

Cytokine and Reward Circuitry Relationships in Treatment-Resistant Depression

Supplement

Table S1. Correlation matrix of demographic measures, clinical measures, and cytokine levels.

Participant variables are listed in columns and rows, with correlations between variables in cells. Highlighted measures indicate significant associations at $p < 0.05$. Note that: * indicates $p < 0.05$; ** indicates $p < 0.01$; *** indicates $p < 0.001$. IL-6 and TNF α are described in pg/mL (log-transformed), age in years, and BMI in kg/m². Abbreviations: CTQ, Childhood Trauma Questionnaire; EA, Emotional Abuse; EN, Emotional Neglect; PA, Physical Abuse; PN, Physical Neglect; SA, Sexual Abuse; MADRS, Montgomery-Asberg Depression Rating Scale.

	TNF α	Age	BMI	MADRS	CTQ	CTQ PA	CTQ SA	CTQ EA	CTQ EN	CTQ PN
IL-6	0.328**	0.12	0.445***	0.128	0.027	-0.026	0.073	0.038	0.027	-0.04
TNF α		-0.033	0.07	-0.151	-0.102	-0.016	-0.227	-0.027	-0.011	-0.125
Age			0.289*	-0.084	-0.119	0.009	-0.148	-0.075	-0.138	-0.07
BMI				0.12	0.091	0.169	0.029	0.16	-0.021	0.013
MADRS					0.224	0.138	0.151	0.151	0.143	0.311**
CTQ						0.745***	0.598***	0.884***	0.841***	0.705***
CTQ PA							0.364**	0.65***	0.492***	0.409***
CTQ SA								0.35**	0.26*	0.291*
CTQ EA									0.755***	0.492***
CTQ EN										0.601***

Table S1.2. Table of differences based on biological sex of variables. Independent samples t-tests were performed to assess differences in demographic measures, clinical measures, and cytokine levels based on biological sex group (male or female). IL-6 and TNF α are described in pg/mL (log-transformed), age in years, and BMI in kg/m².

	Female	Male		
n	48	26		
	Mean	Mean	T-statistic	P value
IL-6	-0.04	0.02	-0.98	0.33
TNF α	0.44	0.51	-1.19	0.24
Age	36.46	35.85	0.23	0.82
BMI	28.79	27.19	1.07	0.29
MADRS	33.38	32.12	0.95	0.35
CTQ	53.08	49.44	0.8	0.43
CTQ PA	7.71	8.28	-0.57	0.57
CTQ SA	8.23	6.56	1.45	0.15
CTQ EA	13.75	11.84	1.28	0.21
CTQ EN	14.83	14.64	0.14	0.89
CTQ PN	8.56	8.12	0.52	0.6

Table S2. Sensitivity analysis examining medical illness and medications.

Sensitivity analysis excluding participants (n=18) with history of medical illnesses (e.g., HIV, cancer, eczema) or taking current medications (e.g., loratadine, NSAIDS) potentially affecting immune system function for significant regression models as identified in the main text. Beta values and p values of the Independent Variable (IV) are reported. Interactions effects are denoted by an asterisk between interacting variables. Abbreviations: CTQ, Childhood Trauma Questionnaire; EN, Emotional Neglect.

Variables		IV Statistics		
DV (connectivity score)	IV	n	Unstandardized Beta Weights	P value
LVS-LBA11	IL-6	56	-0.066	0.014
LVS-RBA11	IL-6	56	-0.06	0.005
RVS-RBA11	TNF α *CTQ Total	55	0.004	0.021
RVS-RBA11	TNF α *CTQ-EN	55	0.013	0.024
RVS-RBA10	IL-6*CTQ-EN	55	0.018	0.005
RVS-RBA10	IL-6*CTQ-EN	55	0.018	0.008

Table S3. Sensitivity analysis of cytokines and covariates.

Sensitivity analysis of significant primary findings in the main text, reporting beta values and unadjusted p values of IV in regression models with IV and DV and covariate of interest (COI) in regression model with independent variables of the IV (as described below), age, sex, BMI, race (dichotomized), batch, and the COI. Interactions effects are denoted by an asterisk between interacting variables, and these models also included the main effects of the interacting variables. A reference row reflecting unadjusted analyses (e.g., without adjustment for any covariate of interest) is also presented, reflecting the findings as described in the primary manuscript. Alcohol and cigarette use was defined by use of either of these in the past year (dichotomized for presence/absence). Recreational drug use was defined by active recreational drug use (dichotomized for presence/absence). Also, we conducted parallel identical analysis to those in the primary main text examining PROMIS anxiety scores in place of CTQ scores for moderation analyses and found that the interaction of PROMIS anxiety scores and cytokine levels did not predict connectivity scores (p 's > 0.15), supporting the specificity of the current findings to childhood trauma exposure per se, rather than to internalizing psychopathology more broadly.

A. Regression models with DV as LVS-LBA11 connectivity score and IV as IL-6

Covariate of Interest	n	IL-6 Statistics	
		Unstandardized Beta Weights	P value
Alcohol Use	74	-0.068	0.004
Cigarette Use	74	-0.07	0.003
CTQ Total	73	-0.07	0.002
Current Neuroleptic Use	74	-0.07	0.002
Current SSRI/SNRI Use	74	-0.068	0.003
MADRS	74	-0.07	0.002
PROMIS Anxiety	74	-0.068	0.003
Recreational Drug Use	74	-0.069	0.003
Reference (unadjusted analysis)	74	-0.069	0.003

B. Regression models with DV as LVS-RBA11 connectivity score and IV as IL-6

Covariate of Interest	n	IL-6 Statistics	
		Unstandardized Beta Weights	P value
Alcohol Use	74	-0.049	0.008
Cigarette Use	74	-0.046	0.011
CTQ Total	73	-0.048	0.009
Current Neuroleptic Use	74	-0.049	0.009
Current SSRI/SNRI Use	74	-0.047	0.01
MADRS	74	-0.049	0.008
PROMIS Anxiety	74	-0.048	0.008
Recreational Drug Use	74	-0.049	0.007
Reference (unadjusted analysis)	74	-0.048	0.009

C. Regression models with DV as RVS-RBA11 connectivity and IV as TNF α *CTQ Total

Covariate of Interest	n	TNF α *CTQ Total Statistics	
		Unstandardized Beta Weights	P value
Alcohol Use	73	0.004	0.005
Cigarette Use	73	0.004	0.004
Current Neuroleptic Use	73	0.004	0.003
Current SSRI/SNRI Use	73	0.005	0.001
MADRS	73	0.004	0.007
PROMIS Anxiety	73	0.004	0.004
Recreational Drug Use	73	0.004	0.004
Reference (unadjusted analysis)	73	0.004	0.005

Table S4. Moderation effects of childhood trauma

Table reporting unstandardized beta values and unadjusted p values of IV in regression models examining moderating effects of childhood trauma with IV and DV in regression model with independent variables of the IV (as described below), age, sex, BMI, race (dichotomized), and batch. Interactions effects are denoted by an asterisk between interacting variables, and these models also included the main effects of the interacting variables. Significant associations ($p < 0.05$) are highlighted in yellow, while trend-level associations ($p < 0.1$) are highlighted in grey. N=73.

DV (connectivity index)	IV Statistics			
	IL-6*CTQ Total		TNF α *CTQ Total	
	Beta	P value	Beta	P value
LVS-LBA10	-0.0002	0.933	0.0014	0.561
LVS-LBA11	-0.0011	0.33	-0.0005	0.722
LVS-RBA10	0.0004	0.83	0.0007	0.774
LVS-RBA11	-0.0008	0.348	0.0009	0.392
RVS-LBA10	0.0034	0.062	0.0042	0.051
RVS-LBA11	0.0009	0.477	0.0037	0.013
RVS-RBA10	0.0024	0.136	0.0027	0.167
RVS-RBA11	0.002	0.076	0.0038	0.005

Table S5. Exploratory: Moderation effects of childhood trauma subtypes

Table reporting unstandardized beta values and unadjusted p values of IV (cytokine by CTQ subtype) in regression models examining moderating effects of childhood trauma subtypes with IV and DV in regression model with independent variables of the IV (and main effects of interacting variables), age, sex, BMI, race (dichotomized), and batch. Significant associations prior to multiple comparisons adjustment (unadjusted $p < 0.05$) are highlighted in yellow, while trend-level associations (unadjusted $p < 0.1$) are highlighted in grey. $N=73$. Adjusted P values reflect FDR-adjusted p values across the eight connectivity indices as described in the primary manuscript.

CTQ Subtype	Connectivity Measure	Cytokine*CTQ Subtype Statistics					
		IL-6			TNF α		
		Beta	P value	Adjusted P Value	Beta	P value	Adjusted P Value
CTQ Emotional Abuse	LVS-LBA10	0.0024	0.701	0.801	-0.003	0.63	0.72
CTQ Emotional Abuse	LVS-LBA11	-0.002	0.549	0.732	-0.004	0.354	0.72
CTQ Emotional Abuse	LVS-RBA10	-0.0001	0.985	0.985	-0.003	0.617	0.72
CTQ Emotional Abuse	LVS-RBA11	-0.002	0.479	0.732	0	0.962	0.962
CTQ Emotional Abuse	RVS-LBA10	0.0112	0.046	0.123	0.004	0.483	0.72
CTQ Emotional Abuse	RVS-LBA11	0.0046	0.239	0.478	0.007	0.112	0.448
CTQ Emotional Abuse	RVS-RBA10	0.012	0.013	0.092	0.004	0.513	0.72
CTQ Emotional Abuse	RVS-RBA11	0.0081	0.023	0.092	0.008	0.039	0.308
CTQ Physical Abuse	LVS-LBA10	-0.0032	0.801	0.801	-0.004	0.72	0.881
CTQ Physical Abuse	LVS-LBA11	-0.0061	0.38	0.76	-0.006	0.341	0.683
CTQ Physical Abuse	LVS-RBA10	0.0047	0.708	0.801	0.001	0.923	0.923
CTQ Physical Abuse	LVS-RBA11	-0.005	0.375	0.76	0.002	0.642	0.881
CTQ Physical Abuse	RVS-LBA10	0.0114	0.326	0.76	0.012	0.233	0.622
CTQ Physical Abuse	RVS-LBA11	0.002	0.799	0.801	0.012	0.08	0.622
CTQ Physical Abuse	RVS-RBA10	0.0159	0.116	0.76	0.003	0.771	0.881
CTQ Physical Abuse	RVS-RBA11	0.0024	0.748	0.801	0.008	0.215	0.622
CTQ Sexual Abuse	LVS-LBA10	-0.0089	0.095	0.43	0.01	0.29	0.463
CTQ Sexual Abuse	LVS-LBA11	-0.0046	0.11	0.43	0.003	0.51	0.582
CTQ Sexual Abuse	LVS-RBA10	-0.0043	0.408	0.653	0.002	0.809	0.809
CTQ Sexual Abuse	LVS-RBA11	-0.0032	0.161	0.43	0.007	0.102	0.235
CTQ Sexual Abuse	RVS-LBA10	-0.0023	0.638	0.804	0.013	0.118	0.235
CTQ Sexual Abuse	RVS-LBA11	-0.0013	0.703	0.804	0.014	0.009	0.05
CTQ Sexual Abuse	RVS-RBA10	-0.0043	0.323	0.645	0.005	0.467	0.582
CTQ Sexual Abuse	RVS-RBA11	0.0001	0.976	0.976	0.013	0.013	0.05
CTQ Emotional Neglect	LVS-LBA10	0.0083	0.253	0.337	0.002	0.842	0.842
CTQ Emotional Neglect	LVS-LBA11	-0.0002	0.953	0.953	-0.001	0.821	0.842
CTQ Emotional Neglect	LVS-RBA10	0.0097	0.175	0.28	-0.002	0.798	0.842
CTQ Emotional Neglect	LVS-RBA11	-0.0007	0.823	0.941	0.003	0.373	0.596
CTQ Emotional Neglect	RVS-LBA10	0.0203	0.001	0.007	0.015	0.053	0.172
CTQ Emotional Neglect	RVS-LBA11	0.0062	0.175	0.28	0.01	0.065	0.172
CTQ Emotional Neglect	RVS-RBA10	0.0175	0.002	0.007	0.007	0.265	0.53
CTQ Emotional Neglect	RVS-RBA11	0.0088	0.031	0.083	0.015	0.001	0.01
CTQ Physical Neglect	LVS-LBA10	0.0195	0.1	0.295	0.014	0.247	0.395
CTQ Physical Neglect	LVS-LBA11	<0.0001	0.997	0.997	-0.002	0.745	0.745
CTQ Physical Neglect	LVS-RBA10	0.0165	0.154	0.295	0.014	0.221	0.395
CTQ Physical Neglect	LVS-RBA11	-0.0034	0.507	0.579	0.002	0.671	0.745
CTQ Physical Neglect	RVS-LBA10	0.0243	0.022	0.175	0.019	0.07	0.395
CTQ Physical Neglect	RVS-LBA11	0.0062	0.406	0.541	0.007	0.345	0.46
CTQ Physical Neglect	RVS-RBA10	0.0128	0.185	0.295	0.014	0.146	0.395
CTQ Physical Neglect	RVS-RBA11	0.0097	0.154	0.295	0.009	0.207	0.395

Further information on Clinical Measures

CTQ scores ranged from 25 to 125. Supplementary analyses examined specific effects of trauma subtypes, using five CTQ subscales ranging from 5 to 25 measuring a spectrum of abuse (emotional, physical and sexual) and neglect (emotional and physical). Higher CTQ and CTQ subscale scores reflect worse trauma severity. The Montgomery-Asberg Depression Rating Scale (MADRS) is a clinician rated measure of depressive symptoms and was used in sensitivity analyses(1). The MADRS was administered by a trained clinician. MADRS scores range between 0 and 60, with higher scores indicating worse depression severity. The Patient-Reported Outcomes Measurement Information System Anxiety Item bank consisting of 29 items is a well-validated computerized adaptive self-report measure (PROMIS Anxiety) broadly measuring anxiety severity (administering typically 4 to 8 questions which may be variable between participants) and allows determination of T-scores with mean of 50 and standard deviation of 10, with higher scores indicating worse anxiety severity(2).

Supplemental References

1. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *The British journal of psychiatry : the journal of mental science.* 134:382-389.
2. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, et al. (2011): Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. *Assessment.* 18:263-283.