

Online Data Supplement

The peripheral blood transcriptome and post-septic cognitive impairment: the Cognition After Sepsis (CASS) observational pilot study

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Supplemental Methods

Weighted Network Analysis

WNA is a robust, mature analytic technology(1-6) for this application. In the first phase of WNA, we construct the correlation matrix corresponding to a weighted network formed from the results of deep sequencing. Next, we used average linkage hierarchical clustering with agglomerative partitioning to cluster patients according to their correlation profiles within the network. This approach operated by converting the correlation profiles into distance metrics and successively merging similar pairs of subjects.(7) The result was a *dendrogram* or cluster tree where patients are grouped into clusters with similar correlation profiles across the deep sequencing results. We then “pruned” the dendrogram in a semi-supervised manner using the dynamic tree-cut procedure to identify the relevant network modules. Modules represent clusters of genes whose expression profiles are correlated; they are expected to approximate biological pathways.

Network modules are typically simplified through principal components analysis, where the first principal component of the module, dubbed the “module eigengene,” summarizes the entire module. In this research, we were interested in the “eigengenes” of two network modules. First, our primary, pre-specified analysis evaluated the association between the first principal component of the network module containing APOE and the 6-month Hayling test. Second, in an exploratory analysis, we sought to identify the network module that was most significantly associated with the 6-month Hayling test.

Secondary Weighted Network Analysis

Because the primary WNA showed a large cluster of low-expression genes, we performed a post hoc analysis using WNA after more strict exclusion of low-expression transcripts (an analysis which excluded APOE). For this analysis, after plotting baseMean transcript counts against log2Foldchange, we identified a group of sparsely expressed genes

which were excluded before re-running the WNA. This process excluded 3500 additional genes with low expression. We then performed standard WNA as outlined above.

Supplemental Results

Primary Weighted Network Analysis Results

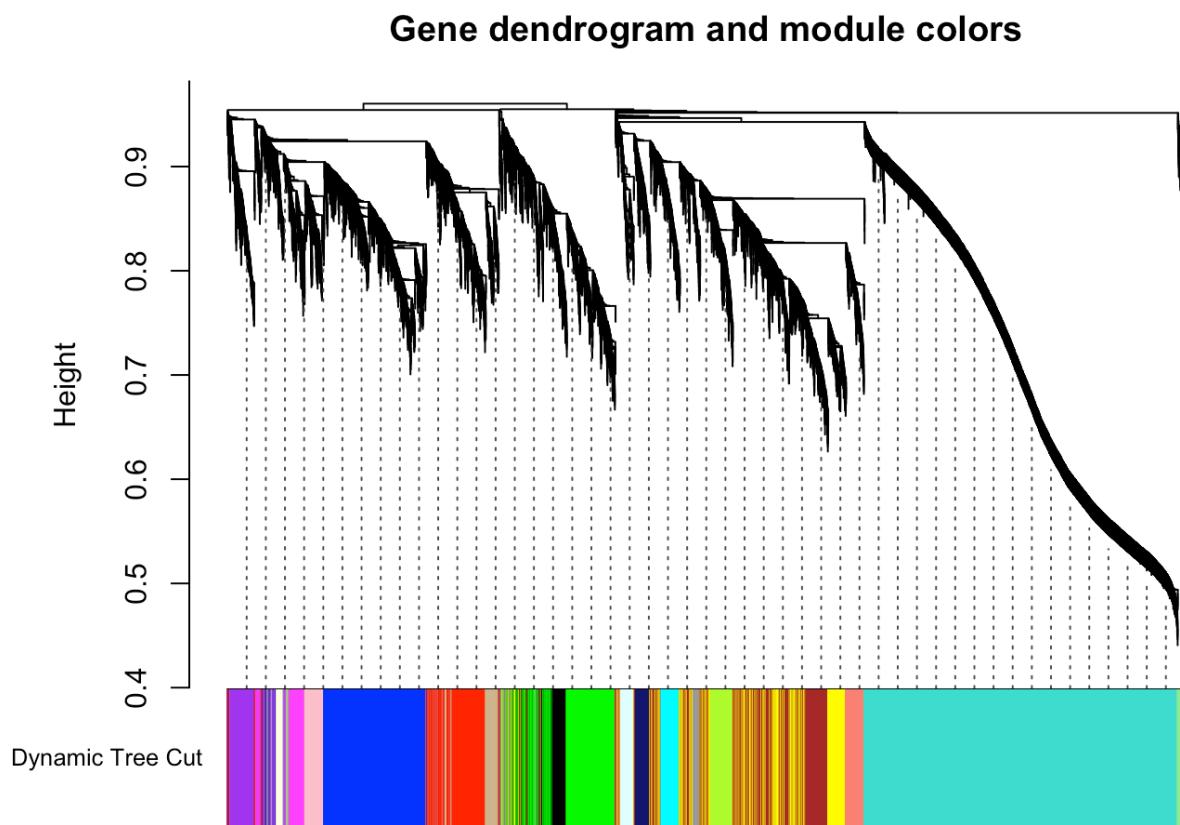
Within WNA, a soft-thresholding power of 6 was chosen based on the empirical appearance of the scale independence figure. Clustering returned 19 discrete modules (eFigure 1). APOE was in the largest cluster (marked as turquoise in eFigure 1). The eigengene of that cluster was not significantly associated with Hayling scores at 6 months. Nor were the eigengenes of the other clusters (eTable 3). We evaluated Gene Ontology enrichment within the modules. eTable 2 lists the top 10 Gene Ontology terms for each of the modules identified within WNA. We employed the Biological Process ontology for the analysis presented in eTable 2.

Secondary Weighted Network Analysis Results

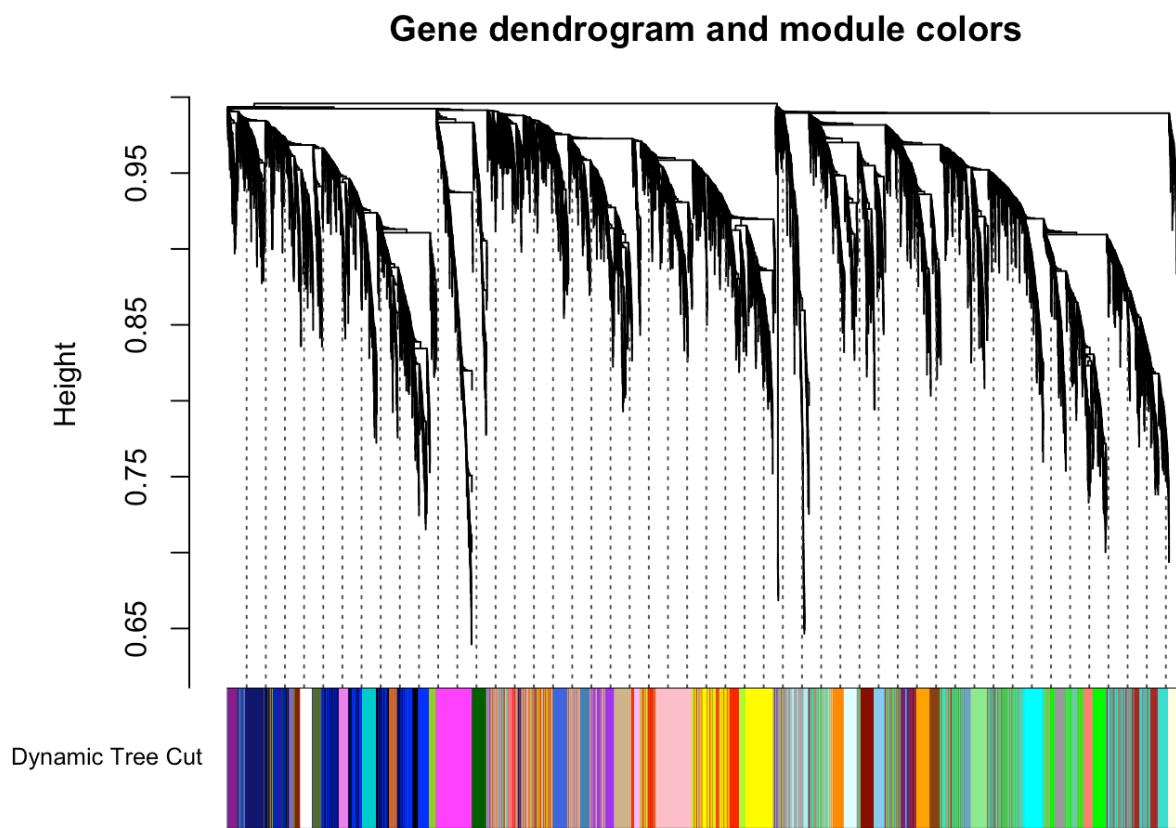
A soft-thresholding power of 12 was chosen based on the empirical appearance of the scale independence figure. Clustering returned 40 discrete modules (eFigure 2). After adjustment for multiple comparisons, no module eigengenes were associated with the primary endpoint (eTable 6). On enrichment analysis, three modules were enriched with significant genes (with p values based on Fisher exact comparison for proportion of significant genes against the background universe of genes): turquoise ($p<10^{-31}$), green ($p<10^{-27}$), and lightyellow ($p=0.01$). Gene ontology categories that were differentially expressed in the two most significant modules are displayed in eTable 7. The primary findings were of an association between oxidoreductase activity and cognitive outcomes in the turquoise module and hormone activity and cognitive outcomes in the green module. The differentially expressed genes in the Gene Ontology oxidoreductase activity category are displayed in eTable 8. The large majority had lower expression among patients with cognitive impairment. The gene with the lowest p value and largest log2-fold change was CYP1B1, a cytochrome P450 enzyme implicated in

suppression of oxidative stress.(8, 9) This may suggest that, consistent with other evidence outside transcriptomics(10-12), higher oxidation activity overall is associated with worse cognitive outcomes.

eFigure 1. Gene dendrogram for primary Weighted Network Analysis



eFigure 2. Gene dendrogram for secondary Weighted Network Analysis



eTable 1. Comparison of the enrolled cohort with the analytic cohort

Variable	Enrolled cohort (N=39)	Analytic cohort (N=30)
Demographics		
Age	57 (47 - 67)	56 (47 - 69)
Race		
American Indian or Alaskan Native	0 (0%)	0 (0%)
Asian	1 (3%)	1 (3%)
Black	0 (0%)	0 (0%)
Native Hawaiian or other Pacific Islander	1 (3%)	1 (3%)
White	37 (95%)	28 (93%)
Female sex	21 (54%)	17 (57%)
Peak educational attainment		
Less than high school	5 (13%)	3 (10%)
High school completed	8 (21%)	7 (23%)
Some college	11 (28%)	10 (33%)
Associate's degree	4 (10%)	2 (7%)
Bachelor's degree	7 (18%)	5 (17%)
Master's, Doctorate or other professional degrees	4 (10%)	3 (10%)
Median annual income for census block (US\$)	69667 (52947 - 86126)	71390 (55038 - 90932)
Baseline living arrangement		
Home	36 (92%)	27 (90%)
Hospital ward	1 (3%)	1 (3%)
Skilled nursing facility	1 (3%)	1 (3%)
Rehabilitation facility	1 (3%)	1 (3%)
Assisted living facility	0 (0%)	0 (0%)
Baseline employment status		
Working full time (at least 32 hours/week)	13 (33%)	11 (37%)
Working part time	2 (5%)	2 (7%)
Unemployed and looking for work	3 (8%)	2 (7%)
Homemaker	3 (8%)	3 (10%)
Retired	12 (31%)	9 (30%)
Receiving disability payments	4 (10%)	2 (7%)
Other	2 (5%)	1 (3%)
Comorbidities and risk factors		
Comorbidities		
Congestive heart failure	4 (10%)	3 (10%)
Depression requiring treatment	7 (18%)	6 (20%)
Anxiety requiring treatment	8 (21%)	7 (23%)
Chronic kidney failure requiring dialysis	4 (10%)	2 (7%)
Diabetes mellitus	10 (26%)	8 (27%)
Ever drink alcohol	16 (41%)	13 (43%)
Current smoker	10 (26%)	6 (20%)

Anti-depressant medications	9 (23%)	7 (23%)
Narcotic pain relievers	12 (31%)	9 (30%)
Mood stabilizers	2 (5%)	2 (7%)
Acute illness attributes		
Admission APACHE II	20 (15 - 26)	18 (13 - 24)
Admission SOFA score	8 (6 - 12)	8 (5 - 11)
Days of delirium	0 (0 - 1)	0 (0 - 0)
Ever delirious	10 (26%)	7 (23%)
Ever mechanically ventilated	11 (28%)	7 (23%)
Ever on vasopressor agents	17 (44%)	10 (33%)
Sepsis etiology		
Pneumonia	13 (33%)	11 (37%)
Urosepsis	8 (21%)	7 (23%)
Central Nervous System	0 (0%)	0 (0%)
Unknown	4 (10%)	3 (10%)
Catheter related	1 (3%)	0 (0%)
Abdominal	6 (15%)	4 (13%)
Skin and soft tissue	7 (18%)	5 (17%)
Endocarditis/bacteremia	0 (0%)	0 (0%)
ICU-free days to day 28	24 (23 - 26)	25 (23 - 26)
ICU length of stay	3.0 (1.9 - 4.1)	3.0 (1.6 - 4.0)
Hospital length of stay	5.7 (4.1 – 9.5)	5.6 (3.9 - 8.9)
Discharge destination		
Home	28 (72%)	24 (80%)
Death	2 (5%)	0 (0%)
Nursing home	5 (13%)	5 (17%)
Rehabilitation facility	2 (5%)	1 (3%)
Hospice	1 (3%)	0 (0%)
Missing	1 (3%)	0 (0%)
Hayling at 6 months	6 (6 - 6)	6 (6 - 6)

eTable 2. Gene Ontology terms within primary WNA modules

Term ID	Term Name	module	n	Module Size	Term Size	Enrichment P value	Bonferroni P value
GO:00023 66 BP	leukocyte activation involved in immune response	black	45	362 (12.4 %)	614 (7.3%)	1.3E-09	2E-05
GO:00022 63 BP	cell activation involved in immune response	black	45	362 (12.4 %)	617 (7.3%)	1.6E-09	2E-05
GO:00450 55 BP	regulated exocytosis	black	47	362 (13%)	677 (6.9%)	3.2E-09	4E-05
GO:00432 99 BP	leukocyte degranulation	black	36	362 (9.9%)	478 (7.5%)	3.4E-08	0.0004
GO:00453 21 BP	leukocyte activation	black	59	362 (16.3 %)	1030 (5.7%)	3.6E-08	0.0004
GO:00024 43 BP	leukocyte mediated immunity	black	44	362 (12.2 %)	664 (6.6%)	4.3E-08	0.0005
GO:00068 87 BP	exocytosis myeloid	black	47	362 (13%)	757 (6.2%)	1E-07	0.0012
GO:00022 74 BP	leukocyte activation	black	39	362 (10.8 %)	572 (6.8%)	1.3E-07	0.0015
GO:00017 75 BP	cell activation	black	62	362 (17.1 %)	1150 (5.4%)	1.4E-07	0.0016
GO:00023 76 BP	immune system process	black	103	362 (28.5 %)	2334 (4.4%)	1.6E-07	0.002
GO:00094 51 BP	RNA modification	blue	30	1548 (1.9%)	95 (31.6%)	1.9E-07	0.0022
GO:00450 58 BP	T cell selection	blue	17	1548 (1.1%)	40 (42.5%)	8.1E-07	0.0097
GO:00067 68 BP	biotin metabolic process	blue	7	1548 (0.5%)	4527 (77.8%)	8.5E-06	0.1017
GO:00464 83 BP	heterocycle metabolic process	blue	603	1548 (39%)	288 (13.3%)	1.5E-05	0.175
GO:00300 98 BP	lymphocyte differentiation	blue	57	1548 (3.7%)	288 (19.8%)	4E-05	0.4786

GO:00104 67 BP	gene expression cellular nitrogen compound	blue	543	1548 (35.1% %)	4067 (13.4%)	4.3E-05	0.5174
GO:00346 41 BP	metabolic process	blue	648	1548 (41.9% %)	4944 (13.1%)	4.8E-05	0.5698
GO:00346 45 BP	cellular macromolecule biosynthetic process	blue	497	1548 (32.1% %)	3707 (13.4%) 204	7.5E-05	0.8937
GO:00302 17 BP	T cell differentiation	blue	43	1548 (2.8%)	211 (26.4% 91)	7.8E-05	0.9341
GO:00080 33 BP	tRNA processing protein modification by small protein conjugation	blue	24	1548 (1.6%)	773 (15%) 701	8.6E-05	1
GO:00324 46 BP	protein ubiquitination	brown	116	1167 (9.9%)	701 (15.3%)	4.6E-09	5E-05
GO:00165 67 BP	mRNA processing	brown	107	1167 (9.2%)	373 (18%) 657	7.5E-09	9E-05
GO:00063 97 BP	mRNA metabolic process	brown	67	1167 (5.7%)	525 (15.2%)	1.1E-08	0.0001
GO:00160 71 BP	proteolysis involved in	brown	100	1167 (8.6%)	328 (17.7%)	2.8E-08	0.0003
GO:00516 03 BP	cellular protein catabolic process	brown	82	1167 (7%)	315 (17.8%)	1.7E-07	0.0021
GO:00083 80 BP	RNA splicing regulation of	brown	58	1167 (5%)	106 (25.5%)	1.9E-07	0.0022
GO:00450 88 BP	innate immune response	brown	63	1167 (5.4%)	271 (17%)	2.5E-07	0.003
GO:00450 89 BP	positive regulation of	brown	56	1167 (4.8%)	315 (17.8%)	2.5E-07	0.003
GO:00436 20 BP	innate immune response regulation of	brown	27	1167 (2.3%)	106 (25.5%) 271	3.1E-07	0.0037
GO:00022 18 BP	DNA-templated transcription in response to stress	brown	50	1167 (4.3%)	1167 (18.5%)	3.5E-07	0.0042

	mitochondrial electron transport, NADH to ubiquinone	cyan	15	269 (5.6%)	46 (32.6%)		
GO:00061 20 BP) 106	8E-15	1E-10
GO:00061 19 BP	oxidative phosphorylation	cyan	19	269 (7.1%)	(17.9%)	3.4E-13	4E-09
GO:00329 81 BP	mitochondrial respiratory chain complex I assembly	cyan	14	269 (5.2%)	48 (29.2%)	3.7E-13	4E-09
GO:00427 75 BP	mitochondrial ATP synthesis coupled electron transport	cyan	16	269 (5.9%)	70 (22.9%)	4.9E-13	6E-09
GO:00229 04 BP	respiratory electron transport chain	cyan	16	269 (5.9%)	85 (18.8%)	1.2E-11	1E-07
GO:00331 08 BP	mitochondrial respiratory chain complex assembly	cyan	14	269 (5.2%)	61 (23%)	1.4E-11	2E-07
GO:00453 33 BP	cellular respiration	cyan	20	269 (7.4%)	147 (13.6%)	1.6E-11	2E-07
GO:00460 34 BP	ATP metabolic process	cyan	23	269 (8.6%)	241 (9.5%)	7.1E-10	8E-06
GO:00070 05 BP	mitochondrion organization	cyan	28	(10.4 %)	362 (7.7%)	1.2E-09	1E-05
GO:00159 80 BP	energy derivation by oxidation of organic compounds	cyan	21	269 (7.8%)	216 (9.7%)	2.9E-09	3E-05
GO:00161 92 BP	vesicle-mediated transport	green	191	(18.4 %)	1038 (12.1%)	1.2E-10	1E-06
GO:00098 93 BP	positive regulation of metabolic process	green	284	1038 (27.4 %)	2620 (10.8%)	4.3E-10	5E-06
GO:00313 25 BP	positive regulation of cellular metabolic process	green	260	1038 (25%)	2398 (10.8%)	3.3E-09	4E-05
GO:00063 66 BP	transcription by RNA polymerase II	green	232	1038 (22.4 %)	2090 (11.1%)	4E-09	5E-05
GO:19035 08 BP	positive regulation of nucleic acid-	green	145	1038 (14%)	1169 (12.4%)	7.4E-09	9E-05

	templated transcription positive regulation of RNA biosynthetic process	green	145	1038 (14%)	1170 (12.4%)	7.9E-09	9E-05
GO:19026 80 BP	cellular protein modification process	green	322	1038 (31%)	3148 (10.2%)	1.4E-08	0.0002
GO:00064 64 BP	protein modification process	green	322	1038 (31%)	3148 (10.2%)	1.4E-08	0.0002
GO:00362 11 BP	transcription, DNA-templated	green	288	1038 (27.7%)	2758 (10.4%)	1.7E-08	0.0002
GO:00063 51 BP	RNA biosynthetic process	green	292	1038 (%)	2809 (10.4%)	2E-08	0.0002
GO:00327 74 BP	neutrophil mediated immunity	greenyellow	37	313 (11.8%)	452 (8.2%)	3.6E-11	4E-07
GO:00432 99 BP	leukocyte degranulation	greenyellow	38	313 (12.1%)	478 (7.9%)	4.6E-11	6E-07
GO:00433 12 BP	neutrophil degranulation	greenyellow	36	313 (11.5%)	442 (8.1%)	7.9E-11	9E-07
GO:00022 83 BP	neutrophil activation involved in immune response	greenyellow	36	313 (11.5%)	444 (8.1%)	9E-11	1E-06
GO:00421 19 BP	vesicle-mediated transport leukocyte activation involved in immune response	greenyellow	76	313 (24.3%)	1575 (4.8%)	5.3E-10	6E-06
GO:00023 66 BP	cell activation involved in immune response	greenyellow	41	313 (13.1%)	614 (6.7%)	1.6E-09	2E-05
GO:00022 63 BP	myeloid leukocyte activation	greenyellow	41	313 (13.1%)	617 (6.6%)	1.8E-09	2E-05
GO:00022 74 BP		greenyellow	39	313 (12.5%)	572 (6.8%)	2.3E-09	3E-05

GO:00024 43 BP	leukocyte mediated immunity regulation of metabolic process	greenyellow w	42	313 (13.4 %)	664 (6.3%)	4.8E-09	6E-05
GO:00192 22 BP	regulation of nitrogen compound	grey60	79	144 (54.9 %)	4943 (1.6%)	1.2E-05	0.1467
GO:00511 71 BP	metabolic process nucleobase- containing compound	grey60	71	144 (49.3 %)	4329 (1.6%)	2.3E-05	0.2748
GO:00061 39 BP	protein modification by small protein	grey60	72	144 (50%)	4415 (1.6%)	2.3E-05	0.2779
GO:00324 46 BP	conjugation	grey60	22	144 (15.3 %)	773 (2.8%)	3E-05	0.3582
GO:00104 68 BP	regulation of gene expression	grey60	59	144 (41%)	3375 (1.7%)	3.1E-05	0.3649
GO:00160 70 BP	RNA metabolic process	grey60	60	144 (41.7 %)	3481 (1.7%)	3.9E-05	0.4632
GO:00027 64 BP	immune response- regulating signaling pathway	grey60	16	144 (11.1 %)	468 (3.4%)	4.9E-05	0.5804
GO:00464 83 BP	heterocycle metabolic process	grey60	72	144 (50%)	4527 (1.6%)	5.9E-05	0.7053
GO:00165 67 BP	protein ubiquitination	grey60	20	144 (13.9 %)	701 (2.9%)	6.9E-05	0.8277
GO:00067 25 BP	cellular aromatic compound metabolic process	grey60	72	144 (50%)	4560 (1.6%)	7.7E-05	0.9183
GO:00512 76 BP	compounds	lightcyan	94	191 (49.2 %)	905 (10.4%)	9.4E-59	1E-54
GO:00063 23 BP	DNA packaging	lightcyan	50	191 (26.2 %)	153 (32.7%)	1.8E-55	2E-51
GO:00711 03 BP	DNA	lightcyan	56	191 (29.3 %)	231 (24.2%)	4.1E-54	5E-50
GO:00063 34 BP	conformation change	lightcyan	42	191 (22%)	104 (40.4%)	4.4E-51	5E-47

)		
GO:00314 97 BP	chromatin assembly	lightcyan	42	191 (22%)	121 (34.7%))	1E-47	1E-43
GO:00002 78 BP	mitotic cell cycle protein-DNA complex	lightcyan	78	191 (40.8%)	191 (10.2%))	7.6E-47	9E-43
GO:00650 04 BP	assembly	lightcyan	46	191 (24.1%)	173 (26.6%))	3.3E-46	4E-42
GO:00347 28 BP	nucleosome organization	lightcyan	42	191 (22%)	133 (31.6%))	1.1E-45	1E-41
GO:00070 49 BP	cell cycle chromatin assembly or disassembly	lightcyan	97	191 (50.8%)	1381 (7%))	2.9E-45	3E-41
GO:00063 33 BP		lightcyan	42	191 (22%)	145 (29%))	6.9E-44	8E-40
GO:00069 52 BP	defense response	lightgreen	59	110 (53.6%)	1204 (4.9%))	7.1E-33	9E-29
GO:00450 87 BP	innate immune response	lightgreen	47	110 (42.7%)	699 (6.7%))	2.6E-31	3E-27
GO:00516 07 BP	defense response to virus	lightgreen	30	110 (27.3%)	186 (16.1%))	7.5E-31	9E-27
GO:00096 15 BP	response to virus	lightgreen	33	110 (30%)	260 (12.7%))	1.9E-30	2E-26
GO:00517 07 BP	response to other organism	lightgreen	43	110 (39.1%)	668 (6.4%))	1.3E-27	2E-23
GO:00432 07 BP	response to external biotic stimulus	lightgreen	43	110 (39.1%)	669 (6.4%))	1.4E-27	2E-23
GO:00343 40 BP	response to type I interferon	lightgreen	20	110 (18.2%)	74 (27%))	1.6E-25	2E-21
GO:00603 37 BP	type I interferon signaling pathway	lightgreen	19	110 (17.3%)	70 (27.1%))	2.5E-24	3E-20
GO:00713 57 BP	cellular response to type I interferon	lightgreen	19	110 (17.3%)	70 (27.1%))	2.5E-24	3E-20
GO:00023 76 BP	immune system process	lightgreen	64	110 (58.2%)	2334 (2.7%))	1.1E-21	1E-17
GO:00025	platelet	lightyellow	11	102	104)	4E-10	5E-06

76 BP	degranulation		(10.8 %)	(10.6%)			
			102				
GO:00420			(17.6 %)	414			
60 BP	wound healing	lightyellow	18	(4.3%)	2.3E-09	3E-05	
			102				
GO:00096			(18.6 %)	498			
11 BP	response to wounding	lightyellow	19	(3.8%)	6.6E-09	8E-05	
			102				
GO:00075			(13.7 %)	259			
96 BP	blood coagulation	lightyellow	14	(5.4%)	1.1E-08	0.0001	
			102				
GO:00508			(13.7 %)	261			
17 BP	coagulation	lightyellow	14	(5.4%)	1.2E-08	0.0001	
			102				
GO:00075			(13.7 %)	263			
99 BP	hemostasis	lightyellow	14	(5.3%)	1.3E-08	0.0002	
GO:00301			102	125			
68 BP	platelet activation	lightyellow	10	(8%)	4E-08	0.0005	
			102				
GO:00508			(14.7 %)	384			
78 BP	regulation of body fluid levels	lightyellow	15	(3.9%)	2.3E-07	0.0027	
GO:00610			102	104			
41 BP	regulation of wound healing	lightyellow	7	(6.7%)	1.5E-05	0.179	
			102				
GO:00071			(20.6 %)	1049			
55 BP	cell adhesion	lightyellow	21	(2%)	4E-05	0.4769	
GO:00063			344	592			
25 BP	chromatin organization	magenta	33	(5.6%)	2.9E-05	0.3519	
GO:00310			344	115			
56 BP	regulation of histone modification	magenta	12	(10.4%)	4.3E-05	0.5161	
			344				
GO:00018			53				
36 BP	release of cytochrome c from mitochondria	magenta	8	(15.1%)	6.1E-05	0.7252	
			344				
GO:00023			344				
76 BP	immune system process	magenta	89	(2.3%)	6.5E-05	0.782	
			344				
GO:19022			2334				
75 BP	regulation of chromatin organization	magenta	13	(3.8%)	6.6E-05	0.7915	
			344				
GO:20012			139				
42 BP	regulation of intrinsic apoptotic signaling pathway	magenta	13	(9.4%)	6.6E-05	0.7915	
			344				
GO:00355			2086				
56 BP	intracellular signal transduction	magenta	81	(3.9%)	8.4E-05	1	
GO:00096			344				
11 BP	response to wounding	magenta	28	(5.6%)	0.0001	1	
			344				

GO:00400 11 BP	locomotion small GTPase	magenta	55	344 (16%)	1283 (4.3%)	0.00013	1
GO:00072 64 BP	mediated signal transduction nucleobase- containing compound	magenta	24	344 (7%)	402 (6%)	0.00013	1
GO:00061 39 BP	metabolic process heterocycle	midnightbl ue	105	196 (53.6)	4415 (2.4%)	3.3E-09	4E-05
GO:00464 83 BP	metabolic process cellular aromatic compound	midnightbl ue	106	196 (54.1)	4527 (2.3%)	6.5E-09	8E-05
GO:00067 25 BP	metabolic process cellular nitrogen compound	midnightbl ue	106	196 (54.1)	4560 (2.3%)	1E-08	0.0001
GO:00346 41 BP	metabolic process cellular response	midnightbl ue	111	196 (56.6)	4944 (2.2%)	2.4E-08	0.0003
GO:00069 74 BP	to DNA damage stimulus	midnightbl ue	30	196 (15.3)	677 (4.4%)	6.4E-08	0.0008
GO:00062 81 BP	DNA repair SRP-dependent cotranslational	midnightbl ue	22	196 (11.2)	429 (5.1%)	3.8E-07	0.0045
GO:00066 14 BP	protein targeting to membrane protein localization to	midnightbl ue	10	196 (5.1%)	91 (11%)	9E-07	0.0108
GO:00709 72 BP	endoplasmic reticulum cotranslational	midnightbl ue	11	196 (5.6%)	115 (9.6%)	1E-06	0.0124
GO:00066 13 BP	protein targeting to membrane	midnightbl ue	10	196 (5.1%)	94 (10.6%)	1.2E-06	0.0146
GO:00450 47 BP	protein targeting to ER cholesterol	midnightbl ue	10	196 (5.1%)	96 (10.4%)	1.5E-06	0.0178
GO:00082 03 BP	metabolic process acetyl-CoA	pink	10	347 (2.9%)	109 (9.2%)	0.00057	1
GO:00060 84 BP	metabolic process cobalamin	pink	5	347 (1.4%)	27 (18.5%)	0.0006	1
GO:00092 35 BP	metabolic process	pink	4	347 (1.2%)	16 (25%)	0.00065	1

GO:00161 25 BP	sterol metabolic process	pink	10	347 (2.9%)	119 (8.4%)	0.00113	1
GO:00011 88 BP	RNA polymerase I preinitiation complex assembly	pink	3	347 (0.9%)	9 (33.3%)	0.00133	1
	positive regulation of glucose mediated signaling pathway	pink	2	347 (0.6%)	3 (66.7%)	0.00201	1
GO:19026 61 BP	chromatin remodeling	pink	10	347 (2.9%)	132 (7.6%)	0.00246	1
GO:00063 38 BP	negative regulation of androgen receptor signaling pathway	pink	3	347 (0.9%)	11 (27.3%)	0.00251	1
GO:00063 51 BP	transcription, DNA-templated	pink	94	347 (27.1%)	2758 (3.4%)	0.00273	1
GO:00311 24 BP	mRNA 3'-end processing	pink	7	347 (2%)	73 (9.6%)	0.00294	1
GO:00067 78 BP	porphyrin-containing compound metabolic process	purple	11	326 (3.4%)	31 (35.5%)	9.2E-11	1E-06
GO:00067 79 BP	porphyrin-containing compound biosynthetic process	purple	9	326 (2.8%)	25 (36%)	4.3E-09	5E-05
GO:00421 68 BP	heme metabolic process	purple	9	326 (2.8%)	26 (34.6%)	6.4E-09	8E-05
GO:00156 71 BP	oxygen transport heme	purple	6	326 (1.8%)	9 (66.7%)	1.7E-08	0.0002
GO:00067 83 BP	biosynthetic process	purple	8	326 (2.5%)	21 (38.1%)	1.9E-08	0.0002
GO:00465 01 BP	protoporphyrinogen IX metabolic process	purple	6	326 (1.8%)	99 (60%)	4.1E-08	0.0005
GO:00302 18 BP	erythrocyte differentiation	purple	14	326 (4.3%)	10 (14.1%)	1.3E-07	0.0015

GO:00488 21 BP	erythrocyte development	purple	8	326 (2.5%)	27 (29.6%) 136	1.8E-07	0.0022
GO:00158 93 BP	drug transport	purple	16	326 (4.9%)	11.8% 107	2.2E-07	0.0027
GO:00341 01 BP	erythrocyte homeostasis	purple	14	326 (4.3%)	13.1% 175	3.5E-07	0.0041
GO:00422 54 BP	ribosome biogenesis ribonucleoprotein complex	red	53	819 (6.5%)	30.3% 289	3.3E-23	4E-19
GO:00226 13 BP	biogenesis	red	68	819 (8.3%)	23.5% 134	1.8E-22	2E-18
GO:00063 64 BP	rRNA processing	red	43	819 (5.3%)	32.1% 168	3.9E-20	5E-16
GO:00160 72 BP	rRNA metabolic process	red	47	819 (5.7%)	28% 528	4E-19	5E-15
GO:00430 43 BP	peptide biosynthetic process	red	89	819 (10.9%)	16.9% 510	1.3E-18	2E-14
GO:00064 12 BP	translation amide	red	86	819 (10.5%)	16.9% 638	5.2E-18	6E-14
GO:00436 04 BP	peptide biosynthetic process	red	98	819 (12%)	15.4% 621	1.5E-17	2E-13
GO:00065 18 BP	metabolic process	red	96	819 (11.7%)	15.5% 4944	2.2E-17	3E-13
GO:00346 41 BP	cellular nitrogen compound metabolic process	red	418	819 (51%)	8.5% 661	9.7E-17	1E-12
GO:00063 96 BP	RNA processing	red	98	819 (12%)	14.8% 106	1.7E-16	2E-12
GO:00061 19 BP	oxidative phosphorylation	salmon	18	270 (6.7%)	17% 4944	4E-12	5E-08
GO:00346 41 BP	cellular nitrogen compound metabolic process	salmon	155	270 (57.4%)	3.1% 4944	1E-11	1E-07
GO:00427 75 BP	mitochondrial ATP synthesis	salmon	14	270 (5.2%)	20% 70	1.1E-10	1E-06
GO:00229 04 BP	coupled electron transport	salmon	15	270 (5.6%)	17.6% 85	1.5E-10	2E-06
	respiratory electron transport	salmon					

		chain)			
GO:00229 00 BP	electron transport chain	salmon	18	270 (6.7%)	141 (12.8%)		5.4E-10	6E-06
GO:00061 39 BP	nucleobase- containing compound metabolic process	salmon	136	270 (50.4)	4415 (3.1%)		3.7E-09	4E-05
GO:00067 25 BP	cellular aromatic compound metabolic process	salmon	138	270 (51.1)	4560 (3%)		8.9E-09	0.0001
GO:00464 83 BP	heterocycle metabolic process	salmon	137	270 (50.7)	4527 (3%)		1.1E-08	0.0001
GO:00068 07 BP	nitrogen compound metabolic process	salmon	192	270 (71.1)	7443 (2.6%)		2.3E-07	0.0027
GO:00453 33 BP	cellular respiration	salmon	15	270 (5.6%)	147 (10.2%)		3.1E-07	0.0037
GO:00064 12 BP	translation	tan	74	267 (27.7)	510 (14.5%)		2.2E-43	3E-39
GO:00430 43 BP	peptide biosynthetic process	tan	75	267 (28.1)	528 (14.2%)		2.5E-43	3E-39
GO:00065 18 BP	peptide metabolic process	tan	78	267 (29.2)	621 (12.6%)		3.6E-41	4E-37
GO:00436 04 BP	amide biosynthetic process	tan	75	267 (28.1)	638 (11.8%)		1.9E-37	2E-33
GO:00436 03 BP	cellular amide metabolic process	tan	79	267 (29.6)	820 (9.6%)		2.5E-33	3E-29
GO:00066 14 BP	SRP-dependent cotranslational protein targeting to membrane	tan	32	267 (12%)	91 (35.2%)		1.1E-31	1E-27
GO:00064 13 BP	translational initiation	tan	40	267 (15%)	172 (23.3%)		1.8E-31	2E-27
GO:00066 13 BP	cotranslational protein targeting	tan	32	267 (12%)	94 (34%)		3.6E-31	4E-27
GO:00450 47 BP	to membrane	tan	32	267 (12%)	96 (33.3%)		7.8E-31	9E-27

)		
	establishment of protein localization to endoplasmic reticulum						
GO:00725 99 BP	endoplasmic reticulum	tan	32	267 (12%)	100 (32%)	3.5E-30	4E-26
706							
GO:00508 77 BP	nervous system process	turquoise	394	4262 (9.2%)	4262 (55.8%)	1.5E-40	2E-36
))		
379							
GO:00076 00 BP	sensory perception	turquoise	236	4262 (5.5%)	4262 (62.3%)	2.8E-34	3E-30
))		
1173							
GO:00072 67 BP	cell-cell signaling	turquoise	550	4262 (12.9%)	4262 (46.9%)	2.2E-28	3E-24
))		
1731							
GO:00073 99 BP	nervous system development	turquoise	757	4262 (17.8%)	4262 (43.7%)	1.6E-27	2E-23
))		
3848							
GO:00072 75 BP	multicellular organism development	turquoise	150	4262 (35.3%)	4262 (39.1%)	2.3E-27	3E-23
			3))		
3450							
GO:00487 31 BP	system development	turquoise	135	4262 (31.7%)	4262 (39.2%)	2.2E-24	3E-20
			1))		
473							
GO:00072 68 BP	chemical synaptic transmission	turquoise	257	4262 (6%)	4262 (54.3%)	3.1E-24	4E-20
))		
4418							
GO:00325 02 BP	developmental process	turquoise	166	4262 (39.1%)	4262 (37.7%)	2.5E-22	3E-18
			7))		
1193							
GO:00068 11 BP	ion transport	turquoise	535	4262 (12.6%)	4262 (44.8%)	5E-22	6E-18
))		
1187							
GO:00220 08 BP	neurogenesis	turquoise	527	4262 (12.4%)	4262 (44.4%)	1.5E-20	2E-16
))		
1575							
GO:00161 92 BP	vesicle-mediated transport	yellow	278	4262 (23.5%)	4262 (17.7%)	3.2E-32	4E-28
))		
572							
GO:00022 74 BP	myeloid leukocyte activation	yellow	142	1182 (12%)	1182 (24.8%)	4.5E-31	5E-27
))		
1182							
GO:00024 46 BP	neutrophil mediated immunity	yellow	122	1182 (10.3%)	1182 (27%)	2.3E-30	3E-26
))		
452							
GO:00433 12 BP	neutrophil degranulation	yellow	119	1182 (10.1%)	1182 (26.9%)	1.6E-29	2E-25
))		
442							
GO:00022 83 BP	neutrophil activation	yellow	119	1182 (10.1%)	1182 (26.8%)	2.5E-29	3E-25
))		

	involved in immune response			%))		
GO:00421 19 BP	neutrophil activation	yellow	120	1182 (10.2%)	452 (26.5%)	3.8E-29	5E-25
GO:00432 99 BP	leukocyte degranulation	yellow	122	1182 (10.3%)	478 (25.5%)	6.7E-28	8E-24
GO:00024 43 BP	leukocyte mediated immunity	yellow	146	1182 (12.4%)	664 (22%)	5.5E-26	7E-22
GO:00069 55 BP	immune response	yellow	262	1182 (22.2%)	1582 (16.6%)	1.1E-25	1E-21
GO:00068 87 BP	exocytosis	yellow	156	1182 (13.2%)	757 (20.6%)	1.4E-24	2E-20

eTable 3. Module eigengene summary by cognitive impairment status for primary Weighted Network Analysis.

Module Eigengene Median (IQR)	Overall (N=30)	With cognitive impairment (N=6)	Without cognitive impairment (N=24)	p-value*
Black	-0.03 (-0.11, +0.08)	-0.11 (-0.17, -0.02)	+0.00 (-0.08, +0.09)	0.52
Blue	+0.00 (-0.16, +0.11)	+0.20 (+0.17, +0.24)	-0.07 (-0.17, +0.07)	0.16
Brown	-0.02 (-0.15, +0.13)	-0.14 (-0.16, -0.08)	+0.05 (-0.10, +0.14)	0.39
Cyan	+0.02 (-0.07, +0.08)	-0.08 (-0.21, -0.01)	+0.06 (-0.05, +0.09)	0.39
Green	-0.01 (-0.12, +0.07)	-0.01 (-0.09, +0.02)	-0.01 (-0.13, +0.07)	0.91
Greenyellow	-0.01 (-0.12, +0.13)	-0.17 (-0.22, -0.04)	+0.08 (-0.07, +0.14)	0.16
Grey60	-0.01 (-0.09, +0.11)	-0.01 (-0.07, +0.05)	-0.01 (-0.09, +0.13)	0.91
Lightcyan	-0.02 (-0.12, +0.11)	-0.01 (-0.19, +0.00)	-0.04 (-0.11, +0.12)	0.88
Lightgreen	-0.01 (-0.12, +0.08)	-0.06 (-0.17, +0.02)	-0.01 (-0.10, +0.11)	0.67
Lightyellow	+0.02 (-0.12, +0.16)	+0.09 (-0.05, +0.16)	-0.01 (-0.14, +0.14)	0.67
Magenta	+0.04 (-0.14, +0.16)	+0.13 (+0.06, +0.17)	-0.01 (-0.16, +0.14)	0.39
Midnightblue	+0.00 (-0.06, +0.13)	+0.07 (-0.05, +0.22)	-0.01 (-0.06, +0.13)	0.64
Pink	-0.02 (-0.11, +0.10)	+0.10 (+0.04, +0.13)	-0.04 (-0.11, +0.08)	0.50
Purple	+0.00 (-0.13, +0.10)	+0.12 (+0.05, +0.14)	-0.07 (-0.15, +0.06)	0.16
Red	+0.01 (-0.13, +0.14)	+0.13 (+0.00, +0.17)	+0.01 (-0.14, +0.10)	0.52
Salmon	+0.02 (-0.07, +0.11)	-0.07 (-0.13, +0.07)	+0.04 (-0.07, +0.12)	0.64
Tan	+0.05 (-0.05, +0.12)	+0.08 (+0.06, +0.10)	+0.02 (-0.07, +0.13)	0.67
Turquoise[∂]	-0.06 (-0.08, -0.04)	-0.06 (-0.08, -0.05)	-0.06 (-0.09, -0.02)	1.00
Yellow	+0.01 (-0.13, +0.13)	-0.24 (-0.25, -0.17)	+0.08 (-0.06, +0.14)	0.16

* Wilcoxon rank sum test, adjusted for multiple comparisons using the false discovery rate approach

∂ Module containing APOE

eTable 4. Weighted Network Analysis (WNA) module membership for genes identified by the differential expression analysis

<i>Gene Name</i>	<i>Description</i>	<i>P value*</i>	<i>module</i>
LIG3	DNA ligase 3	0.042	blue
GAS7	growth arrest specific 7	0.018	greenyellow
POLA2	DNA polymerase alpha 2, accessory subunit	0.047	red
ACPP	acid phosphatase, prostate	0.007	turquoise
DERA	deoxyribose-phosphate aldolase	0.045	brown
CD44	CD44 molecule (Indian blood group) amyloid beta precursor protein binding family A member 2	0.009	greenyellow
APBA2		0.050	blue
HSPA5	heat shock protein family A (Hsp70) member 5	0.034	yellow
SOAT1	sterol O-acyltransferase 1	0.045	yellow
YIPF1	Yip1 domain family member 1	0.026	yellow
DGAT2	diacylglycerol O-acyltransferase 2	0.032	greenyellow
MTMR1	myotubularin related protein 1	0.033	greenyellow
ACSL4	acyl-CoA synthetase long-chain family member 4	0.008	yellow
LAPTM4A	lysosomal protein transmembrane 4 alpha	0.020	brown
CLEC2D	C-type lectin domain family 2 member D	0.007	blue
MAPK6	mitogen-activated protein kinase 6	0.000	yellow
CLTCL1	clathrin heavy chain like 1	0.045	turquoise
PPP1R12B	protein phosphatase 1 regulatory subunit 12B	0.024	magenta
GPR137B	G protein-coupled receptor 137B	0.007	turquoise
ACER3	alkaline ceramidase 3	0.019	yellow
SLC1A3	solute carrier family 1 member 3	0.004	yellow
APLP2	amyloid beta precursor like protein 2	0.044	yellow
CD82	CD82 molecule	0.001	yellow
C3orf18	chromosome 3 open reading frame 18	0.047	blue
SIGLEC1	sialic acid binding Ig like lectin 1	0.042	turquoise
XRN2	5'-3' exoribonuclease 2	0.012	yellow
SPG21	spastic paraparesis 21 (autosomal recessive, Mast syndrome)	0.012	greenyellow
NLRC4	NLR family CARD domain containing 4	0.032	yellow
PSMD5	proteasome 26S subunit, non-ATPase 5	0.030	greenyellow
NANS	N-acetylneuraminate synthase	0.029	yellow
CRISP3	cysteine rich secretory protein 3	0.017	brown
SH3GLB1	SH3 domain containing GRB2 like endophilin B1	0.050	yellow

HSD3B7	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 7	0.048	yellow
GADD45B	growth arrest and DNA damage inducible beta	0.016	yellow
PIK3IP1	phosphoinositide-3-kinase interacting protein 1	0.040	blue
HMOX1	heme oxygenase 1	0.016	turquoise
KIAA0930	KIAA0930	0.039	greenyellow
CTSG	cathepsin G	0.007	blue
DICER1	dicer 1, ribonuclease III	0.007	yellow
CINP	cyclin dependent kinase 2 interacting protein	0.050	greenyellow
	solute carrier organic anion transporter family member		
SLCO4A1	4A1	0.042	greenyellow
VSIG1	V-set and immunoglobulin domain containing 1	0.050	blue
TNFSF13B	tumor necrosis factor superfamily member 13b	0.040	brown
DGKH	diacylglycerol kinase eta	0.001	blue
AP3B2	adaptor related protein complex 3 beta 2 subunit	0.001	yellow
TRPS1	transcriptional repressor GATA binding 1	0.048	yellow
SPAG1	sperm associated antigen 1	0.015	turquoise
PLIN3	perilipin 3	0.043	yellow
COA1	cytochrome c oxidase assembly factor 1 homolog		
	phosphatidylinositol glycan anchor biosynthesis class		
PIGL	L	0.019	blue
GALK1	galactokinase 1	0.006	yellow
SYNGR2	synaptogyrin 2	0.048	yellow
	FAM20A, golgi associated secretory pathway		
FAM20A	pseudokinase	0.000	yellow
TMEM33	transmembrane protein 33	0.042	yellow
BST1	bone marrow stromal cell antigen 1	0.021	yellow
VWA5A	von Willebrand factor A domain containing 5A	0.032	turquoise
MS4A6A	membrane spanning 4-domains A6A	0.017	yellow
MS4A4A	membrane spanning 4-domains A4A	0.001	yellow
ST3GAL4	ST3 beta-galactoside alpha-2,3-sialyltransferase 4	0.004	greenyellow
CD69	CD69 molecule	0.010	midnightblue
TBC1D30	TBC1 domain family member 30	0.013	yellow
SMIM8	small integral membrane protein 8	0.042	turquoise
FIG4	FIG4 phosphoinositide 5-phosphatase	0.042	yellow
LMNB1	lamin B1	0.007	yellow
SEC24A	SEC24 homolog A, COPII coat complex component	0.039	yellow
NIT2	nitrilase family member 2	0.007	blue
ATP6V1A	ATPase H ⁺ transporting V1 subunit A	0.046	greenyellow
HEMK1	HemK methyltransferase family member 1	0.026	blue
STEAP3	STEAP3 metalloreductase	0.043	yellow
RHOU	ras homolog family member U	0.031	brown

LAMTOR2	late endosomal/lysosomal adaptor, MAPK and MTOR activator 2	0.038	yellow
RAB32	RAB32, member RAS oncogene family	0.031	yellow
PTPA	protein phosphatase 2 phosphatase activator pleckstrin homology and RhoGEF domain containing G1	0.004	yellow
PLEKHG1		0.004	yellow
SCPEP1	serine carboxypeptidase 1	0.045	yellow
TSHZ3	teashirt zinc finger homeobox 3	0.024	black
COPA	coatomer protein complex subunit alpha	0.033	yellow
NCKAP1L	NCK associated protein 1 like	0.049	yellow
G0S2	G0/G1 switch 2	0.049	yellow
PARD6B	par-6 family cell polarity regulator beta 5-methyltetrahydrofolate-homocysteine methyltransferase reductase	0.004	blue
MTRR		0.007	yellow
SIGLEC9	sialic acid binding Ig like lectin 9 neural precursor cell expressed, developmentally down-regulated 8	0.035	greenyellow
NEDD8		0.035	brown
NECTIN2	nectin cell adhesion molecule 2	0.002	yellow
SH3BGRL	SH3 domain binding glutamate rich protein like	0.041	brown
CAPN7	calpain 7	0.040	red
CHSY1	chondroitin sulfate synthase 1	0.035	yellow
ENOSF1	enolase superfamily member 1	0.037	blue
EMILIN2	elastin microfibril interfacer 2	0.004	yellow
CTNNBL1	catenin beta like 1	0.042	yellow
CCNA1	cyclin A1	0.049	yellow
KL	klotho	0.050	greenyellow
STARD13	StAR related lipid transfer domain containing 13	0.048	turquoise
ATP13A3	ATPase 13A3	0.020	turquoise
RSAD2	radical S-adenosyl methionine domain containing 2	0.026	lightgreen
CTSL	cathepsin L	0.024	cyan
LMO2	LIM domain only 2	0.004	yellow
CD63	CD63 molecule	0.050	yellow
ITGA7	integrin subunit alpha 7 biogenesis of lysosomal organelles complex 1 subunit 1	0.018	yellow
BLOC1S1		0.042	yellow
ACVR1B	activin A receptor type 1B	0.031	greenyellow
GNS	glucosamine (N-acetyl)-6-sulfatase	0.001	yellow
DRAM1	DNA damage regulated autophagy modulator 1	0.007	yellow
IL10	interleukin 10	0.003	yellow
RPS6KC1	ribosomal protein S6 kinase C1	0.023	yellow
SLC31A1	solute carrier family 31 member 1	0.021	yellow
CASP5	caspase 5	0.030	turquoise

CYP19A1	cytochrome P450 family 19 subfamily A member 1	0.000	greenyellow
CYP1B1	cytochrome P450 family 1 subfamily B member 1	0.000	yellow
STAT4	signal transducer and activator of transcription 4	0.007	blue
PARP16	poly(ADP-ribose) polymerase family member 16	0.044	magenta
BMP2K	BMP2 inducible kinase	0.050	turquoise
NEIL1	nei like DNA glycosylase 1	0.039	turquoise
CLTC	clathrin heavy chain	0.033	greenyellow
EFHD2	EF-hand domain family member D2	0.031	black
C1orf43	chromosome 1 open reading frame 43	0.050	brown
GALNT2	polypeptide N-acetylgalactosaminyltransferase 2	0.009	yellow
METTL21A	methyltransferase like 21A	0.042	red
CSRNP1	cysteine and serine rich nuclear protein 1	0.048	yellow
PLAC8	placenta specific 8 TRAF interacting protein with forkhead associated domain	0.001	yellow
TIFA		0.045	yellow
PDGFC	platelet derived growth factor C	0.005	greenyellow
MYO10	myosin X	0.008	yellow
FAM105A	family with sequence similarity 105 member A	0.016	yellow
KRBOX4	KRAB box domain containing 4	0.047	blue
PROSC	proline synthetase cotranscribed homolog (bacterial) globoside alpha-1,3-N-acetylgalactosaminyltransferase 1	0.048	yellow
GBGT1		0.044	greenyellow
GSTO1	glutathione S-transferase omega 1	0.007	yellow
NPAT	nuclear protein, coactivator of histone transcription	0.043	blue
ROM1	retinal outer segment membrane protein 1	0.017	yellow
FCGR1A	Fc fragment of IgG receptor Ia	0.007	yellow
PTS	6-pyruvoyltetrahydropterin synthase	0.048	turquoise
CAST	calpastatin	0.050	greenyellow
MERTK	MER proto-oncogene, tyrosine kinase	0.017	greenyellow
HS2ST1	heparan sulfate 2-O-sulfotransferase 1	0.026	yellow
OXNAD1	oxidoreductase NAD binding domain containing 1	0.047	blue
APCDD1	APC down-regulated 1	0.036	turquoise
SLC25A28	solute carrier family 25 member 28	0.038	yellow
PIK3AP1	phosphoinositide-3-kinase adaptor protein 1 potassium calcium-activated channel subfamily M alpha 1	0.007	yellow
KCNMA1		0.042	turquoise
TDRD9	tudor domain containing 9	0.012	greenyellow
WDR19	WD repeat domain 19 brain and reproductive organ-expressed (TNFRSF1A modulator)	0.013	blue
BRE		0.045	greenyellow
COPG2	coatomer protein complex subunit gamma 2	0.012	yellow
FCER1G	Fc fragment of IgE receptor Ig	0.042	yellow

LBHD1	LBH domain containing 1	0.042	blue
ACP6	acid phosphatase 6, lysophosphatidic	0.001	green
PDLIM5	PDZ and LIM domain 5	0.050	greenyellow
TGFBR2	transforming growth factor beta receptor 2	0.012	yellow
CD200R1	CD200 receptor 1	0.021	turquoise
RPL9	ribosomal protein L9	0.045	red
PCOLCE2	procollagen C-endopeptidase enhancer 2	0.007	greenyellow
PLSCR2	phospholipid scramblase 2	0.042	yellow
GYG1	glycogenin 1	0.013	yellow
PLB1	phospholipase B1	0.017	greenyellow
CCR1	C-C motif chemokine receptor 1	0.001	yellow
ZDHHC19	zinc finger DHHC-type containing 19	0.032	greenyellow
ZNF589	zinc finger protein 589	0.049	blue
KIF27	kinesin family member 27	0.031	magenta
SPTSSA	serine palmitoyltransferase small subunit A	0.045	brown
CYYR1	cysteine and tyrosine rich 1	0.045	greenyellow
SERPINB8	serpin family B member 8	0.040	turquoise
PDIA3	protein disulfide isomerase family A member 3	0.041	brown
LAIR1	leukocyte associated immunoglobulin like receptor 1	0.025	yellow
YIF1B	Yip1 interacting factor homolog B, membrane trafficking protein	0.042	yellow
IRF2BP2	interferon regulatory factor 2 binding protein 2	0.045	blue
SIGLEC7	sialic acid binding Ig like lectin 7	0.004	yellow
METTL7B	methyltransferase like 7B	0.007	yellow
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	0.039	greenyellow
FPR1	formyl peptide receptor 1	0.012	yellow
LRRC8C	leucine rich repeat containing 8 family member C	0.043	yellow
SLFN12	schlafen family member 12	0.040	brown
SMPDL3A	sphingomyelin phosphodiesterase acid like 3A	0.008	yellow
OLR1	oxidized low density lipoprotein receptor 1	0.023	magenta
RBM4	RNA binding motif protein 4	0.029	blue
GNG5	G protein subunit gamma 5	0.045	yellow
ANKRD36C	ankyrin repeat domain 36C	0.042	blue
ADGRE1	adhesion G protein-coupled receptor E1	0.002	greenyellow
PARL	presenilin associated rhomboid like	0.044	yellow
CDK5R1	cyclin dependent kinase 5 regulatory subunit 1	0.031	magenta
BASP1	brain abundant membrane attached signal protein 1	0.014	greenyellow
CD163L1	CD163 molecule like 1	0.005	greenyellow
ZNF366	zinc finger protein 366	0.003	greenyellow
CTC1	CST telomere replication complex component 1	0.036	magenta

SELENOW	selenoprotein W	0.011	yellow
CALR	calreticulin	0.035	yellow
SEPHS2	selenophosphate synthetase 2	0.042	yellow
RNF135	ring finger protein 135	0.034	yellow
FAM89A	family with sequence similarity 89 member A	0.001	greenyellow
EXT1	exostosin glycosyltransferase 1	0.044	greenyellow
SPATA13	spermatogenesis associated 13	0.024	yellow
MCEMP1	mast cell expressed membrane protein 1	0.044	greenyellow
SELENOF	selenoprotein F	0.042	brown
TNFAIP8L3	TNF alpha induced protein 8 like 3	0.001	yellow
ZNF438	zinc finger protein 438	0.012	yellow
SEPT5	septin 5	0.042	magenta
ATL3	atlastin GTPase 3	0.007	yellow
F8	coagulation factor VIII	0.031	yellow
TARSL2	threonyl-tRNA synthetase like 2 interferon induced protein with tetratricopeptide repeats 1	0.049	blue
IFIT1		0.032	lightgreen
FFAR3	free fatty acid receptor 3	0.004	yellow
CYP4F3	cytochrome P450 family 4 subfamily F member 3	0.015	magenta
LILRB4	leukocyte immunoglobulin like receptor B4	0.035	black
ISG15	ISG15 ubiquitin-like modifier	0.050	lightgreen
RINL	Ras and Rab interactor like	0.047	greenyellow
TREML4	triggering receptor expressed on myeloid cells like 4	0.000	yellow
ADAT2	adenosine deaminase, tRNA specific 2	0.049	blue
FAM217B	family with sequence similarity 217 member B	0.048	yellow
TCF4	transcription factor 4	0.013	yellow
SERPINA1	serpin family A member 1	0.042	black
ENTPD7	ectonucleoside triphosphate diphosphohydrolase 7	0.000	yellow
FCGR1B	Fc fragment of IgG receptor Ib	0.025	yellow
SFI1	SFI1 centrin binding protein	0.020	blue
ZNF43	zinc finger protein 43	0.034	red
LIPN	lipase family member N	0.031	yellow
AIF1	allograft inflammatory factor 1	0.044	brown
TRIM27	tripartite motif containing 27	0.047	yellow
TRIM71	tripartite motif containing 71	0.004	yellow
DDAH2	dimethylarginine dimethylaminohydrolase 2 protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent 1N (putative)	0.037	yellow
PPM1N		0.032	yellow
CCNL2	cyclin L2	0.007	blue
WBP1	WW domain binding protein 1	0.043	blue
PLEKHO2	pleckstrin homology domain containing O2	0.047	black

NAIP	NLR family apoptosis inhibitory protein	0.001	yellow
KIAA1147	KIAA1147	0.029	blue
CEP95	centrosomal protein 95	0.033	blue
KLF14	Kruppel like factor 14	0.002	greenyellow
CD24	CD24 molecule	0.046	brown

*P value is adjusted for a 5% false discovery rate and is based on a Fisher exact comparison to the background universe of all genes assigned to the Gene Ontology

eTable 5. Potentially enriched pathways for normal vs. abnormal cognitive function from the primary Weighted Network Analysis

Pathway	Size	Leading edge	Enrichment Score	p value*
Ribosome	83	63	0.62	<10-7
Primary immunodeficiency	28	17	0.59	0.002
ABC transporters	26	6	0.54	0.04
Phosphatidylinositol signaling system	59	16	0.42	0.049
Oxidative phosphorylation	97	70	-0.6	<10-7
Proteasome	41	33	-0.68	<10-7
Parkinsons Disease	95	55	-0.51	<10-7
Alzheimers Disease	126	75	-0.47	<10-3
Cardiac muscle contraction	32	21	-0.62	<10-3
Huntingtons Disease	141	75	-0.46	0.001
Lysosome	104	46	-0.47	0.001
Complement and coagulation Pathogenic Escherichia coli infection	26	16	-0.59	0.01
Glutathione metabolism	30	16	-0.55	0.02
RIG-I-like receptor signaling pathway	46	14	-0.49	0.02
Fc gamma R-mediated phagocytosis	78	28	-0.44	0.02
Toll Like Receptor signaling	70	37	-0.44	0.03
NOD Like Receptor signaling	48	14	-0.46	0.03
Regulation of actin cytoskeleton	130	51	-0.38	0.03
Leishmania infection	58	22	-0.45	0.03
Glycosaminoglycan degradation	15	9	-0.60	0.04
Arginine and proline metabolism	25	13	-0.52	0.04
O Glycan biosynthesis	17	6	-0.57	0.05

*p value is adjusted for a false discovery rate of 5%. This analysis used Gene Set Enrichment Analysis (GSEA)

eTable 6. Module eigengene summary by cognitive status for secondary WNA

Module Eigengene Median (IQR)	Overall (N=30)	With cognitive impairment (N=6)	Without cognitive impairment (N=24)	p-value*
Black	-0.05 (-0.12, +0.09)	+0.19 (+0.10, +0.26)	-0.09 (-0.13, +0.05)	0.22
Blue	-0.06 (-0.10, +0.07)	-0.07 (-0.10, +0.03)	-0.04 (-0.10, +0.07)	0.84
Brown	-0.02 (-0.14, +0.10)	+0.21 (+0.13, +0.24)	-0.07 (-0.14, +0.07)	0.22
Cyan	+0.01 (-0.06, +0.10)	-0.18 (-0.32, -0.09)	+0.03 (-0.02, +0.11)	0.22
Darkgreen	-0.02 (-0.13, +0.06)	-0.08 (-0.20, -0.01)	-0.01 (-0.09, +0.10)	0.50
Darkgrey	+0.02 (-0.10, +0.15)	+0.08 (-0.07, +0.15)	+0.00 (-0.15, +0.15)	0.78
Darkmagenta	-0.02 (-0.11, +0.09)	-0.03 (-0.23, +0.06)	-0.02 (-0.10, +0.11)	0.81
Darkolivegreen	+0.03 (-0.06, +0.12)	+0.06 (+0.01, +0.11)	+0.02 (-0.09, +0.11)	0.81
Darkorange	+0.01 (-0.13, +0.12)	+0.11 (+0.03, +0.17)	-0.04 (-0.14, +0.12)	0.48
Darkred	+0.01 (-0.11, +0.12)	-0.07 (-0.15, -0.02)	+0.03 (-0.10, +0.13)	0.52
Darkturquoise	-0.01 (-0.12, +0.08)	+0.09 (+0.05, +0.13)	-0.03 (-0.12, +0.05)	0.48
Green	+0.00 (-0.15, +0.17)	-0.18 (-0.22, -0.09)	+0.10 (-0.10, +0.18)	0.22
Greenyellow	-0.02 (-0.10, +0.12)	+0.05 (-0.03, +0.12)	-0.02 (-0.17, +0.12)	0.76
Grey60	+0.04 (-0.07, +0.11)	+0.04 (-0.04, +0.06)	+0.03 (-0.07, +0.13)	0.81
Lightcyan	-0.04 (-0.10, +0.04)	-0.01 (-0.05, +0.03)	-0.06 (-0.10, +0.04)	0.81
Lightgreen	+0.04 (-0.14, +0.13)	+0.08 (+0.04, +0.12)	-0.02 (-0.14, +0.15)	0.74
Lightyellow	+0.02 (-0.11, +0.11)	-0.15 (-0.25, +0.05)	+0.05 (-0.08, +0.11)	0.50
Magenta	-0.03 (-0.15, +0.12)	-0.09 (-0.16, -0.06)	+0.04 (-0.11, +0.13)	0.50
Mediumpurple3	+0.03 (-0.13, +0.09)	+0.04 (-0.01, +0.06)	+0.00 (-0.14, +0.10)	0.84
Midnightblue	+0.03 (-0.09, +0.13)	-0.02 (-0.10, +0.12)	+0.03 (-0.08, +0.13)	0.90
Orange	-0.02 (-0.08, +0.11)	+0.03 (-0.03, +0.21)	-0.02 (-0.09, +0.10)	0.72
Orangered4	+0.03 (-0.08, +0.11)	-0.02 (-0.09, +0.11)	+0.04 (-0.07, +0.11)	0.84
Paleturquoise	-0.03 (-0.12,	-0.07 (-0.12, -0.05)	+0.01 (-0.11,	0.54

	+0.11)		+0.16)	
Pink	+0.00 (-0.13, +0.10)	+0.12 (+0.05, +0.14)	-0.07 (-0.15, +0.06)	0.22
Plum1	-0.01 (-0.10, +0.08)	+0.02 (-0.02, +0.11)	-0.02 (-0.10, +0.07)	0.72
Purple	-0.03 (-0.14, +0.12)	+0.14 (+0.10, +0.17)	-0.07 (-0.15, +0.10)	0.48
Red	-0.03 (-0.12, +0.08)	-0.01 (-0.06, +0.04)	-0.05 (-0.13, +0.09)	0.90
Royalblue	-0.04 (-0.11, +0.09)	-0.11 (-0.17, -0.05)	-0.01 (-0.10, +0.10)	0.50
Saddlebrown	+0.03 (-0.15, +0.11)	-0.04 (-0.14, +0.14)	+0.07 (-0.14, +0.11)	0.90
Salmon	-0.03 (-0.15, +0.15)	+0.17 (+0.15, +0.18)	-0.07 (-0.16, +0.09)	0.32
Sienna3	+0.00 (-0.11, +0.09)	+0.12 (+0.09, +0.16)	-0.02 (-0.13, +0.03)	0.25
Skyblue	+0.01 (-0.10, +0.12)	+0.04 (+0.02, +0.12)	-0.03 (-0.13, +0.09)	0.50
Skyblue3	+0.00 (-0.08, +0.09)	+0.04 (-0.05, +0.09)	+0.00 (-0.09, +0.08)	0.81
Steelblue	+0.02 (-0.08, +0.09)	-0.09 (-0.23, +0.00)	+0.07 (-0.05, +0.09)	0.49
Tan	+0.05 (-0.11, +0.13)	+0.14 (+0.04, +0.16)	+0.04 (-0.12, +0.07)	0.50
Turquoise	+0.01 (-0.10, +0.14)	-0.24 (-0.31, -0.16)	+0.07 (-0.05, +0.14)	0.22
Violet	-0.03 (-0.10, +0.11)	+0.15 (+0.04, +0.30)	-0.04 (-0.10, +0.08)	0.46
White	-0.04 (-0.13, +0.09)	-0.03 (-0.14, +0.01)	-0.07 (-0.13, +0.12)	0.84
Yellow	+0.03 (-0.12, +0.11)	-0.12 (-0.16, -0.01)	+0.06 (-0.09, +0.12)	0.50
Yellowgreen	+0.00 (-0.10, +0.10)	+0.05 (+0.00, +0.09)	-0.03 (-0.11, +0.11)	0.80

* Wilcoxon rank sum test, adjusted for multiple comparisons using the false discovery rate (5%) approach

eTable 7. Gene ontology categories differentially expressed in the two most significant modules from the secondary Weighted Network Analysis

Gene category	Category ID	Module	Enrichment p	Bonferroni p
oxidoreductase activity	GO:0016491 MF	turquoise	6.94E-06	0.03
calcium ion binding	GO:0005509 MF	turquoise	3.89E-05	0.15
protein binding	GO:0005515 MF	turquoise	4.61E-04	1.00
protein serine/threonine kinase activator activity	GO:0043539 MF	turquoise	4.94E-04	1.00
protein domain specific binding	GO:0019904 MF	turquoise	7.91E-04	1.00
oxidoreductase activity, acting on a sulfur group of donors	GO:0016667 MF	turquoise	1.12E-03	1.00
cofactor binding	GO:0048037 MF	turquoise	1.30E-03	1.00
molecular function regulator	GO:0098772 MF	turquoise	1.56E-03	1.00
calcium-dependent protein binding	GO:0048306 MF	turquoise	1.62E-03	1.00
enzyme regulator activity	GO:0030234 MF	turquoise	1.71E-03	1.00
hormone activity	GO:0005179 MF	green	2.69E-06	0.01
peroxisome targeting sequence binding	GO:0000268 MF	green	7.42E-04	1.00
interleukin-1 receptor activity	GO:0004908 MF	green	1.78E-03	1.00
UDP-glycosyltransferase activity	GO:0008194 MF	green	1.92E-03	1.00
NADPH-hemoprotein reductase activity	GO:0003958 MF	green	3.36E-03	1.00
protein-tyrosine sulfotransferase activity	GO:0008476 MF	green	3.36E-03	1.00
sulfotransferase activity	GO:0008146 MF	green	3.80E-03	1.00
intramolecular transferase activity, phosphotransferases	GO:0016868 MF	green	5.69E-03	1.00
transferase activity,	GO:0016758 MF	green	6.08E-03	1.00

transferring hexosyl groups				
palmitoyltransferase activity	GO:0016409 MF	green	7.44E-03	1.00

eTable 8. Genes in the GO oxidoreductase activity molecular function category with differential expression on the secondary Weighted Network Analysis (WNA)

Gene	Base mean expression	log2-fold change in expression	Adjusted p value*	WNA module
HSD3B7	73	-0.99	0.048	turquoise
HMOX1	387	-0.96	0.016	turquoise
STEAP3	43	-1.01	0.043	green
MTRR	605	-1.04	0.007	green
CYP19A1	477	-1.32	0.0002	green
CYP1B1	4334	-1.66	0.0005	turquoise
GSTO1	1086	-0.98	0.007	turquoise
OXNAD1	474	0.83	0.047	brown
PDIA3	414	-0.55	0.041	turquoise
F8	101	-0.87	0.031	turquoise
CYP4F3	1484	1.10	0.015	darkorange

*p value is adjusted for a false discovery rate of 5%

WNA = Weighted Network Analysis

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