Pro-inflammatory Cytokines, Childhood Trauma, and Neuropsychological Function in Adolescent Depression

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DISSERTATION

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AMD	Any Mood Disorder
AMD-T	Any Mood Disorder – Trauma
BMI	Body Mass Index
CDRS	Children's Depression Rating Scale
CTQ	Childhood Trauma Questionnaire
DKEFS	Delis Kaplan Executive Function System
DSM-IV	Diagnostic and Statistic Manual – Fourth Edition
HC	Healthy Controls
HPA	Hypothalamic Pituitary Adrenal
IL	Interleukin
IQ	Intelligence Quotient
MS	Milliseconds
NIMH	National Institute of Mental Health
NOS	Not Otherwise Specified
PGNG	Parametric Go-No/Go
PGNGS	Parametric Go-No/Go-Stop
RCTF	Rey-Osterrieth Complex Figure Test
RDoC	Research Domain Criteria
SLLT	Semantic List Learning Task
SPSS	Statistical Package for the Social Sciences
TNF	Tumor Necrosis Factor

LIST OF ABBREVIATIONS (CONTINUED)

WAIS-III	Wechsler Adult Intelligence Scale – 3rd Edition
WISC-III	Wechsler Intelligence Scale for Children – 3rd Edition

SUMMARY

A study of inflammation in relation to depressive symptoms and neuropsychological functioning was carried out amongst adolescents using a quantitative, cross-sectional approach. Pro-inflammatory ctyokines were obtained and measure in the serum of adolescents with (AMD) and without depression (HC), a subset of whom also had a history of childhood trauma (AMD-T). All participants also completed diagnostic interviews, depression symptom rating scales, self-reported history of childhood trauma, and a brief neuropsychological testing battery.

AMD-T participants demonstrated reduced psychomotor speed, attentional control, inhibitory control, and verbal learning. IL-6 was elevated in AMD and AMD-T adolescents compared to controls and TNF-α was elevated in AMD participants only, whereas no group differences were found in IL-1β. Additionally, inflammation markers alone were associated with depressed mood and memory dysfunction in adolescents (IL-6), whereas inflammation markers interacted in at-risk, depressed and trauma-exposed teens, to predict somatic complaints (TNF-α) and executive function (IL-1β).

I. Introduction

Immune system response is thought to arise, in part from environmental stressors, and interact with multiple systems (Anderson, 2018), including and possibly resulting in blood brain barrier disruption, neurotransmitter metabolism, neuroendocrine function, and glial cell function, to predispose towards a host of negative mental health outcomes (Hostinar, Nusslock, & Miller, 2017), including depression (Berens, Jensen, & Nelson, 2017) and neuropsychological dysfunction (Brown, McIntyre, Rosenblat, & Hardeland, 2018). Therefore, markers of the inflammatory response may represent a key advance in understanding how biomarkers of stress relate to common areas of impairment, such as mood dysregulation and executive dysfunction, in depression. Indeed, inflammatory markers have increasingly been subject to scientific inquiry in depression (Haapakoski, Mathieu, Ebmeier, Alenius, & Kivimaki, 2015; Kohler, Freitas, Maes, et al., 2017; Kohler, Freitas, Stubbs, et al., 2017; Wiedlocha et al., 2018); several studies have linked inflammation with depressive symptoms (Howren, Lamkin, & Suls, 2009; Khandaker, Pearson, Zammit, Lewis, & Jones, 2014; Khandaker et al., 2017), but few have undertaken the degree to which inflammation may or may not be related to specific subsets of symptom profiles or clusters of symptoms in this heterogeneous disorder (Glaus et al., 2017). Moreover, despite increasing awareness that inflammatory markers in the periphery have implications for central nervous system function (Kempuraj et al., 2017), studies assessing the association between peripheral markers of

inflammation and neuropsychological functioning in depression are strikingly rare (Goldsmith et al., 2016).

It is also remarkable that no studies have collectively integrated markers of inflammation in relation to stress, mood, and cognitive function among children and adolescents, despite significant methodological obstacles to generalizing findings from adults to youth (Mitchell & Goldstein, 2014). This gap is problematic from a public health perspective, as the point prevalence of major depression is estimated between 8-15% among children and adolescents (Gore et al., 2011; Lipari, Hughes, & Williams, 2013; Mojtabai, Olfson, & Han, 2016) and is the leading important source of disability (Thapar, Collishaw, Pine, & Thapar, 2012) mortality (Lewinsohn, Klein, & Seeley, 1995), and interpersonal, family, and educational impairment (Lewinsohn, Rohde, & Seeley, 1998) among youth. Unfortunately, the impact of depression among youth casts an even wider net than what is captured by these statistics employing traditional categorical diagnostic systems. As many as 26% of youth experience symptoms of depression that cause impairment yet fall short of a depression diagnosis (Klein, Shankman, Lewinsohn, & Seeley, 2009). This estimate is especially concerning because depression at a young age is associated with poor prognosis in adulthood (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001). For this reason, and consistent with National Institute of Mental Health's (NIMH) proposed Research Domain Criteria (RDoC; (Cuthbert, 2014), it is important not only to understand whether there exist critical periods of brain development for these constructs, but also to develop a better understanding of how these

correlates of depression function across the full continuum of dysfunction of healthy, high-risk, sub-threshold, and affected youth. The detection of these mechanisms during the unique developmental window of adolescence could potentially inform the development of tailored pharmacological and psychosocial treatments by identifying biochemical protective factors and targets for neuronal re-genesis and facilitated resilience.

A. **Inflammation and Depression**

Indeed, accumulating evidence indicates that immune activation may be one index that could help to better explain the full range of dysfunction associated with depression (Krishnan & Nestler, 2010; Schildkraut, 1995). The involvement of a pro-inflammatory state in major depression has been assessed in recent meta-analyses, based on an influx of studies over the past two decades measuring serum levels of pro-inflammatory cytokines, essential mediators of the immune response to stress (Dowlati et al., 2010; Haapakoski et al., 2015; Kohler, Freitas, Maes, et al., 2017; Kohler, Freitas, Stubbs, et al., 2017; Wiedlocha et al., 2018). Three of the most extensively studied pro-inflammatory cytokines include IL-6, TNF-α, and IL-1β. The most consistent finding among depressed subjects is elevations in circulating levels of IL-6 (Dowlati et al., 2010; Kohler, Freitas, Maes, et al., 2017; Wang & Miller, 2017); further, there is also indication that reductions in IL-6 are correlated with successful anti-depressant treatment (Haapakoski et al., 2015; Kohler, Freitas, Stubbs, et al., 2017; Strawbridge et al., 2015). Aberrations in TNF-a are also reported in MDD but are more variable; both increased and similar levels of TNF-a have been found in MDD patients and HC

(Dowlati et al., 2010; Haapakoski et al., 2015). Likewise, well-controlled studies suggest IL-1β is elevated in depressed subjects, but its effects are often obscured by sub-group differences or moderating factors (Dowlati et al., 2010; Haapakoski et al., 2015).

The coupling of depression and inflammation is lesser studied among youth (Mitchell & Goldstein, 2014), which by virtue of their particularly high-risk for recurrence and chronic illness, has the potential to highlight early signs of vulnerability. Cytokine production differs in youth as compared with adults (Lilic, Cant, Abinun, Calvert, & Spickett, 1997), and findings in adults cannot necessarily be extrapolated to children or adolescents. One systematic review synthesizing the salient findings from six studies among youth with major depression, dysthymia, and suicidality, offered some preliminary evidence for elevated levels inflammatory markers (Mitchell & Goldstein, 2014). However, direct comparisons across these studies were challenging, as studies varied according to clinical features [e.g. psychiatric medication status (Gabbay, Klein, Guttman, et al., 2009; Henje Blom et al., 2012), primary depressive disorder (Brambilla, Monteleone, & Maj, 2004), suicidality (Gabbay, Klein, Guttman, et al., 2009; Pandey et al., 2012), childhood trauma (G. E. Miller & Cole, 2012)], the cytokines of interest, and the methods of cytokine measurement [e.g. serum (G. E. Miller & Cole, 2012), plasma (Brambilla et al., 2004; Gabbay, Klein, Alonso, et al., 2009; Gabbay, Klein, Guttman, et al., 2009; Henje Blom et al., 2012), postmortem neuro-inflammation and protein expression (Pandey et al., 2012)]. Since then, one interesting study purposely sampled a large group of un-

medicated adolescents meeting criteria for heterogeneous internalizing disorders and found support for elevated IL-6 compared to controls (Belem da Silva et al., 2017). This result adds important data that IL-6 in particular, may indeed represent a robust, early sign of immune dysregulation but nevertheless calls for further understanding of possibly moderating factors contributing to variability in other cytokine measurements that have been as consistently replicated.

The reason to suspect that moderating factors might explain inconstant findings is that individual MDD patients values tend to show great inter-individual heterogeneity, raising the notion that increased inflammatory markers might only be present in a certain subgroup of depressed patients or involved in a subset of depressive symptoms (Haroon, Raison, & Miller, 2012; Raison & Miller, 2011). For instance, inflammation is hypothesized to relate primarily to a constellation of “sickness behaviors” that overlap with certain, but not all, aspects of depression (D'Mello & Swain, 2017; Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017). Sickness behaviors include anhedonia, psychomotor retardation, excessive fatigue, and somatic complaints (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Konsman, Parnet, & Dantzer, 2002). These behaviors are thought to arise causally from the inflammatory response; in initial support of this, observations from animal studies indicate that administration of lipopolysaccharides are temporally linked with an increase in depressive-like symptoms and behaviors (Biesmans et al., 2016). Similarly, in humans, administration of recombinant preparation of the cytokine interferon-α for treatment of hepatitis-C induces sickness behaviors resembling depression in a substantial portion of patients

(Lotrich, Ferrell, Rabinovitz, & Pollock, 2009; Lotrich, Rabinovitz, Gironda, & Pollock, 2007; Raison, Demetrashvili, Capuron, & Miller, 2005). From an evolutionary perspective, the sickness behaviors occur in an effort to promote rest and recuperation, however, if the inflammatory response fails to fully resolve, it could relate to prolonged symptoms (Wager-Smith & Markou, 2011) and increased reciprocal vulnerability to psychological stress (Bauer, Pascoe, Wollenhaupt-Aguiar, Kapczinski, & Soares, 2014). Nevertheless, the overall measured effect size for the correlation between inflammation and depressive symptoms using traditional self-report measures is small (Valkanova, Ebmeier, & Allan, 2013). Therefore it is plausible, but untested, that increased is inflammation is not necessarily uniformly associated with depression severity but may be especially pronounced among individuals affected by a sub-set of symptoms that align most closely with sickness behaviors or who are unusually high risk for this response.

B. **Inflammation and Neuropsychological Function**

There is growing awareness that, in addition to likely relationships with mood and behavior, inflammatory processes interact with brain health (A. H. Miller & Raison, 2016) and may be an additional mechanism linking depression and neuropsychological dysfunction (Bollen, Trick, Llewellyn, & Dickens, 2017). Through cholinergic and dopaminergic pathways, inflammatory cytokines modulate neuronal and glial cell function, facilitating either neuronal regeneration or neurodegeneration (Licinio, Kling, & Hauser, 1998; Zarate, Singh, & Manji, 2006). While normal levels of cytokines are essential for preserving cognitive

functions, in excess they can reduce dendritic spines and synapses, resulting in detrimental effects on the structural and functional neuronal integrity of the circuits involved in regulating cognition (Albensi & Mattson, 2000; Bauer et al., 2014). It is hypothesized that this atrophy, in addition to blood-brain barrier disruption, neuronal apoptosis, exposure to reactive oxidative substances, and activation of the hypothalamic-pituitary-adrenal (HPA) axis, is associated with neuronal damage and impaired control over cognitive functions (Dunn, 1992; Licinio et al., 1998).

It is quite clear that this inflammatory cascade plays a pathogenic role in neurodegenerative processes associated with older age (Mosley, 2015), yet a number of recent findings also lend support to the notion that chronic inflammation is related to cognitive deficits earlier in adulthood among individuals with psychiatric disorders. Indeed, peripheral inflammation in schizophrenia and bipolar disorder has been linked with broad cognitive deficits, including general intellectual ability, memory, attention, and executive functioning (Bulzacka et al., 2016; Dickerson, Stallings, Origoni, Boronow, & Yolken, 2007; Dickerson et al., 2013; Frydecka et al., 2015; Johnsen et al., 2016; Micoulaud-Franchi et al., 2015). In depression, existing observations linking inflammation and neuropsychological function are more focal and primarily found in the domains of executive functioning and processing speed (Benson et al., 2017; Goldsmith et al., 2016; Krogh et al., 2014; Smagula et al., 2017), which align with the RDoC cognitive systems of cognitive and interference control. The reasons for more restricted effects in depression are not fully understood, but may relate both to

the targets of inflammation in the central nervous symptom and their overlap with neural abnormalities typically associated with depression (Harrison, 2017). For instance, elevated peripheral cytokines have been linked with alterations in dorsal anterior cingulate (S. E. 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., 2016; Haroon et al., 2014; Savitz et al., 2015; Treadway et al., 2017) structure and function, which are brain regions essential for executive function and also common nodes of dysfunctional neural circuitry in depression (Felger, 2017).

An unanswered question is whether neuropsychological correlates of elevated inflammation are detectable among youth with depression. This is particularly pertinent in light of the fact that several of the cognitive impairments that are associated with depression in adulthood are observable early in the course of illness (Joseph, Frazier, Youngstrom, & Soares, 2008; Nieto & Castellanos, 2011; Pavuluri, West, Hill, Jindal, & Sweeney, 2009; Wagner, Muller, Helmreich, Huss, & Tadic, 2014) and are possibly involved in risk for depression (Davidovich et al., 2016). One recent meta-analysis indicated that relative to control subjects, the most pronounced neuropsychological deficit in children and adolescents with major depression was in inhibitory control (Wagner, Muller, Helmreich, Huss, & Tadic, 2015). As impairments in inhibitory control are linked to difficulties analyzing, planning, and prioritizing activities (Peters et al., 2014), academic problems, and low self-esteem (Biederman et al., 2011; Pavuluri, O'Connor, Harral, Moss, & Sweeney, 2006), it is prudent to

understand whether aberrant inflammatory activity may predispose or exacerbate this specific area of weakness. However, to date, associations between inflammation and cognitive functioning among youth samples have only been tested in populations where increased pro-inflammatory activity is common, including obstructive sleep apnea, traumatic brain injury, and pre-term, low-birth weight youth (Huang et al., 2016; Li et al., 2014; O'Shea et al., 2013; Rose, Vassar, Cahill-Rowley, Hintz, & Stevenson, 2016). Moreover, rarely have psychological factors such as depression or stress been taken into account (but see (Cullen et al., 2017)). Accordingly, understanding the role of inflammation in relation to depression in youth and in the absence of major medical confounds, including the attenuating effects of medications, is essential.

C. **Inflammation and Psychological Stress**

Psychological stress is a trans-diagnostic factor, relevant to the onset and persistence of depressive symptoms (Liu & Alloy, 2010; Luyten & Fonagy, 2017) and neuropsychological problems (Malarbi, Abu-Rayya, Muscara, & Stargatt, 2017). The hypothesized pathway linking stress, brain function, and inflammation is primarily through diminished immune sensitivity to glucocorticoid hormones that are involved in down regulation of the inflammatory cascade (Connor & Leonard, 1998). Stress is associated with secretion of the hormonal products of the HPA (e.g. cortisol) and sympathetic adrenal medullary axes (Licinio et al., 1998; Wager-Smith & Markou, 2011). Continued exposure to high concentrations of these hormones increases the likelihood that white blood cells will mount a counter regulatory response and down-regulate the expression or function of

receptors responsible for binding glucocorticoid hormones. Persistence of psychological stress is therefore thought to be indirectly associated with reduced immune capacity to respond to the anti-inflammatory effects of cortisol (Wilson, Finch, & Cohen, 2002), raising a possible bi-directional immuno-endocrine avenue by which stress can relate to alterations in mood and cognitive function (Connor & Leonard, 1998; Wager-Smith & Markou, 2011).

Early life stress, in particular, is one of the greatest risk factors for depression (Arnow, 2004; Chapman et al., 2004; Danese et al., 2009; Kim, Jin, Jung, Hahn, & Lee, 2017; Widom, DuMont, & Czaja, 2007), associated with altered brain structure and function (including reduced processing speed, attention, and executive function (Saleh et al., 2017)), and also linked with alterations in inflammatory activity later in life (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Coelho, Viola, Walss-Bass, Brietzke, & Grassi-Oliveira, 2014). Not surprisingly, there are noteworthy studies on the interplay between early life stress, inflammation, and depression in adulthood. Case-control designs have indicated that the combination of depression in adulthood and early childhood trauma is associated with elevated peripheral inflammatory markers (Grosse et al., 2014; Lu et al., 2013). In prospective cohorts, a history of childhood maltreatment is predictive of the co-occurrence of depression and inflammation in adulthood (Danese et al., 2009; Danese, Pariante, Caspi, Taylor, & Poulton, 2007). Likewise, another prospective study demonstrated that high levels of IL-6 forecasted the development of depression six months later in individuals with high childhood adversity (G. E. Miller & Cole, 2012).

Although no one of these studies provides a conclusive role of how early child adversity promotes or modulates the inflammatory process, put together, they do provide a clear rationale to concurrently assess the inter-relationships between early life stress and depression in effort to further delineate their interactions with immune function. In particular, we do not yet know the extent to which the bio-behavioral signature of early life stress represents an incubated effect that develops in adulthood or if it is embedded as early as adolescence. It is certainly possible that adolescence is marked by particular susceptibility to stress-related immuno-endocrine changes because myelination processes within the central cortico-limbic circuitry of the brain are still undergoing development (Benes, 1989). Moreover, if adolescent patterns of immune, brain, and behavior relationships resemble those found among adults, it would highlight early biochemical signs of vulnerability that could help inform prevention and intervention efforts through optimal modification of pathways to immune dysfunction.

D. **Inflammatory Markers in Adolescence**

Collectively, adult studies of inflammatory markers point to associations with depression (Hiles, Baker, de Malmanche, & Attia, 2012; Valkanova et al., 2013) and inhibitory control (Albensi & Mattson, 2000; Bauer et al., 2014; Shapira-Lichter et al., 2008); however, compared to studies in youth, studies in adults fail to distinguish between the effects of depression per se and the long-term health consequences of being chronically ill. Fewer studies exist among youth, yet studying these processes earlier in the continuum of morbidity (Berk et

al., 2014; Weisenbach, Marshall, et al., 2014) could identify whether there exist critical periods of development for the constructs. If critical periods are identified, they will sharpen understanding of the mechanisms involved in the development and instantiation of dysfunction and subsequently enhance the precision of intervention to increase effectiveness (Casey, Oliveri, & Insel, 2014). Adolescence, in particular, represents a compelling window for studying inflammatory mechanisms of depression and inhibitory control due to (a) minimized confounds of prolonged illness duration, allostatic load, chronic medical co-morbidities, and obesity (Berk et al., 2014; Lopresti & Drummond, 2013); (b) differences in the phenomenology of depression in youth, such as increased anhedonia and irritability (Bemporad, 1982; Birmaher, Brent, & Benson, 1998); and (c) protracted period of cognitive development that differs in maturity and plasticity from adults (Brooks, Iverson, Sherman, & Roberge, 2010; Hongwanishkul, Happaney, Lee, & Zelazo, 2005; Huizinga, Dolan, & van der Molen, 2006). For these reasons, it is not possible to generalize links between inflammatory processes and depression, stress, or cognitive systems in adults - separate studies among youth are crucial.

E. **Goals of the Study**

Collectively, key questions remain about inflammation during adolescence and its effects on mood and cognitive systems. Specifically, there is currently a lack of studies examining how early childhood adversity relates to the interplay between inflammation, depression, and inhibitory control among youth. As such, the aims of this study were to examine how inflammatory markers relate to

dimensions of depression and neuropsychological function, as well as how early life stress modulates these processes among youth, advancing the field in several novel ways. First, this study utilized dimensions of depression and cognitive systems, across multiple levels of analysis (immunological, neurocognitive/behavioral, self-report) that were agnostic about thresholds of diagnostic severity. It also studied these processes early in development and illness course, to assess whether inflammatory markers can be detected in early disease, as well as how they function in an early-onset cohort.

In line with these goals, associations between inflammation, depression dimensions, and neuropsychological function were tested among: 1) adolescents (ages 12 – 17) with any mood disorder (AMD: depression, dysthymia, adjustment disorder with depressed mood, sub-threshold and unspecified depression (n = 40), a subset of whom reported exposure to significant early childhood trauma (AMD-T; n = 22); and 2) matched healthy control (HC) adolescents with no personal psychiatric history (n = 31). Measures of inflammation included pro-inflammatory markers most consistently studied among adults with depression (e.g. pro-inflammatory [IL-6, IL-1β, and TNF-α].

Aim 1. The first aim of the current study was to a) test for differences between AMD, AMD-T, and HC participants in peripheral inflammatory markers, b) evaluate the association between peripheral inflammatory markers and sub-domains of depression, and c) test whether inflammation-symptom associations were moderated by childhood trauma (AMD-T) or depression only (AMD) subgroups.

Hypothesis 1. It was expected that a) markers of inflammation would be elevated in the AMD and AMD-T groups relative to HC adolescents, b) inflammatory markers would be positively related to latent variables of somatic depressive symptoms, and c) AMD-T youth would exhibit exaggerated immune responses associated with stronger links to somatic depression symptoms. Given the relatively small number of studies examining pro-inflammatory cytokines in youth, we did not have a-priori hypotheses about possible cytokine-specific associations with symptoms.

Aim 2. The second aim of the current study was to a) test for differences between AMD, AMD-T, and HC adolescents in neuropsychological functioning, b) evaluate the association between peripheral inflammatory markers and neuropsychological functioning, and c) test whether inflammation-neuropsychological functioning associations were moderated by childhood trauma (AMD-T) or depression only (AMD) subgroups.

Hypothesis 2. It was hypothesized that a) domain-specific deficits in inhibitory control would be observed in the AMD and AMD-T groups relative to HC adolescents, b) inflammation would be inversely related to inhibitory control on performance-based laboratory tasks, and c) AMD-T youth would exhibit exaggerated immune responses associated with stronger links to inhibitory control. Inhibitory control was intentionally tested separately from attentional control and psychomotor speed domains to evaluate specificity of inhibitory control versus executive

functioning and fluency more broadly. Verbal and visual learning and memory were considered exploratory domains of analysis.

II. Methods

A. Participants

Participants were adolescents (and their consenting parent), ages 12-17 with any mood disorder (AMD: depression, dysthymia, adjustment disorder with depressed mood, sub-threshold and unspecified depressive symptoms [n = 40]) and age-, sex-, and IQ-matched healthy control (HC; n = 31) adolescents with no prior or current psychiatric history. Of the AMD adolescents, 55% (n = 22) reported a history of elevated childhood trauma (AMD-T; refer to Study Measures for additional information). All AMD adolescents were recruited based upon significant parent and self-report of depressive symptoms lasting one week or more, identified initially by a clinician or response to advertisement, and confirmed in a clinical interview. Participants were recruited from outpatient psychiatry clinics (AMD only) in a large, urban, academic medical center and the surrounding community (AMD and HC).

A semi-structured telephone-screening interview determined initial eligibility. On additional in-person screening, all participants met strict eligibility criteria. Inclusion criteria were 1) estimated Verbal IQ in the 'borderline' or higher range [T-score >30], and 2) fluent in English. Exclusion criteria were: 1) current psychiatric medication other than a stimulant, 2) formally diagnosed neurological disorder or other chronic medical condition that affects cognition (e.g. learning disability, epilepsy, developmental delay; however, co-morbid ADHD diagnosis is permitted in the AMD group), 3) active suicidality with plan or intent (passive suicidal thoughts were permitted), 4) history of head injury with loss of

consciousness greater than 10 minutes, 5) full-threshold active substance use (alcohol or illicit drugs) disorder within 30 days or more than five self-reported lifetime instances of use, 6) current smokers, 7) participation in a research protocol that involves taking an investigational medication, and 8) active virus or infection in two weeks prior to enrollment assessed by medical history interview.

B. Procedures

After initial screening, participants were invited for a lab visit that included informed consent/assent procedures and a full eligibility screening (e.g. IQ testing, full-length clinical interview). Eligible participants proceeded with completion of a standardized neuropsychological assessment battery, self-report measures of demographic information and behavioral/emotional functioning, and a non-fasting blood sample obtained by venipuncture (see Cytokine Assays for additional information). Weight in kilograms and height in centimeters was collected, and body mass index (BMI) was calculated. Consistent with university standards, participants were compensated $10 per hour ($40 total) for their time.

C. Measures

1. Clinical Assessment

All participants (AMDs and HCs) 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 past developmentally specific psychiatric diagnoses. Although the enrollment criteria were agnostic about diagnostic categories of depressive disorders, this

instrument was used to ensure variability in clinical severity, and to screen for substance use, and suicidality. Current depression symptom severity was assessed by the clinician using the Children's Depression Rating Scale – Revised (Poznanski et al., 1984). The CDRS is a reliable and valid clinician-rated instrument for measuring the severity of depression in children. The clinician also rated severity of functional impairment using the Children's Global Assessment Scale (Shaffer et al., 1983).

2. **Childhood Trauma Exposure**

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-report measure that provides brief, reliable, and valid screening for histories of abuse and neglect (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997). It is completed by the adolescent and inquires about five subscales of maltreatment - emotional, physical, and sexual abuse, and emotional and physical neglect. The total score of each sub-scale has a range from 5 to 25, thus the total score of CTQ 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. proportion of respondents reporting little to no childhood traumatic experiences). In the current sample, the skewness value was 1.62. To adjust for the degree of skewness, existence of childhood trauma exposure can be determined by a cut-off score of each CTQ sub-scale. Participants who score higher than the threshold of any one sub-scale are

treated as a positive case of early childhood trauma. The cutoffs of each sub-scale for moderate exposure are as follows: 1) emotional abuse ≥10, 2) emotional neglect ≥15, 3) sexual abuse ≥ 8, 4) physical abuse ≥8, and 5) physical neglect ≥ 8. Within the AMD group, 22 participants had a positive history of childhood trauma based on the cut-off scores, forming a sub-group of AMD participants with an early childhood trauma history (AMD-T). The convergent validity of these cut-off scores was evaluated by using an exploratory cluster analysis of the study sample, with item-level CTQ responses as input. The resulting cluster solution identified the same subset of n = 22 AMD-T participants as most similar to each other, relative to AMD-only participants and HCs.

3. **Neuropsychological Assessment**

A brief neuropsychological assessment battery was chosen to capture the full range of conceptually and theoretically appreciated cognitive domains. The following tests were administered:

a. **Estimated IQ**

The Wechsler Abbreviated Scale of Intelligence - 2nd Edition (Wechsler, 1999) is a standardized and validated short form of the WISC-III/WAIS-III that yields an IQ estimate through a verbal (vocabulary) subtest; participants must name objects or define words presented to them providing an index of semantic knowledge.

b. **Parametric Go-No/Go-Stop (PGNGS)**

The PGNGS task measures sustained attention, and set-shifting as the task becomes more difficult; processing speed, including simple and subsequently more challenging conditions of responding with no-go and stop rules; and cognitive control, including the ability to stop an unwanted, pre-potent response (correct rejections) and/or the failure to do so (commissions). The PGNGS task consists of two separate levels, each with three conditions, which were completed in order of ascending difficulty, and are based upon contextual inhibition, wherein the target and lure sets change depending upon the context (e.g., previous response). In the task, a serial stream of letters is presented for 500 ms with no inter-stimulus interval. Responses were 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. Accuracy scores for each set of trials (i.e., Go trials, No-Go trials, and Stop trials) were derived by dividing the number of correct hits by the total possible correct hits (minus errors of commission).

c. **Semantic List Learning Task (SLLT)**

The SLLT is a verbal learning and memory task that consists of three blocks: encoding, distraction, and silent rehearsal, to measure memory and learning strategies with minimal interference of executive functioning abilities (Kassel et al., 2016; Schallmo et

al., 2015; Weisenbach, Kassel, et al., 2014). The task consists of 3 lists of 14 semantically related words, for a total of 42 words. A semantic category cue is visually provided at the beginning of each list, displayed for 3.5 seconds. Following the category cue, 14 words are displayed on a screen one at a time, for an average display time of 3.5 seconds. The inter-stimulus interval is a 1 to 4 second jittered range, where a fixation cross is displayed. The total time for one Encoding block is typically 58.25 seconds. A distractor task immediately follows the last word of each list. This is the “Go” portion of the Parametric Go/No-go (PGNG) task during which “x”, “y”, and “z” are presented (Langenecker, Zubieta, Young, Akil, & Nielson, 2007). Each Distraction block lasts for 14 seconds. The Silent Rehearsal block presents participants with the category cue of the previous list, displayed for 14 seconds. The SLLT then repeats the Encoding, Distractor, and Silent Rehearsal blocks for a new category and list of words. The SLLT includes a delayed cued recall task with semantic category cues provided for all 3 lists, as well as a recognition trial.

d. **Rey-Osterrieth Complex Figure Test**

The RCTF is a test of visuo-spatial learning and memory that requires examinees to reproduce a complicated line drawing, first by copying it freehand (copy), then by recalling it immediately

(immediate recall), and then drawing from memory after a delay (delayed recall)(Loring, Martin, Meador, & Lee, 1990).

e. **Purdue Pegboard**

The Purdue Pegboard assesses manual dexterity and bimanual coordination in complex, visually guided, or coordinated movements (Tiffin & Asher, 1948). The pegboard consists of a board with two parallel rows with 25 holes into which cylindrical metal pegs are placed by the examinee. To begin, there is a brief practice. Trials for preferred, non-preferred, and both hands require the participant to place the pins in the holes as quickly as possible, with the score being the number of pins placed in 30 seconds.

f. **Delis Kaplan Executive Function System (DKEFS) – Trails**

The DKEFS trails subtest (Delis, Kramer, Kaplan, & Holdnack, 2004) measures fluency and flexibility of thinking through a series of visual-motor sequencing task. Participants are required to identify a target letters during visual scanning, sequence target numbers in order, sequence target letters in order, switching between connecting target letters and numbers, respectively in numerical and alphabetical order, and to trace non-alpha-numeric targets as a measure of psychomotor speed. The goal of the test is for the participant to finish all conditions as quickly as possible without making any errors.

D. **Data Reduction**

In order to test the hypothesis that inflammation would be associated with specific aspects of heterogeneous depression symptoms (i.e. proclivity for association with somatic versus cognitive aspects of depression), we computed depression subscales of 'somatic symptoms' and 'reported mood' from the CDRS, which optimally represent these desired dimensions. These subscales are derived from the CDRS factor structure put forth in the largest sample published data (n = 314) from children and adolescents (Guo, Nilsson, Heiligenstein, Wilson, & Emslie, 2006). Subscales were computed by weighting CDRS individual item ratings according to their previously identified factor loading and summing the weighted items for each factor (Table I).

Table I. Depression and Neuropsychological Factor Scores in HC and Depressed Adolescents

Factor	Test - Variable	Reliability (alpha)	Factor Loading
Depression Factors from Guo et al 2006^			
Reported Mood[a]	CDRS – Self Esteem	.85	.38
	CDRS – Depressed Feelings		.45
	CDRS – Excessive Weeping		.63
Somatic Symptoms[a]	CDRS – Sleep Disturbance	.85	.43
	CDRS – Excessive Fatigue		.58
	CDRS – Physical Complaints		.42
	CDRS – Impaired Schoolwork[b]		.40
Neuropsychological^			
Inhibitory Control	PGNGS – 2T GNG Hits	.78	.65
	PGNGS – 2T GS Hits		.60
	PGNGS – 2T GS Rejections		.72
	PGNGS – 3T GNG Hits		.57
	PGNGS – 3T GS Hits		.69

	PGNGS – 3T GS Rejections		.72
Attentional Control	PGNGS – 2T Go Hits	.76	.66
	PGNGS – 2T GS Hits		.86
	PGNGS – 3T Go Hits		.54
	PGNGS – 3T GS Hits		.76
Psychomotor Speed	DKEFS Trails – Number ss[b]	.74	.85
	DKEFS Trails – Trails Letter ss		.64
	DKEFS Trails – Trails Letter Number ss		.61
	DKEFS Trails – Trails Motor ss		.50
	Pegboard – Dominant z-score		.56
	Pegboard – Non-Dominant z-score		.61
	Pegboard – Both z-score		.60
Verbal Learning	SLLT – % Recall Primacy	--	.85
	SLLT – % Recognition Primacy		.85
Verbal Memory	SLLT – Recall Hits	.73	.81
	SLLT – % Recall Middle		.70
	SLLT – Average Recall		.79
	SLLT – Recognition Hits		.81
	SLLT – % Recognition Middle		.82
	SLLT – Average Recognition		.87
	SLLT – % Recalled Recognized		.69
	SLLT – % Recognized Recalled		.75
Visual Learning & Memory	RCFT – Immediate T-score	.80	.96
	RCFT – Delayed T-score		.95
	RCFT – Recognition T-score		.60

[a]Factor loadings from Guo et al 2006 used for weighted sum of variables. [b]CDRS analogue for 'Work and Activities' on the Hamilton Depression Rating Scale. ^FA for symptoms and neuropsychological functioning were conducted independently.

Separately, due to the large number of dependent variables yielded by neuropsychological tests, we also conducted a series of exploratory factor analyses (principal axis factor analysis with oblique rotation, extraction of with Eigen-values greater than 1), with variables entered based upon construct and theoretic knowledge of the tests employed (Langenecker, Saunders, Kade, Ransom, & McInnis, 2010; Ryan et al., 2012). These theoretically and empirically driven neuropsychological dimensions included Inhibitory Control, Attentional Control, Psychomotor Speed, Verbal Learning, Verbal Memory, and Visual

Learning/Memory (Table I). All scales were converted prior to analysis such that higher scores reflect better performance. Resulting factor scores were saved as z-scores. Bivariate correlations within and between depression and neuropsychological dimensions are reported in Table II.

E. **Cyotkine Assays**

Levels of pro-inflammatory cytokines were determined in plasma/serum aliquots by enzyme-linked immunosorbent assay using commercially available 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 the levels of cytokines 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. Pro-inflammatory cytokine values were not normally distributed; therefore, values were log-transformed for use in the analysis.

Table I. Bivariate Correlations for Depression and Neuropsychological Functioning Dimensions

Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
CDRS Total (1)	1.00								
Reported Mood (2)	.90**	1.00							
	(.81)**								
Somatic Symptoms (3)	.90**	.79**	1.00						
	(.80)**	(.63)**							
Psychomotor Speed (4)	-.23	-.24*	-.16	1.00					
	(-.32)*	(-.29)	(-.20)						
Attentional Control (5)	-.38**	-.26*	-.25*	-.11	1.00				
	(-.35)*	(-.15)	(-.08)	(.13)					
Inhibitory Control (6)	-.14	-.06	-.12	.02	.10	1.00			
	(-.03)	(.09)	(.02)	(.08)	(.13)				
Verbal Learning (7)	-.18	-.12	-.06	-.03	.36**	.30*	1.00		
	(-.11)	(-.02)	(.09)	(-.11)	(.31)	(.34)*			
Verbal Memory (8)	-.14	-.07	-.11	-.09	.23	.03	.36*	1.00	
	(-.16)	(-.01)	(-.11)	(-.18)	(.33)*	(.09)	(.29)		
Visual Learning/Memory (9)	.03	.07	.05	-.06	.22	.22	.24*	.19	1.00
	(.04)	(.12)	(.09)	(-.14)	(.45)**	(.22)	(.24)	(.26)	

*p<.05, **p<.01, () Denotes correlation coefficient in AMD and AMD-T participants only

F. **Statistical Analyses**

Statistical analyses were performed in SPSS (v24.0). Group differences between HC, AMD, and AMD-T participants in demographic, clinical, and neuropsychological test variables were compared using one-way analysis of variance and chi-squared tests, as appropriate (Aims 1a and 2a). Pro-inflammatory cytokine values were not normally distributed; therefore, group differences were compared using Kruskal-Wallis H tests. The cytokine variables achieved a normal distribution after log-transformation, and subsequently, log-transformed values were used in regression analyses.

Multiple linear regression analyses were run via the Process Macro for SPSS (Hayes, 2017), with each inflammatory cytokine as a focal predictor of each dimension of depression and neuropsychological function resulting from the confirmatory factor analyses. Models involved the hierarchical entry of the inflammatory marker (main effect, Aims 1b and 2b), diagnostic group (main effect), and their interaction (Aims 1c and 2c). Diagnostic group was dummy coded, using indicator coding, with the HC group as the reference group. Significant interactions were followed-up using a standard simple slopes approach (Aiken, West, & Reno, 1991). Specifically, the effect of the inflammatory cytokine in relationship to the dependent depression or neuropsychological dimension was tested at each level of the categorical moderator variable (i.e. HC, AMD, and AMD-T diagnostic groups), allowing for inferences regarding associations of inflammation in HC, depressed, and trauma-exposed depressed participants.

III. Results

A. Demographic and Clinical Characteristics

The demographic and clinical characteristics of the study sample are shown in Table III. HC participants were equivalent to AMD and AMD-T participants on age, sex, verbal IQ estimate, race/ethnicity, and body mass. AMD and AMD-T participants did not significantly differ in the distribution of primary current DSM-IV mood disorder diagnosis. Across all participants with a current depressive disorder diagnosis, 42.5% (n = 17) met criteria for a current major depressive episode, 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 the participants meeting current criteria for dysthymia or depression NOS (n = 20), 35.0% (n = 7) previously met criteria for a past major depressive episode.

B. Inflammatory Cytokines

A statistically significant difference in the omnibus test between AMD, AMD-T, and HC groups (Table III) was observed for serum levels of IL-6 (p = .021) and TNF-α (p = .045). Post-hoc pairwise comparisons indicated that for IL-6 levels, both AMD and AMD-T participants exhibited elevations relative to healthy controls, and did not differ significantly from each other. These group differences corresponded to Cohen's d effect sizes of 0.89 (large) and d = .60 (medium) in AMD and AMD-T participants, respectively. For TNF-α, post-hoc pairwise comparisons indicated that AMD participants demonstrated elevated serum levels relative to HC and AMD-T participants, associated with effect size

Table III. Demographic, Clinical, and Serum Cytokine Variables

	HC (n = 31)		AMD (n = 18)		AMD-T (n = 22)		Omnibus Test	
	M	**SD**	**M**	**SD**	**M**	**SD**	***F***	***p*-value**
Age	14.58	1.43	14.61	1.46	14.45	1.54	.06	.941
Verbal IQ Estimate^	55.16	8.76	54.44	9.90	50.23	9.77	1.92	.155
Body Mass Index	23.15	3.28	22.68	4.96	22.10	4.56	.39	.681
Global Functioning^^[a,b,c]	91.39	5.86	69.28	9.14	60.95	9.20	105.54	<.001
CDRS Total	19.58	1.80	38.28	10.04	47.95	11.61	80.62	<.001
Reported Mood[a,b]	1.59	.27	3.25	1.21	3.96	1.51	35.56	<.001
Somatic Symptoms[a,b]	2.33	.47	4.57	1.82	5.63	1.66	42.17	<.001
Age of Onset	--	--	12.00	2.00	12.33	.298	.35	.710
	N	**%**	**N**	**%**	**N**	**%**	**χ^2**	***p*-value**
Sex (% Female)	20	64.5	10	55.6	14	63.6	.43	.808
Ethnicity								
Hispanic	7	22.6	6	33.3	7	31.8	.86	.650
Non-Hispanic	24	77.4	12	66.7	15	68.2	--	--
Race								
Caucasian	17	54.8	13	76.5	10	45.5	12.41	.134
African American	8	25.8	0	0.0	8	36.4	--	--
Asian	5	16.1	2	11.8	1	4.5	--	--
American Indian/Alaskan Native	0	0.0	0	0.0	1	4.5	--	--
Other/Unknown	1	3.2	2	11.8	2	9.1	--	--
Post Pubertal	21	67.7	12	66.7	16	72.7	.22	.899
Current DSM-IV Diagnosis								
Major Depression	--	--	5	27.8	12	54.5	2.90	.088
Dysthymia	--	--	5	27.8	3	13.6	1.24	.266
Depressive d/o NOS	--	--	7	38.8	5	22.7	2.20	.138
Adjustment d/o Depressed Mood	--	--	1	5.5	2	9.1	1.72	.189
	M	**SD**	**M**	**SD**	**M**	**SD**	**χ^2**	***p*-value**
IL-6[a,b]	1.08	.54	1.84	1.08	1.53	.90	7.75	.021
TNF-α[a,c]	.59	.25	.76	.30	.56	.23	6.21	.045
Il-1β	.09	.06	.09	.06	.10	.05	.255	.880

^Vocabulary sub-test T-Score from the WASI-II; ^^Children's Global Assessment Scale. [a]Significant ($p < .05$) post-hoc pairwise comparison, AMD vs. HC; [b]Significant ($p < .05$) post-hoc pairwise comparison, AMD-T vs. HC; [c]Significant ($p < .05$) post-hoc pairwise comparison, AMD-T vs. AMD

estimates of 0.63 (medium) and 0.74 (medium), respectively. No between-group differences were detected in Il-1β (p = .880).

C. **Inflammation and Depression Symptom Dimensions**

Multiple regression analyses (Table IV) supported a significant main effect of IL-6 on reported depressed mood, whereby IL-6 levels were positively associated with the reported depressed mood across all subjects. There were no main effects of TNF-α or IL-1β on any symptom dimensions across groups (Table IV). Additionally, a TNF-α x diagnostic group interaction significantly contributed to the model predicting somatic symptoms, whereby TNF-α levels were positively associated with somatic symptoms in AMD (b = 3.74, SE = 1.49, p = .015), but not in AMD-T (b = 1.29, SE = .79, p = .107) or HC (b = .33, SE = 1.01, p = .740) participants. There were no interactions between IL-6 or IL-1β and diagnostic group in relation to symptom dimensions (Table III).

D. **Neuropsychological Performance**

The omnibus test for between-group (HC, AMD, AMD-T) differences in neuropsychological domains was significant for psychomotor speed [F (2, 70) = 5.45, p = .023], verbal learning [F (2, 70) = 4.64, p = .035], interference resolution [F (2, 70) = 5.54, p = .021], and inhibitory control [F (2, 70) = 3.99, p = .050]. There were no between-group differences in verbal memory [F (2, 70) = .712 p = .402] or visual memory [F (2, 70) = .038, p = .845].

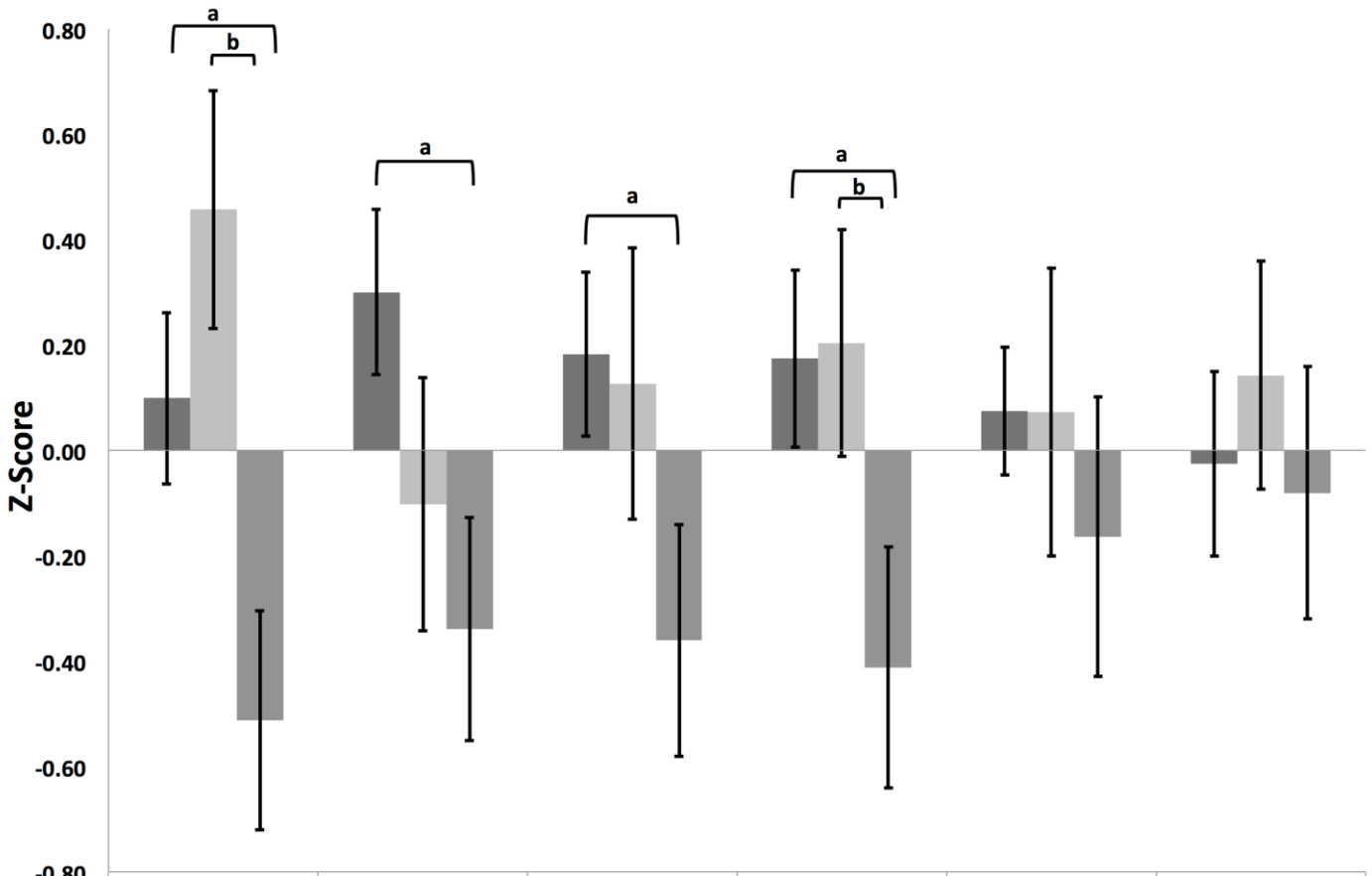
As illustrated in Figure 1, post-hoc pair-wise comparisons indicated that AMD-T participants were characterized by slower psychomotor speed relative to both HC (p = .023, Cohen's d = .65 [medium]) and AMD participants (p = .002,

Table IV. Inflammatory cytokines in relation to depression symptom dimensions in HC, AMD, and AMD-T adolescents

	Dependent Variable											
Focal Predictor	**Reported Mood**				**Somatic Symptoms**				**CDRS Total**			
IL-6	*β*	*SE*	*p*	R^2	*β*	*SE*	*p*	R^2	*β*	*SE*	*p*	R^2
IL-6	1.45	.70	**.047**	.51**	.69	1.29	.590	.57**	3.09	7.93	.697	.71**
AMD	1.63	.36	**<.001**		2.45	.45	**<.001**		19.91	2.77	**<.001**	
AMD-T	2.34	.32	**<.001**		3.35	.40	**<.001**		29.29	2.48	**<.001**	
AMD x IL-6	-.19	1.36	.892		-1.89	1.71	.272		-9.93	10.55	.350	
AMD-T x IL-6	-.09	1.40	.947		-1.23	1.76	.487		-11.07	10.85	.312	
TNF-α												
TNF-α	-.59	.82	.478	.55**	.34	1.02	.740	.61**	-1.84	6.67	.783	.71**
AMD	1.58	.42	**<.001**		2.74	.53	**<.001**		18.23	3.46	**<.001**	
AMD-T	2.91	.42	**<.001**		3.64	.52	**<.001**		29.97	3.44	**<.001**	
AMD x TNF-α	-.96	1,46	.510		3.41	1.70	**.049**		-4.35	11.84	.714	
AMD-T x TNF-α	1.74	1.04	.099		.96	1.29	.460		5.11	8.45	.547	
IL-1β												
IL-1β	.12	.84	.886	.52**	.25	1.07	.817	.55**	-.32	6.65	.961	.70*
AMD	.96	1.33	.471		2.17	1.71	.209		15.65	10.57	.143	
AMD-T	3.70	1.44	**.012**		3.14	1.57	**.050**		34.22	11.47	**.004**	
AMD x IL-1β	-.62	1.17	.597		-.06	1.51	.967		-2.59	9.32	.781	
AMD-T x IL-1β	1.26	1.32	.344		-.13	1.71	.937		5.60	10.56	.597	

*p<.05, **p<.01

Figure 1. Neuropsychological factor score performance in HC, AMD, and AMD-T Adolescents



	Psychomotor Speed	Attentional Control	Inhibitory Control	Verbal Learning	Verbal Memory	Visual Learning/ Memory
HC	0.10	0.30	0.18	0.17	0.07	-0.03
AMD	0.46	-0.10	0.13	0.20	0.07	0.14
AMD-T	-0.51	-0.34	-0.36	-0.41	-0.16	-0.08

[a]AMD-T vs. HC, [b]AMD-T vs. AMD

Cohen's *d* = 1.01 [large]). Similarly, for verbal learning, AMD-T participants performed significantly worse relative to both HC (*p* = .035, Cohen's *d* = .65 [medium]) and AMD participants (*p* = .050, Cohen's *d* = .61 [medium]). Whereas AMD and AMD-T participants did not differ on interference resolution (*p* = .447) or inhibitory control (*p* = .124), AMD-T participants performed significantly worse than HC on interference resolution (*p* = .021, Cohen's *d* = .58 [medium]) and inhibitory control (*p* = .049, Cohen's *d* = .56 [medium]).

E. **Inflammation and Executive Functioning Dimensions**

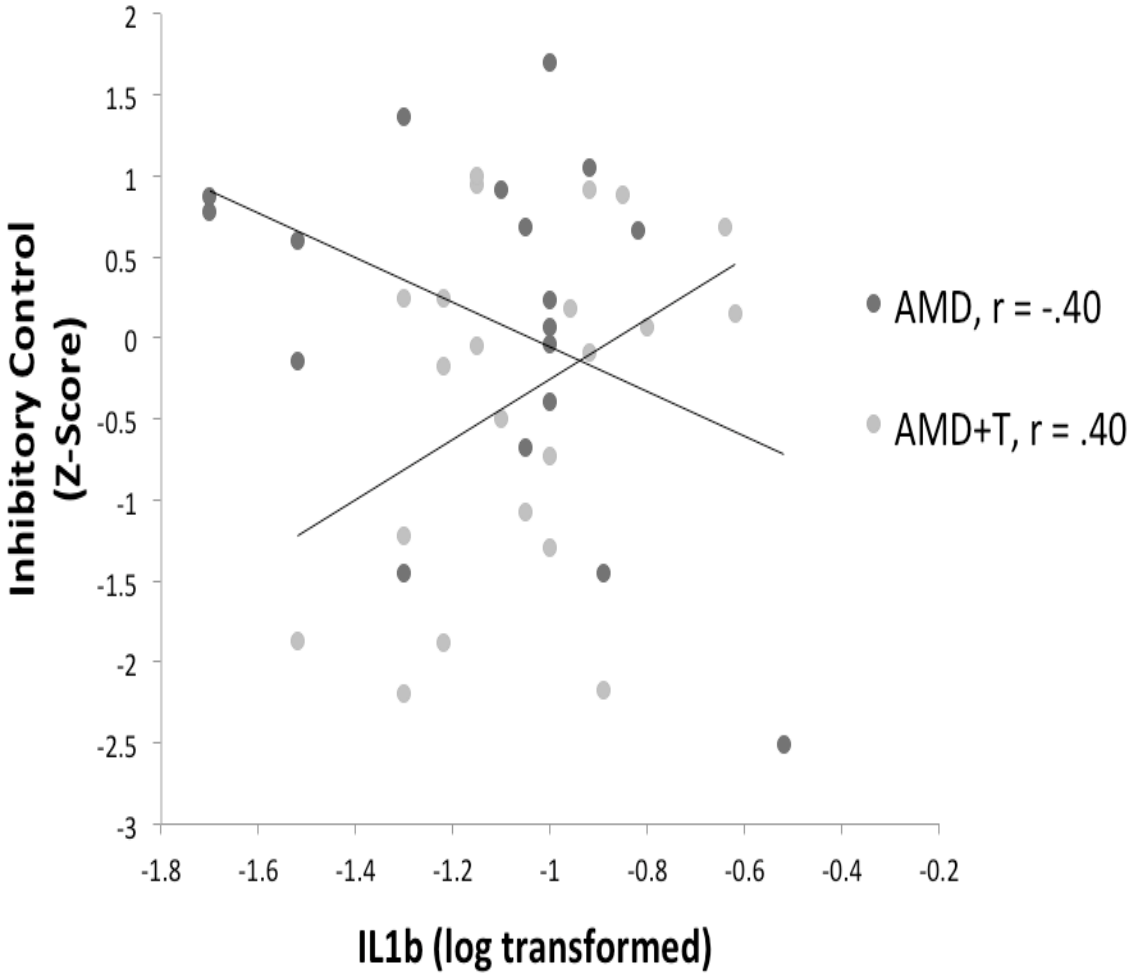
Table V reports the regression models testing the association between inflammatory cytokines and inhibitory control, attentional control, and psychomotor speed. No main effects of any inflammatory cytokine were observed in relation to inhibitory control, attentional control, or psychomotor speed. Analyses did support a significant IL-1β x diagnostic group interaction in relation to the *a-priori* domain of inhibitory control (Figure 2). Follow up tests indicated that whereas there was no relationship between Il-1β and inhibitory control in HCs (*b* = -.36, *SE* = .75, *p* = .630), IL-1β was associated with poorer inhibitory control in AMD (*b* = -1.40, *SE* = .70, *p* = .050), and associated with better inhibitory control in AMD-T (*b* = 1.84, *SE* = .91, *p* = .048). There was no significant interaction between IL-1β and diagnostic group in relation to attentional control or psychomotor speed. Moreover, no interactions between diagnostic group and IL-6 or TNF-α were supported.

Table V. Inflammatory cytokines in relation to executive functioning and fluency in HC, AMD, and AMD-T adolescents

	Dependent Variable											
Focal Predictor	Inhibitory Control				Attentional Control				Psychomotor Speed			
IL-6	*β*	*SE*	*p*	R^2	*β*	*SE*	*p*	R^2	*β*	*SE*	*p*	R^2
IL-6	-1.39	.94	.144	.09	-.11	.95	.905	.08	1.43	.85	.099	.26**
AMD	.04	.32	.112		-.42	.32	.188		.17	.28	.552	
AMD-T	-.41	.29	.155		-.64	.29	**.031**		-.82	.26	**.003**	
AMD x IL-6	1.69	1.25	.181		.41	1.26	.749		-.83	1.13	.466	
AMD-T x IL-6	1.29	1.29	.320		.38	1.30	.772		.66	1.17	.575	
TNF-α												
TNF-α	-1.08	.77	.168	.12	-.39	.78	.619	.10	1.07	.73	.147	.21**
AMD	.09	.31	.768		-.52	.31	.103		.41	.30	.174	
AMD-T	-.57	.27	**.043**		-.60	.27	**.033**		-.56	.26	**.036**	
AMD x TNF-α	-.18	1.37	.895		1.57	1.38	.262		-1.69	1.30	.200	
AMD-T x TNF-α	.52	.98	.598		.82	.99	.412		-.09	.93	.916	
IL-1β												
IL-1β	-.36	.75	.633	.16*	-.08	.78	.921	.09	.62	.75	.416	.16*
AMD	-.12	.28	.689		-.43	.30	.158		.39	.29	.180	
AMD-T	-.57	.27	.036		-.65	.28	**.023**		-.60	.27	**.028**	
AMD x IL-1β	-1.02	1.05	.338		-.30	1.10	.779		-.03	1.06	.976	
AMD-T x IL-1β	2.20	1.09	.**048**		.49	1.24	.691		-.74	1.19	.538	

*p<.05, **p<.01

Figure 2. Il-1β interacts with diagnostic group in association with inhibitory control



F. **Inflammation and Learning and Memory Dimensions**

Table VI reports the regression models testing the association between inflammatory cytokines and verbal learning, verbal memory, and visual learning/memory.

Table VI. Inflammatory cytokines in relation to learning and memory in HC, AMD, and AMD-T adolescents

	Dependent Variable											
Focal Predictor	Verbal Learning				Verbal Memory				Visual Learning/Memory			
IL-6	*β*	*SE*	*p*	R^2	*β*	*SE*	*p*	R^2	*β*	*SE*	*p*	R^2
IL-6	-.76	.48	.120	.11	-.16	.49	.742	.03	-2.09	.94	**.030**	.10*
AMD	.17	.31	.586		-.04	.33	.915		.39	.32	.221	
AMD-T	-.50	.28	.085		-.19	.29	.537		.16	.29	.571	
AMD x IL-6	-.20	1.24	.870		.76	1.29	.557		1.72	1.25	.175	
AMD-T x IL-6	-.06	1.28	.959		-.55	1.37	.683		1.15	1.29	.373	
TNF-α												
TNF-α	.36	.43	.407	.09	-.03	.44	.939	.07	.55	.43	.212	.04
AMD	-.06	.31	.861		.06	.32	.846		.04	.33	.898	
AMD-T	-.59	.27	.036		-.29	.28	.293		-.06	.28	.829	
AMD x TNF-α	.35	1.39	.801		-1.88	1.41	.187		.15	1.43	.915	
AMD-T x TNF-α	-.48	.99	.628		-1.84	1.01	.073		-.84	1.02	.412	
IL-1β												
IL-1β	-1.12	.45	**.016**	.15*	-.07	.48	.881	.09	.22	.48	.642	.02
AMD	.02	.28	.945		-.03	.29	.927		.20	.31	.516	
AMD-T	-.53	.26	**.048**		-.26	.28	.345		-.04	.29	.879	
AMD x IL-1β	.64	1.04	.537		-.35	1.09	.745		.05	1.13	.961	
AMD-T x IL-1β	.55	1.17	.639		2.45	1.24	.052		.50	1.28	.698	

*p<.05, **p<.01

Analyses indicated a significant main effect of Il-1β in relation to verbal learning across all subjects, whereby higher Il-1β was associated with poorer verbal learning. Neither IL-6 nor TNF-α were related to verbal learning. Additionally, there was a main effect IL-6 in relation to visual learning/memory, whereby increases in Il-6 were associated with poorer visual learning/memory. Neither IL-1β nor TNF-α were associated with visual learning/memory. None of the inflammatory cytokines were associated with verbal memory, nor did any of the inflammatory cytokines interact with diagnostic group in relation to any of the learning and memory domains.

IV. Discussion

A. Summary

In this study we found that young, non-medicated, depressed adolescents with and without a history of childhood trauma showed significantly higher serum levels of IL-6 as compared with healthy adolescents without depression. Adolescents with depression and no trauma history demonstrated elevated levels of TNF-α. There was no difference between groups in serum levels of IL-1β. Associations with clinical and neuropsychological data revealed that inflammation alone was associated, linearly, with increased depressed mood, verbal learning, and visual learning/memory dysfunction amongst all adolescents. By contrast, inflammation interacted in at-risk, depressed and trauma-exposed youth, in association with somatic complaints and executive dysfunction. Cumulatively, these findings add important data on inflammatory markers during a critical period of development. Cytokine production may represent an early sign of immune dysregulation during the course of depression and also contribute to the early identification of risk for concomitant neuropsychological dysfunction.

B. Group Differences in Inflammatory Cytokines

To our knowledge, this is the first study reporting elevations in IL-6 among an *un-medicated* sample of depressed adolescents. Two prior studies of un-medicated adolescents have reported consistent findings of elevated IL-6 in samples with primarily clinical 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). Through their interactions with

neurotransmitter function, HPA-axis, and glial cells, there are multiple pathways by which antidepressants could be involved in the inhibition of pro-inflammatory mediators (Galecki, Mossakowska-Wojcik, & Talarowska, 2018). Consequently, in the absence of any pharmacological influences on immune function, our findings raise the possibility that IL-6 is an independent biomarker of early course depression.

Additionally, TNF-α was elevated in AMD participants relative to AMD-T and HC adolescents. Although we expected that adolescents with depression would uniformly demonstrate elevated TNF-α, it is curious that this finding was only present in adolescents without a childhood trauma history. One possible explanation relates to the fact that childhood trauma is known to have adverse effects on healthy physical, emotional, and neural development (Berens et al., 2017). The clear and present dangers might necessitate *efficient* immune functioning for defense, resilience, or repair. By contrast, the immune response among youth who are not exposed to significant trauma may be *inefficient* and have maladaptive consequences when threats or stressors are perceived. This is consistent with the evolutionary model of pathogen-host defense in inflammatory response (Raison & Miller, 2017), which proposes that depression, in part, evolved as an immune, anti-pathogen defense strategy. Paradoxically, the immune response has grown less necessary over time with evolution of the conveniences and protections associated with a more developed, modern world (Raison & Miller, 2017). Nevertheless, subsequent study of TNF-α in larger adolescent samples will be paramount because as it stands, there is significant

variability in directionality of existing findings (Mitchell & Goldstein, 2014). For instance, there are reports of *decreased* TNF-α in depressed adolescents reporting suicidality (Gabbay, Klein, Guttman, et al., 2009) and in adolescent dysthymia (Brambilla et al., 2004). Therefore, we can speculate, but do not yet fully understand whether increased or decreased TNF-α is more adaptive. It might be that different clinical syndromes are associated with inflammatory activity at both high and low ends of a u-curve, which warrants testing with sufficient power. It is also possible, if even likely, that inflammatory markers are different across stages of development and with disease progression.

C. Associations between Inflammation and Depression Symptom Dimensions

IL-6 was positively associated with the dimension of 'reported mood symptoms', but not the CDRS composite index of depression. This finding offers some developmental specificity to the myriad studies that report associations of IL-6 with a more general, cumulative index of depression severity in adulthood (Howren et al., 2009). As the link between IL-6 and depressed mood was present across the full spectrum of healthy, sub-threshold, and affected adolescents, this speculatively, might reflect that IL-6 is not only a state marker of depression, but has some possible involvement in risk for depressed mood (Giletta et al., 2017). Such a hypothesis will require future study using a rigorous longitudinal design. Moreover, seeing as IL-6 concentrations were equally elevated in depressed adolescents with and without a childhood trauma history, longitudinal studies might also reveal whether subtle, within-group differences in child trauma history

emerge or predict recurrence in adulthood. Alternatively, adolescent depression is typically associated with a more severe course of illness (Fombonne et al., 2001), which might confer different neurobiological risk and course relative to those with onset of MDD as adults.

Additionally, TNF-α was positively associated with somatic symptoms, which is expected given its role in suppressing appetite and inducing fever through stimulation of the HPA-axis (Popa, Netea, van Riel, van der Meer, & Stalenhoef, 2007). The initiation of these “sickness” behaviors, represent why TNF-α is regarded as one of the initial mediators of the immune repair process (Biesmans et al., 2015). However, as aforementioned, the specificity of the association between TNF-α and somatic symptoms to depressed adolescents without a childhood trauma history was unanticipated. One consideration is that the AMD only group was overall of milder clinical severity. Therefore, increased TNF-α could be a marker of partial remission/recovery. Through this lens, the correlation between TNF-a and somatic symptoms may be indicative of an active, but not fully resolved, immune repair process. Alternatively, ongoing TNF-a activity may facilitate resilience to subsequent major episodes at the cost of mild residual somatic symptoms.

D. **Group Differences in Neuropsychological Functioning**

A novel design feature of this study is the inclusion of neuropsychological measures and convergent relationships for inflammation, mood, and childhood trauma on cognitive functioning. By in large, childhood trauma and inflammation demonstrated independent associations with cognitive domains. For instance,

deficits in psychomotor speed, interference resolution, inhibitory control, and verbal learning were unique to depressed adolescents with a childhood trauma history. This is broadly consistent with one prior study among adolescent inpatients with diverse psychopathology where childhood maltreatment history was associated with impaired executive function (Kavanaugh, Holler, & Selke, 2015), yet sheds additional light that the specific coupling of depression and childhood trauma may have more diffuse effects on learning, fluency, and retention, in addition to executive functioning. In the current study, the areas of neuropsychological dysfunction associated with childhood trauma substantially overlapped with the cognitive impairments typically found in first-episode depressed adults (Ahern & Semkovska, 2017), suggesting the possibility that early life adversity is a primary driver of impairment in processing speed, learning, and executive function in depression. Indeed, there is at least one longitudinal study to support that childhood trauma prospectively predicts executive dysfunction and nonverbal reasoning into adulthood (Nikulina & Widom, 2013). Nevertheless, these findings must be interpreted in light of the fact that youth exposed to childhood trauma were generally more symptomatic; future studies among asymptomatic, remitted adolescents, would lend additional credence to a possible neuropsychological specificity of childhood trauma.

E. **Associations between Inflammation and Executive Functioning**

Whereas the neuropsychological footprint of childhood trauma was diffuse, inflammation and childhood trauma interacted in a domain-specific manner in relation to inhibitory control. IL-1β was associated with impaired

inhibitory control amongst depressed adolescents without trauma history. The inverse was true among depressed adolescents with a trauma history, where IL-1β was associated with relatively better inhibitory control. Although we expected inflammation and trauma to interact in association with inhibitory control, this directionality was initially, somewhat surprising. However, it is important to consider that trauma-exposed depressed participants showed a *deficit* in inhibitory control, whereas AMD only participants did not differ in performance from controls. It is also noteworthy that IL-1β was the only cytokine tested that showed *no* differences across control, AMD, and AMD-T participants. Cumulatively, these results might also be in line with the pathogen-defense model of immune functioning (Raison & Miller, 2017). Under these circumstances, we speculate that increases in IL-1β might play an adaptive or restorative role in response to childhood trauma and its related disruptions to inhibitory control. Alternatively, IL-1β may elicit concomitant neuro-plastic processes to achieve adaptive functioning. By contrast, increases in IL-1β may be unnecessary and deleterious among adolescents who are not exposed to veritable adversity or threat; therefore in excess, the inflammation may result in detrimental effects to the neural circuitry underlying inhibitory control.

It is also noteworthy that this observed cross over interaction implies possible differential function of pro-inflammatory mediators, whereas the hypothesized pattern of interaction was that the negative impact of inflammation would be present across subjects, but most pronounced in at-risk depressed and trauma-exposed youth. It is therefore likely that limited power to test group

interactions within a relatively small sample precluded the ability to detect subtle emergent differences in slopes, especially seeing as cognitive performance was likely further obscured by variations in development. Nevertheless, it was also surprising that we did not observe an overall domain specific effect of inflammatory markers in relation inhibitory control. From a methodological standpoint, one explanation for this null finding might relate to measurement issues associated with inhibitory control. For instance, while inhibitory control is broadly defined individual's ability to override pre-potent responses to a stimulus in order to implement more adaptive goal-oriented behaviors, successful inhibition can vary substantially in different contexts, with degree of difficulty, or when shifting between rule-sets (e.g. avoid distractors vs. avoid distractors and lures). For instance, there is some suggestion that early course depression may be associated with novel inhibitory deficits (initial but not subsequent exposures (Peters et al., 2017)), obscured by ceiling effects for two-target inhibitory trials (Langenecker et al., 2007), and may be best differentiated by automatic and not controlled inhibition (Verbruggen & Logan, 2008). In the current study, the inhibitory control performance data was collapsed across these factors, and therefore, subsequent exploratory analyses within these sub-domains are warranted.

There are also some conceptual issues involved in detecting or failure to detect a possible impact of inflammation in executive functioning, more broadly. Firstly, executive functioning skills, including interference resolution, attentional control, and inhibitory control, are still undergoing development during

adolescence, and this development can be both protracted and uneven, in part due to variations in age, pubertal status, pubertal hormones. Therefore, chronic inflammation may very well reduce efficiency in cognitive function once executive functioning skills are consolidated in adulthood, but the marked natural variability in executive functioning during adolescence may supersede subtle effects of low-grade inflammation early on. Stated another way, absent a pre-inflammation baseline, there is no way to attribute any weakness to inflammation vs. delayed development or some other factor. Secondly, many of the associations between inflammation and cognition have been detected in cohorts enriched with cerebrovascular risk factors (Windham et al., 2014). Indeed, cerebrovascular risk factors, brain structure abnormalities, inflammation, and cognition (particularly executive functioning and processing speed) are interrelated and it is thought that inflammation at least partly mediates cognitive decline through arteriosclerotic disease in the brain (McAfoose & Baune, 2009). By design, the present study was carefully screened for many health factors (e.g. obesity) and chronic medical conditions known to influence inflammation and increase vascular risk later in life. Therefore, it is possible and likely, that inflammatory markers interact with other health-related risk factors and lifestyle variables (exercise, diet, etc.) to impact executive functioning over time with chronic illness.

F. **Associations between Inflammation and Learning and Memory**

There are other associations between pro-inflammatory markers and neuropsychological functioning that warrant attention. Namely, IL-6 was associated with reduced visual learning/memory performance and IL-1β was

associated with poorer verbal learning. These findings are striking because links between pro-inflammatory markers and learning and memory have thus far, predominantly been detected in the elderly who are typically aging (Jordanova, Stewart, Davies, Sherwood, & Prince, 2007; Weaver et al., 2002), depressed (Charlton et al., 2017; Elderkin-Thompson, Irwin, Hellemann, & Kumar, 2012), or affected by dementia (C. Holmes et al., 2009). The prevailing hypothesis underlying the coupling of inflammation and memory decline in the elderly is that age-related sensitization of microglia lead to a magnified *neuro-inflammatory* response that impairs synaptic plasticity and hippocampal dysfunction, in turn, contributing to memory loss. Remarkably, our findings suggest that peripheral inflammation might disrupt neurodevelopment and pose risk for memory impairments much earlier in life. Future probes or proxies of *neuro*-inflammation among adolescents, such as in the cerebrospinal fluid, in integration with structural and functional neuroimaging, would help to corroborate whether inflammation-related memory disruptive during adolescence is sub-served by similar mechanisms. To date, elevated pro-inflammatory cytokines have been detected post-mortem in the brains of adolescent suicide victims (Pandey et al., 2012).

One interesting aspect of this pattern of associations between inflammatory markers and measures of memory function is that IL-1β was related to reduced memory for verbal content learned in the initial block of the word-list, but not overall recall or recognition of words. This suggests that the impact of peripheral inflammation on semantic list learning may relate specifically to

reduced initial attention and encoding of verbal information. Most learning contexts are a single trial exposure, so the relationship of IL-1β and memory is worth pursuing further in clinical and research contexts. This pattern is different from that observed in older adults and aging cohorts, where pro-inflammatory cytokines are shown to relate to both verbal learning and retention (Charlton et al., 2017; Elderkin-Thompson et al., 2012; C. Holmes et al., 2009; Jordanova et al., 2007; Weaver et al., 2002), theoretically due, in part, to the involvement of chronic inflammation in medial temporal atrophy. As retentive memory disturbance is not typical of adolescence, it is possible that the link between IL-1β and initial verbal learning does reflect a component of attention or organizational rehearsal strategies, even within a task design that utilizes semantic cues to facilitate the executive functioning components of encoding. The association between IL-6 and visual learning and memory may further support this notion, as the RCTF test is quite complex, requiring a substantial reliance on executive function (e.g. planning, organization) for adequate performance.

G. **Limitations**

The current study must be interpreted in light of some limitations. Primarily, the cross-sectional design of the study limits any causal inferences. Second, the current panel of cytokines included only traditional *pro*-inflammatory mediators. Thus, we cannot comment on whether mood disruption and cognitive impairments in adolescence are at all related to the imbalance of cells that up-regulate (i.e. pro-inflammatory) versus inhibit (i.e. anti-inflammatory) the immune response. Third, cytokine physiologies are complex and are likely to include

mediators and moderators that were not investigated here, such as soluble receptors and their buffers. Fourth, childhood trauma was assessed retrospectively and via self-report; this represents a subjective versus objective measure of stress, which could be biased by recall errors and by mood-congruent reporting and might especially apply for the clinically depressed participants. Therefore, the “impact” of childhood trauma on neuropsychological function and in interaction with inflammation is proposed with significant caution; we cannot confidently conclude that childhood trauma predated the observed domains of dysfunction. With a modest sample size, we were not powered to detect whether different types of trauma confer specific risks. For instance, there is some empirical support that increased inflammation might show specificity to sexual and physical abuse (Baumeister et al., 2016). Moreover, sample size also precluded the study of whether social, familial, or environmental supports buffer against inflammation or early childhood adversity. Last, our analyses could be strengthened in future designs by collecting and adjusting for circadian measures, proxies of endocrine/hormonal function, and homeostatic mechanisms, such as temperature, which likely add a further layer of complexity to the immune response (Bansal, Mejia, & Simmons, 2017).

H. **Conclusions**

This study also benefited from several strengths, including recruitment of a representative and diverse adolescent sample free of medications, that was well matched in terms of age, sex, ethnic background, and body mass index and carefully screened for confounds to inflammatory activity such as chronic medical

co-morbidities, obesity, and substance/alcohol/nicotine use. Collectively, the findings do sharpen understanding of the mechanisms involved in the development and instantiation of depression and neuropsychological dysfunction during development. Namely, there appear to be independent effects of both pro-inflammatory mediators and childhood trauma on depressed mood and memory function early in life. These effects are evident even early in the disease process. Thus, interventions to reduce early life stress and inflammation during childhood or adolescence represent possible innovations for forestalling these specific areas of co-occurring dysfunction. Moreover, there may be a specific sub-set of adolescents characterized by inefficient or exaggerated immune response, in the absence of authentic endangerment that poses liability for impaired inhibitory control and somatic symptoms. These associations raise the question of whether interventions that modify physiological hyper-vigilance to perceived stress might represent a viable target for this sub-group. In total, these findings support immune dysregulation affecting adolescents along the spectrum of depression severity. An additional exciting avenue of future research will be whether these basal markers of inflammation confer risk for recurrence or progression of other adverse clinical and neuropsychological sequelae.

Cited Literature

Ahern, E., & Semkovska, M. (2017). Cognitive functioning in the first-episode of major depressive disorder: A systematic review and meta-analysis. *Neuropsychology, 31*(1), 52-72. doi:10.1037/neu0000319

Aiken, L. S., West, S. G., & Reno, R. R. (1991). *Multiple regression: Testing and interpreting interactions*: Sage.

Albensi, B. C., & Mattson, M. P. (2000). Evidence for the involvement of TNF and NF-kappaB in hippocampal synaptic plasticity. *Synapse, 35*(2), 151-159. doi:10.1002/(SICI)1098-2396(200002)35:2<151::AID-SYN8>3.0.CO;2-P

Anderson, G. (2018). Linking the biological underpinnings of depression: Role of mitochondria interactions with melatonin, inflammation, sirtuins, tryptophan catabolites, DNA repair and oxidative and nitrosative stress, with consequences for classification and cognition. *Prog Neuropsychopharmacol Biol Psychiatry, 80*(Pt C), 255-266. doi:10.1016/j.pnpbp.2017.04.022

Arnow, B. A. (2004). Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. *J Clin Psychiatry, 65 Suppl 12*, 10-15.

Bansal, A., Mejia, J. H., & Simmons, R. A. (2017). Immune system: an emerging player in mediating effects of endocrine disruptors on metabolic health. *Endocrinology*. doi:10.1210/en.2017-00882

Bauer, I. E., Pascoe, M. C., Wollenhaupt-Aguiar, B., Kapczinski, F., & Soares, J. C. (2014). Inflammatory mediators of cognitive impairment in bipolar disorder. *J Psychiatr Res, 56*, 18-27. doi:10.1016/j.jpsychires.2014.04.017

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol Psychiatry, 21*(5), 642-649. doi:10.1038/mp.2015.67

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 Neuropsychopharmacol Biol Psychiatry, 77*, 133-137. doi:10.1016/j.pnpbp.2017.03.023

Bemporad, J. R. (1982). Management of childhood depression: developmental considerations. *Psychosomatics, 23*(3), 272-279. doi:10.1016/S0033-3182(82)73417-6

Benes, F. M. (1989). Myelination of cortical-hippocampal relays during late adolescence. *Schizophr Bull, 15*(4), 585-593.

Benson, S., Brinkhoff, A., Lueg, L., Roderigo, T., Kribben, A., Wilde, B., . . . Elsenbruch, S. (2017). Effects of acute systemic inflammation on the interplay between sad mood and affective cognition. *Transl Psychiatry, 7*(12), 1281. doi:10.1038/s41398-017-0043-0

Berens, A. E., Jensen, S. K. G., & Nelson, C. A., 3rd. (2017). Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Med, 15*(1), 135. doi:10.1186/s12916-017-0895-4

Berk, M., Berk, L., Dodd, S., Cotton, S., Macneil, C., Daglas, R., . . . Malhi, G. S. (2014). Stage managing bipolar disorder. *Bipolar Disord, 16*(5), 471-477. doi:10.1111/bdi.12099

Bernstein, D. P., Ahluvalia, T., Pogge, D., & Handelsman, L. (1997). Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(3), 340-348.

Biederman, J., Petty, C. R., Wozniak, J., Wilens, T. E., Fried, R., Doyle, A., . . . Faraone, S. V. (2011). Impact of executive function deficits in youth with bipolar I disorder: a controlled study. *Psychiatry Res, 186*(1), 58-64. doi:10.1016/j.psychres.2010.08.029

Biesmans, S., Bouwknecht, J. A., Ver Donck, L., Langlois, X., Acton, P. D., De Haes, P., . . . Nuydens, R. (2015). Peripheral Administration of Tumor Necrosis Factor-Alpha Induces Neuroinflammation and Sickness but Not Depressive-Like Behavior in Mice. *Biomed Res Int, 2015*, 716920. doi:10.1155/2015/716920

Biesmans, S., Matthews, L. J., Bouwknecht, J. A., De Haes, P., Hellings, N., Meert, T. F., . . . Ver Donck, L. (2016). Systematic Analysis of the Cytokine and Anhedonia Response to Peripheral Lipopolysaccharide Administration in Rats. *Biomed Res Int, 2016*, 9085273. doi:10.1155/2016/9085273

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. doi:10.1016/j.jpsychores.2017.01.002

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. doi:10.1016/S0165-0327(02)00315-4

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. doi:10.1080/09084280903526083

Brown, G. M., McIntyre, R. S., Rosenblat, J., & Hardeland, R. (2018). Depressive disorders: Processes leading to neurogeneration and potential novel treatments. *Prog Neuropsychopharmacol Biol Psychiatry, 80*(Pt C), 189-204. doi:10.1016/j.pnpbp.2017.04.023

Bulzacka, E., Boyer, L., Schurhoff, F., Godin, O., Berna, F., Brunel, L., . . . Group, F.-S. (2016). Chronic Peripheral Inflammation is Associated With Cognitive Impairment in Schizophrenia: Results From the Multicentric FACE-SZ Dataset. *Schizophr Bull, 42*(5), 1290-1302. doi:10.1093/schbul/sbw029

Casey, B. J., Oliveri, M. E., & Insel, T. (2014). A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biol Psychiatry, 76*(5), 350-353. doi:10.1016/j.biopsych.2014.01.006

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *J Affect Disord, 82*(2), 217-225. doi:10.1016/j.jad.2003.12.013

Charlton, R. A., Lamar, M., Zhang, A., Ren, X., Ajilore, O., Pandey, G. N., & Kumar, A. (2017). Associations between pro-inflammatory cytokines, learning, and memory in late-life depression and healthy aging. *Int J Geriatr Psychiatry*. doi:10.1002/gps.4686

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. doi:10.1111/acps.12217

Connor, T. J., & Leonard, B. E. (1998). Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci, 62*(7), 583-606.

Cullen, A. E., Tappin, B. M., Zunszain, P. A., Dickson, H., Roberts, R. E., Nikkheslat, N., . . . 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. doi:10.1016/j.bbi.2017.07.002

Cuthbert, B. N. (2014). The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry, 13*(1), 28-35. doi:10.1002/wps.20087

D'Mello, C., & Swain, M. G. (2017). Immune-to-Brain Communication Pathways in Inflammation-Associated Sickness and Depression. *Curr Top Behav Neurosci, 31*, 73-94. doi:10.1007/7854_2016_37

Danese, A., Moffitt, T. E., Harrington, H., Milne, B. J., Polanczyk, G., Pariante, C. M., . . . 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. doi:10.1001/archpediatrics.2009.214

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. doi:10.1073/pnas.0610362104

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci, 9*(1), 46-56. doi:10.1038/nrn2297

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. doi:10.1016/j.jad.2016.03.049

Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: an update. *J Int Neuropsychol Soc, 10*(2), 301-303. doi:10.1017/S1355617704102191

Dickerson, F., Stallings, C., Origoni, A., Boronow, J., & Yolken, R. (2007). C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia. *Schizophr Res, 93*(1-3), 261-265. doi:10.1016/j.schres.2007.03.022

Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Khushalani, S., & Yolken, R. (2013). Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. *J Affect Disord, 150*(2), 456-459. doi:10.1016/j.jad.2013.04.039

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctot, K. L. (2010). A meta-analysis of cytokines in major depression. *Biol Psychiatry, 67*(5), 446-457. doi:10.1016/j.biopsych.2009.09.033

Dunn, A. J. (1992). Endotoxin-induced activation of cerebral catecholamine and serotonin metabolism: comparison with interleukin-1. *J Pharmacol Exp Ther, 261*(3), 964-969.

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. doi:10.1016/j.biopsych.2010.06.010

Eisenberger, N. I., Moieni, M., Inagaki, T. K., Muscatell, K. A., & Irwin, M. R. (2017). In Sickness and in Health: The Co-Regulation of Inflammation and Social Behavior. *Neuropsychopharmacology, 42*(1), 242-253. doi:10.1038/npp.2016.141

Elderkin-Thompson, V., Irwin, M. R., Hellemann, G., & Kumar, A. (2012). Interleukin-6 and memory functions of encoding and recall in healthy and depressed elderly adults. *Am J Geriatr Psychiatry, 20*(9), 753-763. doi:10.1097/JGP.0b013e31825d08d6

Felger, J. C. (2017). Imaging the role of inflammation in mood and anxiety-related disorders. *Curr Neuropharmacol*. doi:10.2174/1570159X15666171123201142

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 Psychiatry, 21*(10), 1358-1365. doi:10.1038/mp.2015.168

Fombonne, E., Wostear, G., Cooper, V., Harrington, R., & Rutter, M. (2001). The Maudsley long-term follow-up of child and adolescent depression. 1. Psychiatric outcomes in adulthood. *Br J Psychiatry, 179*, 210-217.

Frydecka, D., Misiak, B., Pawlak-Adamska, E., Karabon, L., Tomkiewicz, A., Sedlaczek, P., . . . Beszlej, J. A. (2015). Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. *Eur Arch Psychiatry Clin Neurosci, 265*(6), 449-459. doi:10.1007/s00406-014-0533-5

Gabbay, V., Klein, R. G., Alonso, C. M., Babb, J. S., Nishawala, M., De Jesus, G., . . . Gonzalez, C. J. (2009). Immune system dysregulation in adolescent major depressive disorder. *J Affect Disord, 115*(1-2), 177-182. doi:10.1016/j.jad.2008.07.022

Gabbay, V., Klein, R. G., Guttman, L. E., Babb, J. S., Alonso, C. M., Nishawala, M., . . . 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. doi:10.1089/cap.2008.0140

Galecki, P., Mossakowska-Wojcik, J., & Talarowska, M. (2018). The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. *Prog Neuropsychopharmacol Biol Psychiatry, 80*(Pt C), 291-294. doi:10.1016/j.pnpbp.2017.03.016

Giletta, M., Slavich, G. M., Rudolph, K. D., Hastings, P. D., Nock, M. K., & Prinstein, M. J. (2017). Peer victimization predicts heightened inflammatory reactivity to social stress in cognitively vulnerable adolescents. *J Child Psychol Psychiatry*. doi:10.1111/jcpp.12804

Glaus, J., von Kanel, R., Lasserre, A. M., Strippoli, M. F., Vandeleur, C. L., Castelao, E., . . . Merikangas, K. R. (2017). Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study. *Psychol Med*, 1-13. doi:10.1017/S0033291717002744

Goldsmith, D. R., Haroon, E., Woolwine, B. J., Jung, M. Y., Wommack, E. C., Harvey, P. D., . . . Miller, A. H. (2016). Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. *Brain Behav Immun, 56*, 281-288. doi:10.1016/j.bbi.2016.03.025

Gore, F. M., Bloem, P. J., Patton, G. C., Ferguson, J., Joseph, V., Coffey, C., . . . Mathers, C. D. (2011). Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet, 377*(9783), 2093-2102. doi:10.1016/S0140-6736(11)60512-6

Grosse, L., Carvalho, L. A., Wijkhuijs, A. J., Bellingrath, S., Ruland, T., Ambree, O., . . . Arolt, V. (2014). Clinical characteristics of inflammation-associated depression: Monocyte gene expression is age-related in major depressive disorder. *Brain Behav Immun*. doi:10.1016/j.bbi.2014.08.004

Guo, Y., Nilsson, M. E., Heiligenstein, J., Wilson, M. G., & Emslie, G. (2006). An exploratory factor analysis of the children's depression rating scale-revised. *J Child Adolesc Psychopharmacol, 16*(4), 482-491. doi:10.1089/cap.2006.16.482

Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H., & Kivimaki, M. (2015). Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun, 49*, 206-215. doi:10.1016/j.bbi.2015.06.001

Haroon, E., Fleischer, C. C., Felger, J. C., Chen, X., Woolwine, B. J., Patel, T., . . . Miller, A. H. (2016). Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. *Mol Psychiatry, 21*(10), 1351-1357. doi:10.1038/mp.2015.206

Haroon, E., Raison, C. L., & Miller, A. H. (2012). Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology, 37*(1), 137-162. doi:10.1038/npp.2011.205

Haroon, E., Woolwine, B. J., Chen, X., Pace, T. W., Parekh, S., Spivey, J. R., . . . Miller, A. H. (2014). IFN-alpha-induced cortical and subcortical glutamate changes assessed by magnetic resonance spectroscopy. *Neuropsychopharmacology, 39*(7), 1777-1785. doi:10.1038/npp.2014.25

Harrison, N. A. (2017). Brain Structures Implicated in Inflammation-Associated Depression. *Curr Top Behav Neurosci, 31*, 221-248. doi:10.1007/7854_2016_30

Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*: Guilford Publications.

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. doi:10.1016/j.jad.2011.10.002

Hiles, S. A., Baker, A. L., de Malmanche, T., & Attia, J. (2012). A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. *Brain Behav Immun, 26*(7), 1180-1188. doi:10.1016/j.bbi.2012.06.001

Holmes, C., Cunningham, C., Zotova, E., Woolford, J., Dean, C., Kerr, S., . . . Perry, V. H. (2009). Systemic inflammation and disease progression in Alzheimer disease. *Neurology, 73*(10), 768-774. doi:10.1212/WNL.0b013e3181b6bb95

Holmes, S. E., Hinz, R., Conen, S., Gregory, C. J., Matthews, J. C., Anton-Rodriguez, J. M., . . . 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. doi:10.1016/j.biopsych.2017.08.005

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. doi:10.1207/s15326942dn2802_4

Hostinar, C. E., Nusslock, R., & Miller, G. E. (2017). Future Directions in the Study of Early-Life Stress and Physical and Emotional Health: Implications of the Neuroimmune Network Hypothesis. *J Clin Child Adolesc Psychol*, 1-15. doi:10.1080/15374416.2016.1266647

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med, 71*(2), 171-186. doi:10.1097/PSY.0b013e3181907c1b

Huang, Y. S., Guilleminault, C., Hwang, F. M., Cheng, C., Lin, C. H., Li, H. Y., & Lee, L. A. (2016). Inflammatory cytokines in pediatric obstructive sleep apnea. *Medicine (Baltimore), 95*(41), e4944. doi:10.1097/MD.0000000000004944

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. doi:10.1016/j.neuropsychologia.2006.01.010

Johnsen, E., Fathian, F., Kroken, R. A., Steen, V. M., Jorgensen, H. A., Gjestad, R., & Loberg, E. M. (2016). The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis. *BMC Psychiatry, 16*, 60. doi:10.1186/s12888-016-0769-x

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. doi:10.1002/gps.1772

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. doi:10.1089/cap.2008.064

Kassel, M. T., Rao, J. A., Walker, S. J., Briceno, E. M., Gabriel, L. B., Weldon, A. L., . . . Langenecker, S. A. (2016). Decreased Fronto-Limbic Activation and Disrupted Semantic-Cued List Learning in Major Depressive Disorder. *J Int Neuropsychol Soc, 22*(4), 412-425. doi:10.1017/S1355617716000023

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . 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. doi:10.1097/00004583-199707000-00021

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. doi:10.1080/21622965.2013.789964

Kempuraj, D., Thangavel, R., Selvakumar, G. P., Zaheer, S., Ahmed, M. E., Raikwar, S. P., . . . Zaheer, A. (2017). Brain and Peripheral Atypical Inflammatory Mediators Potentiate Neuroinflammation and Neurodegeneration. *Front Cell Neurosci, 11*, 216. doi:10.3389/fncel.2017.00216

Khandaker, G. M., Pearson, R. M., Zammit, S., Lewis, G., & Jones, P. B. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA Psychiatry, 71*(10), 1121-1128. doi:10.1001/jamapsychiatry.2014.1332

Khandaker, G. M., Stochl, J., Zammit, S., Goodyer, I., Lewis, G., & Jones, P. B. (2017). Childhood inflammatory markers and intelligence as predictors of subsequent persistent depressive symptoms: a longitudinal cohort study. *Psychol Med*, 1-12. doi:10.1017/S0033291717003038

Kim, J. S., Jin, M. J., Jung, W., Hahn, S. W., & Lee, S. H. (2017). Rumination as a Mediator between Childhood Trauma and Adulthood Depression/Anxiety

in Non-clinical Participants. *Front Psychol, 8*, 1597. doi:10.3389/fpsyg.2017.01597
Klein, D. N., Shankman, S. A., Lewinsohn, P. M., & Seeley, J. R. (2009). Subthreshold depressive disorder in adolescents: predictors of escalation to full-syndrome depressive disorders. *J Am Acad Child Adolesc Psychiatry, 48*(7), 703-710. doi:10.1097/CHI.0b013e3181a56606
Kohler, C. A., Freitas, T. H., Maes, M., de Andrade, N. Q., Liu, C. S., Fernandes, B. S., . . . Carvalho, A. F. (2017). Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand, 135*(5), 373-387. doi:10.1111/acps.12698
Kohler, C. A., Freitas, T. H., Stubbs, B., Maes, M., Solmi, M., Veronese, N., . . . Carvalho, A. F. (2017). Peripheral Alterations in Cytokine and Chemokine Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic Review and Meta-Analysis. *Mol Neurobiol*. doi:10.1007/s12035-017-0632-1
Konsman, J. P., Parnet, P., & Dantzer, R. (2002). Cytokine-induced sickness behaviour: mechanisms and implications. *Trends Neurosci, 25*(3), 154-159.
Krishnan, V., & Nestler, E. J. (2010). Linking molecules to mood: new insight into the biology of depression. *Am J Psychiatry, 167*(11), 1305-1320. doi:10.1176/appi.ajp.2009.10030434
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. doi:10.1016/j.bbi.2013.08.014
Langenecker, S. A., Saunders, E. F., Kade, A. M., Ransom, M. T., & McInnis, M. G. (2010). Intermediate: cognitive phenotypes in bipolar disorder. *J Affect Disord, 122*(3), 285-293. doi:10.1016/j.jad.2009.08.018
Langenecker, S. A., Zubieta, J. K., Young, E. A., Akil, H., & Nielson, K. A. (2007). A task to manipulate attentional load, set-shifting, and inhibitory control: convergent validity and test-retest reliability of the Parametric Go/No-Go Test. *J Clin Exp Neuropsychol, 29*(8), 842-853. doi:10.1080/13803390601147611
Lewinsohn, P. M., Klein, D. N., & Seeley, J. R. (1995). Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry, 34*(4), 454-463.
Lewinsohn, P. M., Rohde, P., & Seeley, J. R. (1998). Treatment of adolescent depression: frequency of services and impact on functioning in young adulthood. *Depress Anxiety, 7*(1), 47-52.
Li, X., Robertson, C. M., Yu, X., Cheypesh, A., Dinu, I. A., & Li, J. (2014). Early postoperative systemic inflammatory response is an important determinant for adverse 2-year neurodevelopment-associated outcomes after the Norwood procedure. *J Thorac Cardiovasc Surg, 148*(1), 202-206. doi:10.1016/j.jtcvs.2013.07.079

Licinio, J., Kling, M. A., & Hauser, P. (1998). Cytokines and brain function: relevance to interferon-alpha-induced mood and cognitive changes. *Semin Oncol, 25*(1 Suppl 1), 30-38.
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. doi:10.1203/00006450-199708000-00018
Lipari, R. N., Hughes, A., & Williams, M. (2013). State Estimates of Major Depressive Episode among Adolescents: 2013 and 2014 *The CBHSQ Report* (pp. 1-7). Rockville (MD).
Liu, R. T., & Alloy, L. B. (2010). Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. *Clin Psychol Rev, 30*(5), 582-593. doi:10.1016/j.cpr.2010.04.010
Lopresti, A. L., & Drummond, P. D. (2013). Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. *Prog Neuropsychopharmacol Biol Psychiatry, 45*, 92-99. doi:10.1016/j.pnpbp.2013.05.005
Loring, D. W., Martin, R. C., Meador, K. J., & Lee, G. P. (1990). Psychometric construction of the Rey-Osterrieth complex figure: Methodological considerations and interrater reliability. *Archives of Clinical Neuropsychology, 5*(1), 1-14.
Lotrich, F. E., Ferrell, R. E., Rabinovitz, M., & Pollock, B. G. (2009). Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. *Biol Psychiatry, 65*(4), 344-348. doi:10.1016/j.biopsych.2008.08.009
Lotrich, F. E., Rabinovitz, M., Gironda, P., & Pollock, B. G. (2007). Depression following pegylated interferon-alpha: characteristics and vulnerability. *J Psychosom Res, 63*(2), 131-135. doi:10.1016/j.jpsychores.2007.05.013
Lu, S., Peng, H., Wang, L., Vasish, S., Zhang, Y., Gao, W., . . . Li, L. (2013). Elevated specific peripheral cytokines found in major depressive disorder patients with childhood trauma exposure: a cytokine antibody array analysis. *Compr Psychiatry, 54*(7), 953-961. doi:10.1016/j.comppsych.2013.03.026
Luyten, P., & Fonagy, P. (2017). The stress-reward-mentalizing model of depression: An integrative developmental cascade approach to child and adolescent depressive disorder based on the research domain criteria (RDoC) approach. *Clin Psychol Rev*. doi:10.1016/j.cpr.2017.09.008
Malarbi, S., Abu-Rayya, H. M., Muscara, F., & Stargatt, R. (2017). Neuropsychological functioning of childhood trauma and post-traumatic stress disorder: A meta-analysis. *Neurosci Biobehav Rev, 72*, 68-86. doi:10.1016/j.neubiorev.2016.11.004
McAfoose, J., & Baune, B. T. (2009). Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev, 33*(3), 355-366. doi:10.1016/j.neubiorev.2008.10.005
Meier, T. B., Drevets, W. C., Wurfel, B. E., Ford, B. N., Morris, H. M., Victor, T. A., . . . 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. doi:10.1016/j.bbi.2015.11.003
Micoulaud-Franchi, J. A., Faugere, M., Boyer, L., Fond, G., Richieri, R., Faget, C., . . . Lancon, C. (2015). Elevated C-reactive protein is associated with sensory gating deficit in schizophrenia. *Schizophr Res, 165*(1), 94-96. doi:10.1016/j.schres.2015.03.018
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. doi:10.1038/nri.2015.5
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. doi:10.1016/j.biopsych.2012.02.034
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. doi:10.1016/j.jaac.2013.11.013
Mojtabai, R., Olfson, M., & Han, B. (2016). National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults. *Pediatrics, 138*(6). doi:10.1542/peds.2016-1878
Mosley, R. L. (2015). Adaptive Immunity in Neurodegenerative and Neuropsychological Disorders. *J Neuroimmune Pharmacol, 10*(4), 522-527. doi:10.1007/s11481-015-9640-y
Muscatell, K. A., Dedovic, K., Slavich, G. M., Jarcho, M. R., Breen, E. C., Bower, J. E., . . . 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. doi:10.1016/j.bbi.2014.06.201
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, 40*(2), 266-280. doi:10.1080/15374416.2011.546049
Nikulina, V., & Widom, C. S. (2013). Child maltreatment and executive functioning in middle adulthood: a prospective examination. *Neuropsychology, 27*(4), 417-427. doi:10.1037/a0032811
O'Shea, T. M., Shah, B., Allred, E. N., Fichorova, R. N., Kuban, K. C., Dammann, O., . . . Investigators, E. S. (2013). Inflammation-initiating illnesses, inflammation-related proteins, and cognitive impairment in extremely preterm infants. *Brain Behav Immun, 29*, 104-112. doi:10.1016/j.bbi.2012.12.012
Pandey, G. N., Rizavi, H. S., Ren, X., Fareed, J., Hoppensteadt, D. A., Roberts, R. C., . . . Dwivedi, Y. (2012). Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res, 46*(1), 57-63. doi:10.1016/j.jpsychires.2011.08.006
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. doi:10.1016/j.biopsych.2006.03.027

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. doi:10.1097/CHI.0b013e318196b907

Peters, A. T., Jacobs, R. H., Crane, N. A., Ryan, K. A., Weisenbach, S. L., Ajilore, O., . . . Langenecker, S. A. (2017). Domain-specific impairment in cognitive control among remitted youth with a history of major depression. *Early Interv Psychiatry, 11*(5), 383-392. doi:10.1111/eip.12253

Peters, A. T., Peckham, A. D., Stange, J. P., Sylvia, L. G., Hansen, N. S., Salcedo, S., . . . Deckersbach, T. (2014). Correlates of real world executive dysfunction in bipolar I disorder. *J Psychiatr Res, 53*, 87-93. doi:10.1016/j.jpsychires.2014.02.018

Popa, C., Netea, M. G., van Riel, P. L., van der Meer, J. W., & Stalenhoef, A. F. (2007). The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res, 48*(4), 751-762. doi:10.1194/jlr.R600021-JLR200

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.

Raison, C. L., Demetrashvili, M., Capuron, L., & Miller, A. H. (2005). Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs, 19*(2), 105-123.

Raison, C. L., & Miller, A. H. (2011). Is depression an inflammatory disorder? *Curr Psychiatry Rep, 13*(6), 467-475. doi:10.1007/s11920-011-0232-0

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, 42*(1), 5-27. doi:10.1038/npp.2016.194

Rose, J., Vassar, R., Cahill-Rowley, K., Hintz, S. R., & Stevenson, D. K. (2016). Neonatal Biomarkers of Inflammation: Correlates of Early Neurodevelopment and Gait in Very-Low-Birth-Weight Preterm Children. *Am J Perinatol, 33*(1), 71-78. doi:10.1055/s-0035-1557106

Ryan, K. A., Vederman, A. C., McFadden, E. M., Weldon, A. L., Kamali, M., Langenecker, S. A., & McInnis, M. G. (2012). Differential executive functioning performance by phase of bipolar disorder. *Bipolar Disord, 14*(5), 527-536. doi:10.1111/j.1399-5618.2012.01032.x

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. doi:10.1017/S0033291716002403

Savitz, J., Dantzer, R., Meier, T. B., Wurfel, B. E., Victor, T. A., McIntosh, S. A., . . . Drevets, W. C. (2015). Activation of the kynurenine pathway is

associated with striatal volume in major depressive disorder. *Psychoneuroendocrinology, 62*, 54-58. doi:10.1016/j.psyneuen.2015.07.609

Schallmo, M. P., Kassel, M. T., Weisenbach, S. L., Walker, S. J., Guidotti-Breting, L. M., Rao, J. A., . . . Langenecker, S. A. (2015). A new semantic list learning task to probe functioning of the Papez circuit. *J Clin Exp Neuropsychol, 37*(8), 816-833. doi:10.1080/13803395.2015.1052732

Schildkraut, J. J. (1995). The catecholamine hypothesis of affective disorders: a review of supporting evidence. 1965. *J Neuropsychiatry Clin Neurosci, 7*(4), 524-533; discussion 523-524.

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 Psychiatry, 40*(11), 1228-1231.

Shapira-Lichter, I., Beilin, B., Ofek, K., Bessler, H., Gruberger, M., Shavit, Y., . . . Yirmiya, R. (2008). Cytokines and cholinergic signals co-modulate surgical stress-induced changes in mood and memory. *Brain Behav Immun, 22*(3), 388-398. doi:10.1016/j.bbi.2007.09.006

Smagula, S. F., Lotrich, F. E., Aizenstein, H. J., Diniz, B. S., Krystek, J., Wu, G. 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. doi:10.1002/gps.4512

Strawbridge, R., Arnone, D., Danese, A., Papadopoulos, A., Herane Vives, A., & Cleare, A. J. (2015). Inflammation and clinical response to treatment in depression: A meta-analysis. *Eur Neuropsychopharmacol, 25*(10), 1532-1543. doi:10.1016/j.euroneuro.2015.06.007

Thapar, A., Collishaw, S., Pine, D. S., & Thapar, A. K. (2012). Depression in adolescence. *Lancet, 379*(9820), 1056-1067. doi:10.1016/S0140-6736(11)60871-4

Tiffin, J., & Asher, E. J. (1948). The Purdue Pegboard: Norms and studies of reliability and validity. *Journal of applied psychology, 32*(3), 234.

Treadway, M. T., Admon, R., Arulpragasam, A. R., Mehta, M., Douglas, S., Vitaliano, G., . . . 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. doi:10.1016/j.biopsych.2017.02.1183

Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord, 150*(3), 736-744. doi:10.1016/j.jad.2013.06.004

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. doi:10.1016/j.bbi.2016.10.019

Verbruggen, F., & Logan, G. D. (2008). Automatic and controlled response inhibition: associative learning in the go/no-go and stop-signal paradigms. *J Exp Psychol Gen, 137*(4), 649-672. doi:10.1037/a0013170

Wager-Smith, K., & Markou, A. (2011). Depression: a repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition? *Neurosci Biobehav Rev, 35*(3), 742-764. doi:10.1016/j.neubiorev.2010.09.010

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. *Eur Child Adolesc Psychiatry*. doi:10.1007/s00787-014-0559-2

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. doi:10.1007/s00787-014-0559-2

Wang, A. K., & Miller, B. J. (2017). Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression. *Schizophr Bull*. doi:10.1093/schbul/sbx035

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., Kassel, M. T., Rao, J., Weldon, A. L., Avery, E. T., Briceno, E. M., . . . Langenecker, S. A. (2014). Differential prefrontal and subcortical circuitry engagement during encoding of semantically related words in patients with late-life depression. *Int J Geriatr Psychiatry, 29*(11), 1104-1115. doi:10.1002/gps.4165

Weisenbach, S. L., Marshall, D., Weldon, A. L., Ryan, K. A., Vederman, A. C., Kamali, M., . . . 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. doi:10.1002/gps.4084

Widom, C. S., DuMont, K., & Czaja, S. J. (2007). A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. *Arch Gen Psychiatry, 64*(1), 49-56. doi:10.1001/archpsyc.64.1.49

Wiedlocha, M., Marcinowicz, P., Krupa, R., Janoska-Jazdzik, M., Janus, M., Debowska, W., . . . Szulc, A. (2018). Effect of antidepressant treatment on peripheral inflammation markers - A meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry, 80*(Pt C), 217-226. doi:10.1016/j.pnpbp.2017.04.026

Wilson, C. J., Finch, C. E., & Cohen, H. J. (2002). Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc, 50*(12), 2041-2056.

Windham, B. G., Simpson, B. N., Lirette, S., Bridges, J., Bielak, L., Peyser, P. A., . . . Mosley, T. H. (2014). Associations between inflammation and cognitive function in African Americans and European Americans. *J Am Geriatr Soc, 62*(12), 2303-2310. doi:10.1111/jgs.13165

Zarate, C. A., Jr., Singh, J., & Manji, H. K. (2006). Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry, 59*(11), 1006-1020. doi:10.1016/j.biopsych.2005.10.021

VITA
Amy Peters

EDUCATION

University of Illinois at Chicago (UIC) **Chicago, IL**

2017 – 2018 *Clinical Psychology Intern* in *Psychiatry*

2012 – 2018 *Clinical Psychology Doctoral Program*

- Masters of Arts, 2013
- Doctor of Philosophy, 2018

2006 – 2010 **Boston College** **Chestnut Hill, MA**

Bachelor of Arts, Psychology

- University & Departmental Honors

HONORS AND AWARDS

2017 Chair's Choice Travel Award, *Society for Biological Psychiatry*

2017 Leonard D. Eron Award for Outstanding Scholarly Accomplishment, *UIC Psychology Department*

2016 Outstanding Student Researcher Award, *Society for a Science of Clinical Psychology*

2016 Student Liaison Committee Student Research Award, *International Neuropsychological Society*

2016 Samuel Gershon Junior Investigator Award, *International Society for Bipolar Disorders*

2014 Early Career Investigator Travel Scholarship Award, *Society of Biological Psychiatry*

2013 Travel Award, *UIC Graduate Student Council*

2013 Travel Award, *UIC Psychology Department*

2013 Travel Award, *UIC College of Liberal Arts and Sciences*

2013 Travel Award, *UIC Graduate College*

GRANTS AND FELLOWSHIPS

2018 – **National Institute of Mental Health** T32 MH 112485-1

Post-doctoral Fellow $59,482 (direct costs)

"Translational Neuroscience Training for Clinicians"

Principal Investigator: Roffman

Role: Post-doctoral Fellow

2018 – 2020 **Cognitive Neuroscience Center, University of Illinois at Chicago**

Neuroimaging Pilot Grant $6,000 (scan costs)

"Brain and Behavioral Measures of Affect and Motivational Reactivity in Daughters and their Mothers"

Principal Investigator: Burkhouse

Role: Co-Investigator

2016 – 2017 **American Psychological Foundation**

Elizabeth Munsterburg Koppitz Child Psychology Graduate Fellowship $25,000

"Neurobiology of Adolescent Mood Disorders: Inflammation, Depression, and Neuropsychological Functioning"
Principal Investigator: Peters

2015 – 2018 **National Institute of Mental Health** F31 MH108258-01
Ruth L. Kirschstein National Research Service Award $129,360 (direct costs)
"Neurodevelopmental Perspective on Inflammation, Loss, and Neurocognition"
Principal Investigator: Peters

2014 – 2015 **National Institute of Mental Health** T32 MH067631
Pre-doctoral Fellow $25,282 (direct costs)
"Training in the Neuroscience of Mental Health"
Principal Investigator: Rasenick
Role: Pre-doctoral Fellow

2014 **University of Illinois at Chicago** $3,000 (research funds)
Provost Award for Graduate Research
"Inflammatory Markers in Late-Adolescent Remitted Depression: Association with Executive Functions and Cognitive Control"
Principal Investigator: Peters

2013 – 2015 **University of Illinois at Chicago**
Chancellor's Graduate Research Fellowship $8,000 (stipend)
"Stage Modeling Mood Disorders"
Principal Investigator: Peters

2009 **Boston College**
Senior Thesis Research Grant $3,000 (stipend)
"Directed Forgetting in the Context of Anxiety and Depression"
Principal Investigator: Peters

PEER-REVIEWED PUBLICATIONS (32 Total)

1. **Peters, A.T.,** Van Meter, A., Pruitt, P.J., Briceno, E.M., Ryan, K.A., Hagan, M., Weldon, A.L., Kassel, M.T., Vederman, A., Zubieta, J.K., McInnis, M., Weisenbach, S.L., & Langenecker, S.A. Differential fronto-limbic activation during semantically-cued list learning in mood disorders: A pilot study of neuroendocrine correlates. *Journal of Affective Disorders,* (In Press).

2. **Peters, A.T.,** Burkhouse, K., Kujawa, A., Afshar, K., Fitzgerald, K.D., Monk, C.S., Hajcak G., & Phan, K.L. Impact of pubertal timing and depression on error-related brain activity in anxious youth. *Developmental Psychobiology*, (In Press).

3. Gold, A.K, Peters, A.T., Otto, M.W., Sylvia, L.G., Magalhaes, P.V., Miklowitz, D.J., Frank, E., Berk, M., Dougherty, D.D., Nierenberg, A.A., & Deckersbach, T. The impact of substance use disorders on recovery from bipolar depression: Results from the STEP-BD psychosocial trial. *Australian and New Zealand Journal of Psychiatry* (In press).

4. Deckersbach, T., **Peters, A.T.,** Shea, C.V., Gosai, A.K., Stange, J.P., Peckham, A.D., Ellard, K.K., Otto, M.W., Rauch, S.L., Dougherty, D.D., & Nierenberg, A.A. Memory performance predicts response to psychotherapy for depression in bipolar disorder: A pilot randomized controlled trial with exploratory functional magnetic resonance imaging. *Journal of Affective Disorders,* (In Press).

5. Burkhouse, K., Stange, J.P., Jacobs, R.H., Bhaumik, R., Bessette, K.L., **Peters, A.T.,** Crane, N.A., Fitzgerald, K., Monk, C., Welsh, R.C., Phan, K.L., & Langenecker, S.A. Age-related changes in resting-state functional networks among individuals with and without internalizing psychopathologies. *Depression and Anxiety,* (In Press).

6. Weinstein, S.M., Cruz, R., Isaia, A., **Peters, A.T**., & West, A.E. Child- and Family-Focused Cognitive Behavioral Therapy for Pediatric Bipolar Disorder: Applications for suicide prevention. *Suicide and Life Threatening Behavior,* (In Press).

7. **Peters, A.T.,** Weinstein, S.M., Isaia, A., Van Meter, A., Zulauf, C.A., Henry, D.B, & West, A.E. Symptom dimensions and trajectories of functioning among bipolar youth: A cluster analysis. *Journal of Psychiatric Practice,* (In Press).

8. Stange, J.P., Bessette, K.L., Jenkins, L.M., Burkhouse, K.L., **Peters, A.T.,** Feldhaus, C., Crane, N.A., Ajilore, O., Jacobs, R.H., Watkins, E.R., & Langenecker, S.A. Attenuated intrinsic connectivity within the cognitive control network among individuals with remitted depression: Temporal stability and association with negative cognitive styles. *Human Brain Mapping,* (In Press).

9. Burkhouse, K., Jacobs, R.H., **Peters, A.T.,** Ajilore, O., & Langenecker, S.A. Neural correlates of rumination in adolescents with remitted major depressive disorder and healthy controls. *Cognitive, Affective, and Behavioral Neuroscience,* (In Press).

10. Jacobs, R.H., Watkins, E.R., **Peters, A.T.,** Feldhaus, C.G., Barba, A., Carbray, J., & Langenecker, S.A. Targeting ruminative thinking in adolescents at risk for depressive relapse: Rumination-focused cognitive behavior therapy in a pilot randomized controlled trial with resting state fMRI. *PLoS ONE,* (In Press).

11. **Peters, A.T.,** Van Meter, A., Pruitt, P.J., Briceno, E.M., Ryan, K.A., Hagan, M., Weldon, A.L., Kassel, M.T., Vederman, A., Zubieta, J.K., McInnis, M., Weisenbach, S.L., & Langenecker, S.A (2016). Acute cortisol reactivity attenuates engagement of fronto-parietal and striatal regions during emotion processing in negative mood disorders. *Psychoneuroendocrinology*, 73: 67-78.

12. Sylvia, L.G., Salcedo, S., **Peters, A.T.,** Magalhaes, P.V., Frank, E., Miklowitz, D., Otto, M.W., Berk, M., Nierenberg, A.A., & Deckersbach, T. Do sleep disturbances moderate response to psychotherapy in bipolar disorder? *Journal of Nervous and Mental Disease,* (In Press).

13. **Peters, A.T.**, Jacobs, R.H., Feldhaus, C., Dion, C., & Langenecker, S.A. (2016). Aberrant resting-state functional connectivity in limbic and cognitive control networks relates to depressive rumination and mindfulness: A pilot study among adolescents with a history of depression**.** *Journal of Affective Disorders,* 200: 178-81.

14. Deckersbach, T., **Peters, A.T.,** Sylvia, L.G., Gold, A. Magalhaes, P.V., Henry, D.B., Frank, E., Otto, M.W., Berk, M., Dougherty, D.D., Nierenberg, A.A., & Miklowitz, D.J. (2016). A cluster analytic approach to predictors and moderators of psychosocial treatment for bipolar depression. *Journal of Affective Disorders,* 203: 152-57.

15. **Peters, A.T.**, Shesler, L.W., Magalhaes, P.V., Frank, E., Miklowitz, D., Otto, M.W., Berk, M., Nierenberg, A.A., Sylvia, L.G, & Deckersbach, T. (2016). Medical burden, body mass index, and the outcome of psychosocial interventions for bipolar depression. *Australian and New Zealand Journal of Psychiatry,* 50(7): 667-77.

16. **Peters, A.T.,** Jacobs, R.H., Feldhaus, C., Henry, D.B., Silva, S.G., Langenecker, S.A., Albano, A.M., Reinecke, M.A., & Curry, J.F. (2016). Trajectories of functioning into emerging adulthood following treatment for adolescent depression. *Journal of Adolescent Health,* 58(3): 253-9.

17. **Peters, A.T.,** West, A.E., Eisner, L.R., Baek, J.H., & Deckersbach, T (2016). The burden of recurrent mood episodes in bipolar I disorder: Results from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), *Journal of Nervous and Mental Disease,* 204(2): 87-94.

18. **Peters, A.T.,** Shankman, S.A., Deckersbach, T. & West, A.E. (2015). Predictors of first episode major depression in individuals with and without sub-threshold symptoms: A prospective, population-based study. *Psychiatry Research*, 230(2):150-6.

19. **Peters, A.T.,** Jacobs, R.H., Crane, N.A., Lamar, M., Ryan, K.A., Weisenbach, S.L., Ajilore, O., Kassel, M.T., Gabriel, L.B., West, A.E., Zubieta, J., & Langenecker, S.A. (2015). Domain-specific impairment in cognitive control among remitted youth with a history of major depression. *Early Intervention in Psychiatry,* (In Press).

20. Weinstein, S.M., Henry, D., Katz, A.C., **Peters, A.T.,** & West, A.E. (2015). Treatment moderators of child and family focused cognitive behavioral therapy (CFF-CBT) for pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(2): 116-125.

21. Weinstein, S.M., Van Meter, A., Katz, A.C., **Peters, A.T.,** & West, A.E. (2015). Cognitive and family correlates of current suicidal ideation in children with bipolar disorder. *Journal of Affective Disorders,* 173: 15-21.

22. West, A.E., Weinstein, S.M., **Peters, A.T.,** Katz, A.C., Pavuluri, M., & Henry, D. (2014). A randomized controlled trial of child and family focused cognitive behavioral therapy (CFF-CBT) for pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 53(11): 1168-78.

23. Jacobs, R.H., Jenkins, L.M., Gabriel, L.B., Barba, A., Ryan, K.A., Weisenbach, S.L., Verges, A., Baker, A.M., **Peters, A.T.**, Crane, N.A., Gotlib, I.H., Zubieta, J., Phan, K.L., Langenecker, S.A., & Welsh, R.C. (2014). Increased coupling of intrinsic networks in remitted depressed youth predicts rumination and cognitive control. *PLoS ONE*, 9(8).

24. **Peters, A.T.**, Henry, D.B., & West, A.E. (2014). Caregiver characteristics and symptoms of pediatric bipolar disorder. *Journal of Child and Family Studies*, 24(5): 1469-1480.

25. **Peters, A.T.,** Sylvia, L.G., Magalhaes, P.V., Frank, E., Otto, M.W., Miklowitz, D., Dougherty, D., Berk, M., Nierenberg, A.A, & Deckersbach, T. (2014). Age of onset, course of illness and psychotherapy treatment outcome for bipolar disorder: Evidence from STEP-BD. *Psychological Medicine,* 44(16):3455-67.

26. **Peters, A.T.,** Peckham, A.D., Stange, J.P., Sylvia, L.G., Rauch, S.L., Nierenberg, A.A., Dougherty, D.D. & Deckersbach, T. (2014). Correlates of real world executive dysfunction in bipolar I disorder. *Journal of Psychiatric Research,* 53: 87- 93.
27. Deckersbach, T., **Peters, A.T.,** Sylvia, L.G., Urdahl, A., Magalhaes, P.V., Otto, M.W., Frank, E., Miklowitz, D., Berk, M., Kinrys, G., & Nierenberg, A.A (2014). Do co-morbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? Results from STEP-BD. *American Journal of Psychiatry, 171* (2): 178-86.

28. Sachs, G.S., **Peters, A.T.** Sylvia, L.G., & Grunze, H. (2014) Polypharmacy and bipolar disorder: What's personality got to do with it? *International Journal of Neuropsychoparmacology,* 17(7):1053-61.

29. Sylvia, L.G., **Peters, A.T.,** Deckersbach, T. & Nierenberg, A.A (2013). Nutrient-based therapies for bipolar disorder. A systematic review. *Psychotherapy & Psychosomatics, 82 (1); 10-9*

30. McMurrich, S., Sylvia, L.G., Dupuy, J.M., Peckham, A.D., **Peters, A.T,** & Perlis, RH. (2012). Course, outcomes, and psychosocial interventions for first-episode mania. *Bipolar Disorders, 14 (8); 797-808*

31. **Peters, A.T.** & Nierenberg, A.A. (2011). Stepping back to step forward: What lessons do we take from STEP-BD? *Journal of Clinical Psychiatry*, *72 (10):* 1-3

32. **Peters, A.T.,** Nierenberg, A.A., & Deckersbach, T. (2011). A 32-year-old male with mania, leg pain, migraines. *Psychiatric Annals, 41 (7):* 363-6

RESEARCH EXPERIENCE

2017 – **MOOD AND ANXIETY DISORDERS RESEARCH PROGRAM** **Chicago, IL**
Clinical Psychology Intern**,** UIC Department of Psychiatry
Supervisors: K. Luan Phan, M.D., Katie Burkhouse, Ph.D.

2013 – **COGNITIVE NEUROSCIENCE CENTER** **Chicago, IL**
Graduate Research Assistant**,** UIC Department of Psychiatry
Supervisors: Scott Langenecker, Ph.D., Ghanshyam Pandey, Ph.D., Rachel Jacobs, Ph.D.

2012 – 2016 **PEDIATRIC INTERVENTION RESEARCH IN MOOD DISORDERS** **Chicago, IL**
Graduate Research Assistant, UIC Institute for Juvenile Research

Supervisors: Amy E. West, Ph.D., Sally M. Weinstein, Ph.D.

2010 – 2012 BIPOLAR CLINIC AND RESEARCH PROGRAM Boston, MA
Clinical Research Coordinator, Massachusetts General Hospital Department of Psychiatry
Supervisors: Thilo Deckersbach, Ph.D., Louisa G. Sylvia, Ph.D., Andrew A. Nierenberg, M.D., Dan Iosifescu, M.D., Gary S. Sachs, M.D., Roy H. Perlis, M.D., M.Sc.

2008 – 2010 LAB FOR COGNITIVE AND AFFECTIVE NEUROSCIENCE Chestnut Hill, MA
Thesis Student/Research Assistant, Boston College Department of Psychology
Supervisor: Elizabeth Kensinger, Ph.D.

NEUROPSYCHOLOGICAL ASSESSMENT CLINICAL EXPERIENCE

2017 – ADULT NEUROPSYCHOLOGY SERVICE Chicago, IL
Clinical Neuropsychology Intern**,** UIC Neuropsychiatric Institute
Supervisors: Neil Pliskin, Ph.D. ABPP-CN, Woojin Song, Ph.D;, Jason Soble, Ph.D., ABPP-CN

2016 – 2017 LIFESPAN NEUROPSYCHOLOGY MOOD DISORDERS CLINIC Chicago, IL
Clinical Neuropsychology Extern**,** UIC Neuropsychiatric Institute
Supervisor*:* Scott Langenecker, Ph.D.
Didactic Instructor: Neil Pliskin, Ph.D., ABPP-CN

2015 - 2017 PEDIATRIC NEUROPSYCHOLOGICAL SERVICES Evanston, IL
Pyschometrician (2016 - 2017) & Clinical Neuropsychology Extern (2015 – 2016)**,** NorthShore University Health System/University of Chicago Pritzker School of Medicine
Supervisors: Elizabeth Heideman, Ph.D., ABPP-CN, Victoria Tuchscherer, Ph.D.

2012 – 2014 PRACTICUM IN PSYCHOLOGICAL ASSESSMENT Chicago, IL
Clinical Practicum Student, Office of Applied Psychological Services
Supervisors: Amanda Lorenz, Ph.D., Ellen Herbener, Ph.D.

2011 – 2012 PSYCHIATRIC NEUROSCIENCE/NEUROTHERAPEUTICS Charlestown, MA
Neuropsychological Technician, Massachusetts General Hospital Department of Psychiatry
Supervisors: Thilo Deckersbach, Ph.D., Darin Dougherty, M.D.

2010 – 2012 BIPOLAR CLINIC AND RESEARCH PROGRAM Boston, MA
Independent Evaluator, Massachusetts General Hospital Department of Psychiatry
Supervisor: Thilo Deckersbach, Ph.D.

CLINICAL INTAKES & PSYCHOTHERAPY EXPERIENCE

2014 – PEDIATRIC MOOD DISORDERS CLINIC Chicago, IL
Psychology Intern, *UIC Department of Psychiatry*
Psychology Extern, UIC Colbeth Clinic and Institute for Juvenile Research
Supervisors: Amy E. West, Ph.D., Sally M. Weinstein, Ph.D, Katie L. Burkhouse

2013 – **COGNITIVE NEUROSCIENCE CENTER** **Chicago, IL**
Independent Evaluator, UIC Department of Psychiatry
Supervisors: Rachel Jacobs, Ph.D., Scott Langenecker, Ph.D.

2012 – 2014 **PRACTICUM IN PSYCHOTHERAPY** **Chicago, IL**
Clinical Practicum Student, Office of Applied Psychological Services
Supervisors: Gloria Balague, Ph.D., Nancy Dassoff, Ph.D., & Amanda Lorenz, Ph.D.

2010 – 2012 **BIPOLAR CLINIC AND RESEARCH PROGRAM** **Boston, MA**
Dialectical Behavior Therapy Group Leader*,* Massachusetts General Hospital Department of Psychiatry
Supervisors: Thilo Deckersbach, Ph.D., Lori Eisner, Ph.D.

First-Episode Program Clinical Assistant, Massachusetts General Hospital
Supervisors: Roy Perlis, M.D. & Stephanie McMurrich, Ph.D.

Triage Coordinator, Massachusetts General Hospital Department of Psychiatry
Supervisors: Andrew Nierenberg, M.D., Thilo Deckersbach, Ph.D.

2009 – 2010 **OBSESSIVE COMPULSIVE DISORDERS INSTITUTE** **Belmont, MA**
Behavioral Coach, Mclean Hospital Department of Psychiatry
Supervisor: Szu-Hui Lee, Ph.D.

2007 **PSYCHOLOGICAL SEVICES CLINIC** **Storrs, CT**
Clinical Practicum Observation, University of Connecticut Department of Psychology
Supervisor: Marianne L. Barton, Ph.D.

RESEARCH TRAININGS

January 2015 **"fMRI Image Acquisition and Analyses Course** **Boulder, CO**
The Mind Research Network & University of Colorado at Boulder
Instructors: Kent Kiehl, Ph.D.; Vince Calhoun, Ph.D.; Tor Wager, Ph.D.

May 2014 "**Mixed Effects Regression for Longitudinal Data Analysis"** **Chicago, IL**
University of Illinois at Chicago
Instructor: Don Hedeker, Ph.D.

CLINICAL WORKSHOPS

June 2016 **"Mindfulness-Based Stress Reduction"** **Chicago, IL**
University of Illinois at Chicago
Instructor: Elana Rosenbaum, MS.W.

June 2014 **"Motivational Interviewing in Health Care**" **Chicago, IL**
University of Illinois at Chicago
Instructor: Kelly Walker Lowry, Ph.D.

TEACHING EXPERIENCE

2013, 2016 **UNIVERSITY OF ILLINOIS AT CHICAGO,** PSYCHOLOGY DEPT. **Chicago, IL**
Teaching Assistant*, Abnormal Psychology*
- Professor: Karina Reyes, Ph.D.

2008 – 2009 **BOSTON COLLEGE,** LYNCH SCHOOL OF EDUCATION **Chestnut Hill, MA**
- **Teaching Assistant***, First Year Experience Seminar*

PROFESSIONAL AFFILIATIONS

International Neuropsychological Society
American Academy of Clinical Neuropsychology
International Society for Bipolar Disorders
International Society for Affective Disorders
Society for a Science of Clinical Psychology
American Psychological Association,
Division 40, Clinical Neuropsychology
Division 53, Child and Adolescent Psychology
Association for Behavioral and Cognitive Therapies
Neurocognitive Therapies/Translational Research Special Interest Group
Bipolar Disorder Special Interest Group