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Interplay between pro-inflammatory cytokines, childhood trauma, and executive function in depressed adolescents

Amy T. Peters[a,b,*], Xinguo Ren[c], Katie L. Bessette[c,d], Benjamin I. Goldstein[e,f], Amy E. West[g], Scott A. Langenecker[d], Ghanshyam N. Pandey[c]

[a] Massachusetts General Hospital, Department of Psychiatry, USA
[b] Harvard Medical School, Department of Psychiatry, USA
[c] University of Illinois at Chicago, Department of Psychiatry, USA
[d] University of Utah, Department of Psychiatry, USA
[e] Sunnybrook Health Sciences Centre, Department of Psychiatry, Canada
[f] University of Toronto, Department of Pharmacology and Toxicology & Department of Psychiatry, Canada
[g] Keck School of Medicine of the University of Southern California, Department of Pediatrics, USA

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ABSTRACT

Background: Pro-inflammatory cytokines have been linked to depression, early childhood trauma, and impairment in executive function in adults. Whether these links are present during adolescence, a time when vulnerability to depression is heightened, a point more proximal to childhood trauma, and a critical period of brain development, is not well understood.

Method: Serum levels of interleukin (IL)-6, IL-1β, and tumor necrosis factor alpha (TNF-α) were measured in 70 adolescents aged 12–17, including 40 with a DSM-IV depressive disorder (DEP), a sub-set (n = 22) of whom reported a history of childhood trauma (DEP-T), and 30 healthy controls (HCs). Participants completed performance-based (Parametric Go/No-Go Task) and observer-rated (Behavior Rating Inventory of Executive Function) measures of executive function. Procedures were conducted at a subspecialty clinic (Dec 2015–June 2017).

Results: IL-6 was elevated in DEP and DEP-T adolescents compared to controls ($p = .014$) and TNF-α was elevated in DEP participants only ($p = .040$) compared to controls, whereas no group differences were found in IL-1β ($p = .829$). Additionally, DEP-T participants demonstrated relative deficits in performance-based ($p = .044$) and observer-rated inhibitory control ($p = .049$) compared to controls. Across the whole sample, TNF-α was associated with performance-based ($r = -0.25$, $p = .039$) and observer-rated ($r = 0.32$, $p = .009$) inhibitory control deficits. In subgroup analyses, TNF-α was associated with increased observer-rated inhibitory deficits in DEP, and at the trend level, with reduced inhibitory control performance in DEP-T.

Conclusions: The current results suggest that inflammation may be a marker of disease processes in adolescent depression. Though longitudinal studies are needed, depressed adolescents with childhood trauma exposure appear to constitute a uniquely vulnerable group in terms of objective risk for executive dysfunction. Immune dysregulation may partly contribute to this risk.

1. Introduction

There is growing awareness that inflammation affects brain health (Miller and Raison, 2016) and may sub-serve neuropsychological dysfunction in depression (Bollen et al., 2017). Indeed, peripheral inflammation correlates with executive functioning and processing speed in depressed adults (Benson et al., 2017; Goldsmith et al., 2016; Krogh et al., 2014; Smagula et al., 2017). Conceptually, neuropsychological studies converge with neuroimaging, where peripheral cytokines are associated with altered dorsal anterior cingulate (Holmes et al., 2018; Meier et al., 2016; van Velzen et al., 2017), dorsolateral prefrontal cortex (Muscatell et al., 2015), and basal ganglia (Eisenberger et al., 2010; Felger et al., 2016; Haroon et al., 2014, 2016; Savitz et al., 2015; Treadway et al., 2017) structure and function. These brain regions are essential for executive function and common nodes of dysfunctional neurocircuitry in depression (Felger, 2017). It is also appreciated that executive dysfunction is observable in adolescent depression (Joseph et al., 2008; Nieto and Castellanos, 2011; Pavuluri et al., 2009; Wagner

* Corresponding author. Massachusetts General Hospital, Department of Psychiatry, 50 Staniford Street, Suite 580, USA.
E-mail address: amy.peters@mgh.harvard.edu (A.T. Peters).

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et al., 2014), possibly involved in depression risk (Davidovich et al., 2016), and especially pronounced amongst adults with childhood trauma exposure (Marshall et al., 2016). Yet, existing peripheral immune alterations in adolescent depression are somewhat variable, and it is not yet known if inflammation influences executive dysfunction in adolescents, or whether early life trauma affects this possible relationship.

1.1. Inflammation in adolescent depression

Initial studies of youth with various depressive disorders, including major depression, dysthymia, and suicidality, report alterations in serum cytokine levels (for a review (Mitchell and Goldstein, 2014); also see (Belem da Silva et al., 2017; Pallavi et al., 2015)). The most consistent finding is increased IL-6, whereas evidence for reproducible patterns in other cytokines is equivocal (Kim et al., 2014; Mills et al., 2013; Mitchell and Goldstein, 2014). Studies are heterogeneous and vary in psychiatric medication status (Gabbay et al., 2009; Henje Blom et al., 2012), primary depressive disorder (Brambilla et al., 2004), suicidality (Gabbay et al., 2009; Pandey et al., 2012), childhood trauma (G. E. Miller and Cole, 2012)], and the cytokines of interest. Put together, IL-6 may indeed represent an early sign of immune dysregulation, but the variability in existing designs calls for further exploration of peripheral inflammation in adolescents that accounts for these factors.

1.2. Role of inflammation in risk for executive dysfunction in adolescence

While the abovementioned literature suggests that immune dysregulation may be present in depressed adolescents, whether this inflammation relates to the emergence of cognitive deficits typically present in the initial stages of depression is largely unknown (Cullen et al., 2017). A meta-analysis of neuropsychological studies in youth depression identified a domain specific deficit in inhibitory control (Wagner et al., 2015), an aspect of executive function that involves selecting, maintaining, and updating goal representations, while overriding pre-potent responses. Because impaired inhibitory control predicts behavioral, academic, and psychological difficulties (Biederman et al., 2011; Pavuluri et al., 2006; Peters et al., 2014a), it is prudent to understand whether inflammation disrupts development and functioning of inhibitory skills in adolescence.

1.3. Interplay of depression with childhood trauma and inflammation

In understanding the possible role of inflammation in inhibitory control deficits during adolescence, it is essential to consider differences in childhood trauma exposure, which has been implicated in both immune dysregulation and increased risk of inhibitory control deficits. Childhood trauma exposure may increase risk for inhibitory control deficits and inflammation in depression. For instance, in adults, the coupling together of childhood trauma and depression predicts alterations in brain structure and function, including reduced processing speed, attention, and executive function (Quinn et al., 2018; Saleh et al., 2017). Moreover, childhood trauma predicts the co-occurrence of depression and alterations in inflammatory activity later in life (Baumeister et al., 2016a; Coelho et al., 2014; Danese et al., 2007, 2009; Grosse et al., 2014; Lu et al., 2013; Miller and Cole, 2012). However, whether childhood trauma exaggerates inhibitory controls deficits, inflammation, or their co-occurrence during adolescence is unclear. Because brain development is ongoing and uneven during this period, especially in regions essential for regulation of behavior, the adolescent brain may be particularly vulnerable to the effects of early childhood trauma.

1.4. Adolescence as a critical period of risk

To unite these fragmented areas of research, it is important to study inflammation and its role in regulating cognition, both in the context of adolescent depression, childhood trauma, and their combination. In particular, evaluating these constructs during adolescence could help identify a critical period for when and how inflammatory-related mood and cognitive changes develop. Findings cannot be extrapolated from adult studies due to possible contributions of chronic depression burden and comorbidities (Berk et al., 2014; Weisenbach et al., 2014). Adolescence is a compelling window due to (a) minimized confounds of prolonged illness duration, allostatic load, chronic medical co-morbidities, and obesity (Berk et al., 2014; Lopresti and Drummond, 2013); (b) differences in the phenomenology of depression in adolescence, such as increased anhedonia and irritability (Bemporad, 1982; Birmaher et al., 1998); (c) protracted period of cognitive development that differs in maturity and plasticity from adults (Brooks et al., 2010; Hongwanishkul et al., 2005; Huizinga et al., 2006), and d) differences in cytokine production (Lilic et al., 1997).

To address these gaps in the literature, we measured three of the most extensively studied pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) and inhibitory control (performance-based and observer-rated) amongst adolescents with depressive disorders (naïve to psychotropic treatment for their mood disorder), with and without exposure to significant childhood trauma, and healthy control (HC) adolescents. These cytokines, in particular, were selected because IL-6 and TNF-α negatively impact serotonin production and integrity (Linthorst et al., 1995), which may increase risk for depression. Further, the release of TNF-α, as well as IL-1β, is thought to induce synaptic pruning, leading to impaired neuroplasticity and structural brain changes that then negatively impact cognition (Rosenblat et al., 2014). Consistent with the Research Domain Criteria Framework (RDoC), our sampling strategy aimed to capture the full range of negative mood disturbance, including major depression, dysthymia, adjustment disorder with depressed mood, and depression not otherwise specified diagnoses. The first aim was to compare groups in inflammation. We expected elevated cytokines in depressed adolescents, especially those with childhood trauma, relative to HC. The second aim was to compare groups in inhibitory control. We predicted inhibitory control deficits in depressed adolescents, especially those with childhood trauma, relative to HC. The third aim was to evaluate associations between inflammation and inhibitory control. We anticipated that inflammation would predict poorer inhibitory control, and that this association would be strongest in depressed adolescents with childhood trauma.

2. Method

2.1. Participants and procedures

This study was designed in-line with the RDoC initiative and supported by the National Institute of Mental Health. All study procedures were approved by the appropriate Institutional Review Board. Participants were assenting adolescents (and their consenting parent), ages 12–17 with any depressive mood disorder (DEP: depression, dysthymia, adjustment disorder with depressed mood, sub-threshold and unspecified depressive symptoms [n = 40]) and HC (n = 30) adolescents with no psychiatric history, equivalent in age, sex, and IQ. Of the DEP adolescents, 55% (n = 22) met threshold for childhood trauma (DEP-T; Study Measures for detail). DEP adolescents were recruited based on self-report of depressive symptoms, identified initially by a clinician or response to advertisement, and confirmed in a structured clinical interview. Participants were recruited from outpatient psychiatry clinics (DEP only) in a large, urban, academic medical center and surrounding community (DEP and HC).

A semi-structured telephone-screening interview determined initial eligibility. At in-person screening, all participants met the following inclusion criteria: 1) estimated Verbal IQ in 'borderline' or higher range [T-score > 30, Wechsler Abbreviated Scale of Intelligence - 2nd Edition Vocabulary Test (Wechsler, 1999)], and 2) English fluency. Exclusion criteria were: 1) psychiatric medication (except for stimulant use,

which was permitted among [n = 2] DEP with co-morbid ADHD in order to provide an ideal testing environment for neurocognitive tasks, as stimulants are not known to interfere with measurement of inflammation (Baumeister et al., 2016b; Kittel-Schneider et al., 2016), 2) neurological or medical condition affecting cognition (e.g. learning disability, epilepsy, developmental delay) 3) active suicidality with plan or intent requiring acute intervention, 4) prior head injury with loss of consciousness > 10 min, 5) current substance or alcohol use disorder within 30 days or more than five self-reported lifetime instances of use, 6) current smokers, 7) participation in an investigational medication research protocol, and 8) active virus or infection within two weeks prior to enrollment, as assessed by medical history interview. Eligible HC participants denied 1st degree family history of depression or other psychiatric disorders during screening.

2.2. Procedures

Eligible participants completed executive function measures, self-reports of demographics, behavior, and emotion, and a non-fasting blood sample obtained by venipuncture (Cytokine Assays for detail). Height/weight were collected via physical history questionnaire, and body mass index (BMI) was calculated. Consistent with university standards, participants were compensated $10 per hour.

2.3. Measures

2.3.1. Clinical assessment

Participants were interviewed by a clinically trained, masters-level mental health professional using the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (Kaufman et al., 1997) to yield current and lifetime DSM-IV psychiatric diagnoses. Training for all raters (n = 3) included scoring two consecutive (and randomly selected) interview recordings that achieved a kappa reliability statistic of > 0.80). Although enrollment criteria were agnostic about diagnostic depression categories, this instrument was used to ensure variability in clinical severity, screen for substance use, and evaluate for suicidality. Clinicians rated depression symptom severity on the Children's Depression Rating Scale – Revised (Poznanski et al., 1984) and functional impairment using the Children's Global Assessment Scale (Shaffer et al., 1983).

2.3.2. Childhood trauma exposure

The Childhood Trauma Questionnaire (CTQ) is a brief, reliable, and valid 28-item adolescent self-report measure that inquires about five types of maltreatment history - emotional, physical, and sexual abuse, and emotional and physical neglect (Bernstein et al., 1997). Each subscale score ranges from 5 to 25, thus the total CTQ score fluctuates from 25 to 125.

Although the total score of the CTQ is intended to represent the cumulative severity of childhood trauma exposure, the distribution of the measure is often skewed by the base-rate of childhood trauma (i.e., a high proportion of respondents reporting little to no childhood traumatic experiences). To adjust for the degree of skewness (1.62), clinically significant childhood trauma exposure can be determined by a cut-off score for each sub-scale (Bevilacqua et al., 2012; Gibb et al., 2009; Johnson et al., 2011; Kudinova et al., 2015; Walker et al., 1999). Participants above threshold on any one sub-scale are positive cases of early childhood trauma. Per the CTQ manual, the following cutoffs for moderate exposure were used: emotional abuse ≥13, emotional neglect ≥15, sexual abuse ≥8, physical abuse ≥10, and physical neglect ≥10. Additionally, within-sample, convergent validity of moderate cut-off scores was evaluated with exploratory cluster analysis, using item-level CTQ responses as input.

2.3.3. Parametric Go-No/Go (PGNG)

The PGNG assesses contextual inhibitory control, where target and lure sets change depending upon the previous response. A serial stream of letters is presented for 500 ms with no inter-stimulus interval. Responses are made by key press using the right index finger. No targets were repeated without at least one intervening distractor – thus responses delayed by up to 1000 ms were included for a relevant target. The primary dependent variable is inhibitory control (hereafter inhibitory accuracy), which measures the ability to stop an unwanted, pre-potent response. It represents the number of correct rejections divided by total possible correct rejections (rejections + commissions). Additionally, the PGNG measures sustained attention (hereafter attentional control), which is derived by dividing the number of correct hits by the total possible correct hits (hits + omissions) for No-Go trials. Response time is an index of processing speed, computed by averaging response time for Go trials.

2.3.4. Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF is a reliable and valid 86-item parent-report questionnaire of real-world executive function behaviors for youth ages 5–18. It consists of eight behavioral and meta-cognitive executive function subscales. For convergence with performance-based inhibitory control, we used the inhibit subscale (α = 0.83), which inquires about the adolescent's ability to control impulses and stop engaging in a behavior.

2.4. Cytokine collection and assays

Blood draws were acquired throughout the day between the hours of 8 a.m. and 7 p.m., which was systematically recorded. Time of collection was not significantly correlated with Il-1β (r = 0.08, p = .53), TNF-α (r = −0.13, p = .27), or IL-6 (r = 0.11, p = .39) levels. Participants were instructed to refrain from exercise on the day of their study visit until all study procedures were completed, which was confirmed at screening. However, the blood draw was non-fasting and participants were instructed to adhere to their normal dietary patterns, given evidence that intermittent and even a single bout of fasting can attenuate pro-inflammatory cytokines and induce anti-inflammatory effects (Aksungar et al., 2007; Faris et al., 2012; Lavin et al., 2011; Speaker et al., 2016).

Serum was separated, centrifuged at 6,000 rpm for 10 min, and stored at −80 °C before batch analysis. Laboratory staffs measuring cytokines were blinded to participant diagnosis. Cytokine levels were determined in plasma/serum aliquots by enzyme-linked immunosorbent assay using Quantakine® kits (R&D Systems, Inc., Minneapolis, MN, USA) for human IL-1β, TNF-α, and IL-6. Briefly, 100 μL of incubation buffer and 100 μL of serum/plasma or standard is added to each well and incubated for 3 h at room temperature (RT) on the orbital shaker. After washing wells six times with Wash Buffer, 200 μL of Conjugate is added to each well, incubated for 2 h at room temperature, washed using Wash Buffer as before, 50 μL of Substrate Solution is added to each well and incubated for 60 min at room temperature. Following this, 50 μL of Amplifier Solution is added to each well, incubated for 30 min at room temperature and 50 μL of Stop Solution is added to each well. The optical density of each well is determined within 30 min using a microplate reader set to 490 nm, and wavelength correction is set to 650 nm, and cytokine levels are calculated. Standard curve was generated by plotting the mean absorbance for each standard, and data points are linearized. The cytokines concentration in each sample was determined by reading it against the standard curve.

2.5. Statistical analyses

Differences between HC, DEP, and DEP-T participants in demographic and clinical factors were compared using one-way analysis of variance and chi-squared tests, as appropriate. Pro-inflammatory cytokine values were not normally distributed; therefore, group

differences in cytokines were compared using Kruskal-Wallis H tests (Aim 1). As demographic differences, including age, sex, and IQ, are reported in relation to performance-based (Garavan et al., 2006; Lee et al., 2015; Votruba and Langenecker, 2013) and observer-rated measures (Gioia et al., 2000; Huizinga and Smidts, 2010) of inhibitory control, one-way analysis of co-variance was used to compare groups in executive functioning measures, adjusting for these variables within the same model (Aim 2). Associations between cytokine levels and executive functioning variables (Aim 3) used Pearson's bivariate correlations in the full study sample, with coefficients in DEP and DEP-T subgroups reported separately. Significant bivariate associations were then subjected to multivariate analyses using generalized linear models. Main and interactive effects of cytokines, group, and their interaction were tested, adjusting per above for age, sex, and IQ, as well as BMI. Cytokine variables achieved a normal distribution after log-transformation and therefore log-transformed values were used in correlational and regression analyses.

3. Results

3.1. Childhood trauma exposure

Twenty-two DEP met threshold for significant maltreatment, forming a sub-group of DEP with childhood trauma history (DEP-T). We note that this classification was not altered when using slight variations in the cut-offs reported in select prior studies (Bevilacqua et al., 2012; Walker et al., 1999). The cluster solution identified the same subset of twenty-two DEP-T as most similar to each other relative to DEP-only and HCs. Of note, one additional HC participant reported CTQ score above threshold and aligned with DEP-T participants in the cluster analysis solution, thus was excluded from the overall study sample and all analyses. Among DEP only participants, 38.9% (n = 7 of 18) met threshold for low levels of trauma, as well as 30.0% (n = 9 of 30) of HC participants.

3.2. Demographic and clinical characteristics

Demographic and clinical characteristics of the sample are shown in Table 1. HCs were equivalent to DEP and DEP-T on age, sex, verbal IQ, and BMI. Across participants, age, sex, and verbal IQ were unrelated to any cytokine measurement (all p's $> .09$). BMI was positively correlated with IL-6 ($r = 0.24$, $p = .05$), but unrelated to TNF-α ($r = 0.07$, $p = .58$) or IL-1β ($r = 0.02$, $p = .89$).

DEP and DEP-T did not significantly differ in the distribution of current DSM-IV depression diagnosis, though there was a trend for a greater proportion of DEP-T participants with MDD (54.5% vs. 27.8%), $X^2 = 2.90$, $p = .09$. Of currently depressed patients, 42.5% (n = 17) met criteria for major depression (MDD), 20.0% (n = 8) for dysthymia, 30.0% (n = 12) for depressive disorder not otherwise specified (NOS), and 7.5% (n = 3) for adjustment disorder with depressed mood. Of participants with current dysthymia or depression NOS (n = 20), 35.0% (n = 7) met criteria for a past major depressive episode. Across the full sample, the proportion of participants meeting threshold for childhood trauma amongst each depression spectrum diagnosis was 70.0% for major depression (n = 12 of 17), 37.5% for dysthymia (n = 3 of 8), 41.7% for depressive disorder NOS (n = 5 of 12), and 66.7% for adjustment disorder with depressed mood (n = 2 of 3).

3.3. Inflammatory cytokines

There was a statistically significant omnibus difference between DEP, DEP-T, and HC (Table 2) for IL-6 and TNF-α levels. Post-hoc pairwise comparisons indicated that IL-6 levels were elevated in both DEP ($d = 0.91$) and DEP-T ($d = 0.63$) relative to HCs, and did not differ significantly from each other. For TNF-α, post-hoc pairwise comparisons indicated that DEP ($d = 0.65$) had elevated serum levels relative to HC and DEP-T ($d = 0.74$). No group differences were detected in Il-1β.

3.4. Executive functioning

Performance. The omnibus test (Table 2) for between-group (HC, DEP, DEP-T) differences was significant for inhibitory accuracy. Post-hoc pair-wise comparisons indicated that DEP-T demonstrated poorer inhibitory accuracy relative to HC ($d = 0.54$) but not DEP ($d = 0.40$), Fig. 1a. DEP did not differ from HC in inhibitory accuracy ($d = 0.15$). There were no group differences in attentional control or response time.

Observer Report. 94% of parents completed the observer report rating scale; data were missing for four subjects (n = 1 HC, n = 1 DEP, and n = 2 DEP-T). The omnibus test (Table 2) for between-group differences was significant for observer report of inhibitory control. As illustrated in Fig. 1b, post-hoc pair-wise comparisons indicated that DEP-T parents reported greater inhibitory problem behavior relative to HCs ($d = .62$) but not DEP ($d = 0.06$). DEP parents reported greater inhibitory problem behavior at the trend level compared to HC ($d = .64$).

3.5. Bivariate associations between inflammatory cytokines and executive functioning dimensions

Table 3 shows exploratory correlations between cytokines and executive functioning in the full sample, and DEP and DEP-T, separately (e.g., individual differences analysis). Across the full sample, TNF-α and inhibitory accuracy were inversely related ($r = -.25$, $p = .04$, Fig. 2a). Follow-up correlations indicated a trend in DEP-T ($r = -0.39$, $p = .07$), but not in DEP ($r = -0.32$, $p = .19$), or HC ($r = -0.11$, $p = .56$) groups. TNF-α was associated with parent report of more inhibitory problem behavior across the full sample ($r = 0.32$, $p = .01$, Fig. 2b). Follow-up correlations indicated a trend in DEP-T ($r = 0.37$, $p = .09$), significant correlation in DEP ($r = 0.56$, $p = .02$), but not HC ($r = 0.13$, $p = .49$). TNF-α was not associated with attentional control or response time. IL-6 and IL-1β were not associated with executive function.

3.6. Multivariate modeling of inflammatory cytokines and executive functioning dimensions

Partial correlations across the full sample remained significant between TNF-α and inhibitory accuracy ($r = -0.27$, $p = .03$), as well as between TNF-α and parent-reported inhibitory problem behavior ($r = 0.31$, $p = .02$) after adjusting for age, sex, IQ, and BMI. In a multivariate generalized linear model (Table 4) predicting inhibitory accuracy, the effects of age, sex, IQ, and BMI were non-significant, and TNF-α remained significantly associated with reduced inhibitory accuracy. There was a trend for an interaction between group and TNF-α (Table 4), such that the negative correlation between TNF-α and inhibitory accuracy was most pronounced in DEP-T. The simple slope was significant in DEP-T ($b = -0.34$, $se = 0.13$, $p = .01$). In a multivariate generalized linear model predicting inhibitory problem behavior (Table 4), older age significant predicted reduced inhibitory problem behavior; TNF-α remained significantly associated with increased inhibitory problem behavior. There was a trend for an interaction between group and TNF-α (Table 4), such that the association between TNF-α and inhibitory problem behavior was most pronounced in DEP. The simple slope was significant in DEP ($b = 10.38$, $se = 4.88$, $p = .04$).

4. Discussion

In this study, depressed adolescents with and without a history of childhood trauma and naïve to pharmacological treatment for depression showed higher serum levels of IL-6 compared to HCs. Adolescents with depression and no trauma history demonstrated elevated TNF-α.

Table 1
Demographic, clinical, and serum cytokine variables in HC, DEP, and DEP-T adolescents.

	HC (n = 30)		DEP (n = 18)		DEP-T (n = 22)		Omnibus Test	
	M	SD	M	SD	M	SD	*F*	*p*-value
Age	14.67	1.37	14.61	1.46	14.45	1.54	.12	.88
Verbal IQ Estimate^	55.63	8.49	54.44	9.90	50.23	9.77	2.25	.11
Body Mass Index	22.98	3.21	22.68	4.96	22.10	4.56	.27	.76
Global Functioning^^[a,b,c]	91.70	5.69	69.28	9.14	60.95	9.20	106.76	< .001
CDRS Total[a,b,c]	19.47	1.72	38.28	10.04	47.95	11.61	78.98	< .001
Age of Onset	–	–	12.00	2.00	12.33	.298	.35	.71
	N	**%**	**N**	**%**	**N**	**%**	χ^2	***p*-value**
Sex (% Female)	19	63.3	10	55.6	14	63.6	.35	.84
Household Income (% < 60K)^^^	7	26.9	6	35.3	9	47.4	2.01	.38
Ethnicity								
Hispanic	6	20.0	6	33.3	7	31.8	1.36	.51
Non-Hispanic	24	80.0	12	66.7	15	68.2	–	–
Race								
Caucasian	16	53.3	13	76.5	10	45.5	12.44	.13
African American	8	26.7	0	0.0	8	36.4	–	–
Asian	5	16.7	2	11.8	1	4.5	–	–
American Indian/Alaskan Native	0	0.0	0	0.0	1	4.5	–	–
Other/Unknown	1	3.3	2	11.8	2	9.1	–	–
Post Pubertal	23	76.6	12	66.7	16	72.7	1.44	.96
Current DSM-IV Diagnosis^^^								
Major Depression	–	–	5	27.8	12	54.5	2.90	.09
Dysthymia	–	–	5	27.8	3	13.6	1.24	.27
Depressive d/o NOS	–	–	7	38.8	5	22.7	2.20	.14
Adjustment d/o Depressed Mood	–	–	1	5.5	2	9.1	1.72	.19
Comorbid DSM-IV Diagnoses								
Panic Disorder	–	–	1	5.6	3	13.6	.72	.61
Simple Phobia	–	–	0	0.0	1	2.5	.84	.99
Social Phobia	–	–	2	11.1	9	22.5	2.4	.15
Agoraphobia	–	–	1	5.6	0	2.5	1.25	.45
Generalized Anxiety Disorder	–	–	9	50.0	8	47.1	.75	.52
Post Traumatic Stress Disorder	–	–	1	5.6	4	18.2	1.44	.36
Attention Deficit/Hyperactivity	–	–	1	5.6	5	22.7	2.29	.20
Oppositional Defiant Disorder	–	–	1	5.6	1	4.5	.02	.99

[a]Significant ($p < .05$) post-hoc pairwise comparison, DEP vs. HC; [b]Significant ($p < .05$) post-hoc pairwise comparison, DEP-T vs. HC; [c]Significant ($p < .05$) post-hoc pairwise comparison, DEP-T vs. DEP.
^Vocabulary sub-test T-Score from the WASI-II; ^^Children's Global Assessment Scale; ^^^Calculated based on percent of available cases; household income not reported for HC: n = 4, DEP: n = 1, DEP-T: n = 3. ^^^^There was a trend for greater CDRS scores in DEP-T participants without MDD (M = 42.50, SD = 10.22) versus DEP participants without MDD (M = 34.69, SD = 8.64), $F = 3.83$, $p = .06$. Additionally, CDRS scores were higher in DEP-T with MDD (M = 52.50, SD = 11.05) versus DEP-T without MDD (M = 42.50, SD = 10.22), $F = 4.78$, $p = .04$). CTQ subscale scores for physical abuse (p = .67), sexual abuse (p = .19), and physical neglect (p = .75) were equivalent in DEP-T with and without MDD. Emotional neglect was higher in DEP-T with MDD (M = 15.00, SD = 4.80) versus DEP-T without MDD (M = 10.00, SD = 4.49), $F = 6.26$, $p = .02$). Emotional abuse was higher in DEP-T with MDD (M = 13.75, SD = 5.03) versus DEP-T without MDD (M = 8.70, SD = 3.23), $F = 7.47$, $p = .01$).

Table 2
Between group differences in cytokine levels and executive functioning measures.

	HC (n = 30)		DEP (n = 18)		DEP-T (n = 22)		Omnibus Test	
Cytokines	M	SD	M	SD	M	SD	χ^2	*p*-value
IL-6[a,b*]	1.06	.54	1.84	1.08	1.53	.90	8.55	.014
TNF-α[a,c*]	.58	.25	.76	.30	.56	.23	6.44	.040
Il-1β	.09	.06	.09	.06	.10	.05	.38	.829
Executive Function	**M**	**SD**	**M**	**SD**	**M**	**SD**	***F***	***p*-value**
Inhibitory Accuracy[b]	.72	.19	.70	.21	.60	.25	3.28	.044
Attentional Control	.85	.13	.85	.12	.78	.16	.56	.575
Response Time	577.54	81.74	573.71	58.94	592.21	72.15	.895	.414
Observer-Rated Inhibition[b]	11.65	3.06	13.88	3.87	14.15	4.77	3.18	.049

[a]Significant ($p < .05$) post-hoc pairwise comparison, DEP vs. HC.
[b]Significant ($p < .05$) post-hoc pairwise comparison, DEP-T vs. HC.
[c]Significant ($p < .05$) post-hoc pairwise comparison, DEP-T vs. DEP.
*Significant group differences were sustained when testing log-transformed values in a general linear model for IL-6, $F(2, 69) = 9.50$, $p = .009$, as well as for TNF-α, $F(2, 69) = 4.53$, $p = .038$. There remained no difference between groups in IL-1β when using log transformed values, $F(2, 69) = 0.90$, $p = .631$.

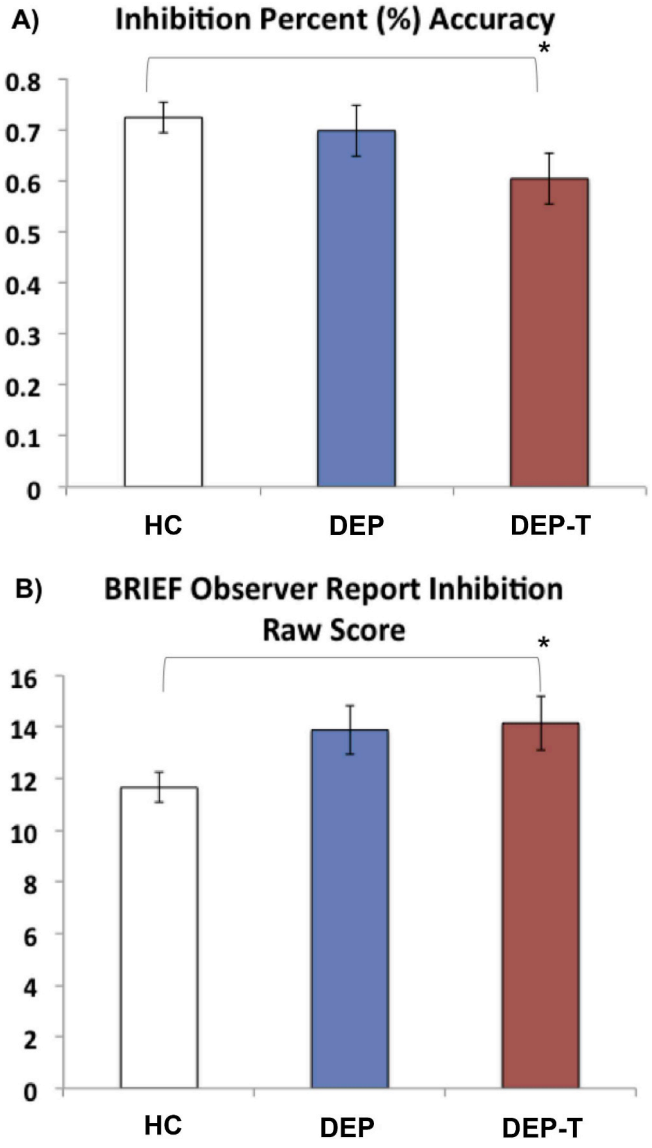

Fig. 1. Performance-Based (A) and Observer-Rated (B) Measures of Executive Function in HC, DEP, and DEP-T Adolescents. *Denotes significant difference, $p < .05$.

Additionally, DEP-T demonstrated deficits in inhibitory control. Increased TNF-α was associated with poorer inhibitory control. Moreover, there was a trend to suggest that the association between TNF-α and performance-based inhibitory control may be most pronounced in DEP-T, whereas the relationship with subjective ratings was more marked in DEP. These findings were robust to adjustment for demographics and BMI. Cumulatively, these findings implicate cytokine production as a sign of immune dysregulation in early-onset depression and potential risk marker for executive dysfunction.

4.1. Inflammatory cytokines

Our finding of elevated IL-6 among depressed adolescents who are naïve to pharmacological treatment of their mood disorder is consistent with existing literature, which has largely been conducted in samples with some proportion of participants taking medication for depression (Mitchell and Goldstein, 2014; Pallavi et al., 2015). Two prior studies of un-medicated adolescents also report elevated IL-6 in patients with primarily anxiety disorders (small minority of depressed participants (Belem da Silva et al., 2017)) and females with mixed mood and anxiety disorders (Henje Blom et al., 2012). Because there are multiple neurotransmitter, neuroendocrine, and glial pathways by which antidepressants could be involved in the inhibition of pro-inflammatory mediators (Galecki et al., 2018), our findings raise the possibility that IL-6 is a biomarker of early course depression independent of pharmacological influences.

However, the observed pattern of IL-6 alterations is only partly consistent with our hypothesis that inflammation would be elevated in depression, but most pronounced in depressed youth with childhood trauma. It was also somewhat surprising and inconsistent with our hypotheses that TNF-α was elevated only in DEP participants *without* a childhood trauma history. One possible explanation is that the clear and present dangers of childhood trauma to physical-, emotional-, and neuro-development (Berens et al., 2017) might necessitate *efficient* immune functioning for defense, resilience, or repair. By contrast, elevated inflammation in the absence of threat may be *inefficient* and have deleterious effects (Raison and Miller, 2017). It is also possible that clinical and diagnostic heterogeneity could obscure effects; different clinical syndromes may be associated with inflammatory activity at both high and low ends of a u-curve. For instance, *decreased* TNF-α is reported in suicidal adolescents (Gabbay et al., 2009) and in adolescent dysthymia (Brambilla et al., 2004). Third, unclear interactions between different kinds of inflammatory markers (e.g. pro- and anti-inflammatory ratios) may contribute to heterogeneity in measurement. Subsequent longitudinal study of TNF-α will be paramount for clarifying variability (Mitchell and Goldstein, 2014).

4.2. Executive functioning

Consistent with our hypothesis, DEP-T participants demonstrated deficits in performance-based and observer-rated measures of inhibitory control, but not other aspects of executive function such as attentional control or response time. Childhood maltreatment has predicted executive dysfunction in adolescent inpatients with diverse psychopathology (Kavanaugh et al., 2015), but our work suggests that inhibitory control, specifically, may be particularly sensitive to its effects in depression. Moreover, as childhood trauma prospectively predicts executive dysfunction into adulthood (Nikulina and Widom, 2013), it is possible that early life adversity is involved in the instantiation of inhibitory dysfunction in depression (Marshall et al., 2016).

4.3. Associations between inflammation and executive functioning

As expected, increased TNF-α was associated with inhibitory control deficits but not attentional control or response time. This converges with a community youth study, where increased salivary C-reactive protein correlated with poorer Stroop inhibition and switching (Cullen et al., 2017). These findings are striking because the prevailing hypothesis underlying inflammation and cognitive dysfunction is that age-related sensitization of microglia magnifies *neuro-inflammation*, impairing synaptic plasticity and cortical function, and in turn, cognitive functions (Aiken et al., 1991; Holmes et al., 2009; Jordanova et al., 2007; Weaver et al., 2002). However, peripheral inflammation might disrupt typical neurodevelopment of inhibitory control much earlier in life. If replicated, TNF-α may offer an avenue for prevention, potentially alleviating downstream effects of chronic illness on brain function and cognition.

DEP-T demonstrated inhibitory control deficits and a trend for preferential association with TNF-α, but it is perplexing that TNF-α was not elevated in DEP-T. It is likely an issue of statistical power, as the correlations (−.39 and −0.32) are in the same direction and of the same general effect size. An alternative interpretation is that it is possible brain changes embedded from early trauma (Heany et al., 2018) may catalyze vulnerability and sensitivity to low-level, and even normative, fluctuations in cytokine signaling. Equally, childhood trauma

Table 3
Bivariate correlations for inflammatory cytokine and executive functioning dimensions.

Full Sample	IL6	TNF-α^	Il-1β	Inhibitory Accuracy	Attentional Control	Response Time	Observer Inhibition
IL6							
TNF-α	0.14						
Il-1β	0.10	−0.13					
Inhibitory Accuracy	−0.06	−0.25*	−0.06				
Attentional Control	−0.01	0.13	0.21	−0.27*			
Response Time	0.01	−0.10	0.04	0.04	−0.16		
Observer Inhibition	0.17	0.32**	−0.06	−0.27*	−0.16	0.15	
CDRS	−0.17	−0.01	0.003	−0.07	−0.21	0.13	0.17
DEP							
IL6							
TNF-α	0.12						
Il-1β	0.03	0.19					
Inhibitory Accuracy	−0.02	−0.32	−0.34				
Attentional Control	−0.10	−0.08	0.23	−0.18			
Response Time	0.02	−0.12	−0.29	0.38	−0.27		
Observer Inhibition	0.05	0.56*	0.10	−0.02	−0.53*	0.39	–
DEP-T							
IL6							
TNF-α	0.12						
Il-1β	0.35	−0.20					
Inhibitory Accuracy	−0.15	−0.39[t]	0.08				
Attentional Control	0.01	0.21	0.25	−0.41			
Response Time	0.09	0.05	0.12	−0.13	0.07		
Observer Inhibition	0.15	0.37[t]	−0.25	−0.52*	0.10	0.18	–

RT = Response Time, *Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), [t]Denotes statistical trend at $p < .10$; ^Full sample correlations remained significant between TNF-α and inhibitory accuracy ($r = -0.27$, $p = .04$), as well as between TNF-α and Observer Inhibition ($r = 0.35$, $p = .01$) after controlling for group.

may modulate anti-inflammatory mediators, not investigated here, and potentiate effects of the imbalance between pro- and anti-inflammatory cytokines on the brain. Related, in individual differences analyses it was paradoxical that elevated TNF-α predicted observer report of inhibitory problem behavior in DEP, despite only marginal, non-significant observed performance deficits. Discordance between parent ratings and performance (Table 3) could be in line with the notion that parental criticism and impaired perspective taking engender inflammatory responses in offspring (Ehrlich et al., 2015; Human et al., 2014; Manczak et al., 2016). On the other hand, given the relatively small sample sizes of subgroups, we are also cautious not to over interpret variations in the strength of cytokine and executive functioning correlations, which could relate to statistical power.

4.4. Possible mechanisms for peripheral cytokine effects on the brain

Mechanistically, how might inflammation promote executive dysfunction, possibly disproportionately in depressed youth with trauma exposure? There are multifactorial pathways by which peripheral cytokines may enhance neural-immune crosstalk. The first involves afferent vagus nerve fibers, which sense peripheral inflammatory molecules and convey signals to the brain (Pavlov and Tracey, 2012). In a second, humoral pathway, production of cytokines from Toll-like receptors on macrophage-like cells in the circumventricular organs and the choroid plexus can enter the brain by volume diffusion (Vitkovic et al., 2000). Third, in excess, cytokine transporters at the blood–brain barrier can gain access to the brain through saturable transport (Banks, 2006). Epigenetic alterations related to stress and psychiatric disorders (Tsankova et al., 2007; Vanden Berghe et al., 2006), as well as alterations in central serotonergic activity (Maes et al., 2011) may be involved in particular vulnerability for depressed youth with trauma exposure.

Given that there are multiple complex pathways from the periphery to the brain, why might executive dysfunction relate specifically to TNF-α? TNF-α is involved in myelin degeneration (Selmaj and Raine, 1988) and white matter volume alterations (Diniz et al., 2015; Frodl and Amico, 2014; Smagula et al., 2017), and TNF-α antagonism has antidepressant effects in some patients (Raison et al., 2013). Accordingly, TNF-α might alter typical age-related frontal-subcortical white matter maturation (Barnea-Goraly et al., 2005) sub-serving executive function (Peters et al., 2014b), possibly particularly so in depressed youth (Aghajani et al., 2014; Bessette et al., 2014; LeWinn et al., 2014). Indeed, the impact of white matter integrity on executive control is more pronounced in depressed adults versus controls (Rizk et al., 2017). Additionally, TNF-α influences glutamate reuptake and release in the basal ganglia and dorsal anterior cingulate (Haroon et al., 2015, 2016), which contribute to inhibition within a functional executive control brain network (McTeague et al., 2016). Therefore, inflammation may relate to inhibition through effects on glutamate in the brain. On the other hand, while increased TNF-α uniquely predicted reduced executive function here, the cognitive correlates of inflammation might be subtle in adolescents and could interact over time with multiple biomarkers, like oxidative stress and BDNF (Newton et al., 2017).

4.5. Strengths and limitations

These findings must be interpreted within the context of the study's strengths and weaknesses. Strengths include enrollment of a diverse sample of depressed adolescents, equivalent to HCs in demographics and carefully screened for confounds to inflammation. On the other hand, a major limitation of the study is that the cross-sectional design limits any causal inferences. Second, cytokine physiologies are complex; effects of imbalance between cells that up-regulate versus inhibit (i.e., anti-inflammatory) immune response or mediators not investigated here (e.g., soluble receptors and their buffers) are unknown. Moreover, cytokines were measured peripherally and the direct link to brain function is unconfirmed. Third, childhood trauma was assessed retrospectively via self-report, which could be biased by recall errors

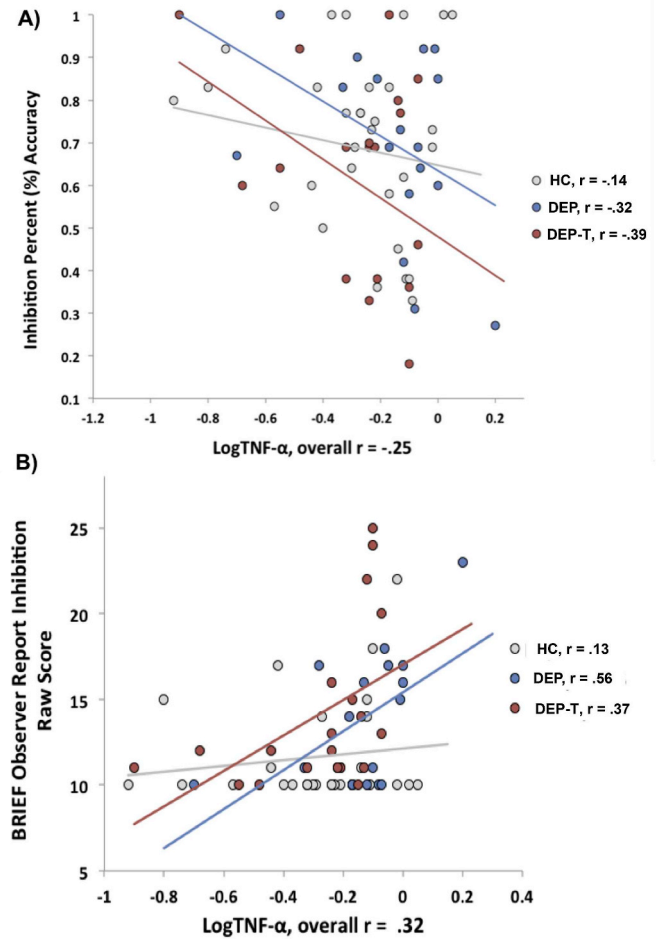

Fig. 2. Association between inflammatory cytokines and performance-based (A) and observer-rated (B) measures of inhibitory control.

and mood-congruent reporting, especially as DEP-T youth had higher CDRS and lower global functioning scores, and trend towards a greater proportion of participants with MDD. Fourth, we were underpowered to detect whether specific traumas (e.g., sexual and physical abuse (Baumeister et al., 2016a)) confer unique risks or whether psychosocial supports buffer against inflammation or childhood trauma. Last, future designs could address possible circadian and endocrine influences in the immune response (Bansal et al., 2018).

5. Summary and clinical implications

In sum, both immune function and childhood trauma impact inhibitory control early in the disease process of adolescent depression. The coupling of early childhood adversity and depression may potentiate a phenotype of executive dysfunction, which may be partly related to inflammation. Specifically, TNF-α may be a target of interest, which if demonstrated in future studies, could have clinical applications for anti-inflammatory therapy. More broadly, the findings contribute to an emerging consensus that childhood social conditions are important in establishing differential developmental vulnerability to disease and disability. It will be highly important to study whether earlier identification and intervention affects subsequent inflammatory and cognitive processes. Future research should also evaluate whether basal markers of inflammation confer risk for progression of clinical and neuropsychological sequelae.

Table 4
Multivariate modeling of inflammatory cytokines and executive functioning dimensions in DEP-T, DEP, and HC.

	Inhibitory Accuracy			
	b	*se*	*p*	R^2
Age	−0.02	0.02	.29	0.20
Sex	0.05	0.05	.30	
Verbal IQ Estimate	−0.002	−0.003	.43	
BMI	−0.001	0.01	.86	
DEP	−0.25	0.11	**.02**	
DEP-T	−0.48	0.13	**< .001**	
TNF-α	−0.34	0.12	**.004**	
TNF-α*DEP	−0.27	0.26	.29	
TNF-α*DEP-T	−0.34	0.19	.07[t]	
	Observer Inhibition			
	b	*se*	*p*	R^2
Age	−0.8	0.31	**.01**	0.35
Sex	−0.85	0.91	.35	
Verbal IQ Estimate	−0.05	0.05	.33	
BMI	0.03	0.12	.77	
DEP	5.24	1.86	**.01**	
DEP-T	6.48	2.32	**.01**	
TNF-α	4.39	2.07	**.03**	
TNF-α*DEP	9.23	5.05	.06[t]	
TNF-α*DEP-T	3.23	3.31	.33	

BOLD denotes significant at $p < .05$, [t]Denotes statistical trend at $p < .10$.
IQ = Intelligence Quotient, BMI = Body Mass Index.

Previous presentation of data

May 2018 Meeting of the Society for Biological Psychiatry.

Conflicts of interest

None of the authors have conflicts of interests to report.

Disclosures

None.

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References

Aghajani, M., Veer, I.M., van Lang, N.D., Meens, P.H., van den Bulk, B.G., Rombouts, S.A., Vermeiren, R.R., van der Wee, N.J., 2014. Altered white-matter architecture in treatment-naive adolescents with clinical depression. Psychol. Med. 44 (11), 2287–2298.

Aiken, L.S., West, S.G., Reno, R.R., 1991. Multiple Regression: Testing and Interpreting Interactions. Sage.

Aksungar, F.B., Topkaya, A.E., Akyildiz, M., 2007. Interleukin-6, C-reactive protein and biochemical parameters during prolonged intermittent fasting. Ann. Nutr. Metab. 51 (1), 88–95.

Banks, W.A., 2006. The blood-brain barrier in psychoneuroimmunology. Neurol. Clin. 24 (3), 413–419.

Bansal, A., Mejia, J.H., Simmons, R.A., 2018 Jan 1. Immune system: an emerging player in mediating effects of endocrine disruptors on metabolic health. Endocrinology 159 (1), 32–45. https://doi.org/10.1210/en.2017-00882.

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C.C., Reiss, A.L., 2005. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. Cerebr. Cortex 15 (12), 1848–1854.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016a. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive

protein, interleukin-6 and tumour necrosis factor-alpha. Mol. Psychiatr. 21 (5), 642–649.
Baumeister, D., Ciufolini, S., Mondelli, V., 2016b. Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment? Psychopharmacology (Berlin) 233 (9), 1575–1589.
Belem da Silva, C.T., de Abreu Costa, M., Kapczinski, F., de Aguiar, B.W., Salum, G.A., Manfro, G.G., 2017. Inflammation and internalizing disorders in adolescents. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 77, 133–137.
Bemporad, J.R., 1982. Management of childhood depression: developmental considerations. Psychosomatics 23 (3), 272–279.
Benson, S., Brinkhoff, A., Lueg, L., Roderigo, T., Kribben, A., Wilde, B., Witzke, O., Engler, H., Schedlowski, M., Elsenbruch, S., 2017. Effects of acute systemic inflammation on the interplay between sad mood and affective cognition. Transl. Psychiatry 7 (12), 1281.
Berens, A.E., Jensen, S.K.G., Nelson 3rd, C.A., 2017. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. BMC Med. 15 (1), 135.
Berk, M., Berk, L., Dodd, S., Cotton, S., Macneil, C., Daglas, R., Conus, P., Bechdolf, A., Moylan, S., Malhi, G.S., 2014. Stage managing bipolar disorder. Bipolar Disord. 16 (5), 471–477.
Bernstein, D.P., Ahluvalia, T., Pogge, D., Handelsman, L., 1997. Validity of the childhood trauma questionnaire in an adolescent psychiatric population. J. Am. Acad. Child Adolesc. Psychiatry 36 (3), 340–348.
Bessette, K.L., Nave, A.M., Caprihan, A., Stevens, M.C., 2014. White matter abnormalities in adolescents with major depressive disorder. Brain Imag. Behav. 8 (4), 531–541.
Bevilacqua, L., Carli, V., Sarchiapone, M., George, D.K., Goldman, D., Roy, A., Enoch, M.A., 2012. Interaction between FKBP5 and childhood trauma and risk of aggressive behavior. Arch. Gen. Psychiatr. 69 (1), 62–70.
Biederman, J., Petty, C.R., Wozniak, J., Wilens, T.E., Fried, R., Doyle, A., Henin, A., Bateman, C., Evans, M., Faraone, S.V., 2011. Impact of executive function deficits in youth with bipolar I disorder: a controlled study. Psychiatr. Res. 186 (1), 58–64.
Birmaher, B., Brent, D.A., Benson, R.S., 1998. Summary of the practice parameters for the assessment and treatment of children and adolescents with depressive disorders. American Academy of Child and Adolescent Psychiatry. J. Am. Acad. Child Adolesc. Psychiatry 37 (11), 1234–1238.
Bollen, J., Trick, L., Llewellyn, D., Dickens, C., 2017. The effects of acute inflammation on cognitive functioning and emotional processing in humans: a systematic review of experimental studies. J. Psychosom. Res. 94, 47–55.
Brambilla, F., Monteleone, P., Maj, M., 2004. Interleukin-1beta and tumor necrosis factor-alpha in children with major depressive disorder or dysthymia. J. Affect. Disord. 78 (3), 273–277.
Brooks, B.L., Iverson, G.L., Sherman, E.M., Roberge, M.C., 2010. Identifying cognitive problems in children and adolescents with depression using computerized neuropsychological testing. Appl. Neuropsychol. 17 (1), 37–43.
Coelho, R., Viola, T.W., Walss-Bass, C., Brietzke, E., Grassi-Oliveira, R., 2014. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr. Scand. 129 (3), 180–192.
Cullen, A.E., Tappin, B.M., Zunszain, P.A., Dickson, H., Roberts, R.E., Nikkheslat, N., Khondoker, M., Pariante, C.M., Fisher, H.L., Laurens, K.R., 2017. The relationship between salivary C-reactive protein and cognitive function in children aged 11-14years: does psychopathology have a moderating effect? Brain Behav. Immun. 66, 221–229.
Danese, A., Moffitt, T.E., Harrington, H., Milne, B.J., Polanczyk, G., Pariante, C.M., Poulton, R., Caspi, A., 2009. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch. Pediatr. Adolesc. Med. 163 (12), 1135–1143.
Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc. Natl. Acad. Sci. U. S. A. 104 (4), 1319–1324.
Davidovich, S., Collishaw, S., Thapar, A.K., Harold, G., Thapar, A., Rice, F., 2016. Do better executive functions buffer the effect of current parental depression on adolescent depressive symptoms? J. Affect. Disord. 199, 54–64.
Diniz, B.S., Sibille, E., Ding, Y., Tseng, G., Aizenstein, H.J., Lotrich, F., Becker, J.T., Lopez, O.L., Lotze, M.T., Klunk, W.E., Reynolds, C.F., Butters, M.A., 2015. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. Mol. Psychiatr. 20 (5), 594–601.
Ehrlich, K.B., Miller, G.E., Chen, E., 2015. Harsh parent-child conflict is associated with decreased anti-inflammatory gene expression and increased symptom severity in children with asthma. Dev. Psychopathol. 27 (4 Pt 2), 1547–1554.
Eisenberger, N.I., Berkman, E.T., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2010. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol. Psychiatry 68 (8), 748–754.
Faris, M.A., Kacimi, S., Al-Kurd, R.A., Fararjeh, M.A., Bustanji, Y.K., Mohammad, M.K., Salem, M.L., 2012. Intermittent fasting during Ramadan attenuates proinflammatory cytokines and immune cells in healthy subjects. Nutr. Res. 32 (12), 947–955.
Felger, J.C., 2017. Imaging the role of inflammation in mood and anxiety-related disorders. Curr. Neuropharmacol.
Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., Miller, A.H., 2016. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol. Psychiatr. 21 (10), 1358–1365.
Frodl, T., Amico, F., 2014. Is there an association between peripheral immune markers and structural/functional neuroimaging findings? Prog. Neuro-Psychopharmacol. Biol. Psychiatry 48, 295–303.
Gabbay, V., Klein, R.G., Guttman, L.E., Babb, J.S., Alonso, C.M., Nishawala, M., Katz, Y., Gaite, M.R., Gonzalez, C.J., 2009. A preliminary study of cytokines in suicidal and nonsuicidal adolescents with major depression. J. Child Adolesc. Psychopharmacol. 19 (4), 423–430.
Galecki, P., Mossakowska-Wojcik, J., Talarowska, M., 2018. The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 80 (Pt C), 291–294.
Garavan, H., Hester, R., Murphy, K., Fassbender, C., Kelly, C., 2006. Individual differences in the functional neuroanatomy of inhibitory control. Brain Res. 1105 (1), 130–142.
Gibb, B.E., Schofield, C.A., Coles, M.E., 2009. Reported history of childhood abuse and young adults' information-processing biases for facial displays of emotion. Child. Maltreat. 14 (2), 148–156.
Gioia, G.A., Isquith, P.K., Guy, S.C., Kenworthy, L., 2000. Behavior Rating Inventory of Executive Function: BRIEF. Psychological Assessment Resources Odessa, FL.
Goldsmith, D.R., Haroon, E., Woolwine, B.J., Jung, M.Y., Wommack, E.C., Harvey, P.D., Treadway, M.T., Felger, J.C., Miller, A.H., 2016. Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. Brain Behav. Immun. 56, 281–288.
Grosse, L., Carvalho, L.A., Wijkhuijs, A.J., Bellingrath, S., Ruland, T., Ambree, O., Alferink, J., Ehring, T., Drexhage, H.A., Arolt, V., 2014. Clinical characteristics of inflammation-associated depression: monocyte gene expression is age-related in major depressive disorder. Brain Behav. Immun.
Haroon, E., Felger, J.C., Woolwine, B.J., Chen, X., Parekh, S., Spivey, J.R., Hu, X.P., Miller, A.H., 2015. Age-related increases in basal ganglia glutamate are associated with TNF, reduced motivation and decreased psychomotor speed during IFN-alpha treatment: preliminary findings. Brain Behav. Immun. 46, 17–22.
Haroon, E., Fleischer, C.C., Felger, J.C., Chen, X., Woolwine, B.J., Patel, T., Hu, X.P., Miller, A.H., 2016. Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. Mol. Psychiatr. 21 (10), 1351–1357.
Haroon, E., Woolwine, B.J., Chen, X., Pace, T.W., Parekh, S., Spivey, J.R., Hu, X.P., Miller, A.H., 2014. IFN-alpha-induced cortical and subcortical glutamate changes assessed by magnetic resonance spectroscopy. Neuropsychopharmacology : Off. Publ. Am. Coll. Neuropsychopharmacol. 39 (7), 1777–1785.
Heany, S.J., Groenewold, N.A., Uhlmann, A., Dalvie, S., Stein, D.J., Brooks, S.J., 2018. The neural correlates of Childhood Trauma Questionnaire scores in adults: a meta-analysis and review of functional magnetic resonance imaging studies. Dev. Psychopathol. 30 (4), 1475–1485.
Henje Blom, E., Lekander, M., Ingvar, M., Asberg, M., Mobarrez, F., Serlachius, E., 2012. Pro-inflammatory cytokines are elevated in adolescent females with emotional disorders not treated with SSRIs. J. Affect. Disord. 136 (3), 716–723.
Holmes, C., Cunningham, C., Zotova, E., Woolford, J., Dean, C., Kerr, S., Culliford, D., Perry, V.H., 2009. Systemic inflammation and disease progression in Alzheimer disease. Neurology 73 (10), 768–774.
Holmes, S.E., Hinz, R., Conen, S., Gregory, C.J., Matthews, J.C., Anton-Rodriguez, J.M., Gerhard, A., Talbot, P.S., 2018. Elevated translocator protein in anterior cingulate in major depression and a role for inflammation in suicidal thinking: a positron emission tomography study. Biol. Psychiatry 83 (1), 61–69.
Hongwanishkul, D., Happaney, K.R., Lee, W.S., Zelazo, P.D., 2005. Assessment of hot and cool executive function in young children: age-related changes and individual differences. Dev. Neuropsychol. 28 (2), 617–644.
Huizinga, M., Dolan, C.V., van der Molen, M.W., 2006. Age-related change in executive function: developmental trends and a latent variable analysis. Neuropsychologia 44 (11), 2017–2036.
Huizinga, M., Smidts, D.P., 2010. Age-related changes in executive function: a normative study with the Dutch version of the Behavior Rating Inventory of Executive Function (BRIEF). Child Neuropsychol. 17 (1), 51–66.
Human, L.J., Chan, M., DeLongis, A., Roy, L., Miller, G.E., Chen, E., 2014. Parental accuracy regarding adolescent daily experiences: relationships with adolescent psychological adjustment and inflammatory regulation. Psychosom. Med. 76 (8), 603–610.
Johnson, A.L., Benas, J.S., Gibb, B.E., 2011. Depressive implicit associations and adults' reports of childhood abuse. Cognit. Emot. 25 (2), 328–333.
Jordanova, V., Stewart, R., Davies, E., Sherwood, R., Prince, M., 2007. Markers of inflammation and cognitive decline in an African-Caribbean population. Int. J. Geriatr. Psychiatry 22 (10), 966–973.
Joseph, M.F., Frazier, T.W., Youngstrom, E.A., Soares, J.C., 2008. A quantitative and qualitative review of neurocognitive performance in pediatric bipolar disorder. J. Child Adolesc. Psychopharmacol. 18 (6), 595–605.
Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36 (7), 980–988.
Kavanaugh, B., Holler, K., Selke, G., 2015. A neuropsychological profile of childhood maltreatment within an adolescent inpatient sample. Appl. Neuropsychol. Child 4 (1), 9–19.
Kim, J.W., Szigethy, E.M., Melhem, N.M., Saghafi, E.M., Brent, D.A., 2014. Inflammatory markers and the pathogenesis of pediatric depression and suicide: a systematic review of the literature. J. Clin. Psychiatry 75 (11), 1242–1253.
Kittel-Schneider, S., Spiegel, S., Renner, T., Romanos, M., Reif, A., Reichert, S., Heupel, J., Schnetzler, L., Stopper, H., Jacob, C., 2016. Cytogenetic effects of chronic methylphenidate treatment and chronic social stress in adults with attention-deficit/hyperactivity disorder. Pharmacopsychiatry 49 (4), 146–154.
Krogh, J., Benros, M.E., Jorgensen, M.B., Vesterager, L., Elfving, B., Nordentoft, M., 2014. The association between depressive symptoms, cognitive function, and inflammation in major depression. Brain Behav. Immun. 35, 70–76.
Kudinova, A.Y., Gibb, B.E., McGeary, J.E., Knopik, V.S., 2015. Brain derived neurotrophic factor (BDNF) polymorphism moderates the interactive effect of 5-HTTLPR polymorphism and childhood abuse on diagnoses of major depression in women.

Psychiatr. Res. 225 (3), 746–747.
Lavin, D.N., Joesting, J.J., Chiu, G.S., Moon, M.L., Meng, J., Dilger, R.N., Freund, G.G., 2011. Fasting induces an anti-inflammatory effect on the neuroimmune system which a high-fat diet prevents. Obesity (Silver Spring) 19 (8), 1586–1594.
Lee, H.W., Lo, Y.H., Li, K.H., Sung, W.S., Juan, C.H., 2015. The relationship between the development of response inhibition and intelligence in preschool children. Front. Psychol. 6, 802.
LeWinn, K.Z., Connolly, C.G., Wu, J., Drahos, M., Hoeft, F., Ho, T.C., Simmons, A.N., Yang, T.T., 2014. White matter correlates of adolescent depression: structural evidence for frontolimbic disconnectivity. J. Am. Acad. Child Adolesc. Psychiatry 53 (8), 899–909 909 e891-897.
Lilic, D., Cant, A.J., Abinun, M., Calvert, J.E., Spickett, G.P., 1997. Cytokine production differs in children and adults. Pediatr. Res. 42 (2), 237–240.
Linthorst, A.C., Flachskamm, C., Muller-Preuss, P., Holsboer, F., Reul, J.M., 1995. Effect of bacterial endotoxin and interleukin-1 beta on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: an in vivo microdialysis study. J. Neurosci. 15 (4), 2920–2934.
Lopresti, A.L., Drummond, P.D., 2013. Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 45, 92–99.
Lu, S., Peng, H., Wang, L., Vasish, S., Zhang, Y., Gao, W., Wu, W., Liao, M., Wang, M., Tang, H., Li, W., Li, W., Li, Z., Zhou, J., Zhang, Z., Li, L., 2013. Elevated specific peripheral cytokines found in major depressive disorder patients with childhood trauma exposure: a cytokine antibody array analysis. Compr. Psychiatr. 54 (7), 953–961.
Maes, M., Leonard, B.E., Myint, A.M., Kubera, M., Verkerk, R., 2011. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (3), 702–721.
Manczak, E.M., Basu, D., Chen, E., 2016. The price of perspective taking: child depressive symptoms interact with parental empathy to predict immune functioning in parents. Clin. Psychol. Sci. 4 (3), 485–492.
Marshall, D.F., Passarotti, A.M., Ryan, K.A., Kamali, M., Saunders, E.F., Pester, B., McInnis, M.G., Langenecker, S.A., 2016. Deficient inhibitory control as an outcome of childhood trauma. Psychiatr. Res. 235, 7–12.
McTeague, L.M., Goodkind, M.S., Etkin, A., 2016. Transdiagnostic impairment of cognitive control in mental illness. J. Psychiatr. Res. 83, 37–46.
Meier, T.B., Drevets, W.C., Wurfel, B.E., Ford, B.N., Morris, H.M., Victor, T.A., Bodurka, J., Teague, T.K., Dantzer, R., Savitz, J., 2016. Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder. Brain Behav. Immun. 53, 39–48.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16 (1), 22–34.
Miller, G.E., Cole, S.W., 2012. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol. Psychiatry 72 (1), 34–40.
Mills, N.T., Scott, J.G., Wray, N.R., Cohen-Woods, S., Baune, B.T., 2013. Research review: the role of cytokines in depression in adolescents: a systematic review. JCPP (J. Child Psychol. Psychiatry) 54 (8), 816–835.
Mitchell, R.H., Goldstein, B.I., 2014. Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. J. Am. Acad. Child Adolesc. Psychiatry 53 (3), 274–296.
Muscatell, K.A., Dedovic, K., Slavich, G.M., Jarcho, M.R., Breen, E.C., Bower, J.E., Irwin, M.R., Eisenberger, N.I., 2015. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. Brain Behav. Immun. 43, 46–53.
Newton, D.F., Naiberg, M.R., Andreazza, A.C., Scola, G., Dickstein, D.P., Goldstein, B.I., 2017. Association of lipid peroxidation and brain-derived neurotrophic factor with executive function in adolescent bipolar disorder. Psychopharmacology (Berlin) 234 (4), 647–656.
Nieto, R.G., Castellanos, F.X., 2011. A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. J. Clin. Child Adolesc. Psychol.: Off. J. Soc. Clin. Child Adoles. Psychol., Am. Psychol. Assoc., Div. 53 40 (2), 266–280.
Nikulina, V., Widom, C.S., 2013. Child maltreatment and executive functioning in middle adulthood: a prospective examination. Neuropsychology 27 (4), 417–427.
Pallavi, P., Sagar, R., Mehta, M., Sharma, S., Subramanium, A., Shamshi, F., Sengupta, U., Pandey, R.M., Mukhopadhyay, A.K., 2015. Serum cytokines and anxiety in adolescent depression patients: gender effect. Psychiatr. Res. 229 (1–2), 374–380.
Pandey, G.N., Rizavi, H.S., Ren, X., Fareed, J., Hoppensteadt, D.A., Roberts, R.C., Conley, R.R., Dwivedi, Y., 2012 Jan. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. J. Psychiatr. Res. 46 (1), 57–63. https://doi.org/10.1016/j.jpsychires.2011.08.006. Epub 2011 Sep 8.
Pavlov, V.A., Tracey, K.J., 2012. The vagus nerve and the inflammatory reflex–linking immunity and metabolism. Nat. Rev. Endocrinol. 8 (12), 743–754.
Pavuluri, M.N., O'Connor, M.M., Harral, E.M., Moss, M., Sweeney, J.A., 2006. Impact of neurocognitive function on academic difficulties in pediatric bipolar disorder: a clinical translation. Biol. Psychiatry 60 (9), 951–956.
Pavuluri, M.N., West, A., Hill, S.K., Jindal, K., Sweeney, J.A., 2009. Neurocognitive function in pediatric bipolar disorder: 3-year follow-up shows cognitive development lagging behind healthy youths. J. Am. Acad. Child Adolesc. Psychiatry 48 (3), 299–307.
Peters, A.T., Peckham, A.D., Stange, J.P., Sylvia, L.G., Hansen, N.S., Salcedo, S., Rauch, S.L., Nierenberg, A.A., Dougherty, D.D., Deckersbach, T., 2014a. Correlates of real world executive dysfunction in bipolar I disorder. J. Psychiatr. Res. 53, 87–93.
Peters, B.D., Ikuta, T., DeRosse, P., John, M., Burdick, K.E., Gruner, P., Prendergast, D.M., Szeszko, P.R., Malhotra, A.K., 2014b. Age-related differences in white matter tract microstructure are associated with cognitive performance from childhood to adulthood. Biol. Psychiatry 75 (3), 248–256.
Poznanski, E.O., Grossman, J.A., Buchsbaum, Y., Banegas, M., Freeman, L., Gibbons, R., 1984. Preliminary studies of the reliability and validity of the children's depression rating scale. J. Am. Acad. Child Psychiatry 23 (2), 191–197.
Quinn, M.E., Stange, J.P., Jenkins, L.M., Corwin, S., DelDonno, S.R., Bessette, K.L., Welsh, R.C., Langenecker, S.A., 2018. Cognitive control and network disruption in remitted depression: a correlate of childhood adversity. Soc. Cognit. Affect Neurosci. 13 (10), 1081–1090.
Raison, C.L., Miller, A.H., 2017. Pathogen-host defense in the evolution of depression: insights into epidemiology, genetics, bioregional differences and female preponderance. Neuropsychopharmacology : Off. Publ. Am. Coll. Neuropsychopharmacol. 42 (1), 5–27.
Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 70 (1), 31–41.
Rizk, M.M., Rubin-Falcone, H., Keilp, J., Miller, J.M., Sublette, M.E., Burke, A., Oquendo, M.A., Kamal, A.M., Abdelhameed, M.A., Mann, J.J., 2017. White matter correlates of impaired attention control in major depressive disorder and healthy volunteers. J. Affect. Disord. 222, 103–111.
Rosenblat, J.D., Cha, D.S., Mansur, R.B., McIntyre, R.S., 2014. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 53, 23–34.
Saleh, A., Potter, G.G., McQuoid, D.R., Boyd, B., Turner, R., MacFall, J.R., Taylor, W.D., 2017. Effects of early life stress on depression, cognitive performance and brain morphology. Psychol. Med. 47 (1), 171–181.
Savitz, J., Dantzer, R., Meier, T.B., Wurfel, B.E., Victor, T.A., McIntosh, S.A., Ford, B.N., Morris, H.M., Bodurka, J., Teague, T.K., Drevets, W.C., 2015. Activation of the kynurenine pathway is associated with striatal volume in major depressive disorder. Psychoneuroendocrinology 62, 54–58.
Selmaj, K.W., Raine, C.S., 1988. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. Ann. Neurol. 23 (4), 339–346.
Shaffer, D., Gould, M.S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., Aluwahlia, S., 1983. A children's global assessment scale (CGAS). Arch. Gen. Psychiatr. 40 (11), 1228–1231.
Smagula, S.F., Lotrich, F.E., Aizenstein, H.J., Diniz, B.S., Krystek, J., Wu, G.F., Mulsant, B.H., Butters, M.A., Reynolds 3rd, C.F., Lenze, E.J., 2017. Immunological biomarkers associated with brain structure and executive function in late-life depression: exploratory pilot study. Int. J. Geriatr. Psychiatry 32 (6), 692–699.
Speaker, K.J., Paton, M.M., Cox, S.S., Fleshner, M., 2016. A single bout of fasting (24 h) reduces basal cytokine expression and minimally impacts the sterile inflammatory response in the white adipose tissue of normal weight F344 rats. Mediat. Inflamm. 1698071 2016.
Treadway, M.T., Admon, R., Arulpragasam, A.R., Mehta, M., Douglas, S., Vitaliano, G., Olson, D.P., Cooper, J.A., Pizzagalli, D.A., 2017. Association between interleukin-6 and striatal prediction-error signals following acute stress in healthy female participants. Biol. Psychiatry 82 (8), 570–577.
Tsankova, N., Renthal, W., Kumar, A., Nestler, E.J., 2007. Epigenetic regulation in psychiatric disorders. Nat. Rev. Neurosci. 8 (5), 355–367.
van Velzen, L.S., Schmaal, L., Milaneschi, Y., van Tol, M.J., van der Wee, N.J., Veltman, D.J., Penninx, B.W., 2017. Immunometabolic dysregulation is associated with reduced cortical thickness of the anterior cingulate cortex. Brain Behav. Immun. 60, 361–368.
Vanden Berghe, W., Ndlovu, M.N., Hoya-Arias, R., Dijsselbloem, N., Gerlo, S., Haegeman, G., 2006. Keeping up NF-kappaB appearances: epigenetic control of immunity or inflammation-triggered epigenetics. Biochem. Pharmacol. 72 (9), 1114–1131.
Vitkovic, L., Konsman, J.P., Bockaert, J., Dantzer, R., Homburger, V., Jacque, C., 2000. Cytokine signals propagate through the brain. Mol. Psychiatr. 5 (6), 604–615.
Votruba, K.L., Langenecker, S.A., 2013. Factor structure, construct validity, and age- and education-based normative data for the Parametric Go/No-Go Test. J. Clin. Exp. Neuropsychol. 35 (2), 132–146.
Wagner, S., Muller, C., Helmreich, I., Huss, M., Tadic, A., 2014. A Meta-Analysis of Cognitive Functions in Children and Adolescents with Major Depressive Disorder. European child & adolescent psychiatry.
Wagner, S., Muller, C., Helmreich, I., Huss, M., Tadic, A., 2015. A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. Eur. Child Adolesc. Psychiatry 24 (1), 5–19.
Walker, E.A., Unutzer, J., Rutter, C., Gelfand, A., Saunders, K., VonKorff, M., Koss, M.P., Katon, W., 1999. Costs of health care use by women HMO members with a history of childhood abuse and neglect. Arch. Gen. Psychiatr. 56 (7), 609–613.
Weaver, J.D., Huang, M.H., Albert, M., Harris, T., Rowe, J.W., Seeman, T.E., 2002. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology 59 (3), 371–378.
Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. Psychological Corporation.
Weisenbach, S.L., Marshall, D., Weldon, A.L., Ryan, K.A., Vederman, A.C., Kamali, M., Zubieta, J.K., McInnis, M.G., Langenecker, S.A., 2014. The double burden of age and disease on cognition and quality of life in bipolar disorder. Int. J. Geriatr. Psychiatry 29 (9), 952–961.