathway overlap. Further exploration is clearly needed, but the present results provide preliminary evidence that this approach might be useful in elucidating genetic biomarkers for cognitive processing and ultimately HAND. In so doing, this approach might also lead to novel ways to organize or select cognitive tests for HAND diagnosis. Indeed, it is worth noting that the cognitive tests used in the present study as well as many similar tests commonly employed were not designed for genetic studies,<sup>14</sup> and current ways of organizing cognitive measures may not map neatly onto gene expression or canonical pathways.

Several caveats should be considered when interpreting these results and addressed in future investigations. First, it remains unclear whether molecular signatures in blood accurately reflect those found in the brain. However, several investigators have reported that the circulating blood may act as a "sentinel tissue", 15 "neural probe", 16 or "surrogate"17 for underlying pathophysiology in brain disorders. In fact, Liew and colleagues<sup>15</sup> reported an 80% overlap between blood and brain gene expression. Furthermore, blood-based approaches allow for better standardization of technical procedures and the ability to profile human subjects in a relatively non-invasive manner.<sup>18,19</sup> Second, we attempted to limit the influence of different subtypes of cells in blood by focusing on leukocytes. Within this cell category, several cell types (ie, neutrophils, eosinophils, basophils, lymphocytes, monocytes, and macrophages) with varying roles in the blood exist and may influence gene expression

profiles.<sup>20</sup> Future blood-based studies may find it advantageous to isolate specific lymphocyte subtypes in an effort to achieve greater sensitivity in detecting gene expression changes. Third, the sample size was small, which may have prohibited detection of effects that would have retained statistical significance in a larger sample, even after correcting for multiple testing. In fact, large expression effects  $(r > \pm 0.49)^{11}$  were observed for a majority of genes for each of the MCCB tests suggesting many of these genes may have been significant in a larger sample and justify further investigation. Fourth, pathway-level analysis was done using one of the largest knowledge bases of biological networks (IPA, Redwood City, CA, USA), a considerable strength. However, IPA is manually curated and relies on previously published findings on mammalian biology. Thus, in some cases cellular component annotation can be missing or incomplete due to the lack of information in protein databases to which IPA is linked (eg, UniProt) and ultimately may underestimate extracellular entities (eg, metabolites, hormones).<sup>21</sup> Fifth, expression profiles were based on samples collected immediately (< 30 minutes) prior to cognitive testing. Thus, expression and pathway profiles observed in this study are not a result of cognitive performance tests but rather potential markers for performance ability. Future longitudinal research that examines expression profiles before and after neurocognitive testing could further elucidate the biological mechanisms underlying neurocognitive performance. Sixth, this study utilized the MATRICS consensus cognitive battery which was designed to evaluate cognitive-enhancing agents and other interventions to treat core cognitive deficits of schizophrenia and not necessarily for the identification of genomic markers for neurocognitive performance or HAND. Thus, it is possible that use of other neurocognitive tests and/or batteries will yield different results. Finally, in an effort to conserve power, potentially influential covariates (eg, age, gender, diet, and exercise) were not adjusted for in our analysis. Future studies with larger samples that have the power to include more covariates are warranted.

Despite these limitations, our work provides preliminary data for the application of genomic expression and pathway analysis to tests of neurocognitive performance. This approach may provide the potential for improving our ability to identify genomic markers of HAND as well as provide guidance to physicians and researchers in HIV medicine and other disciplines in their pursuit of viable genomic biomarkers for neurocognitive impairment.

### **Acknowledgments**

This work was primarily supported by a National Institutes of Health grant R21MH075027 (MTT) but also supported from grants R01DA012846, R01DA018662, R01MH065562, and R01MH071912 (MTT), R01MH079881, R25MH074508, R25MH081482, and R41MH079728 (IPE), R01AG018386, R01AG022381, and R01AG022982 (WSK), P50MH081755 (Eric Courchesne/SJG), the UCSD Center for AIDS Research Genomics Core, and a NARSAD Young Investigator Award (SJG).

## Disclosure

The authors report no conflicts of interest in this work.

### References

- Levine AJ, Singer EJ, Shapshak P. The role of host genetics in the susceptibility for HIV-associated neurocognitive disorders. *AIDS Behav*. 2009;13(1):118–132.
- Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89–95.
- Quinones MP, Kaddurah-Daouk R. Metabolomics tools for identifying biomarkers for neuropsychiatric diseases. *Neurobiol Dis.* 2009;35(2):165–176.
- Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behav*. 2006;5(4): 311–328.
- Nurnberger JI Jr, Blehar MC, Kaufmann CA, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry*. 1994;51(11):849–859; discussion 863–864.
- Glatt SJ, Chandler SD, Bousman CA, et al. Alternatively spliced genes as biomarkers for schizophrenia, bipolar disorder and psychosis: a blood-based spliceome-profiling exploratory study. *Curr Pharmacogenomics Person Med.* 2009;7(3):164.
- Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203–213.
- Kern RS, Nuechterlein KH, Green MF, et al. The MATRICS consensus cognitive battery, part 2: co-norming and standardization. *Am J Psychiatry*. 2008;165(2):214–220.
- Woods SP, Moore DJ, Weber E, Grant I. Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychol Rev.* 2009;19(2):152–168.
- Schroeder A, Mueller O, Stocker S, et al. The RIN: an RNA integrity number for assigning integrity values to RNA measurements. *BMC Mol Biol.* 2006 Jan 31;7:3.
- 11. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-159.
- Whistler T, Taylor R, Craddock RC, Broderick G, Klimas N, Unger ER. Gene expression correlates of unexplained fatigue. *Pharmacogenomics*. 2006;7(3):395–405.
- Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res.* 2004;72(1):29–39.
- Goldberg TE, Weinberger DR. Genes and the parsing of cognitive processes. *Trends Cogn Sci.* 2004;8(7):325–335.
- Liew CC, Ma J, Tang HC, Zheng R, Dempsey AA. The peripheral blood transcriptome dynamically reflects system wide biology: a potential diagnostic tool. *J Lab Clin Med*. 2006;147(3):126–132.

- Gladkevich A, Kauffman HF, Korf J. Lymphocytes as a neural probe: potential for studying psychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(3):559–576.
- Sullivan PF, Fan C, Perou CM. Evaluating the comparability of gene expression in blood and brain. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141B(3):261–268.
- Tsuang MT, Nossova N, Yager T, et al. Assessing the validity of blood-based gene expression profiles for the classification of schizophrenia and bipolar disorder: a preliminary report. *Am J Med Genet B Neuropsychiatr Genet.* 2005;133B(1):1–5.
- Mohr S, Liew CC. The peripheral-blood transcriptome: new insights into disease and risk assessment. *Trends Mol Med*. 2007;13(10):422–432.
- Chana G, Glatt SJ, Everall IP, Tsuang MT. Blood and Brain Gene Expression in Major Psychiatric Disorders: A Search for Biomarkers. Biomarkers for Psychiatric Disorders. New York, NY: Springer; 2008.
- 21. Pospisil P, Iyer LK, Adelstein SJ, Kassis AI. A combined approach to data mining of textual and structured data to identify cancer-related targets. *BMC Bioinformatics*. 2006;7:354.

# Supplementary material

Table SI Top 10 canonical pathways by neurocognitive domain and test

Reasoning and problem         Maxes         Protein ubiquicination padway         3.47E+00         6.44E502           solving         Cospilation system         2.09E+00         1.08E+01           Chemokine signaling         1.33E100         6.67E-02           Call cycle: G2/H DNA damage checkpoint regulation         1.12E+00         6.98E-02           CMPM-mediated signaling         1.11E+00         4.40E-02           Provision metabolism         1.12E+00         8.08E-01           Provision metabolism         1.12E-00         8.08E-01           Orice carbon pool by fokte         8.01E-01         3.26E-00           Orice carbon pool by fokte         8.01E-01         3.26E-00           Orice carbon pool by fokte         8.01E-01         1.28E-01           Orice carbon pool by fokte         8.01E-01         1.28E-01           Orice carbon pool by fokte         9.21E-01         3.26E+00         1.12E-01           Orice carbon pool by fokte         9.21E-01         3.26E+00         1.12E-01           Caramide signaling         2.10E+00         1.12E-01         1.28E-01           Garbardia carbon di motivital response         1.65E+00         1.28E-01           Caramide signaling         2.10E+00         1.28E-01           Caramide signaling	Domain	Test	Canonical pathway	Log p	Ratio
solving         Congulation system         209Eu00         108E-01           Chemokine signaling         152Eu00         6.678-02           Purine metabolism         1.19E-00         3.12E-02           eAPH-mediated signaling         1.19E-00         3.12E-02           eAPH-mediated signaling         1.19E-00         3.02E-02           eAPH-mediated signaling         1.19E-00         3.02E-02           instrot in metabolism         1.12E-01         3.04E-00           Tipte junction signaling         8.48E-01         3.04E-00           One carbon pool by folate         3.04E-00         1.12E-00           Caramide signaling         1.02E-01         1.22E-01           Caramide signaling         1.92E-00         1.12E-01           Caramide signaling         1.92E-00         1.22E-01           Caramide signaling         1.92E-00         1.02E-01           Caradian rhythim signaling	Reasoning and problem	Mazes	Protein ubiquitination pathway	3.47E+00	6.44E-02
Cospitation system         209-100         1.08E-00           Chemokine signaling         1.5514-00         6.67F-02           Cell rycle: G2/M DNA damage checkpoint regulation         1.254-00         6.98E-02           AMP-mediated signaling         1.16E+00         8.00E-02           Inotation metabolism         1.254-01         2.08E-02           Pheryhalpanine metabolism         1.254-01         2.08E-02           Pheryhalpanine metabolism         1.254-01         2.08E-02           Tight junction signaling         2.054-00         1.15E-01           Carcino-mediated endocytosis         3.04E-00         1.15E-01           Carcino-mediated endocytosis         3.04E-00         1.15E-01           Carcino couple receptor signaling         1.95E-00         1.08E-01           Carcino couple receptor signaling         1.95E-00         1.08E-01           Carcina drythm signaling         1.95E-00         1.28E-01           Carcina drythmsis graning         1.95E-00         <	solving				
Working memory         VMS         NMS         NMS         Self-02         Self-02           Verbal learning         1.15E+00         3.1252-00         Self-02         Self-02           Purine metabolism         1.15E+00         3.125-00         Self-02         Self-02           Instact interabolism         1.12E+00         Self-02         Self-02<			Coagulation system	2.09E+00	1.08E-01
Verbal learning         1.21-00         6.988-20.0           Purine metabolism         1.195+00         3.125-02           cAMP-mediated signaling         1.162+00         4.405-02           Inexitol metabolism         1.125+00         8.005-02           Princylalanine metabolism         9.125-01         2.805-02           Tight junction signaling         8.486-01         3.665-02           One carbon pool by folite         6.2116-01         5.265-02           Verbal learning         Hopkins         Charins-mediated endocytosis         3.04-00         1.155-01           Verbal learning         1.925-00         9.416-02         1.226-01         6.707-000         1.226-01           Carande signaling         1.955-00         1.028-01         1.028-01         1.028-01           Carande signaling         1.655-00         1.028-01         1.028-01         1.028-01           Carande signaling         1.655-00         1.028-01         1.028-01         1.028-01           Carande signaling         1.656-00         1.028-01         1.028-01         1.028-01           Carada rythm signaling         1.656-00         1.286-01         1.286-01         1.286-01           Carada regris ginaling         1.656-00         1.286-01         1.286			Chemokine signaling	1.53E+00	6.67E-02
Purine metabolism         1.164-00         3.126-02           cAMP-mediated signaling         1.164-00         4.406-02           Inositol metabolism         9.125-01         2.206-02           Prenybalanine metabolism         9.125-01         2.206-02           Tight junction signaling         8.466-01         3.666-02           One carbon pool by folate         3.218-01         5.266-02           Verbal learning         Hopkins         Clarin-mediated endocytosis         3.044-00         1.185-01           Verbal learning         1.076-01         1.228-01         0.228-01         0.228-01           Verbal learning         1.076-01         1.228-01         0.228-01         0.228-01           Carande signaling         1.368-00         1.228-01         0.228-01         0.228-01           Carande signaling         1.368-00         1.286-01         0.268-01         1.268-01           Caradian trythm signaling         1.368-00         1.286-01         1.268-01         1.268-01           Vorking memory         WMS         MF-48 signaling         3.278-00         1.286-01           Vorking memory         WMS         MF-48 signaling         3.278-00         1.286-01           Vorking memory         WMS         MF-48 signaling			Cell cycle: G2/M DNA damage checkpoint regulation	I.22E+00	6.98E-02
Verthal learning         1.16E-00         4406-02           Honoitol metabolism         1.12E-01         62005-02           Tight junction signaling         848E-01         3.68E-01           Verthal learning         Hopkins         Clatrin-mediated endocytosis         3.04E-00         1.10E-01           Verthal learning         Hopkins         Clatrin-mediated endocytosis         3.04E-00         1.10E-01           PFAR signaling         2.07E-00         1.10E-01         1.22E-00         9.41E-02           Grandan Tydyrin Signaling         1.65E-00         1.22E-01         9.41E-02           Grandan Tydyrin Signaling         1.65E-00         1.22E-01         1.26E-01           Claradan Tydyrin Signaling         1.65E-00         1.28E-01         1.28E-01           Claradan Tydyrin Signaling         1.65E-00         1.28E-01         1.28E-01           Claradan Tydyrin Signaling         1.65E-00         1.28E-01         1.28E-01           Vorking memory         VMS         NF-&S isgnaling         2.08E-00         1.38E-00         1.28E-01           Vorking memory         VMS         NF-&S isgnaling         2.08E-00         1.38E-00         1.28E-01           Vorking memory         VMS         NF-&S isgnaling         2.08E-00         2.08E-00 <td></td> <td></td> <td>Purine metabolism</td> <td>1.19E+00</td> <td>3.12E-02</td>			Purine metabolism	1.19E+00	3.12E-02
Verbal learning         11.21:00         800E-02           Prepylalanine metabolism         9.12:01         2.280E-02           Tight junction signaling         848E-01         5.26E-02           One carbon pool by folate         8.21E-01         5.26E-02           Verbal learning         1.18E-01         5.26E-02           PRA signaling         2.10E-10         1.18E-01           PRA signaling         2.10E-10         1.18E-01           Ceramide signaling         1.96E-00         1.22E-01           G-protein coupled receptor signaling         1.28E-10         0.22E-01           Circadian rhythm signaling         1.68E-10         0.12EE-01           Circadian rhythm signaling         1.68E-10         0.12EE-01           Role of PKR in interferon induction and antiviral response         1.63E-01         0.12EE-01           Verking memory         WMS         NF-K8 signaling         3.78E-00         1.24E-01           Notecreit and invitose         1.38E-10         0.28E-01         1.28E-10           Verking memory         WMS         NF-K8 signaling         2.30E-00         1.30E-01           Notecreit and invitose         1.38E-10         1.38E-10         1.38E-10         1.38E-10           Verking memory         VMS			cAMP-mediated signaling	1.16E+00	4.40E-02
Phenylalinine metabolism         9:12:01         22:06:12           Tigfk junction signaling         6:48:00         3:66:20           One carbon pool by folate         8:21:01         5:25:62           One carbon pool by folate         8:21:01         5:25:62           One carbon pool by folate         8:21:01         1:15:50           NF-AS signaling         2:37:40         1:10:60           Caramide signaling         1:92:10         9:12:22:01           Caramide signaling         1:92:10         9:21:00           Caradian rhythm signaling         1:65:10         1:02:20           Caradian rhythm signaling         1:65:10         1:02:01           Caradian rhythm signaling         1:61:00         1:02:01           Caradian rhythm signaling         1:61:00         1:02:01           Caradian rhythm signaling         1:36:10         1:08:01           Caradian rhythm signaling         1:36:10         1:08:01           Caradian rhythm signaling         1:36:10         1:08:01           Caradian rhythm signaling <td></td> <td></td> <td>Inositol metabolism</td> <td>1.12E+00</td> <td>8.00E-02</td>			Inositol metabolism	1.12E+00	8.00E-02
Tight junction signaling         8.48E-01         3.26E-02           One carbon pool by folace         3.21E-01         5.26E-02           Verbal learning         Hopkins         Clatrin-mediated endocytosis         3.04E+00         1.15E-01           PARA signaling         2.10E+00         1.10E-01         1.10E-01           Caranide signaling         1.95E+00         9.41E-02           Caranide signaling         1.65E+00         1.22E-01           Caranide signaling         1.65E+00         1.22E-01           Circadian rhythm signaling         1.61E+00         1.02E-01           Circadian rhythm signaling         1.61E+00         1.02E-01           Circadian rhythm signaling         1.61E+00         1.02E-01           Circadian rhythm signaling         3.79E+00         1.12E-01           Circadian rhythm signaling         3.79E+00         1.24E-01           Role of PKR in interferon induction and antiviral response         1.38E+00         1.28E-01           Working memory         WMS         NF-4B signaling         2.09E+00         1.38E-01           Nucleotide excision repair pathway         1.61E+00         1.08E-01         1.38E+00         7.51E-02           Circadian of MRR in interferon induction and antiviral response         1.38E+00         7.51E-02<			Phenylalanine metabolism	9.12E-01	2.80E-02
One carbon pool by folate         8.21E-01         5.26E-02           Werbal learning         Hopkins         Clarkin-mediated endocytosis         3.04E+00         I.15E-01           NF-xB signaling         2.37E+00         1.10E-01         PPAA signaling         1.96E+00         1.22E-01           G-protein coupled receptor signaling         1.95E+00         1.22E-01         9.41E-02         1.28E-01           G-protein coupled receptor signaling         1.65E+00         1.26E-01         1.26E-01         1.26E-01           Circadian rhytchin signaling         1.65E+00         1.26E-01         1.26E-01         1.26E-01           Role of PKR in interefron induction and antiviral response         1.63E+00         1.28E-01         1.28E-01           Working memory         WMS         NF-s8 signaling         2.06E+00         1.24E-01           Working memory         WMS         NF-s8 signaling         2.06E+00         1.24E-01           Volceide excitoxion         1.34E+00         1.28E-01         1.28E-01         1.28E-01           Volceide excitoxion repair pathway         1.61E+00         1.08E-01         Notecote         1.36E+00         1.28E-01           Nucleatide excitoxis or signaling         1.61E+00         1.08E-01         Notecote         1.35E+00         1.30E-01 </td <td></td> <td></td> <td>Tight junction signaling</td> <td>8.48E-01</td> <td>3.66E-02</td>			Tight junction signaling	8.48E-01	3.66E-02
Verbal learning         Hopkins         Clatrin-mediated endocytosis         3.04E-00         1.18E-00           PRA signaling         2.10E+00         1.10E-01           PPA signaling         2.10E+00         1.12E-01           Ceramide signaling         1.96E+00         1.22E-00           Ge-protein coupled receptor signaling         1.95E+00         9.41E-02           Extrogen receptor signaling         1.65E+00         1.28E-01           Circadian rhythm signaling         1.65E+00         1.28E-01           Circadian rhythm signaling         1.65E+00         1.28E-01           KXR/RX activation         1.34E-00         9.41E-02           Working memory         WMS         NF+8 signaling         3.79E+00         1.28E-01           Working memory         WMS         NF+8 signaling         3.79E+00         1.28E-01           Role of PKR in interferon induction and antiviral response         1.61E+00         1.08E-01           Role of PKR in interferon induction and antiviral response         1.61E+00         1.08E-01           Nucleotide excision repair pathway         1.51E-00         1.38E-01         1.08E-01           Nucleotide excision repair pathway         1.51E-00         1.48E-00         1.09E-01           Nucleotide excision repair pathway         1.			One carbon pool by folate	8.21E-01	5.26E-02
NF-κ6 signaling       2.07E-00       1.10E-01         PARA signaling       2.10E-00       1.12E-01         G-protein coupled receptor signaling       1.92E-00       9.41E-02         Entrogen receptor signaling       1.85E+00       1.02E-01         Circadian rhythm signaling       1.65E+00       1.02E-01         Circadian rhythm signaling       1.61E+00       1.08E-01         Circadian rhythm signaling       1.61E+00       1.24E-01         Vorking memory       WMS       NF-xB signaling       1.61E+00       1.24E-01         Obel of PKR in interferon induction and antiviral response       1.85E+00       1.126E-01         Obel of PKR in interferon induction and antiviral response       1.85E+00       1.24E-01         Death receptor signaling       1.61E+00       1.08E-01       1.28E-01         Nucleotide excision repair pathway       1.57E+00       1.43E+01       1.08E-01         Nucleotide excision repair pathway       1.57E+00       1.43E+00       1.08E-01         Nucleotide excision repair pathway       1.57E+00       1.43E+00	Verbal learning	Hopkins	Clatrin-mediated endocytosis	3.04E+00	1.15E-01
PPAR signaling         2.106+00         1.12E-01           Ceramide signaling         1.92E+00         9.41E-02           Exrogen receptor signaling         1.85E+00         1.02E-01           Circadian rhythm signaling         1.65E+00         1.56E-01           Role of PKR in interferon induction and antiviral response         1.63E+00         1.28E-01           VOrking memory         WMS         NF-x8 signaling         3.79E+00         1.24E-01           KRIR XR activation         1.34E+00         9.41E-02         1.86E+00         1.28E-01           VOrking memory         WMS         NF-x8 signaling         3.79E+00         1.24E-01           Role of pattern recognition receptors in recognition         2.06E+00         1.30E-01           Death receptor signaling         1.61E+00         1.08E-01           Death receptor signaling         1.61E+00         1.30E-01           Nucleotide excision repair pathway         1.57E+00         1.43E-00           Death receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cytosolic pattern recognition receptors         1.47E+00         9.46E-02           G-protein coupled receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cytosolic pattern recognition receptors         1.47E+00			NF-κB signaling	2.37E+00	1.10E-01
Ceramide signaling         1,96E-80         1.22E-00         9,41E-02           G-protein coupled receptor signaling         1,85E+00         1.02E-01           Circadian rhythm signaling         1,65E+00         1.26E-01           Role of PKR in interferon induction and antiviral response         1,63E+00         1.26E-01           UXRXR activation         1,34E+00         9,41E-02           LXRXRX activation         1,34E+00         9,41E-02           Vorking memory         WMS         NF-x8 signaling         2,08E+00         1,22E-01           NF-x8 signaling         2,08E+00         1,23E+01         1,24E-01           Role of PKR in interferon induction and antiviral response         1,85E+00         1,28E-01           Nucleotide excision repair pathway         1,57E+00         1,28E-01           Nucleotide excision repair pathway         1,57E+00         1,43E-00           Inositol phosphate metabolism         1,33E+00         7,51E-02           G-BAP creeptor signaling         1,49E+00         1,49E-00           LN span         JAK/stat signaling         1,45E+00         1,49E-00           LN span         JAK/stat signaling         1,58E+00         1,49E-00           LN span         JAK/stat signaling         2,45E+00         9,46E-02      <			PPAR signaling	2.10E+00	1.12E-01
G-protein coupled receptor signaling         1,92E+00         9,41E-02           Escrogen receptor signaling         1,85E+00         1,02E-01           Circadian rhythm signaling         1,65E+00         1,28E-01           TOGF-β signaling         1,61E+00         1,28E-01           UXR/RX activation         1,34E+00         9,41E-02           Working memory         WMS         NF-k8 signaling         3,79E+00         1,24E-01           Role of PKR in interferon induction and antiviral response         1,38E+00         1,24E-01           No facteria and viruses         7041-14ke receptor signaling         2,08E+00         1,23E-01           Role of PKR in interferon induction and antiviral response         1,63E+00         1,28E-01           Death receptor signaling         1,61E+00         1,08E-01           Nucleotide excision repair pathway         1,57E+00         1,43E-00           Inositol phosphare metabolism         1,53E+00         7,51E-02           G-protein coupled receptor signaling         1,49E+00         7,92E-02           Activation of IR by cytosolic pattern recognition receptors         1,47E+00         9,46E-02           One carbon pool by folate         1,79E+00         1,08E-01           ILN span         JAK/stat signaling         1,58E+00         9,43E-02			Ceramide signaling	1.96E+00	1.22E-01
Estrogen receptor signaling         1.85E+00         1.26E-01           Circadian rhythm signaling         1.65E+00         1.56E+00           TGF-f) signaling         1.61E+00         1.28E-01           UXR/RX activation         1.34E+00         9.41E-02           WMS         NF-x5 signaling         3.79E+00         1.28E-01           NF-x5 signaling         3.79E+00         1.18E-01         0           of bacteria and viruses         TOI-like receptor signaling         2.08E+00         1.30E-01           Nel of PKR in interferon induction and antiviral response         1.85E+00         1.28E-01           Nucleotide excision regair pathway         1.57E+00         1.48E-01           Nucleotide excision regair pathway         1.57E+00         1.48E-01           Inositol phosphate metabolism         1.53E+00         7.92E-02           GABA receptor signaling         1.49E+00         7.92E-02           GABA receptor signaling         1.49E+00         7.92E-02           GABA receptor signaling         1.49E+00         1.99E-01           TGF-f5 signaling         2.22E+00         8.41E-02           One carbon pool by foltre         1.79E+00         1.06E-01           EGF signaling         1.56E+00         9.43E-02           Domain <td></td> <td></td> <td>G-protein coupled receptor signaling</td> <td>1.92E+00</td> <td>9.41E-02</td>			G-protein coupled receptor signaling	1.92E+00	9.41E-02
Circadian rhythm signaling         1.65E-00         1.56E-01           Role of PKR in interferon induction and antiviral response         1.63E+00         1.28E-01           TGF-β signaling         3.79E+00         1.24E-01           Working memory         WMS         NF-k8 signaling         3.79E+00         1.24E-01           Role of pattern recognition receptors in recognition         2.30E+00         1.38E-01           of bacteria and viruses         70E-11kike receptor signaling         2.08E+00         1.30E-01           Role of PKR in interferon induction and antiviral response         1.85E+00         1.38E-01           Nexk KR in interferon induction and antiviral response         1.61E+00         1.08E-01           Nucleotide excision repair pathway         1.57E+00         1.43E-01           Nucleotide excision repair pathway         1.57E+00         7.51E-02           G-Protein coupled receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cytosolic pattern recognition receptors         1.47E+00         9.46E-02           GABA receptor signaling         2.32E+00         8.41E-02           One carbo nool by folate         1.79E+00         1.06E-01           ILV span         JAK/stat signaling         1.52E+00         7.53E-02           Lift-fold         GABA			Estrogen receptor signaling	1.85E+00	1.02E-01
Working memory         WMS         NF-β signaling LXR/RXR activation         1.38E-00         1.28E-01           Working memory         WMS         NF-κB signaling LXR/RXR activation         3.79E+00         1.24E-01           Role of pattern recognition receptors in recognition of bacteria and viruses         2.08E+00         1.38E-00           Toll-like receptor signaling         2.08E+00         1.38E-01           Nucleotide excision repair pathway         1.57E+00         1.38E-01           Nucleotide excision repair pathway         1.57E+00         1.43E-01           Inositol phosphate metabolism         1.53E+00         7.51E-02           GapArotein coupled receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cryosolic pattern recognition receptors         1.47E+00         9.46E-02           GaBA receptor signaling         1.43E+00         1.09E-01           TGF-β signaling         2.43E+00         9.46E-02           One carbon pool by folate         1.79E+00         1.49E+00           UN span         JAK/stat signaling         2.55E+00         1.19E-01           US spaling         2.43E+00         9.46E-02         0ne carbon pool by folate         1.79E+00         1.05E-01           UN span         JAK/stat signaling         1.54E+00         7.53E-0			Circadian rhythm signaling	1.65E+00	1.56E-01
Working memory         WMS         I.08E-01 LXR/RX activation         1.34E+00         9.41E-02           Working memory         WMS         NF-k8 signaling         3.79E+00         1.24E-01           Role of pattern recognition receptors in recognition         2.30E+00         1.18E-01           of bacteria and viruses         1.08E-01         1.30E-01           Toll-like receptor signaling         2.08E+00         1.28E-01           Death receptor signaling         1.61E+00         1.08E-01           Nucleotide excision repair pathway         1.57E+00         1.43E-00           Inositol phosphate metabolism         1.53E+00         7.51E-02           G-protein coupled receptor signaling         1.47E+00         9.46E-02           GABA receptor signaling         2.43E+00         9.46E-02           One carbon pool by foate         1.79E+00         1.09E-01           LN span         JAK/stat signaling         2.43E+00         9.46E-02           One carbon pool by foate         1.79E+00         1.09E-01           LV span         JAK/stat signaling         2.43E+00         9.46E-02           U. signaling         1.59E+00         1.05E-01         1.95E+00         1.06E-01           EGF signaling         1.79E+00         1.05E-01         1.55E+00 <td></td> <td></td> <td>Role of PKR in interferon induction and antiviral response</td> <td>1.63E+00</td> <td>1.28E-01</td>			Role of PKR in interferon induction and antiviral response	1.63E+00	1.28E-01
UND Right activation         1.34E+00         9.41E-02           Working memory         WMS         NF-xB signaling         3.79E+00         1.24E-01           Role of patterm recognition receptors in recognition         2.30E+00         1.30E-01           Role of patterm recognition receptors in recognition         2.08E+00         1.30E-01           Role of PKR in interferon induction and antiviral response         1.65E+00         1.28E-01           Nucleotide excision repair pathway         1.57E+00         1.43E-01           Inositol phosphare metabolism         1.53E+00         7.51E-02           G-protein coupled receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cytosolic pattern recognition receptors         1.47E+00         9.46E-02           GABA receptor signaling         1.43E+00         1.09E-01           LN span         IAK/stat signaling         2.35E+00         1.47E+00           One carbon pool by folate         1.79E+00         8.41E-02         0:66E-02           One carbon pool by folate         1.79E+00         8.00E-02         1.04E+00           Erythropoietin signaling         1.54E+00         7.53E-02         SAPK/JNK signaling         1.54E+00         7.53E-02           SAPK/JNK signaling         1.44E+00         8.00E-02			TGF- $\beta$ signaling	1.61E+00	1.08E-01
Working memory         WMS         NF-κB signaling Role of pattern recognition recognition         3.79E+00         1.24E-01           Role of pattern recognition recognition         2.30E+00         1.18E-01           of bacteria and viruses         70II-like receptor signaling         2.06E+00         1.30E-01           Death receptor signaling         2.06E+00         1.30E-01           Death receptor signaling         1.61E+00         1.08E-01           Nucleotide excision repair pathway         1.57E+00         1.43E-01           Inositol phosphate metabolism         1.53E+00         7.51E-02           G-protein coupled receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cytosolic pattern recognition receptors         1.47E+00         9.64E-02           GABA receptor signaling         2.32E+00         8.41E-02           One carbon pool by folate         1.79E+00         1.05E-01           Cardernergic signaling         2.32E+00         8.41E-02           One carbon pool by folate         1.79E+00         1.05E-01           EGF signaling         1.56E+00         7.53E-02           Domain         Neuropulni signaling         1.54E+00         7.53E-02           APK/JNK signaling         1.56E+00         5.63E-02         Chemonkine signaling			LXR/RXR activation	I.34E+00	9.41E-02
Role of pattern recognition recognition2.30E+001.18E-01of bacteria and viruses70H1kr erceptor signaling2.00E+001.30E-01Role of PKR in interferon induction and antiviral response1.85E+001.28E-01Death receptor signaling1.61E+001.08E-01Nucleotide excision repair pathway1.57E+001.43E-01Inositol phosphate metabolism1.53E+007.72E-02G-protein coupled receptor signaling1.49E+007.92E-02GAA receptor signaling1.49E+001.09E-01LN spanJAK/stat signaling2.55E+001.19E-01TGF-β signaling2.32E+008.41E-02One carbon pool by folate1.79E+001.05E-01ECF signaling1.54E+007.53E-02Virupopietin signaling1.54E+007.53E-02Neuregulin signaling1.54E+007.53E-02SAPK/L/NK signaling1.54E+007.53E-02Chemokine signaling1.54E+007.53E-02SAPK/L/NK signaling1.54E+007.53E-02Chemokine signaling1.43E+006.58E-02Complement system1.65E+005.63E-02Nicotinate and nicotinamide metabolism1.32E+003.88E-02Nicotinate and nicotinamide metabolism1.32E+003.88E-	Working memory	WMS	NF-κB signaling	3.79E+00	1.24E-01
of batteria and viruses Toll-like receptor signaling Nucleotide excision repair pathway 1.61E+00 1.30E-01 Nucleotide excision repair pathway 1.57E+00 1.53E+00 7.51E-02 G-protein coupled receptor signaling 1.47E+00 7.92E-02 Activation of IRF by cytosolic pattern recognition receptors 1.47E+00 7.92E-02 Activation of IRF by cytosolic pattern recognition receptors 1.47E+00 7.92E-02 0.43E+00 7.92E-02 0.43E+00 7.92E-02 0.43E+00 7.92E-02 0.43E+00 7.92E-02 0.43E+00 7.92E-02 0.43E+00 7.92E-02 0.43E+00 7.92E-00 1.92E+00 1.92E+00 1.92E+00 1.92E+00 1.92E+00 1.92E+00 1.92E+00 1.92E+00 1.92E+00 1.93			Role of pattern recognition receptors in recognition	2.30E+00	1.18E-01
Toll-like receptor signaling       2.08E-00       1.30E-01         Role of PKR in interferon induction and antiviral response       1.85E+00       1.28E-01         Death receptor signaling       1.61E+00       1.08E-01         Nucleotide excision repair pathway       1.57E+00       1.43E-01         Inositol phosphate metabolism       1.53E+00       7.51E-02         G-protein coupled receptor signaling       1.47E+00       7.92E-02         Activation of IRF by cytosolic pattern recognition receptors       1.47E+00       7.92E-02         Activation of IRF by cytosolic pattern recognition receptors       1.47E+00       7.92E-02         Activation of IRF by cytosolic pattern recognition receptors       1.47E+00       7.92E-02         Activation of IRF by cytosolic pattern recognition receptors       1.47E+00       9.46E-02         GABA receptor signaling       2.55E+00       1.19E-01         TGF-β signaling       2.43E+00       9.64E-02         One carbon pool by folate       1.79E+00       1.06E-01         EGF signaling       1.54E+00       7.53E-02         Neuregulin signaling       1.54E+00       7.53E-02         Chemokine signaling       1.54E+00       7.53E-02         Neuregulin signaling in the cardiovascular system       1.56E+00       6.54B-02			of bacteria and viruses		
Role of PKR in interferon induction and antiviral response1.85E+001.28E-01Death receptor signaling1.61E+001.08E-01Nucleotide excision repair pathway1.57E+007.31E-02G-protein coupled receptor signaling1.49E+007.92E-02Activation of IRF by cytosolic pattern recognition receptors1.47E+009.46E-02GABA receptor signaling1.43E+001.09E-01LN spanJAK/stat signaling2.55E+001.19E-01TGF-f \$ signaling2.22E+008.41E-02One carbon pool by folate1.79E+001.05E-01EGF signaling1.55E+009.43E-02One carbon pool by folate1.79E+001.05E-01EGF signaling1.55E+009.43E-02Neuregulin signaling1.54E+007.53E-02SAPK/JNK signaling1.54E+007.53E-02Chemokine signaling1.54E+007.53E-02SAPK/JNK signaling1.54E+007.53E-02Chemokine signaling1.44E+008.33E-02Nucerouplin/TRK signaling1.45E+005.63E-02Complement system1.73E+008.33E-02Nicotinate and nicotinamide metabolism1.53E+003.88E-02Nig/ycan degradation1.99E+003.88E-02Nicotinate and nicotinamide metabolism1.23E+003.88E-02Nicotinate and nicotinamide metabolism1.23E+003.88E-02Nicotinate and nicotinamide metabolism1.32E+003.28E-02Nicotinate and nicotinamide metabolism1.32E+003.28E-02Nicotinate and nicotin			Toll-like receptor signaling	2.08E+00	1.30E-01
Death receptor signaling       1.61E+00       1.08E-01         Nucleotide excision repair pathway       1.57E+00       1.43E-01         Inositol phosphate metabolism       1.53E+00       7.51E-02         G-protein coupled receptor signaling       1.47E+00       7.92E-02         Activation of IRF by cytosolic pattern recognition receptors       1.47E+00       9.46E-02         GABA receptor signaling       1.43E+00       1.09E-01         LN span       JAK/stat signaling       2.55E+00       1.19E-01         G-F signaling       2.43E+00       8.41E-02       0.06 carbon pool by folate       1.79E+00       1.05E-01         EGF signaling       1.53E+00       1.05E-01       1.55E+00       9.43E-02         One carbon pool by folate       1.79E+00       1.05E-01       1.65E-00       9.43E-02         L-2 signaling       1.54E+00       7.53E-02       1.65E-00       9.43E-02         Neuregulin signaling       1.54E+00       7.53E-02       2.6E+00       6.58E-02         Chemokine signaling       1.54E+00       7.53E-02       2.6E+00       6.58E-02         Domain       NeuroguninyTRK signaling       1.5E+00       5.63E-02         Nicotinate and nicotinamide metabolism       1.53E+00       3.38E-02         Nicotinat			Role of PKR in interferon induction and antiviral response	1.85E+00	1.28E-01
Nucleotide excision repair pathway1.57E+001.43E-01Inositol phosphate metabolism1.33E+007.51E-02G-protein coupled receptor signaling1.49E+007.92E-02Activation of IRF by cytosolic pattern recognition receptors1.47E+009.46E-02GABA receptor signaling2.55E+001.19E-01LN spanJAK/stat signaling2.55E+001.19E-01TGF-β signaling2.22E+008.41E-02or-adrenergic signaling2.22E+008.41E-02One carbon pool by folate1.79E+001.05E-01EGF signaling1.59E+008.00E-02IL-2 signaling1.56E+009.43E-02Neuregulin signaling1.54E+007.53E-02Neuregulin signaling1.54E+007.53E-02APK/JNK signaling1.64E+008.00E-02LOmmainNeurotrophin/TRK signaling1.65E+00DomainNeurotrophin/TRK signaling1.65E+00Neotoniate and nicotinamide metabolism1.33E+003.63E-02Nicotinate and nicotinamide metabolism1.33E+003.63E-02Nicotinate and nicotinamide metabolism1.33E+003.08E-02Nicotinate and nicotinamide metabolism1.33E+002.80E-02Nicotinate and nicotinamide metabolism1.32E+002.80E-02Nicotinate and nicotinamide metabolism1.32E+003.28E-02Nicotinate and nicotinamide metabolism1.32E+003.28E-02Nicotinate and nicotinamide metabolism1.32E+003.28E-02Nicotinate and nicotinamide metabolism1.32E+003.			Death receptor signaling	1.61E+00	1.08E-01
Inositol phosphate metabolism         1.53E+00         7.51E-02           G-protein coupled receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cytosolic pattern recognition receptors         1.47E+00         9.46E-02           GABA receptor signaling         1.43E+00         1.09E-01           LN span         JAK/stat signaling         2.55E+00         1.19E-01           Co-adrenergic signaling         2.43E+00         9.64E-02           α-adrenergic signaling         2.22E+00         8.41E-02           One carbon pool by folate         1.79E+00         1.05E-01           EGF signaling         1.73E+00         1.06E-01           Erythropoietin signaling         1.54E+00         7.53E-02           Neuregulin signaling         1.54E+00         7.53E-02           Chemokine signaling         1.54E+00         7.53E-02           Chemokine signaling         1.6E+00         6.58E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.53E+00         3.68E-02           Nicotinate and nicotinamide metabolism         1.53E+00         3.68E-02           Nicotinate and nicotinamide metabolism         1.33E+00         3.68E-02           Nicotinate and			Nucleotide excision repair pathway	1.57E+00	1.43E-01
G-protein coupled receptor signaling         1.49E+00         7.92E-02           Activation of IRF by cytosolic pattern recognition receptors         1.47E+00         9.46E-02           GABA receptor signaling         1.43E+00         1.09E-01           LN span         JAK/stat signaling         2.35E+00         1.19E-01           TGF-β signaling         2.43E+00         9.64E-02           c-adrenergic signaling         2.22E+00         8.41E-02           One carbon pool by folate         1.79E+00         1.05E-01           EGF signaling         1.73E+00         1.06E-01           Erythropoietin signaling         1.54E+00         7.53E-02           Neuregulin signaling         1.54E+00         7.53E-02           Chemokine signaling         1.54E+00         7.53E-02           Chemokine signaling         1.54E+00         7.53E-02           Chemokine signaling         1.54E+00         6.58E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.58E+00         5.63E-02           Nicotinate and nicotinamide metabolism         1.33E+00         6.67E-02           Nicotinate and nicotinamide metabolism         1.32E+00         2.80E-02           Nicotinate and nicotinamide meta			Inositol phosphate metabolism	1.53E+00	7.51E-02
Activation of IRF by cytosolic pattern recognition receptors         1.47E+00         9.46E-02           GABA receptor signaling         1.43E+00         1.09E-01           LN span         JAK/stat signaling         2.55E+00         1.19E-01           TGF-β signaling         2.43E+00         9.64E-02         0           α-adrenergic signaling         2.22E+00         8.41E-02         0         0           One carbon pool by folate         1.79E+00         1.05E-01         0         0.05E-01           EGF signaling         1.59E+00         8.00E-02         0.06E-01         0.05E-01         0.05E-01           LP signaling         1.54E+00         7.53E-02         0.06E-01         0.05E-01         0.05E-02           LL-2 signaling         1.54E+00         7.53E-02         0.06E-02         0.06E-02         0.06E-02           Neuregulin signaling         1.54E+00         7.53E-02         0.06E-02			G-protein coupled receptor signaling	I.49E+00	7.92E-02
GABA receptor signaling         1.43E+00         1.09E-01           LN span         JAK/stat signaling         2.55E+00         1.19E-01           TGF-β signaling         2.43E+00         9.64E-02           α-adrenergic signaling         2.22E+00         8.41E-02           α-adrenergic signaling         1.79E+00         1.05E-01           EGF signaling         1.73E+00         1.05E-01           EGF signaling         1.59E+00         8.00E-02           IL-2 signaling         1.56E+00         9.43E-02           Neuregulin signaling         1.54E+00         7.53E-02           SAPK/JNK signaling         1.54E+00         7.53E-02           Chemokine signaling         1.44E+00         8.00E-02           Domain         Neurotrophin/TRK signaling         1.65E+00         7.53E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.65E+00         5.63E-02           Nicotinate and nicotinamide metabolism         1.33E+00         3.88E-02           Neg/can degradation         1.39E+00         6.67E-02           Phenylalanine metabolism         1.23E+00         3.28E-02           Nicotinate and nicotinamide metabolism         1.38E+00         3.28E-02 <td></td> <td></td> <td>Activation of IRF by cytosolic pattern recognition receptors</td> <td>I.47E+00</td> <td>9.46E-02</td>			Activation of IRF by cytosolic pattern recognition receptors	I.47E+00	9.46E-02
LN span         JAK/stat signaling         2.55E+00         1.19E-01           TGF-β signaling         2.43E+00         9.64E-02           α-adrenergic signaling         2.22E+00         8.41E-02           One carbon pool by folate         1.79E+00         1.05E-01           EGF signaling         1.73E+00         1.06E-01           Erythropoietin signaling         1.59E+00         8.00E-02           IL-2 signaling         1.56E+00         9.43E-02           Neuregulin signaling         1.54E+00         7.53E-02           SAPK/JNK signaling         1.54E+00         7.53E-02           Chemokine signaling         1.44E+00         8.00E-02           Complement system         1.73E+00         6.58E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.65E+00         5.63E-02           Nicotinate and nicotinamide metabolism         1.53E+00         3.88E-02           N-glycan degradation         1.39E+00         6.67E-02           Phenylalanine metabolism         1.23E+00         2.80E-02           NRF2-mediated oxidative stress response         1.12E+00         3.28E-02           Airway inflammation in asthma         1.08E+00         1.67E-01 <td></td> <td></td> <td>GABA receptor signaling</td> <td>I.43E+00</td> <td>1.09E-01</td>			GABA receptor signaling	I.43E+00	1.09E-01
TGF-β signaling       2.43E+00       9.64E-02         α-adrenergic signaling       2.22E+00       8.41E-02         One carbon pool by folate       1.79E+00       1.05E-01         EGF signaling       1.73E+00       1.06E-01         Erythropoietin signaling       1.59E+00       8.00E-02         IL-2 signaling       1.56E+00       9.43E-02         Neuregulin signaling       1.54E+00       7.53E-02         SAPK/JNK signaling       1.54E+00       7.53E-02         Chemokine signaling       1.44E+00       8.00E-02         Domain       Neurotrophin/TRK signaling       2.16E+00       6.58E-02         Complement system       1.73E+00       8.33E-02         Hypoxia signaling in the cardiovascular system       1.65E+00       5.63E-02         Nicotinate and nicotinamide metabolism       1.53E+00       3.88E-02         N-glycan degradation       1.39E+00       6.67E-02         Phenylalanine metabolism       1.23E+00       2.80E-02         NRF2-mediated oxidative stress response       1.12E+00       3.28E-02         Airway inflammation in asthma       1.08E+00       1.67E-01         Histidine metabolism       1.05E+00       2.70E-02         Purine metabolism       1.05E+00       2.70E-02 <td></td> <td>LN span</td> <td>JAK/stat signaling</td> <td>2.55E+00</td> <td>1.19E-01</td>		LN span	JAK/stat signaling	2.55E+00	1.19E-01
α-adrenergic signaling         2.22E+00         8.41E-02           One carbon pool by folate         1.79E+00         1.05E-01           EGF signaling         1.73E+00         1.06E-01           Erythropoietin signaling         1.59E+00         8.00E-02           IL-2 signaling         1.56E+00         9.43E-02           Neuregulin signaling         1.54E+00         7.53E-02           SAPK/JNK signaling         1.54E+00         7.53E-02           Chemokine signaling         1.44E+00         8.00E-02           Domain         Neurotrophin/TRK signaling         2.16E+00         6.58E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.65E+00         5.63E-02           Nicotinate and nicotinamide metabolism         1.53E+00         3.88E-02           Neglvcan degradation         1.39E+00         6.67E-02           Phenylalanine metabolism         1.23E+00         2.80E-02           NRF2-mediated oxidative stress response         1.12E+00         3.28E-02           Airway inflammation in asthma         1.08E+00         1.67E-01           Histidine metabolism         0.05E+00         2.70E-02           Purine metabolism         1.05E+00         2.40E-02 </td <td></td> <td></td> <td>TGF-<math>\beta</math> signaling</td> <td>2.43E+00</td> <td>9.64E-02</td>			TGF- $\beta$ signaling	2.43E+00	9.64E-02
One carbon pool by folate         1.79E+00         1.05E-01           EGF signaling         1.73E+00         1.06E-01           Erythropoietin signaling         1.59E+00         8.00E-02           IL-2 signaling         1.56E+00         9.43E-02           Neuregulin signaling         1.54E+00         7.53E-02           SAPK/JNK signaling         1.54E+00         7.53E-02           Chemokine signaling         1.44E+00         8.00E-02           Domain         Neurotrophin/TRK signaling         2.16E+00         6.58E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.65E+00         5.63E-02           Nicotinate and nicotinamide metabolism         1.39E+00         6.67E-02           Phenylalanine metabolism         1.23E+00         2.80E-02           NRF2-mediated oxidative stress response         1.12E+00         3.28E-02           Airway inflammation in asthma         1.08E+00         1.67E-01           Histidine metabolism         1.03E+00         2.70E-02           Purine metabolism         1.03E+00         2.40E-02			lpha-adrenergic signaling	2.22E+00	8.41E-02
EGF signaling       1.73E+00       1.06E-01         Erythropoietin signaling       1.59E+00       8.00E-02         IL-2 signaling       1.56E+00       9.43E-02         Neuregulin signaling       1.54E+00       7.53E-02         SAPK/JNK signaling       1.54E+00       7.53E-02         Chemokine signaling       1.44E+00       8.00E-02         Domain       Neurotrophin/TRK signaling       2.16E+00       6.58E-02         Complement system       1.73E+00       8.33E-02         Hypoxia signaling in the cardiovascular system       1.65E+00       5.63E-02         Nicotinate and nicotinamide metabolism       1.39E+00       6.67E-02         Phenylalanine metabolism       1.23E+00       2.80E-02         NRF2-mediated oxidative stress response       1.12E+00       3.28E-02         Airway inflammation in asthma       1.08E+00       1.67E-01         Histidine metabolism       1.05E+00       2.70E-02         Purine metabolism       1.03E+00       2.70E-02			One carbon pool by folate	I.79E+00	1.05E-01
Erythropoietin signaling         1.59E+00         8.00E-02           IL-2 signaling         1.56E+00         9.43E-02           Neuregulin signaling         1.54E+00         7.53E-02           SAPK/JNK signaling         1.54E+00         7.53E-02           Chemokine signaling         1.44E+00         8.00E-02           Domain         Neurotrophin/TRK signaling         2.16E+00         6.58E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.65E+00         5.63E-02           Nicotinate and nicotinamide metabolism         1.53E+00         3.88E-02           N-glycan degradation         1.39E+00         6.67E-02           Phenylalanine metabolism         1.23E+00         2.80E-02           NRF2-mediated oxidative stress response         1.12E+00         3.28E-02           Airway inflammation in asthma         1.08E+00         1.67E-01           Histidine metabolism         1.05E+00         2.70E-02           Purine metabolism         1.03E+00         2.40E-02			EGF signaling	1.73E+00	1.06E-01
IL-2 signaling       I.56E+00       9.43E-02         Neuregulin signaling       I.54E+00       7.53E-02         SAPK/JNK signaling       I.54E+00       7.53E-02         Chemokine signaling       I.44E+00       8.00E-02         Domain       Neurotrophin/TRK signaling       2.16E+00       6.58E-02         Complement system       I.73E+00       8.33E-02         Hypoxia signaling in the cardiovascular system       I.65E+00       5.63E-02         Nicotinate and nicotinamide metabolism       I.53E+00       3.88E-02         N-glycan degradation       I.39E+00       6.67E-02         Phenylalanine metabolism       I.23E+00       2.80E-02         Airway inflammation in asthma       I.08E+00       I.67E-01         Histidine metabolism       I.05E+00       2.70E-02         Purine metabolism       I.03E+00       2.40E-02			Erythropoietin signaling	1.59E+00	8.00E-02
Neuregulin signaling         1.54E+00         7.53E-02           SAPK/JNK signaling         1.54E+00         7.53E-02           Chemokine signaling         1.44E+00         8.00E-02           Domain         Neurotrophin/TRK signaling         2.16E+00         6.58E-02           Complement system         1.73E+00         8.33E-02           Hypoxia signaling in the cardiovascular system         1.65E+00         5.63E-02           Nicotinate and nicotinamide metabolism         1.53E+00         3.88E-02           N-glycan degradation         1.39E+00         6.67E-02           Phenylalanine metabolism         1.23E+00         2.80E-02           NRF2-mediated oxidative stress response         1.12E+00         3.28E-02           Airway inflammation in asthma         1.08E+00         1.67E-01           Histidine metabolism         1.05E+00         2.70E-02           Purine metabolism         1.03E+00         2.40E-02			IL-2 signaling	1.56E+00	9.43E-02
SAPK/JNK signaling1.54E+007.53E-02Chemokine signaling1.44E+008.00E-02DomainNeurotrophin/TRK signaling2.16E+006.58E-02Complement system1.73E+008.33E-02Hypoxia signaling in the cardiovascular system1.65E+005.63E-02Nicotinate and nicotinamide metabolism1.53E+003.88E-02N-glycan degradation1.39E+006.67E-02Phenylalanine metabolism1.23E+002.80E-02NRF2-mediated oxidative stress response1.12E+003.28E-02Airway inflammation in asthma1.08E+001.67E-01Histidine metabolism1.05E+002.70E-02Purine metabolism1.03E+002.40E-02			Neuregulin signaling	1.54E+00	7.53E-02
Chemokine signaling1.44E+008.00E-02DomainNeurotrophin/TRK signaling2.16E+006.58E-02Complement system1.73E+008.33E-02Hypoxia signaling in the cardiovascular system1.65E+005.63E-02Nicotinate and nicotinamide metabolism1.53E+003.88E-02N-glycan degradation1.39E+006.67E-02Phenylalanine metabolism1.23E+002.80E-02NRF2-mediated oxidative stress response1.12E+003.28E-02Airway inflammation in asthma1.08E+001.67E-01Histidine metabolism1.05E+002.70E-02Purine metabolism1.03E+002.40E-02			SAPK/JNK signaling	1.54E+00	7.53E-02
DomainNeurotrophin/TRK signaling2.16E+006.58E-02Complement system1.73E+008.33E-02Hypoxia signaling in the cardiovascular system1.65E+005.63E-02Nicotinate and nicotinamide metabolism1.53E+003.88E-02N-glycan degradation1.39E+006.67E-02Phenylalanine metabolism1.23E+002.80E-02NRF2-mediated oxidative stress response1.12E+003.28E-02Airway inflammation in asthma1.08E+001.67E-01Histidine metabolism1.05E+002.70E-02Purine metabolism1.03E+002.40E-02			Chemokine signaling	I.44E+00	8.00E-02
Complement system1.73E+008.33E-02Hypoxia signaling in the cardiovascular system1.65E+005.63E-02Nicotinate and nicotinamide metabolism1.53E+003.88E-02N-glycan degradation1.39E+006.67E-02Phenylalanine metabolism1.23E+002.80E-02NRF2-mediated oxidative stress response1.12E+003.28E-02Airway inflammation in asthma1.08E+001.67E-01Histidine metabolism1.05E+002.70E-02Purine metabolism1.03E+002.40E-02		Domain	Neurotrophin/TRK signaling	2.16E+00	6.58E-02
Hypoxia signaling in the cardiovascular system1.65E+005.63E-02Nicotinate and nicotinamide metabolism1.53E+003.88E-02N-glycan degradation1.39E+006.67E-02Phenylalanine metabolism1.23E+002.80E-02NRF2-mediated oxidative stress response1.12E+003.28E-02Airway inflammation in asthma1.08E+001.67E-01Histidine metabolism1.05E+002.70E-02Purine metabolism1.03E+002.40E-02			Complement system	1.73E+00	8.33E-02
Nicotinate and nicotinamide metabolism1.53E+003.88E-02N-glycan degradation1.39E+006.67E-02Phenylalanine metabolism1.23E+002.80E-02NRF2-mediated oxidative stress response1.12E+003.28E-02Airway inflammation in asthma1.08E+001.67E-01Histidine metabolism1.05E+002.70E-02Purine metabolism1.03E+002.40E-02			Hypoxia signaling in the cardiovascular system	1.65E+00	5.63E-02
N-glycan degradation1.39E+006.67E-02Phenylalanine metabolism1.23E+002.80E-02NRF2-mediated oxidative stress response1.12E+003.28E-02Airway inflammation in asthma1.08E+001.67E-01Histidine metabolism1.05E+002.70E-02Purine metabolism1.03E+002.40E-02			Nicotinate and nicotinamide metabolism	1.53E+00	3.88E-02
Phenylalanine metabolism     1.23E+00     2.80E-02       NRF2-mediated oxidative stress response     1.12E+00     3.28E-02       Airway inflammation in asthma     1.08E+00     1.67E-01       Histidine metabolism     1.05E+00     2.70E-02       Purine metabolism     1.03E+00     2.40E-02			N-glycan degradation	1.39E+00	6.67E-02
NRF2-mediated oxidative stress response     1.12E+00     3.28E-02       Airway inflammation in asthma     1.08E+00     1.67E-01       Histidine metabolism     1.05E+00     2.70E-02       Purine metabolism     1.03E+00     2.40E-02			Phenylalanine metabolism	1.23E+00	2.80E-02
Airway inflammation in asthma       1.08E+00       1.67E-01         Histidine metabolism       1.05E+00       2.70E-02         Purine metabolism       1.03E+00       2.40E-02			NRF2-mediated oxidative stress response	1.12E+00	3.28E-02
Histidine metabolism     1.05E+00     2.70E-02       Purine metabolism     1.03E+00     2.40E-02			Airway inflammation in asthma	1.08F+00	1.67E-01
Purine metabolism I.03E+00 2.40E-02			Histidine metabolism	1.05F+00	2.70F-02
(Continued)			Purine metabolism	1.03F+00	2.40E-02
					(Continued)

### Table SI (Continued)

Domain	Test	Canonical pathway	Log p	Ratio
Visual learning	BVMT	Axonal guidance signaling	3.45E+00	7.42E-02
0		Integrin signaling	2.33E+00	8.29E-02
		Sonic hedgehog signaling	2.19E+00	1.61E-01
		Calcium signaling	1.92E+00	6.93E-02
		Regulation of actin-based motility by rho	1.67E+00	8.70E-02
		Synthesis and degradation of ketone bodies	1.53E+00	1.58E-01
		Lysine biosynthesis	I.47E+00	4.69E-02
		IL-10 signaling	1.33E+00	8.45E-02
		Coagulation system	1.29E+00	1.08E-01
		NF-κB signaling	1.24E+00	6.90E-02
Speed of processing	Category	cAMP-mediated signaling	I.84E+00	8.18E-02
	• •	Valine, leucine and isoleucine degradation	I.74E+00	8.41E-02
		Synthesis and degradation of ketone bodies	I.49E+00	1.58E-01
		Phototransduction pathway	I.40E+00	9.52E-02
		$TGF-\beta$ signaling	I.37E+00	8.43E-02
		Calcium signaling	1.17E+00	5.94E-02
		Glycerophospholipid metabolism	1.10E+00	5.62E-02
		Cell cycle: G2/M DNA damage checkpoint regulation	1.10E+00	9.30E-02
		Caveolar-mediated endocytosis	9.41E-01	7.41E-02
		Pentose phosphate pathway	9.04E-01	5.62E-02
	BACS	Sonic hedgehog signaling	1.89E+00	1.29E-01
		Lysine biosynthesis	1.78E+00	4.69E-02
		Calcium signaling	1.69E+00	5.45E-02
		Aminosugars metabolism	1.69E+00	5.77E-02
		Cell cycle: GI/S checkpoint regulation	I.57E+00	8.62E-02
		NF-κB signaling	I.54E+00	6.21E-02
		Glycolysis/gluconeogenesis	1.51E+00	5.67E-02
		Axonal guidance signaling	1.25E+00	4.35E-02
		Wnt/β-catenin signaling	1.24E+00	5.45E-02
		Integrin signaling	1.15E+00	5.18E-02
	Trails A	N-glycan degradation	2.01E+00	1.00E-01
		Pantothenate and CoA biosynthesis	1.53E+00	4.76E-02
		Neurotrophin/TRK signaling	1.51E+00	5.41E-02
		Glycine, serine and threonine metabolism	1.39E+00	3.47E-02
		Dopamine receptor signaling	1.18E+00	4.40E-02
		Valine, leucine and isoleucine biosynthesis	1.13E+00	4.44E-02
		NRF2-mediated oxidative stress response	1.12E+00	3.31E-02
		ERK/MAPK signaling	1.06E+00	3.28E-02
		Hypoxia signaling in the cardiovascular system	9.63E-01	4.23E-02
		Folate biosynthesis	9.35E-01	2.63E-02
	Domain	N-glycan degradation	2.34E+00	1.33E-01
		Glycosphingolipid biosynthesis – ganglioseries	I.37E+00	6.90E-02
		Aminosugars metabolism	I.06E+00	6.73E-02
		Glycosphingolipid biosynthesis – globoseries	9.76E-01	7.32E-02
		Glycerolipid metabolism	9.01E-01	4.14E-02
		Eicosanoid signaling	8.75E-01	5.95E-02
		Regulation of actin-based motility by rho	8.06E-01	5.43E-02
		C21-steroid hormone metabolism	7.97E-01	5.71E-02
		T helper cell differentiation	7.82E-01	7.89E-02
A	0.77	Phototransduction pathway	7.59E-01	7.94E-02
Attention/vigilance	СРТ	Neurotrophin/ I KK signaling	1.61E00	5.13E-02
		C I LA4 signaling in cytotoxic 1 lymphocytes	1.36E00	4.49E-02
		Frienylaianine metabolism	1.31EUU	2.8E-02
		NICZ-Ineulated oxidative stress response	1.27 EUU	3.24E-UZ
		ra-giycan degradation	1.21EUU	0.0/E-U2

(Continued)

#### Table SI (Continued)

Domain	Test	Canonical pathway	Log p	Ratio
		Phenylalanine, tyrosine and tryptophan biosynthesis	1.18E00	3.12E-02
		Airway inflammation in asthma	1.12E00	1.67E-01
		One carbon pool by folate	1.1E00	5.26E-02
		Angiopoietin signaling	1.09E00	4.17E-02
		Pyrimidine metabolism	1.09E00	2.63E-02
Social cognition	MSCEIT	Tyrosine metabolism	1.71E00	I.08E-02
		Dendritic cell maturation	I.46E00	1.21E-02
		O-glycan biosynthesis	1.17E00	2.33E-02
		Serotonin receptor signaling	1.08E00	2.17E-02
		Retinol metabolism	1.02E00	1.61E-02
		Phenylalanine metabolism	9.94E-01	9.35E-03
		Role of cytokines in mediating communication between	9.79E-01	I.79E-02
		immune cells		
		Lymphotoxin $\beta$ receptor signaling	9.71E-01	I.69E-02
		C21-steroid hormone metabolism	9.43E-01	I.45E-02
		FGF signaling	8.02E-01	1.14E-02

Abbreviations: NAB, Neuropsychological Assessment Battery; HVLT, Hopkins Verbal Learning Test; SSpan, Wechsler Memory Scale-Spatial span; LN span, letter-number span; BVMT, Brief Visuospatial Memory Test; Cat, category test-animals; BACS, Brief Assessment of Cognition in Schizophrenia; CPT, Continuous Performance Test; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test.

#### Neurobehavioral HIV Medicine

### Publish your work in this journal

Neurobehavioral HIV Medicine is an international, peer-reviewed, open access journal focusing on advances in research in HIV/ AIDS, with specific reference to the neurological, psychiatric and behavioral consequences of the disease, concomitant infections and specific antiretroviral therapy. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/journal-of-neurobehavioral-hiv-medicine-journal

submit your manuscript | www.dovepress.com
Dovepress

32

**Dove**press