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DEPRESSIVE SYMPTOMATOLOGY AND INFLAMMATORY CORRELATES

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by

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Abstract

To help understand the psychopathology of mental disorders, recent emphasis has been placed on disaggregating multidimensional constructs into multiple more homogenous constructs. In this context, breaking down depression into specific symptoms and exploring the various correlates (e.g., biological, clinical, psychosocial) of each symptom could provide insight into the underlying pathophysiology as well as potential targets for intervention. This concept is the overarching theme of the present dissertation, which consisted of two studies.

Study 1 examined the latent factors of symptoms using the depression Symptom Checklist (SCL-20) and the Patient Health Questionnaire **(**PHQ-9), in patients with comorbid depression and obesity. Exploratory factor analysis (EFA) was performed on baseline data from 409 patients recruited in primary care. Participants (mean age of 51.0 ± 12.1 years, 70% women) had moderate depression. EFA of the SCL-20 suggested two factors: negative affect (71% of the variance) and anhedonia (15% of the variance). EFA of the PHQ-9 yielded one factor: negative affect (87% of the variance). The most endorsed symptoms on both scales were feeling low energy, overeating and disturbed sleep. The present findings suggest that neurovegetative symptoms of depression may be more prevalent and/or severe compared to affective/cognitive symptoms in patients with comorbid obesity. Both scales capture the negative affect construct. However, the SCL-20 seems more sensitive than the PHQ-9 to capture other depression-related constructs (e.g., anhedonia). One possible reason includes the differences in number of scale items. More factors may have been identified if more indicators were included on the PHQ-9.

Study 2 aimed to measure depression-related constructs more accurately (i.e., by employing a battery of questionnaires and laboratory-based tasks) and to examine how these constructs relate to inflammatory markers in individuals with mild to severe depression. This study consisted of 68 young adults (mean age = 23.5 ± 5.7 years, 78% women). Approximately 55% of the subjects met DSM-5 criteria for a current major depressive episode. Participants underwent well-validated neurocognitive assessments. Blood plasma was quantified for basal inflammation. As expected, only a subset of individuals in our sample exhibited elevated inflammation as measured by C-reactive protein (CRP) (55%). Higher inflammation *was not* associated with higher severity of depression. However, higher levels of CRP (*beta* = .27, *p* = .03), IL-6 (*beta* = .28, *p* = .01) and IL-17 (*beta* = .29, *p* = .01) were significantly associated with worse response inhibition (i.e., higher error rates). In addition, higher CRP was associated with greater total fatigue (*beta* = .31, *p* = .02), general fatigue (*beta* = .31, *p* = .02), mental fatigue (beta = .32, *p* = .02), and reduced activity (*beta* = 27, *p* = .03). Moreover, higher IL-6 was associated with higher physical fatigue (*beta* = .30, *p* = .02), and higher IL-17 was significantly associated with slower motor speed as measured by the finger tapping test-two targets (non-dominant hand only) (*beta* = -.25, *p* = .04). In contrast to our expectation, higher levels of IL-17 were associated with faster psychomotor processing speed (as measured by the trail making test-A) (*beta* = -.27, *p* = .02) as well as higher pleasure (*beta* = .26, *p* = .03). There were no significant associations between CRP or cytokine levels and either episodic or working memory. Preliminary findings from this study suggest that an association exists between inflammation and specific symptoms of depression, including fatigue and low response inhibition.

In sum, the results of the current dissertation support the idea that depression is not a unidimensional construct and relying only on depression sum-scores may mask important information. Breaking down depression into specific symptoms can help elucidate the distinct neurobiological correlates of depressive symptoms and may help clinicians use more targeted treatment strategies that correspond to each clusters' underlying biological mechanisms.

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Adrenocorticotropic hormone (ACTH)
Anterior cingulate cortex (ACC)
Beck depression inventory (BDI)
Binge eating disorder (BED)
Blood Brain Barrier (BBB)
Body mass index (BMI)
Cambridge Neuropsychological Test Automated Battery (CANTAB)
Cerebrospinal fluid (CSF)
Confirmatory factor analyses (CFA)
Corticotropin releasing hormone (CRH)
C-reactive protein (CRP)
Damage/danger activated molecular patters (DAMPs)
Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)
Digit Symbol Test (DST)
Dopamine transporter (DAT)
Dorsolateral prefrontal cortex (DLPFC)
Excitatory amino acid transporters (EAATs)
Exploratory factor analysis (EFA)
Finger Tapping Test (FTT)
Functional magnetic resonance (fMRI)
Hamilton Depression Rating Scale (HAMD)
Hepatitis C virus (HCV)
Hypothalamus pituitary adrenal (HPA)
Indoleamine dioxygenase (IDO)
Interferon (IFN)
Interleukin (IL)
Inventory of Depressive Symptomatology-Self Report (IDS-SR)
Macrophage migratory inhibitory factor (MIF)
Magnetic resonance spectroscopy (MRS)
Major Depressive Disorder (MDD)
Mitogen activated protein kinase (MAPK)
Multidimensional fatigue inventory (MFI)
Non-steroidal anti-inflammatory agents (NSAIDs)
Pattern Comparison Processing (PCP)
Patient health questionnaire-9 (PHQ-9)
Phenylalanine (ph)
Phenylalanine hydroxylase (PAH)
Positron emission tomography (PET)
Research Aimed at Improving Both Mood and Weight (RAINBOW)
Snaith-Hamilton Pleasure Scale (SHAPS)
Sympathetic Nervous System (SNS)
Symptoms checklist-20 (SCL-20)
Temporal Experience of Pleasure Scale (TEPS)
Tetrahydrobiopterin (BH4)

Trail Making Test A (TMT-A)
Tyrosine (tyr)
Tyrosine hydroxylase (TH)
Vesicular monoamine transporter 2 (VMAT2)

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CHAPTER 1: Introduction

1.1 Major Depressive Disorder (MDD): a major public health concern

Unipolar depression is the leading cause of disability worldwide (Friedrich, 2017). In 2010, the economic burden of patients with major depressive disorder was estimated to be $210.5 billion in the United States. Importantly, comorbid conditions accounted for 62% of the financial burden (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). Depression is associated with a wide range of physical conditions, including metabolic syndrome, cardiovascular disease, rheumatoid arthritis, chronic pain, asthma and neurodegenerative disease (Slavich & Irwin, 2014). Comorbid depression is a predictor of worse treatment outcomes and increased mortality in patients suffering from physical conditions (Kessler, 2012). It has been suggested that depression exerts negative effects through various mechanisms, including neurohormonal and immunological alterations, poor health behaviors (e.g., decreases in physical health) and non-adherence to treatment (Kessler, 2012). With this information in mind, depression is acknowledged as a major public health concern.

1.2 Clinical presentation of MDD

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), major depressive disorder has been defined as the presence of five or more of the following symptoms for at least two consecutive weeks (American Psychiatric Association, 2013). One of the symptoms must be either depressed mood (almost every day), or loss of interest/anhedonia (almost every day). Other symptoms include: weight loss or weight gain (e.g., five percent or greater change in body weight in a month) or change in appetite (almost every day), insomnia or hypersomnia (almost every day), psychomotor agitation/retardation, fatigue or loss of energy (almost every day), worthlessness or inappropriate guilt (almost every day),

reduced ability to think or concentrate, and suicidal ideation, thoughts of death, or attempt to commit suicide. In general, these symptoms can be classified into three dimensions: 1) psychological symptoms, a broad concept that often includes core symptoms of depressed mood or anhedonia, as well as other symptoms of worthlessness, guilt, and suicidal thoughts, 2) cognitive symptoms (e.g., impaired ability to think or concentrate), and 3) neurovegetative symptoms (e.g., sleep problems, fatigue or loss of energy, changes in appetite).

1.3 Parsing the heterogeneity of depression

To help understand the psychopathology of mental disorders, recent emphasis has been placed on disaggregating multidimensional constructs (i.e., higher order) into multiple more homogenous constructs (i.e., lower order) (Smith et al., 2009). In the context of depression, breaking down depressive symptoms into more homogenous constructs and exploring the various correlates (e.g., biological, clinical, psychosocial) of each construct could provide insight into the underlying pathophysiology as well as potential targets for intervention. The heterogeneity of depressive symptoms in the context of underlying neurobiology and treatment response is discussed below.

1.3.1 Neural circuitry underlying symptoms of depression

Evidence suggests that altered function of multiple brain circuits mediate specific symptoms of depression. Depressed mood is associated with changes in functional activity of the medial prefrontal cortex including the subgenual (i.e., ventral) part of the anterior cingulate cortex (ACC) and orbitofrontal cortex (Stahl, Zhang, Damatarca, & Grady, 2003; Willner, Scheel-krüger, & Belzung, 2013). Increased activity in the subgenual ACC (sACC) has been shown in depressed patients (Gotlib et al., 2005). Inability to experience pleasure or anhedonia is associated with changes in functional activity of the mesolimbic dopaminergic pathway (which

begins in the ventral tegmental area and projects to the amygdala, hippocampus, and nucleus accumbens). Reduced dopamine release in the nucleus accumbens (i.e., ventral striatum) in response to reward has been shown to be associated with anhedonia in depressed patients (Willner et al., 2013). Anxiety has been linked to altered activity in the amygdala (Stahl, Zhang, et al., 2003; Willner et al., 2013). The amygdala plays a key role in emotional responses to aversive stimuli and fear conditioning (Willner et al., 2013). Compared to controls, depressed patients showed increased amygdala activity when exposed to aversive stimuli (Willner et al., 2013). Feelings of guilt, worthlessness and suicidal ideation might be related to the mesolimbic pathway, the amygdala, and the anterior cingulate cortex (Stahl, Zhang, et al., 2003).

Cognitive dysfunction, including concentration, planning, problem-solving and indecisiveness, is linked with hypoactivity in the dorsal part of the ACC and the dorsolateral prefrontal cortex (DLPFC) in depressed patients (Stahl, Zhang, et al., 2003; Willner et al., 2013). In addition, given that experiencing mental fatigue among depressed patients might be related to apathy, decreased motivation, and cognitive impairment, it has been suggested that reduced DLPFC activity plays a role in mental fatigue symptoms (Stahl, Zhang, et al., 2003).

Physical fatigue and psychomotor retardation observed in depression have been linked to altered activity of brain regions controlling motor function including the striatum (which receives serotonergic and dopaminergic projections) and the cerebellum (which receives noradrenergic projections) (Stahl, Zhang, et al., 2003). Indeed, depressed patients have shown reduced dopamine activity in the caudate nucleus (i.e., dorsal striatum) (Willner et al., 2013). Loss of appetite and weight loss are parts of the vegetative functions of the brain which are controlled by the hypothalamus (Hall, 2016). It has been suggested that the hypothalamus regulates appetite and weight through serotonergic and noradrenergic pathways (Stahl, Zhang, et al., 2003).

According to these findings, not only is depression a heterogeneous disorder by its symptomatology, but also in terms of its underlying neurophysiology. Thus, identifying a panel of biomarkers (such as inflammatory markers, neuroendocrine markers, or neurotransmitters) might be needed to unravel the complex neurobiology underlying symptoms of depression.

1.3.2 Response to antidepressants and symptoms of depression

Because all current antidepressants have comparable efficacy, other factors need to be considered in selecting an appropriate medication, including age, history of prior treatment response, comorbid medical/psychiatric conditions, adverse effect profiles, and concurrent medication use (Koda-Kimble et al., 2012). Interestingly, Zimmerman et al. (2004) found that the presence of specific clinical symptoms was the most common factor that influenced psychiatrists' choice of antidepressant. For example, depressed patients who had symptoms of fatigue/low energy despite taking citalopram (a selective serotonin reuptake inhibitor [SSRI]) were more likely to benefit from augmentation with bupropion (a norepinephrine dopamine reuptake inhibitor) than buspirone (a partial $5HT_{1A}$ agonist) following 14 weeks for treatment (Gaynes et al., 2011). This finding could be explained by distinct pharmacological actions of these two medications; bupropion has activating effects on the central nervous system through enhancing dopamine and norepinephrine levels, whereas buspirone exerts anxiolytic effects by increasing serotonin neurotransmission (Katzung et al., 2012). Given that serotonergic, dopaminergic and noradrenergic pathways are all involved in the regulation of fatigue/energy (Stahl, Zhang, et al., 2003), and that bupropion increases both dopamine and norepinephrine concentrations, it is plausible that add-on treatment with bupropion is more likely to alleviate symptoms of fatigue/energy than buspirone.

Similarly, another study revealed differential efficacy of escitalopram (i.e., selective serotonin reuptake inhibitor) and nortriptyline (i.e., tricyclic antidepressant) on symptom dimensions of depression after 12 weeks of therapy (Uher et al., 2009). Escitalopram was more effective than nortriptyline in improving mood dimension (i.e., depressed mood, psychomotor retardation, anxiety and activity), and cognitive dimension (i.e., guilt, self-dissatisfaction, pessimism, suicidal ideations). In contrast, nortriptyline was more effective than escitalopram in improving neurovegetative symptoms (i.e., impaired sleep, decreased appetite, weight loss and lack of sexual interest). Improvement in mood and cognitive symptoms by an antidepressant that increases serotonin neurotransmission, as well as improvement in neurovegetative symptoms by an antidepressant that increases both serotonin and norepinephrine neurotransmission, further supports the notion that distinct pathophysiology might mediate these symptom dimensions of depression. It is important to note that these differential associations were not evident in relation to total depression score.

Taken together, breaking down depression into different constructs may elucidate the distinct neurobiological correlates of depressive symptoms and may help clinicians use more targeted treatment strategies that correspond to each clusters' underlying biological mechanisms (Stahl, 2003). This may be of critical importance by informing future work on designing more effective and individualized treatments.

1.4 Depression and obesity

The presentation of depression varies greatly across patients. Clinical, behavioral and sociodemographic factors, including weight status, help account for such variation. For example, higher BMI was associated with higher neurovegetative/somatic symptoms of depression (Udo et al., 2015). As previously noted, depression is often comorbid with other physical health

conditions. Obesity is one physical health condition which has been widely studied in relation to depression. In spite of the high comorbidity of depression with obesity, little research has focused on the effect of obesity on symptom profiles of depression. Indeed, understanding the structure of depression in the context of obesity might help identify those constructs that are more prototypical to the concept of depression in this population. This information may have important implications by providing insight into symptoms that could be selectively targeted by treatment.

1.5 Depression and inflammation

Although elevated levels of inflammatory biomarkers have been well-documented in patients with major depressive disorder (meta-analyses by Dowlati et al., 2010; Hiles et al., 2012; Howren et al., 2009; Liu, Ho, & Mak, 2012), significant variability has been found across these studies (Dowlati et al., 2010; Howren et al., 2009). One source of variability might be that depression is a heterogeneous disorder in terms of symptomatology and pathophysiology (Slavich & Irwin, 2014). Most of the studies relating depression to inflammation in medically healthy subjects have examined depression as a broad syndrome and have not assessed whether such associations are symptom-specific. Multiple assessment tools are being used in clinical practice and research settings to assess depressive symptoms including both observer-rated assessments (such as the Hamilton Depression Rating Scale) and patient-rated assessments (such as the Beck Depression Inventory). In the majority of studies relating specific symptoms of depression to inflammation, assessment of the underlying constructs of depression was limited to one or two questions, which could underrepresent each measured construct. This is particularly important in terms of cognitive symptoms of depression given that depression has been linked to

impairment in multiple cognitive domains, many of which are not captured by one or two questions.

Examining the associations between specific depressive symptoms and inflammatory markers may provide valuable information beyond what can be learned from only focusing on total depression scores. This approach would have implications for treatment by providing information that may inform clinicians to use neurobiologically based treatment strategies and select medications that target each symptom in the context of underlying mechanisms.

1.6 The present dissertation

The present dissertation consists of two studies. The aims of these studies are as follows: Given that the presentation of depression varies greatly across patients and little research has focused on the relationship between obesity and symptoms of depression, ***Study 1*** which is presented in chapter 2 aimed to examine the factor structure of depressive symptomatology using exploratory factor analysis in a sample of patients with comorbid depression and obesity. This aim was achieved by conducting a series of secondary data analyses collected in the RAINBOW (Research Aimed at Improving Both Mood and Weight) study. The RAINBOW is a 2-arm randomized controlled trial that employed an integrated, collaborative care model to treat adults with comorbid obesity and depression in primary care. This research will expand the existing literature by identifying those constructs that are more prototypical to the concept of depression in the context of obesity.

Given that investigating inflammatory correlates of depression has been an extensive area of research in recent years, and less attention has been given to dimensional constructs in such associations, ***Study 2*** which is presented in chapter 3 aimed to measure depression-related constructs more accurately (i.e., by employing a battery of questionnaires and laboratory-based

tasks) and to examine how these constructs relate to inflammatory markers in individuals with mild to severe depression. These aims were achieved by conducting a cross-sectional study to: 1) assess multiple constructs within depression by employing a battery of questionnaires and laboratory-based tasks, and 2) quantify inflammatory biomarkers in blood. This research can expand our understanding of the inflammatory correlates of depressive symptoms which could eventually help unravel the complex pathophysiology of depression. The theoretical model for Study 2 aims is shown below:

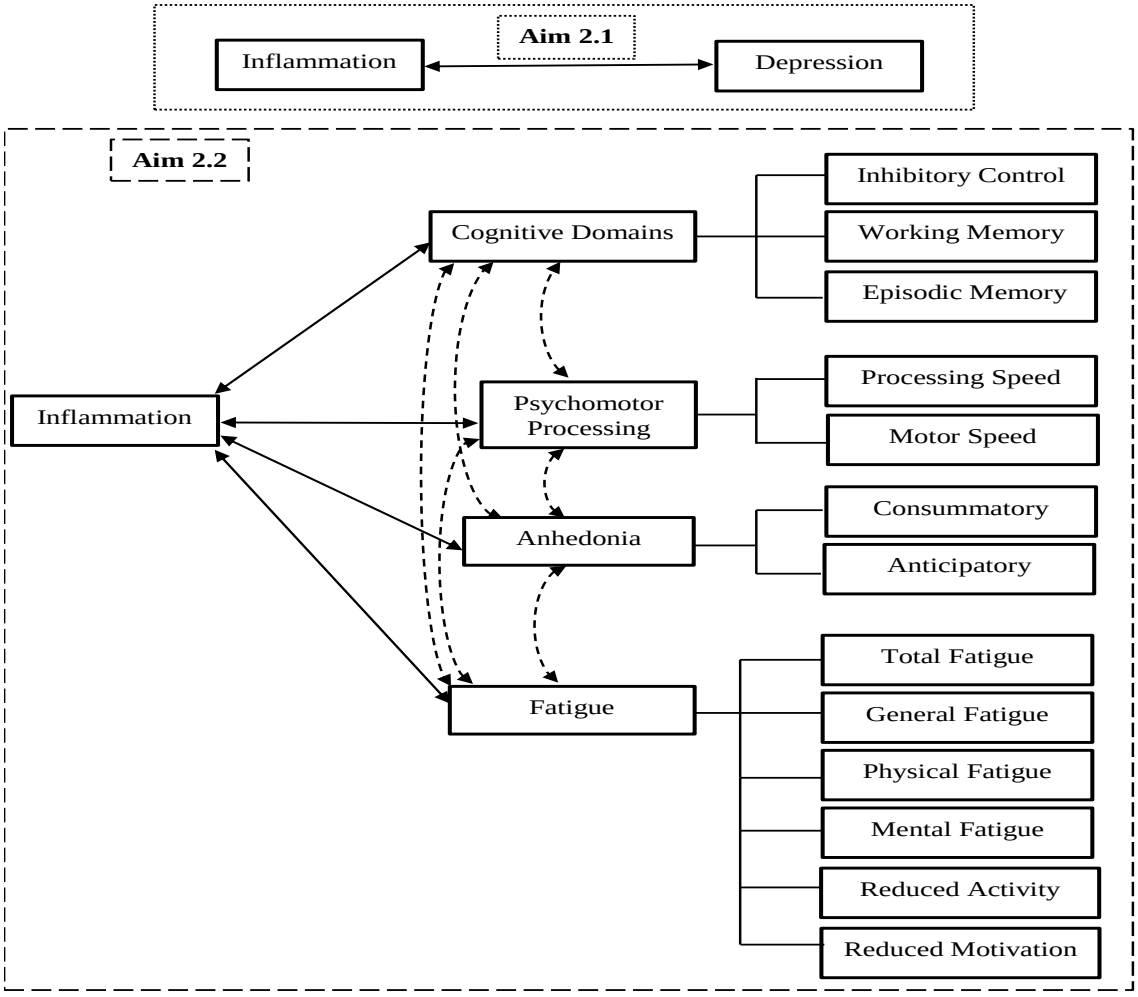

Figure 1. Theoretical model of study 2 aims

References-Chapter 1

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CHAPTER 2: The factor structure of depressive symptoms in patients with comorbid depression and obesity enrolled in the RAINBOW clinical trial

1. Introduction-Study 1

Unipolar depression is predicted to be the number one leading cause of burden of disease globally by 2030 (World Health Organization, 2008). A wide range of physical conditions are associated with depression, including metabolic syndrome, cardiovascular disease, rheumatoid arthritis, chronic pain, and neurodegenerative disease (Slavich & Irwin, 2014). Obesity, defined as a body mass index (BMI) $\geq$30 kg/m^2, often coexists with depression. Indeed, a bidirectional association between depression and obesity has been noted (Luppino et al., 2010). The prevalence of obesity among adults with depression was reported at 53% in 2005-2010 (Pratt and Brody, 2014). In addition, individuals with obesity (BMI $\geq$30 kg/m^2) had a higher lifetime prevalence of major depressive disorder (MDD) than normal weight individuals (Petry et al., 2008).

Commonly used terms in clinical practice, including depression, often reflect a combination of constructs, rather than a single construct (Smith et al., 2009). Based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria, MDD is defined by a constellation of signs and symptoms including affective (e.g., depressed mood), cognitive (e.g., concentration difficulty), and neurovegetative symptoms (e.g., fatigue) (American Psychiatric Association, 2013). Importantly, these constructs may differ in their underlying etiology, prognoses, and medical comorbidities as well as in responsiveness to treatment (Vares, Abrah, & Spanemberg, 2015). Therefore, there has been a call to identify more homogenous constructs within depressive symptomatology rather than only relying on a single score of a multidimensional construct given that the former may provide insight into the

underlying neurobiology as well as inform diagnoses and treatment decisions (Smith et al., 2009).

Importantly, the presentation of depression varies greatly across patients. Clinical, behavioral, and sociodemographic factors, including weight status, help account for such variation. For example, higher BMI was associated with higher neurovegetative/somatic symptoms of depression (Udo et al., 2015). Consistently, patients seeking bariatric surgery reported higher somatic symptoms of depression relative to affective/cognitive symptoms (Munoz et al., 2007). Given that obesity and depression share symptoms (such as fatigue, changes in appetite, low self-esteem), the clinical presentation of depression in patients with comorbid obesity might be different from those without obesity both in terms of severity and the characteristics of depression they experience. In spite of the high comorbidity of depression with obesity, little research has focused on the effect of obesity on symptom profiles of depression. Indeed, understanding the structure of depression in the context of obesity might help identify those constructs that are more prototypical to the concept of depression in patients with comorbid depression and obesity.

Given that a single scale is typically comprised of limited items which cannot accurately assess all dimensions of depression, extensive item pools are needed to capture all components of depressive symptoms (Shafer, 2006). However, there is value in exploring the factor structure of existing depression scales because it will add to our understanding of the components of depression that are being measured by each scale. Research findings regarding the underlying constructs or factor structures of commonly used depression scales vary by setting and population.

The depression Symptom Checklist (SCL-20) has been used in different medical settings, including patients with obesity, chronic illness, epilepsy, and primary care patients (Chaytor et al., 2011; Ciechanowski et al., 2010; Katon et al., 1996; Katon et al., 2010; Linde et al., 2011; Simon et al., 2000). In spite of its widespread use, however, evidence regarding the factor structure of the SCL-20 is scarce. The underlying structure of the Patient Health Questionnaire (PHQ-9) has been explored in broader populations, including patients with cardiovascular disease (de Jonge et al., 2009), spinal cord injury (Kalpakjian et al., 2009; Krause et al., 2008, 2010, 2011; Richardson & Richards, 2008), persistent major depressive disorder (Guo et al., 2017), substance abuse (Dum, Pickren, Sobell, & Sobell, 2008), and primary care patients (Baas et al., 2011; Cameron et al., 2008; Elhai et al., 2012; Huang et al., 2006; Petersen et al., 2015). The majority of these studies supported a 2-factor model (de Jonge et al., 2007; Elhai et al., 2012; Guo et al., 2017; Kalpakjian et al., 2009; Krause et al., 2008, 2010, 2011; Richardson & Richards, 2008; Petersen et al., 2015); the two factors that emerged included "somatic" items (e.g., appetite changes, sleep disturbance) and "non-somatic" items (e.g., loss of interest, depressed mood). In contrast, however, a few studies yielded a 1-factor structure (Baas et al., 2011; Cameron et al., 2008; Dum et al., 2008; Huang et al., 2006), indicating a unidimensional construct of depression. Although the 2-factor structure of the PHQ-9 was relatively prevalent and consistent across studies, there have been inconsistencies in terms of items that load on each factor. These inconsistencies could be explained in part by differences in study sample. Although both the SCL-20 and PHQ-9 have been used in a population of individuals with comorbid depression and obesity (Cassin et al., 2013; Linde et al., 2011; Simon, Ludman, Linde, Belinda, & Jeffery, 2008), no study to our knowledge has explored the underlying structure of these scales in this specific population.

Much of the existing literature in individuals with obesity has examined the factor structure of depressive symptomatology using the Beck depression inventory (BDI). Of five studies that we are aware of, four found a three-factor structure (Hall et al., 2013; Hayden et al., 2010; Hayes et al., 2015; Udo et al., 2015), and one found a 2-factor model (Munoz et al., 2007). It is not clear whether the identified 3-factor structure is a function of the BDI scale or a feature of depression in this specific population. Hence, it is important to explore the factor structure of other depression scales to help answer this important question.

Additional considerations to developing more precise phenotypic definitions of depression include that presenting symptoms of depression often vary across sex and age; we posit that this may further differ across profiles of depressive symptoms. For example, women were more likely to present neurovegetative symptoms of depression (e.g., increased appetite, weight gain, leaden paralysis) than men (Łojko et al., 2015). In addition, greater age was associated with higher neurovegetative/somatic symptoms of depression (Hegeman et al., 2012; Schaakxs et al., 2018; Udo et al., 2015). This evidence highlights the importance of exploring the effects of sex and age on the symptom profiles of depression, which in turn may provide insight into assessment and evaluation of intervention effects for specific subgroups of patients.

The present study aimed to understand the symptom profiles of depression in patients with comorbid depression and obesity. To accomplish this, we had two specific aims. The first aim was to examine the factor structure of depression as assessed by the SCL-20 and PHQ-9 in patients with comorbid depression and obesity using exploratory factor analysis. The factor structure of the SCL-20 and PHQ-9 might be different due to (1) differences in number of scale items, and (2) differences in the aspects of depression they tap into. The SCL-20 items are intended to measure the "*intensity*" of symptoms, whereas the PHQ-9 items are intended to

measure the "*frequency*" of symptoms. Therefore, exploratory factor analysis (EFA) was conducted separately on the SCL-20 and PHQ-9 to explore whether the factor structures differ across these two scales. Although evidence on the factor structure of the SCL-20 is lacking, given that the items on the SCL-20 are similar to the BDI items, and that both scales measure the same aspect of symptoms (i.e., the intensity of symptoms) (see appendix C), we hypothesized that a 3-factor model will emerge from the SCL-20. Given that a 2-factor model of the PHQ-9 was observed in the majority of prior studies, we hypothesized that a 2-factor model will emerge from this scale, with one factor containing neurovegetative items and the other containing affective items. It would be ideal to parse out the cognitive factor from the affective factor given that these two reflect distinct constructs according to the Research Domain Criteria (RDoC) framework. However, commonly used depression rating scales include only a limited number of items, if any, that capture core cognitive elements of depression (e.g., difficulty concentrating). Therefore, we did not expect the affective and cognitive items to diverge. The second aim of this study was to examine whether the severity of the identified factors varies across sex, age groups (18-44, 45- <65, ≥65), and BMI category (27-<35, 35-<40, ≥40). Given the lack of evidence on the moderating effects of these variables on symptom profiles of depression to inform *a priori* hypotheses, this aim is exploratory.

2. Methods-Study 1

2.1 Participants

This study reports a post-hoc analysis of baseline data from the RAINBOW trial, a 2-arm randomized clinical trial that evaluated an integrated, collaborative care intervention to treat adults with comorbid depression and obesity in primary care. Patients were recruited from multiple medical centers of the Palo Alto Medical Foundation. A detailed description of the trial protocol can be found elsewhere (Ma et al., 2015). Inclusion criteria included men and women ≥18 years of age, residing in the Bay Area, California, with BMI ≥ 30.0 kg/m^2 (≥27 if of Asian descent), and clinically significant depression reflected by PHQ-9 ≥ 10. Participants were excluded if they had active suicidal ideation, any axis I disorder (other than minor/major depressive disorder, dysthymia, and/or comorbid anxiety disorder), active Bulimia Nervosa within the past three months, bariatric surgery within the past 12 months, current alcohol/substance use disorder, pre-existing diabetes or cardiovascular disease, or a diagnosis of cancer (for a complete and detailed list of inclusion and exclusion criteria see Ma et al., 2015). This resulted in a sample of 409 participants.

2.2 Assessment and measures

Participants completed a self-reported questionnaire assessing sociodemographic characteristics including age, sex, race, ethnicity, education, income, marital status, and household size. BMI was calculated based on height and weight measured by trained study coordinators. Depressive symptoms were assessed by the SCL-20 and PHQ-9. The SCL-20 is a self-report questionnaire with 20 items that were drawn from the SCL-90 (see appendix A). Respondents answered questions regarding *how much* they were distressed by a symptom over the last two weeks. Each item is rated on a 5-point scale (0 = *not at all*, 1 = *a little bit*, 2 =

moderately, 3 = *quite a bit*, 4 = *extremely*) (Derogatis et al., 1974). The SCL-20 total scores are the mean values of the 20 items, which range from 0 (not at all) to 4 (extremely). A score of 0.75 or less represents minimal depression/remission; the cut-off points of 1.5 and 2, respectively, represent moderate and severe depression (Ma et al., 2019). The PHQ-9 is a self-report questionnaire with 9 items that corresponds to DSM-IV criteria for diagnosis of MDD (see appendix B). Respondents answered questions regarding *how often* a symptom has bothered them over the last two weeks. Each item is rated on a 4-point scale (0 = *not at all*, 1 = *several days*, 2 = *more than half the days*, 3 = *nearly every day*). The PHQ-9 was used to screen participants online or by phone before they were scheduled for baseline visits, at which time the SCL-20 was administered.

2.3 Statistical analysis

Exploratory factor analyses with oblique rotations (Osborne & Banjanovic, 2016) were conducted to examine the factor structure of the SCL-20 and PHQ-9, separately. The unweighted least squares method was used to extract factors because of the non-normal distribution of data (Fabrigar et al., 1999; Nunnally, 1994). Bootstrap resampling method was performed to estimate the precision and potential replicability of identified factors (Diciccio & Efron, 1996). Factor loadings of 0.30 or greater was used to represent that the item loaded onto the factor (Brown, 2014). The number of factors were determined based on three criteria: (1) the Kaiser criterion based on eigenvalues >1.0 (Braeken & van Assen, 2017), (2) inclusion of at least three items for each factor, and (3) interpretability of the identified factors and loaded items in the context of theoretical concepts and empirical evidence. Standardized scoring coefficients were estimated for each scale item with salient loadings on the factor (Osborne & Banjanovic, 2016) and used to compute weighted factor scores. The mean score on each identified factor was estimated by

multiplying the raw values of items with salient loadings on the factor by the standardized scoring coefficients and then averaged. Analysis of variance was conducted to compare overall depression scores and scores of the identified factors across age groups, sex, and BMI categories. All analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina). $P < 0.05$ (2-sided) was considered statistically significant.

3. Results-Study 1

3.1 Subject characteristics

Subject characteristics are shown in Table 1. The study sample consisted of 409 individuals (70% women, 71% non-Hispanic white) with comorbid depression and obesity with a mean age of 51.0 ± 12.1 years. Approximately 74% of the sample reported an annual income of ≥ $75,000, and 61% were married or cohabiting. The mean SCL-20 and PHQ-9 scores were 1.5 ± 0.5 and 13.8 ± 3.1 respectively, representing moderate depressive symptoms. The mean BMI score was 36.7 ± 6.4, indicating moderate obesity. No significant differences were observed between men and women in BMI or in age (*ps* > 0.5).

3.2 Most endorsed depressive symptoms

The top most endorsed symptoms with the highest mean scores on the SCL-20 were feeling low energy/slowed down, overeating, disturbed sleep, and worrying too much. These symptoms had a mean value of greater than 2, indicating that on average the intensity of these items was rated as moderate or greater during the past two weeks (see Supplemental Table 1 [S1]). Similarly, the top most endorsed symptoms with a mean value of 2 or greater on the PHQ-9 were low energy/feeling tired, overeating/poor appetite, and sleep disturbance, indicating that on average they were present more than half the days or nearly every day over the past two weeks (see Table S2).

3.3 Exploratory Factor Analysis

3.3.1 SCL-20

The eigenvalues and factor patterns from EFA on the SCL-20 are shown in Tables 2 and 3. Two factors met all of the three pre-specified criteria. The first factor accounted for 71% of the total variance and it was labeled "**negative affect**" based on the loaded items. Ten items- reflecting "negative mood" and "negative bias"- were retained in factor 1, including blaming yourself (coefficients=0.83), feelings of worthlessness (0.82), guilt (0.78), hopeless (0.72), blue (0.61), being trapped (0.60) and lonely (0.55), worrying too much about things (0.54), crying easily (0.43), and thoughts of death (0.34). The second factor accounted for 15% of the total variance and it was labeled "**anhedonia**." Four items were retained in factor 2, including feeling everything is an effort (0.74), no interest in things (0.62), low energy or slowed down (0.51), and loss of sexual interest or pleasure (0.39). The third factor had an eigenvalue < 1.0 and thus could be unreliable, but it met the three loaded item and interpretability criteria. Factor 3 accounted for 10% of the total variance and was labeled "**sleep disturbance**" based on the three items loaded onto it, which included restless or disturbed sleep (0.86), trouble falling asleep (0.57), and awakening early in the morning (0.42). The item "thoughts of ending life" did not load significantly on any of the factors. The "negative affect" factor correlated moderately with the "anhedonia" factor (r = 0.52, p <0.001) and correlated weakly with the "sleep disturbance" factor (r = 0.18, p <0.001). In addition, the "anhedonia" factor also correlated weakly with the "sleep disturbance" factor (r = 0.18, p <0.001). Inter-factor correlations are shown in Table S3. Total SCL-20 scores correlated strongly with the "negative affect" factor (r = 0.88, p <0.001) and moderately with the "anhedonia" factor (r = 0.71, p <0.001) and the "sleep disturbance" factor (r = 0.46, p <0.001). No significant correlations were observed between BMI and either total SCL-

20 score or the three factors. Among the SCL-20 items, “overeating” correlated weakly with BMI ($r = 0.11$, $p < 0.05$)

The mean score on the “negative affect” factor (0.17 ± 0.10) was significantly lower than the mean score on the “anhedonia” factor (0.49 ± 0.20; $t(408) = -36.83$, $p < 0.0001$) and the mean score on the “sleep disturbance” factor (0.64 ± 0.33; $t(408) = -28.66$, $p < 0.0001$). The mean score on the “anhedonia” factor was significantly lower than the mean score on the “sleep disturbance” factor ($t(408) = -8.47$, $p < 0.0001$). The mean factor scores are shown at the top of Table 5.

3.3.2 PHQ-9

The eigenvalues and factor patterns of the PHQ-9 are shown in Tables 2 and 4. Only the first factor met the three pre-specified criteria. It accounted for 87% of the total variance and was labeled “negative affect.” Three items were retained in factor 1, including feeling down, depressed or hopeless (coefficients=0.64), little interest or pleasure in doing things (0.48), and feeling bad about yourself (0.46). Six items including sleep disturbance, fatigue or low energy, changes in appetite, difficulty concentrating, psychomotor retardation or agitation, and thoughts of death did not load on this factor. The mean score on the negative affect factor is presented at the top of Table 6. Total PHQ-9 scores correlated significantly with the “negative affect” factor ($r = 0.68$, $p < 0.001$). No significant correlations were observed between BMI and either total PHQ-9 score or factor 1. Among the PHQ-9 items, two items of “difficulty concentrating” and “psychomotor retardation/agitation” negatively correlated with BMI, although the strength of correlations was weak ($r = -0.11$, $p < 0.05$ and $r = -0.11$, $p < 0.05$, respectively).

3.3.3 Bootstrap results to test internal validation

The bootstrapped mean eigenvalues for the first four factors of the SCL-20 and two factors of the PHQ-9 are presented in Table 2. Regarding the SCL-20, the mean values for the first four eigenvalues, across 2000 resamples, were consistent with our initial EFA analysis, supporting a two-factor structure. Regarding the PHQ-9, the mean value for the first factor, across 2000 resamples, was greater than 1, supporting a one-factor structure. The average bootstrapped factor loadings are shown in Tables S4-S5. Based on the bootstrapped statistics, the same items were retained in the factors as they were identified in the initial analysis, suggesting the stability of the initial results across 2000 resamples.

3.4 Depression scores across groups

3.4.1 SCL-20

Women scored significantly higher on the SCL-20 total score (F= 4.32, $p = 0.038$) and the potential "sleep disturbance" factor score (F= 8.99, $p = 0.003$) compared to men. No significant differences were found between men and women in two other factor scores ($p > 0.7$). No significant differences were found in the SCL-20 total score or the three factor scores across BMI categories or age groups (all *p's* > 0.05). Results are presented at the bottom of Table 5.

3.4.2 PHQ-9

No significant differences were found between men and women in the PHQ-9 total score (F=3.39, $p = 0.07$) or the "negative affect" factor score ($p = 0.7$). No significant differences were found in the PHQ-9 total score or the "negative affect" factor score across BMI categories or age groups (All *p's* > 0.3). Results are presented at the bottom of Table 6.

4. Discussion-Study 1

The clinical presentation of depression may vary across patients. Comorbidity of depression with other medical conditions may help account for such variation. Obesity is one example of these conditions. Given that these two conditions often co-occur and they share similar symptoms, it is important to explore the characteristics of depression in the context of obesity. This study is the first to examine the factor structure of the PHQ-9 and the SCL-20, two widely used depression rating scales, in patients with comorbid depression and obesity. Our results suggest that both scales capture the "negative affect" construct in these patients. However, the SCL-20 seems more sensitive than the PHQ-9 to capture other depression-related constructs (e.g., anhedonia). Some possible reasons for this observation include: (1) differences in number of scale items, and (2) differences in the aspects of depression they tap into; the SCL-20 measures the severity of depressive symptoms, whereas the PHQ-9 measures the frequency of symptoms. Because the most endorsed symptoms in terms of both severity (as measured by the SCL-20) and frequency (as measured by the PHQ-9) were the same (i.e., low energy/fatigue, sleep disturbance and overeating/changes in appetite), it is more likely that the two different factor structures which emerged from these scales were mainly due to the difference in number of scale items. Overall, these findings provide important information regarding the clinical utility of these scales. Given that the PHQ-9 (or PHQ-2) has increasingly been adopted as a depression screening tool in primary care, our findings suggest that this practice may need to be re-examined in patients with comorbid depression and obesity; that is, insofar as this scale may largely capture only the negative affective dimension of depression, studies that need to screen on other aspects of depression or those seeking to determine sub-types of depression may be better served by considering additional items and/or alternative scales. This approach may have

important implications by providing insight into symptoms that could be selectively targeted by treatment.

In contrast to our findings, most prior studies supported a 2-factor model of the PHQ-9 in other samples (e.g., cardiovascular disease, MDD, substance abuse); the two factors that emerged included "somatic" items (e.g., sleep disturbance, changes in appetite) and "non-somatic" items (e.g., loss of interest, depressed mood) (de Jonge et al., 2007; Elhai et al., 2012; Guo et al., 2017; Kalpakjian et al., 2009; Krause et al., 2008, 2010, 2011; Richardson & Richards, 2008; Petersen et al., 2015). Relatively few studies yielded a 1-factor structure including all nine items (Baas et al., 2011; Cameron et al., 2008; Dum et al., 2008; Huang et al., 2006). Interestingly, in the present study the items related to neurovegetative symptoms (e.g., fatigue, sleep) on the PHQ-9 did not load on the negative affect factor, suggesting that these symptoms may represent a distinct underlying construct. In the majority of the prior studies that found a 2-factor structure on the PHQ-9, the items fatigue/low energy, sleep disturbance and changes in appetite loaded together on the same somatic factor (e.g., de Jonge et al., 2007; Elhai et al., 2012; Krause et al., 2008, 2010, 2011; Richardson & Richards, 2008; Petersen et al., 2015). However, our findings on the SCL-20 suggest that these items did not share the same underlying factor and they tended to load on distinct factors in the present sample. Therefore, more factors may have been identified if more indicators were included on the PHQ-9. Considered together, these data support the notion that the factor structure of the PHQ-9 differs across patient populations.

Evidence on the factor structure of the SCL-20 in individuals with obesity is lacking. However, some prior findings in these individuals revealed a three-factor structure on the BDI scale using factor analysis (Hall et al., 2013; Hayden et al., 2010; Hayes et al., 2015; Udo et al.,

2015). In one study, these factors consisted of the “negative perceptions”, “diminished vigor” and “cognitive dysregulation” factors (Hayes et al., 2015). The first two factors as well as the loaded items on these factors were similar to our results on the SCL-20; the “negative perception” factor included items that represented negative mood and negative bias, and the “diminished vigor” factor included the items loss of energy, fatigue and loss of interest in sex. In other three studies, a three-factor structure represented “negative mood or affective”, “negative self-attitudes or cognitive”, and “somatic” items (Hall et al., 2013; Hayden et al., 2010; Udo et al., 2015). In these studies, items relevant to negative affect (e.g., sadness) and negative bias (e.g., guilty feeling) consistently form two distinct clusters. Conversely, in the present study, affective and negative bias symptoms (as measured by the SCL-20) shared the same latent factor (i.e., loaded on the same factor), suggesting that negative self-perception plays a major role in the experience of depressed mood in our sample. Because our study is the first to examine the factor structure of the SCL-20 and the PHQ-9 in comorbid depression and obesity, future studies need to evaluate the replicability of factors that emerged from our study in this specific sample.

Although the eigenvalue for the sleep disturbance factor was less than one, there may be potential value in reporting the results for this factor as it may provide additional information about other symptom manifestations of depression in this population. In the present study, the item sleep disturbance on the SCL-20 did not cluster with the items loss of energy/fatigue and tended to form a distinct factor, suggesting that these symptoms may have a different underlying construct and/or cause. In contrast, in prior studies among individuals with obesity and depression, the items sleep changes, fatigue and loss of energy on the BDI loaded together and form a separate somatic factor (Hall et al., 2013; Hayden et al., 2010; Udo et al., 2015). The weak correlation between the sleep factor and the negative affect factor in the present study

suggests that sleep problems may not be mainly driven by the underlying construct of depression. There is evidence indicating that sleep and obesity are related. Sleep disturbance may contribute to the development and progression of obesity via several biological and behavioral mechanisms (reviewed by Cooper et al., 2018). For example, sleep deprivation has been associated with increased ghrelin levels (a hormone that stimulates appetite) and decreased leptin (a hormone that inhibits appetite) levels, which in turn contribute to increased appetite and weight gain. Importantly, sleep disturbance may occur secondary to obesity. Indeed, obesity has been linked to the development and severity of obstructive sleep apnea (reviewed by Hargens et al., 2013). However, there is evidence indicating the obesity-sleep association exists independent of sleep apnea (Vgontzas, Bixler, & Chrousos, 2006).

Interestingly, we found that the loss-of-interest item on the SCL-20 did not load on the affective factor and shared the same latent factor as loss of energy and fatigue symptoms. In addition, the anhedonia factor correlated with the negative affect factor and did not correlate with BMI. This suggests that the experience of fatigue and low energy in this sample is a feature of depression and not merely driven by physical problems due to obesity. Examining whether symptoms of anhedonia, low energy and fatigue share a common underlying neurobiology in patients with comorbid depression and obesity would be a fruitful avenue of future research. Existing evidence indicates that inflammation can play a role in the pathophysiology of depression (Dowlati et al., 2010; Hiles et al., 2012; Howren et al., 2009). In addition, evidence suggests that inflammation can alter dopamine in the basal ganglia, resulting in anhedonia, fatigue and psychomotor retardation (reviewed by Felger & Miller, 2012). Given that obesity is characterized by low-grade inflammation (Shelton & Miller, 2010), we speculate based on our preliminary findings that loss of energy, fatigue and loss of interest lumped together partly

because they are interrelated in an inflammatory network. Exploring homogenous constructs within depression with a particular biosignature is an important next step in advancing translational research in the context of comorbid depression and obesity.

We found that patients scored higher on the anhedonia and the sleep disturbance factors compared to the affective factor as measured by the SCL-20 scale. The factor scores showed consistent patterns across sex, age and BMI categories with one exception; women scored higher in the potential sleep disturbance factor compared to men. Prior studies suggest that clinical presentation of depression may differ across sex, with women more likely to exhibit neurovegetative symptoms (e.g., sleep, fatigue) (Delisle et al., 2012; Silverstein, 2002, 1999). In addition, the most endorsed symptoms on both the SCL-20 and the PHQ-9 were low energy/fatigue, sleep disturbance and overeating/changes in appetite. Studies in obesity yielded similar patterns of results. For example, loss of energy, fatigue, changes in sleep patterns or appetite were among the most endorsed depressive symptoms in a sample of obese subjects seeking bariatric surgery (Hall et al., 2013; Hayden et al., 2010; Munoz et al., 2007). These findings, combined with our results, support the notion that neurovegetative symptoms of depression may be more prevalent and/or severe compared to affective/cognitive symptoms in patients with comorbid obesity.

These findings on the symptom domains of depression are constrained by the nature of the scales we examined. Given that the obtained factors are influenced by the number of indicators included in the factor analysis, and that a single scale has a limited number of items, the observed factors likely do not fully capture the heterogeneity of depression. For example, two items (overeating and poor appetite) hinted at the potential presence of an additional factor on the SCL-20 related to the impact of depression on consumptive behavior. However, with only

two items this factor may not have been adequately measured. Overeating, and perhaps associated feelings of shame and guilt, might be a feature of depression in this specific population (Goss & Allan, 2009). Another important example is cognition. Commonly used depression rating scales assess cognitive symptoms using only one or two items, which does not allow for a full representation of this construct (Majd et al., 2020). Indeed, core cognitive elements of depression (indecisiveness or difficulty concentrating) were assessed by only one item on the PHQ-9 and no items on the SCL-20. Therefore, use of additional assessment tools (e.g., objective neurocognitive testing) that more fully capture cognitive function may be important.

Identifying the factor structure of depressive symptoms in the context of obesity may help identify those constructs that are more central to the concept of depression in this population. More generally, this view is in line with the need to identify moderators of treatment response. There is substantial variability in response to treatment across depressed patients (Nierenberg, 2003). Comorbid psychiatric and medical conditions, prolonged depressive episodes, older age, and severity of illness have been identified as potential negative predictors of treatment response (reviewed by Kornstein & Schneider, 2001; Nierenberg, 2003). In addition, there is some evidence suggesting that obesity or higher BMI predicted poor treatment outcomes in patients with depression (Dennehy et al., 2015; Khan et al., 2007; Kloiber et al., 2007; Papakostas et al., 2005; Uher et al., 2009). Interestingly, it has been found that the effects of higher BMI/obesity on response to antidepressants may be treatment and/or symptom-specific (Green et al., 2017; Jha et al., 2018; Uher et al., 2009). For example, depressed patients with higher BMI were more responsive to venlafaxine than escitalopram, and this improvement was particularly evident on neurovegetative symptoms (Green et al., 2017). Hence, understanding

depressive symptomology in the context of obesity will provide insight into more comprehensive assessment tools that capture the heterogeneity of depression. Importantly, this information may inform future efficacy/effectiveness studies to explore whether components of depression respond differentially to treatment. Eventually, these data may help tailor treatment to individuals based on presenting symptoms and could improve treatment outcomes. This notion is in line with precision medicine approaches that aim for improving outcomes for patients.

Limitations

The results of this preliminary study need to be interpreted with some caution. This sample represented moderate depressive symptoms, which may limit generalizability to severe levels of depression. In addition, this study was (albeit by intent) limited to individuals with BMI ≥ 30.0 kg/m^2 ($\geq$27 if of Asian descent), therefore our findings reported here are not meant to generalize to a broader range of BMI values.

Conclusions

Our results suggest that both the SCL-20 and PHQ-9 capture the "negative affect" construct in patients with comorbid depression and obesity. However, the SCL-20 seems more sensitive than the PHQ-9 to capture other depression-related constructs (e.g., anhedonia). This study supports the idea that depression is not a unidimensional construct and relying only on depression sum-scores (i.e. total score) may mask important information in depressed patients with comorbid obesity. In addition, these findings highlight that the aspects of depression that are measured by depression measures may vary across patient populations. Importantly, the clinical utility of depression measures should take into account the reliability and validity of the scales in discerning the underlying constructs (or symptom profiles) of depression given that the latter may inform treatment decisions in patients presenting with varying symptom profiles. Finally, a

comprehensive assessment tool that measures various aspects of depression, particularly cognitive symptoms, fatigue, anhedonia, sleep, and overeating, in addition to negative emotions/affect, may be needed to better characterize the nature of depression in patients with comorbid obesity.

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Tables-Study 1

Table 1
Subject characteristics

	Total sample
N	409
Sex: N (%)	
Women	287 (70)
Men	122 (30)
Age [years]: Mean (SD)	51.0 (12.1)
BMI [kg/m^2]: Mean (SD)	36.7 (6.4)
Ethnicity/ Race: N (%)	
Non-Hispanic white	289 (71)
Black	6 (1)
Asian/Pacific islander	40 (10)
Hispanic	56 (14)
Other	18 (4)
Annual family income: N/total (%)	
<$75,000	93/365 (26)
$75,000– <$150,000	117/365 (32)
≥$150,000	155/365 (42)
Marital status: N/total (%)	
Married or living with partner	247/406 (61)
Single/divorced/separated/widowed	159/406 (39)
Education: N (%)	
≤ High school graduate or GED	27 (7)
Some college	98 (24)
Undergraduate degree	151 (37)
Graduate-level work or degree	133 (32)

Table 2

Eigenvalues for the correlation matrix

	Original results			*Bootstrap results across 2000 resamples*		
	Eigenvalue	Variance	Cumulative variance	Mean Eigenvalue (Min, Max)	95% CI	SD
SCL-20						
Factor 1*	**5.32**	0.71	0.71	**5.38** (4.57, 6.15)	5.37, 5.39	0.24
Factor 2*	**1.15**	0.15	0.86	**1.26** (0.93, 1.72)	1.25, 1.26	0.11
Factor 3*	0.77	0.10	0.96	0.86 (0.86, 1.20)	0.85, 0.86	0.08
Factor 4	0.54	0.07	1.04	0.63 (0.63, 0.88)	0.63, 0.64	0.06
PHQ-9						
Factor 1*	**1.28**	0.87	0.87	**1.33** (1.32, 1.33)	1.25, 1.41	0.12
Factor 2	0.45	0.30	1.18	0.55 (0.31, 0.87)	0.55, 0.56	0.07

*Factor 1 (on both the SCL-20 and the PHQ-9) was labeled "*negative affect*", Factor 2 was labeled "*anhedonia*" and factor 3 was labeled "*sleep disturbance*"

Table 3

Rotated Factor Pattern (Standardized Regression Coefficients) of the SCL20

		Factor 1*	Factor 2*	Factor 3*	Factor 4
SCL 4	Crying easily	**0.43**	-0.06	0.17	0.06
SCL 5	Feeling of being caught or trapped	**0.60**	0.02	0.00	0.04
SCL 6	Blaming yourself for things	**0.83**	-0.12	-0.00	0.05
SCL 7	Feeling lonely	**0.55**	0.03	0.02	0.06
SCL 8	Feeling blue	**0.61**	0.20	0.02	-0.01
SCL 9	Worrying too much about things	**0.54**	0.04	0.19	-0.06
SCL 13	Feeling hopeless about the future	**0.72**	0.08	-0.02	-0.09
SCL 14	Thoughts of death or dying	**0.34**	0.07	-0.05	0.04
SCL 19	Feelings of worthlessness	**0.82**	0.02	-0.12	-0.05
SCL 20	Feelings of guilt	**0.78**	-0.09	0.00	0.039
SCL 1	Feeling low in energy or slowed down	-0.09	**0.51**	0.06	0.10
SCL 10	Feeling no interest in things	0.17	**0.62**	-0.07	-0.09
SCL 11	Loss of sexual interest or pleasure	0.01	**0.39**	0.12	-0.02
SCL 18	Feeling everything is an effort	0.09	**0.74**	-0.02	0.03
SCL 12	Trouble falling asleep	0.04	-0.02	**0.57**	-0.08
SCL 16	Awakening early in the morning	-0.05	0.07	**0.42**	0.06
SCL 17	Sleep that is restless or disturbed	-0.01	0.01	**0.86**	-0.02
SCL 3	Poor appetite	0.12	0.17	0.21	**-0.32**
SCL 15	Overeating	0.08	0.09	0.03	**0.97**
SCL 2	Thoughts of ending your life	0.26	0.03	-0.06	-0.01

*Factor 1 was labeled "*negative affect*", Factor 2 was labeled "*anhedonia*" and factor 3 was labeled "*sleep disturbance*"

Table 4

Factor Pattern of the PHQ-9		**Factor 1***
PHQ1	Little interest or pleasure in doing things	**0.48**
PHQ2	Feeling down, depressed or hopeless	**0.64**
PHQ6	Feeling bad about yourself - or that you are a failure or have let yourself or your family down	**0.46**
PHQ3	Trouble falling or staying asleep, or sleeping too much	0.089
PHQ4	Feeling tired or having little energy	0.17
PHQ5	Poor appetite or overeating	0.05
PHQ7	Trouble concentrating on things, such as reading the newspaper or watching television	0.27
PHQ8	Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0.15
PHQ9	Thoughts that you would be better off dead, or of hurting yourself	0.17

*Factor 1 was labeled "*negative affect*"

Table 5
Mean total SCL-20 and factor scores in the entire sample and across groups

	Sample Size	Total score Mean[a] (SD)	Score on *negative affect* Mean[b] (SD)	Score on *anhedonia* Mean[b] (SD)	Score on *sleep disturbance* Mean[b] (SD)
Total sample	409	1.5 (0.5)	**0.17**[1,2] (0.10)	**0.49**[1,3] (0.20)	**0.64**[2,3] (0.33)
Women	287	**1.5**[4] (0.5)	0.17 (0.10)	0.49 (0.21)	**0.67**[4] **(0.33)**
Men	122	**1.4**[4] (0.5)	0.17 (0.10)	0.48 (0.19)	**0.56**[4] **(0.33)**
BMI					
27 - <35	209	1.5 (0.6)	0.17 (0.10)	0.48 (0.20)	0.63 (0.35)
35 - <40	111	1.5 (0.5)	0.18 (0.10)	0.51 (0.22)	0.67 (0.34)
≥ 40	89	1.5 (0.5)	0.16 (0.10)	0.49 (0.20)	0.64 (0.29)
Age					
18- <45	115	1.6 (0.5)	0.19 (0.10)	0.52 (0.20)	0.62 (0.35)
45- <65	248	1.5 (0.6)	0.17 (0.10)	0.47 (0.20)	0.66 (0.33)
≥ 65	46	1.4 (0.5)	0.16 (0.09)	0.52 (0.21)	0.61 (0.34)

[a]the SCL-20 total scores are the average values for the 20 items, ranging from 0 (not depressed at all) to 4 (extremely depressed)
[b]the mean score on each identified factor was estimated by taking the mean of the raw values of items with salient loadings on the factor multiplied by the standardized scoring coefficients
[1]indicates a significant difference between the mean score on the negative affect factor and anhedonia factor (p <0.0001)
[2]indicates a significant difference between the mean score on the negative affect factor and sleep disturbance factor (p <0.0001)
[3]indicates a significant difference between the mean score on the anhedonia and sleep disturbance factor (p <0.0001)
[4]indicates a significant difference across men and women (p = 0.003)

Table 6

Mean total PHQ-9 and factor score in the entire sample and across groups

	Sample Size	Total score[1] Mean[a] (SD)	Score on *negative affect*[1] Mean[b] (SD)
Total sample	409	13.8 (3.1)	0.40 (0.17)
Women	287	14.0 (3.1)	0.41 (0.17)
Men	122	13.4 (3.2)	0.40 (0.16)
BMI			
27 - <35	209	13.9 (3.2)	0.41 (0.18)
35 - <40	111	13.6 (2.8)	0.38 (0.15)
≥ 40	89	13.8 (3.2)	0.42 (0.16)
Age			
18- <45	115	14.0 (3.3)	0.41 (0.18)
45- <65	248	13.6 (3.0)	0.40 (0.16)
≥ 65	46	14.1 (3.3)	0.44 (0.16)

[a]the PHQ-9 total score is the sum of all 9 items, ranging from 0 to 27

[b]the mean score on the identified factor was estimated by taking the mean of the raw values of items with salient loadings on the factor multiplied by the standardized scoring coefficients

[1]no significant differences were found in the PHQ-9 total score or the "negative affect" factor score across BMI categories or age groups (All *p's* > 0.3)

Supplementary Tables-Study 1

Table S1
Mean and standard deviation (SD) for each item of the SCL-20

Variable	Mean[a]	SD	Label
SCL 1	**2.32**	0.95	Feeling low in energy or slowed down
SCL 2	0.11	0.33	Thoughts of ending your life
SCL 3	0.60	0.92	Poor appetite
SCL 4	0.90	1.01	Crying easily
SCL 5	1.21	1.10	Feeling of being caught or trapped
SCL 6	1.64	1.13	Blaming yourself for things
SCL 7	1.45	1.12	Feeling lonely
SCL 8	1.67	0.98	Feeling blue
SCL 9	**2.12**	1.09	Worrying too much about things
SCL 10	1.68	1.00	Feeling no interest in things
SCL 11	1.82	1.31	Loss of sexual interest or pleasure
SCL 12	1.77	1.28	Trouble falling asleep
SCL 13	1.27	1.04	Feeling hopeless about the future
SCL 14	0.63	0.91	Thoughts of death or dying
SCL 15	**2.30**	1.23	Overeating
SCL 16	1.58	1.28	Awakening early in the morning
SCL 17	**2.14**	1.17	Sleep that is restless or disturbed
SCL 18	1.94	1.02	Feeling everything is an effort
SCL 19	1.12	1.07	Feelings of worthlessness
SCL 20	1.33	1.13	Feelings of guilt

[a]each item was rated from 0 (not depressed at all) to 4 (extremely depressed)

Table S2
Mean and standard deviation (SD) for each item of the PHQ-9

Variable	Mean[a]	SD	Label
PHQ1	1.63	0.82	Little interest or pleasure in doing things
PHQ2	1.41	0.77	Feeling down, depressed or hopeless
PHQ3	**2.17**	0.96	Trouble falling or staying asleep, or sleeping too much
PHQ4	**2.36**	0.74	Feeling tired or having little energy
PHQ5	**2.30**	0.83	Poor appetite or overeating
PHQ6	1.66	0.94	Feeling bad about yourself - or that you are a failure or have let yourself or your family down
PHQ7	1.39	1.01	Trouble concentrating on things, such as reading the newspaper or watching television
PHQ8	0.69	0.88	Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual
PHQ9	0.13	0.34	Thoughts that you would be better off dead, or of hurting yourself

[a]each item was rated from 0 (not at all) to 3 (nearly every day)

Table S3
Inter-factor correlations-SCL-20

	Negative affect	Anhedonia	Sleep disturbance
Negative affect	1.00	**0.52***	**0.18***
Anhedonia		1.00	**0.18***
Sleep disturbance			1.00

*$p<0.001$

Table S4
Bootstrap results for factor loadings for the SCL-20 across 2000 resamples

	Bootstrapped factor loadings Mean (95% CIs)			
	Factor 1	Factor 2	Factor 3	Factor 4
SCL 1	0.08 (0.07, 0.08)	**0.39** (0.39, 0.40)	0.16 (0.16, 0.17)	0.15 (0.14, 0.15)
SCL 2	0.24 (0.24, 0.25)	0.08 (0.07, 0.04)	-0.10 (-0.01, -0.00)	0.04 (0.03, 0.05)
SCL 3	0.17 (0.16, 0.17)	0.17 (0.17, 0.18)	0.19 (0.18, 0.19)	-0.12 (-0.14, -0.10)
SCL 4	**0.41** (0.40, 0.41)	0.11 (0.11, 0.12)	0.18 (0.18, 0.19)	0.09 (0.08, 0.09)
SCL 5	**0.57** (0.57, 0.58)	0.17 (0.17, 0.18)	0.08 (0.08, 0.09)	0.06 (0.06, 0.07)
SCL 6	**0.73** (0.73, 0.74)	0.15 (0.14, 0.15)	0.08 (0.07, 0.08)	0.05 (0.04, 0.05)
SCL 7	**0.54** (0.54, 0.54)	0.18 (0.17, 0.18)	0.10 (0.09, 0.10)	0.06 (0.06, 0.07)
SCL 8	**0.64** (0.63, 0.64)	0.32 (0.31, 0.32)	0.13 (0.13, 0.14)	0.04 (0.04, 0.05)
SCL 9	**0.54** (0.54, 0.54)	0.21 (0.20, 0.21)	0.22 (0.22, 0.22)	0.02 (0.01, 0.03)
SCL 10	0.34 (0.34, 0.34)	**0.50** (0.49, 0.52)	0.01 (0.09, 0.11)	-0.00 (-0.01, 0.00)
SCL 11	0.13 (0.13, 0.13)	**0.35** (0.34, 0.35)	0.19 (0.19, 0.20)	0.05 (0.04, 0.05)
SCL 12	0.08 (0.08, 0.09)	0.09 (0.08, 0.10)	**0.46** (0.45, 0.48)	0.01 (0.01, 0.02)
SCL 13	**0.70** (0.70, 0.71)	0.24 (0.24, 0.25)	0.08 (0.08, 0.09)	-0.01 (-0.02, -0.01)
SCL 14	**0.33** (0.32, 0.33)	0.14 (0.14, 0.15)	0.02 (0.02, 0.03)	0.08 (-0.07, 0.09)
SCL 15	0.15 (0.14, 0.15)	0.19 (0.18, 0.19)	0.12 (0.12, 0.13)	**0.40** (0.38, 0.42)
SCL 16	0.01 (0.01, 0.01)	0.13 (0.12, 0.14)	**0.37** (0.36, 0.38)	0.08 (0.07, 0.09)
SCL 17	0.07 (0.07, 0.07)	0.16 (0.15, 0.17)	**0.70** (0.68, 0.71)	0.08 (0.07, 0.09)
SCL 18	0.32 (0.32, 0.32)	**0.59** (0.58, 0.60)	0.16 (0.15, 0.18)	0.11 (0.10, 0.11)
SCL 19	**0.76** (0.75, 0.76)	0.22 (0.21, 0.23)	-0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)
SCL 20	**0.69** (0.69, 0.70)	0.16 (0.15, 0.17)	0.08 (0.08, 0.09)	0.06 (0.06, 0.07)

Table S5 Bootstrap results for factor loadings for the PHQ-9 across 2000 resamples	
	Bootstrapped factor loadings Mean (95% CIs)
	Factor 1
PHQ1	**0.50** (0.50, 0.50)
PHQ2	**0.73** (0.72, 0.74)
PHQ3	0.05 (0.04, 0.05)
PHQ4	0.11 (0.11, 0.12)
PHQ5	-0.03 (-0.03, -0.02)
PHQ6	**0.44** (0.43, 0.44)
PHQ7	0.17 (0.16, 0.17)
PHQ8	0.05 (0.05, 0.06)
PHQ9	0.18 (0.18, 0.19)

References-Study 1

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CHAPTER 3: Depressive symptoms and inflammation

1. Introduction-Study 2

1.1 Overview of evidence linking depression and inflammation

Several lines of research support the notion that inflammation plays a role in the pathophysiology of depression. *First*, the similarities between sickness behavior and depressive symptoms; sickness behavior is characterized by a constellation of symptoms including anhedonia, malaise, loss of appetite, sleep changes, and social withdrawal (Dantzer et al., 2008). *Second*, increased levels of inflammatory biomarkers IL-6, TNF-α, IL-1β and CRP have been found in patients with MDD and individuals with subclinical levels of depression (Dowlati et al., 2010; Hiles, Baker, de Malmanche, & Attia, 2012a; Howren, Lambkin & Suls, 2009). *Third*, both clinical and animal studies found that inflammation can induce depressive symptoms (Anisman, Kokkinidis, & Merali, 2002; Capuron, Ravaud, & Dantzer, 2000; Dantzer, 2001; Yirmiya, 1996). Indeed, 30% to 40% of patients receiving interferon-α (IFN-α) therapy experience depressive symptoms during the course of treatment (which may result in discontinuation of this therapy) (Capuron & Miller, 2004). *Fourth*, individuals who experience chronic inflammation (such as autoimmune disorders) are at increased risk for developing major depression than the general population (Slavich & Irwin, 2014). *Fifth*, it has been suggested that higher baseline inflammation predicts non-response to antidepressant treatment (reviewed by Strawbridge et al., 2015). *Sixth*, several studies examined the antidepressant effects of anti-inflammatory agents, including non-steroidal anti-inflammatory agents (NSAIDs) and cytokine inhibitors. A meta-analysis by Köhler et al. (2014) suggested that anti-inflammatory medications,

especially celecoxib (a selective cyclooxygenase-2 inhibitor) had beneficial effects on depressive symptoms. In addition, Raison et al. (2013) studied the effect of infliximab (a TNF-α antagonist) in depressed patients who were moderately treatment resistant. Overall, no difference was observed between treatment and control groups in depressive symptom improvement; however, infliximab-treated patients with baseline CRP values of greater than 5mg/L had greater reduction in depression scores compared to placebo-treated patients, suggesting patients with depressive disorders who have higher inflammation may benefit from anti-inflammatory therapy.

Taken together, these observations indicate that inflammation is involved in the pathophysiology of depression at least in subgroups of patients. This evidence raises the question of which biological processes link depression and inflammation, which will be discussed in the next section.

1.2 Mechanisms by which depression contributes to elevated inflammation

Depression and stress are tightly linked. Stress can lead to depression and/or it might occur secondary to depression (Belmaker & Agam, 2008). Pathways through which depression could contribute to elevated inflammation are discussed below.

First, psychological and physical stress cause increases in peripheral neutrophils, and monocytes, which ultimately will lead to proinflammatory cytokine release (Hodes, Kana, Menard, Merad, & Scott, 2015). Reduced sensitivity of immune cells to glucocorticoids has been shown as a result of chronic stress, thus contributing to enhanced release of inflammatory cytokines by immune cells (Hawkley et al., 2007). *Second*, corticotropin releasing hormone (CRH) induces macrophage migratory inhibitory factor (MIF), which is a pro-inflammatory

cytokine secreted by monocytes/macrophages and T cells. It has been suggested that psychological stressors enhance MIF levels. Importantly, MIF release can counter-regulate the anti-inflammatory properties of glucocorticoids, consequently resulting in the production of cytokines in the presence of glucocorticoids. Thus, increased plasma levels of MIF might contribute to glucocorticoid resistance of immune cells reported under conditions of chronic stress (Hawkley et al., 2007). *Third*, depression could lead to a more sedentary lifestyle and/or unhealthy diet, which could lead to obesity. In turn, adipose tissue secretes inflammatory cytokines such as IL-6 and TNF-α (Shelton & Miller, 2010). *Fourth*, more frequent and/or prolonged periods of acute stress experienced by depressed individuals might contribute to sustained increases in glucocorticoid levels observed in a subset of depressed patients (Hawkley et al., 2007). Psychological and/or physiological stress stimulate danger signals (i.e., damage/danger activated molecular patters [DAMPs]), and danger molecules consequently activate the HPA axis and sympathetic nervous system (SNS) (Hodes et al., 2015). If the HPA axis works properly, glucocorticoids downregulate the HPA axis through negative feedback on the hypothalamus (inhibits CRF release) and on the anterior pituitary gland (inhibits release of ACTH) (Hawkley et al., 2007; Nestler et al., 2002). However, evidence shows that chronic stress can cause dysregulation of the HPA axis. Normally, the release of glucocorticoids enhances the inhibitory effect of the hippocampus on the HPA axis. However, sustained increases in glucocorticoid levels under conditions of chronic stress exert detrimental effects on the hippocampus neurons and reduce neurogenesis. Thus, it has been proposed that the inhibitory effect of the hippocampus on the HPA axis would be impaired, causing further release of

glucocorticoids which could consequently damage the hippocampus neurons (e.g., reduction in dendritic branching) (Nestler et al., 2002).

Together, these changes can reduce the anti-inflammatory effects of glucocorticoids, which ultimately could contribute to exaggerated inflammatory responses to psychological and/or physiological stress. It should be noted that inflammatory cytokines are potent inducers of the HPA axis, thus further contributing to impaired inhibitory control of the hippocampus which lead to more release of glucocorticoids and changes in the hippocampus.

1.3 Mechanisms by which inflammation may cause depression

Under conditions of infection or inflammatory-related disorders, peripheral immune cells produce inflammatory cytokines. These peripherally released cytokines can signal the brain and cause sickness behavior. TNF-α and IL-1β are mainly involved in sickness behavior. While sickness behavior is an adaptive response to infection and lasts for a limited period of time, depression is a maladaptive response that tends to be chronic and may occur as a result of prolonged and/or heightened activation of innate immunity (e.g., in vulnerable individuals who have physiological or psychological risk factors for depression such as excessive ACTH release or in conditions with enhanced activity of innate immunity such as obesity). In line with this, it has been shown that IFN-treated patients who developed depression during IFN therapy had greater ACTH and cortisol release following the first administration of IFN-α than those who did not develop depression (Capuron & Miller, 2004).

The question of how inflammation is related not only to sickness behavior, but the development of depression could be answered by evidence showing that inflammation is capable

of changing the structure and function of the brain through multiple mechanisms, including reduced monoamine metabolism, increases in glutamatergic neurotransmission, and reduced neurogenesis in different brain regions such as the hippocampus. Although these mechanisms were not directly examined in this study, a description of them in the present dissertation may have merit.

1.4 Effects of inflammation on neurotransmitters

Multiple pathways exist by which peripheral inflammation can signal the brain and contribute to the development and progression of depression, including stimulation of vagal or other nerve afferents, saturable transport systems, circumventricular organs, and disruptions in the blood brain barrier (BBB) (Konsman, Parnet, & Dantzer, 2002; Quan & Banks, 2007). Inflammatory cytokines may alter neurotransmitter function such as serotonin, dopamine and glutamate in the brain.

1.4.1 Effects of inflammation on the serotonergic system

Elevated inflammation can alter the synthesis and reuptake of serotonin (Capuron & Miller, 2004). Tryptophan, which is a precursor of serotonin, can undergo two pathways as presented in Figure 2. The second pathway can be affected by elevated inflammation. Indeed, cytokines can activate indoleamine 2,3 dioxygenase (IDO) at the periphery and in the brain. IDO is an enzyme that breaks down tryptophan into kynurenine. Then, kynurenine is converted to kynurenic acid (by the enzyme kynurenine aminotransferase) and quinolinic acid (by the enzyme kynurenine monooxygenase). In the brain, astrocytes and microglia produce kynurenic acid and quinolinic acid, respectively. Kynurenic acid is neuroprotective, whereas quinolinic acid is

neurotoxic. In addition, cytokines reduce the availability of tetrahydrobiopterin (BH4) which is a cofactor of tryptophan hydroxylase (an enzyme responsible for serotonin synthesis). These mechanisms might be responsible for inflammation-induced "tryptophan starvation" which results in reduced bioavailability of serotonin (Dantzer, 2016). Consistent with this notion, patients who developed major depression in the course of interferon therapy had increased plasma kynurenine and reduced tryptophan levels compared to IFN-α-treated patients who did not develop depression. Such reduction in tryptophan levels has been associated with mood and cognitive symptoms of depression (Capuron & Miller, 2004).

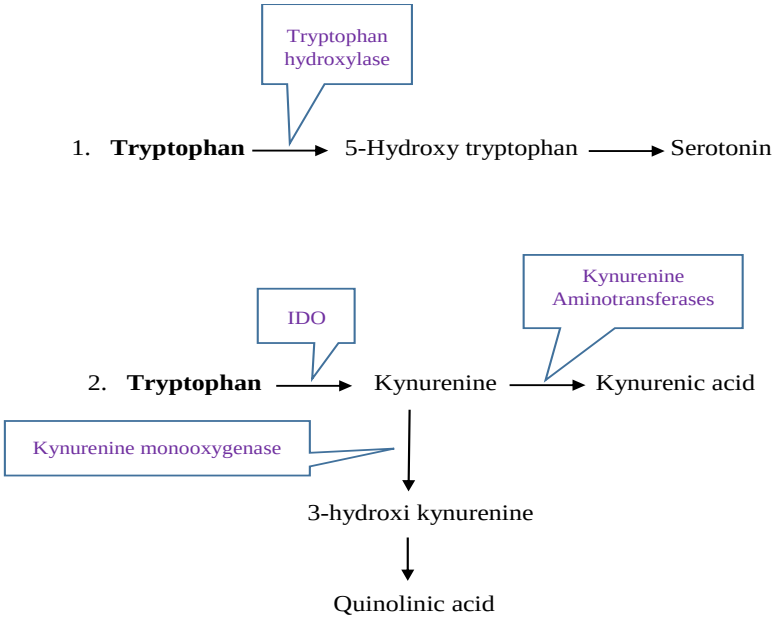

Figure 2. Tryptophan & kynurenine metabolism pathway (Dantzer, 2007)

1.4.2 Effects of inflammation on the dopaminergic system

Inflammation can affect several brain regions containing dopaminergic neurons, such as the nucleus accumbens (ventral striatum), and the caudate nucleus and putamen (dorsal striatum).

The nucleus accumbens is part of the mesolimbic dopaminergic pathway; this pathway begins in the ventral tegmental area (where the cell bodies of dopaminergic neurons are located) and sends axons to the amygdala, hippocampus and nucleus accumbens (Willner et al., 2013). The caudate nucleus and putamen (dorsal striatum) are part of the nigrostriatal pathway. These regions receive dopaminergic signaling from the substantia nigra (Willner et al., 2013). Alterations in the activity of the nucleus accumbens have been attributed to anhedonia in depressed patients. In addition, altered function of the caudate and putamen has been shown to be related to fatigue and psychomotor retardation in depression (Capuron et al., 2007; Stahl et al., 2003).

The pathway of dopamine synthesis is as follows: Phenylalanine → Tyrosine → L-DOPA → Dopamine; phenylalanine (ph) is converted to tyrosine by the enzyme phenylalanine hydroxylase (PAH). Then, tyrosine (tyr) is converted to L-DOPA by the enzyme tyrosine hydroxylase (TH). Finally, L-DOPA is converted to dopamine by the enzyme DOPA decarboxylase. The enzymes PAH and TH need a cofactor tetrahydrobiopterin (BH4). There are three potential mechanisms by which inflammation might reduce dopamine synthesis and function (reviewed by Felger & Miller, 2012).

First, the effects of inflammation on the synthesis of dopamine. Given that BH4 is a cofactor involved in nitric oxide synthesis, inflammatory cytokines appear to decrease the availability of BH4 by inducing nitric oxide synthesis (Kitagami et al., 2003). Thus, reduced activity of BH4 is one potential pathway by which inflammation might reduce dopamine synthesis. Some observations support this notion. Increased peripheral levels of phenylalanine have been shown in patients with inflammation-related conditions such as sepsis (Neurauter et

al., 2008). In addition, an elevated peripheral blood ph/tyr ratio has been found among elderly individuals with low levels of inflammation, suggesting that inflammation is associated with a lower conversion of phenylalanine to tyrosine (Capuron et al., 2011). Additionally, in another study IFN-α treated patients showed an elevated ph/tyr ratio in blood and reduced dopamine in the CSF after 12 weeks of therapy (Felger et al., 2013). The elevated ph/tyr ratio was correlated with fatigue. There was a positive correlation between elevated IL-6 levels and reduced BH4 levels (both measured in the CSF). *Second*, inflammation could influence the packaging and release of dopamine (reviewed by Felger & Miller, 2012). The vesicular monoamine transporter 2 (VMAT2) plays an important role in packaging of dopamine into vesicles. Inflammatory cytokines have been shown to reduce the expression of VMAT2, thus resulting in impaired release of dopamine (Kazumori et al., 2004; Felger, 2016). *Third*, inflammation could diminish reuptake of dopamine from the synaptic cleft back into the presynaptic neuron. Indeed, inflammatory cytokines activate mitogen activated protein kinase (MAPK). MAPK has been shown to increase the expression of dopamine transporter (DAT), thus causing diminished dopamine turnover (Morón et al., 2003).

1.4.3 Effects of inflammation on the glutamatergic system

There is a bidirectional association between inflammation and glutamate release. Inflammatory cytokines activate NMDA receptors by increasing glutamate release and producing quinolinic acid (in microglia). These processes may activate microglia, and thus contribute to further release of inflammatory cytokines (McNally, Bhagwagar, & Hannestad, 2008). Increases in synaptic glutamate can trigger apoptosis and cell death. Cytokines can activate both peripheral

and central IDO, which breaks down tryptophan to kynurenine. Then, kynurenine is converted to quinolinic acid, which is mainly produced in microglia. Peripheral kynurenine can cross the BBB through an amino acid transporter (i.e., LAT1). It has been shown that under conditions of systemic inflammation, peripherally released kynurenine is mainly responsible for producing quinolinic acid in the brain. Given than quinolinic acid is an NMDA receptor agonist, it increases glutamatergic neurotransmission. In addition, activated microglia have been shown to express glutamate receptors, further contributing to glutamate release (Haroon & Miller, 2016).

Inflammation can increase glutamatergic neurotransmission by interfering with astrocytic glutamate uptake (Haroon & Miller, 2016). Astrocytes play an important role in glutamate clearance. Glutamate transporters, known as excitatory amino acid transporters (EAATs) play a role in glutamate clearance. EAATs, which are located on the presynaptic surface of glial cells (such as astrocytes, activated microglia), transport extracellular glutamate into astrocytic cytoplasm, where glutamate is converted to glutamine (i.e., detoxification). Inflammation can reverse this flow, and contribute to further release of glutamate. Reduction in the expression and function of EAATs has been shown under conditions of inflammation, thus interfering with glutamate clearance (Haroon & Miller, 2016).

Taken together, inflammation can alter the function of neurotransmitters in multiple brain regions. In the next section, evidence from neuroimaging studies regarding the effects of inflammation on neurocircuits and related depressive symptoms are discussed.

1.5 Supporting evidence from neuroimaging studies

Neuroimaging studies, using techniques such as functional magnetic resonance (fMRI), magnetic resonance spectroscopy (MRS) and positron emission tomography (PET), have identified neurocircuits and neurotransmitters involved in inflammation-associated depression. There is strong evidence that altered dopamine function in the basal ganglia is a primary target of inflammatory biomarkers (reviewed by Felger & Miller, 2012). Indeed, this effect has been found to mediate depressive symptoms, particularly anhedonia, fatigue and psychomotor retardation (both motor and cognitive components). Although the present study did not use neuroimaging techniques, an overview of the existing literature in this regard may have merit.

Two studies have examined the link between increased inflammation and brain activity in reward-related regions among 48 unmedicated patients with MDD who were otherwise healthy. Using fMRI, elevated CRP levels were associated with reduced connectivity between the ventral striatum and ventromedial prefrontal cortex (vmPFC), which in turn correlated with anhedonia (Felger et al., 2016). Interestingly, while patients with CRP < 1 mg/L (defined as low inflammation) showed marked connectivity between these two regions, patients with CRP > 3 mg/L (defined as high inflammation) showed no significant connectivity between the two regions. In addition, elevated CRP levels were associated with reduced connectivity between the dorsal striatum and vmPFC, which in turn correlated with psychomotor slowing (Felger et al., 2016).

In a separate study among 50 patients with MDD, increased CRP levels were associated with elevated glutamate concentrations in the left basal ganglia as measured by MRS, which in

turn correlated with anhedonia (assessed by the "anhedonia" items of the inventory of depressive symptomatology) and psychomotor slowing (assessed objectively by using neurocognitive tasks) (Haroon et al., 2016). Subgroup analyses also revealed that MDD patients with CRP > 3mg/L had greater glutamate concentrations than those with CRP < 1 mg/L, supporting a positive association between inflammation and glutamate concentration. These studies suggest that elevated inflammation is associated with behaviors related to the basal ganglia.

Further support relating inflammation to anhedonia and psychomotor slowing comes from neuroimaging studies among patients receiving IFN therapy or typhoid vaccination. HCV patients who underwent IFN therapy for 4-6 weeks had reduced activity in the ventral striatum during the win versus lose condition of a gambling task, suggesting reduced response to rewarding stimuli (Capuron et al., 2012). Such reduced activity correlated with higher scores on depression, anhedonia and fatigue. Similarly, endotoxin challenge in healthy volunteers was associated with reduced ventral striatum activity during reward anticipation, which correlated with depressed mood (Eisenberger et al., 2010). Regarding psychomotor changes, higher IL-6 levels following typhoid vaccination in healthy men were associated with increased activity of the substantia nigra while performing a cognitive task (i.e., Stroop test) as well as prolonged reaction time (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008).

Together, elevated inflammation has been linked to reduced activity in the ventral and dorsal striatum and decreased connectivity between the striatum and vmPFC. Indeed, alterations in these neurocircuits correlated with depressive symptoms particularly anhedonia, fatigue and

psychomotor slowing. In the next section, cross-sectional studies relating inflammation to dimensions of depression will be discussed.

1.6 Studies relating depressive dimensions to inflammation

Although the depression-inflammation connection has been widely documented, relatively little research has focused on relating inflammation to dimensions of depression in depressed patients who are otherwise healthy. To date, 14 cross-sectional studies have examined the association between inflammatory biomarkers and dimensions of depression in clinical and community samples. Findings from these studies are discussed below.

***Mood/cognitive symptoms and inflammation*.** Among the fourteen cross-sectional studies relating mood/cognitive symptoms of depression to inflammation, twelve reported null results (Bremmer, Beekman, Deeg, & Penninx, 2008; Case & Stewart, 2014; Chang et al., 2012; Dannehl et al., 2014; Duivis, Vogelzangs, Kupper, De Jonge, & Penninx, 2013; Elovainio et al., 2009; Euteneuer et al., 2012; Euteneuer et al., 2017; Jokela, Virtanen, Batty, & Kivimäki, 2016; Michal et al., 2013; Schmidt et al., 2016; White et al., 2017). Of these studies, three found that mood/cognitive symptoms were associated with higher CRP levels *prior* to adjustment for neurovegetative symptoms (Case et al., 2014; Jokela et al., 2016; White et al., 2017). Two studies found a positive association between cognitive symptoms and increased CRP levels, independent of covariates (Köhler-Forsberg et al., 2017; Krogh et al., 2014). These two studies did not adjust for neurovegetative symptoms. Of the fourteen studies, only two examined objective measures of cognitive function; one found worse cognitive functioning in relation to higher CRP (Krogh et al., 2014), whereas the other found no association (Chang et al., 2012).

Studies that examined mood/cognitive symptoms in relation to IL-6 and TNF-α levels reported null results (Bremmer et al., 2008; Dannehl et al., 2014; Duivis et al., 2012; Euteneuer et al., 2017; Krogh et al., 2014).

Together, this evidence does not support a strong association between mood/cognitive symptoms and inflammation. In addition, this evidence suggests that the associations between mood/cognitive symptoms and inflammation might be explained by neurovegetative symptoms of depression. These findings need to be interpreted with caution, given that the majority of studies measured mood/cognitive symptoms by a few items as part of a depression rating scale. More details on limitations of these studies will be discussed in the section "gaps in the literature."

Neurovegetative/somatic symptoms and inflammation. Among the twelve studies relating neurovegetative/somatic symptoms of depression to CRP, six reported null results (Bremmer et al., 2008; Euteneuer et al., 2017; Köhler-Forsberg et al., 2017; Krogh et al., 2014; Michal et al. 2013; Schmidt et al., 2016), and five found positive associations between CRP and either the summed neurovegetative score or the individual items (Case et al., 2014; Duivis et al., 2012; Elovaino et al., 2008; Jokela et al., 2016; White et al., 2017). In addition, one study objectively measured motor speed (by the finger tapping test) and found that higher CRP was associated with lower motor speed (Chang et al., 2012). Case et al. (2014) found that neurovegetative symptoms related to higher CRP levels independent of cognitive symptoms. White et al. (2017) and Jokela et al. (2016) reported the same pattern of results; the associations between the neurovegetative symptoms and CRP remained significant after simultaneous

adjustment for other depressive symptoms. Among the five studies relating neurovegetative/somatic symptoms to IL-6, four found null results (Bremmer et al., 2008; Euteneuer et al., 2017; Dannehl et al., 2014; Krogh et al., 2014), and one found a positive association (Duivis et al., 2012). Among the three studies relating neurovegetative/somatic symptoms to TNF-α, one found a negative correlation (Schmidt et al., 2016) and two found a positive association (Dannehl et al., 2014; Duivis et al., 2012).

Together, this evidence suggests that an association exists between neurovegetative symptoms and inflammation beyond potentially confounding factors (including mood and cognitive symptoms). Overall, these findings need to be interpreted with caution, as there is a wide range of variability across the studies that warrants closer scrutiny before making any conclusions. In particular, classifications of depressive symptoms (i.e., "depressed mood," "cognitive" or "neurovegetative") differ across studies. Discrepancies in this literature are discussed in the next section.

1.7 Gaps in the literature

Multiple assessment tools are being used in clinical practice and research settings to assess depressive symptoms including both observer-rated assessments (e.g., HAMD) and patient-rated assessments (e.g., BDI, PHQ-9). In the research setting, especially in studies of community samples, the use of self-report questionnaires is more common and convenient. In the majority of studies that have examined inflammation in relation to specific symptoms of depression, assessment of the underlying constructs of depression was limited to one or two questions, which could underrepresent each measured construct. Thus, measuring depression-

related constructs more accurately by using assessment tools that specifically address each construct and examining how each construct relates to inflammation would be an important next step in this research domain. Given evidence linking inflammation to specific symptoms of depression including anhedonia, cognitive symptoms, psychomotor retardation and fatigue, limitations in the existing literature regarding assessments of these constructs will be discussed below.

Anhedonia: Loss of interest/ pleasure or anhedonia is defined as a core symptom of depression. Most studies that related inflammation to specific symptoms of depression have conceptualized anhedonia along with other symptoms under the cognitive dimension. In addition, in these studies (discussed in the previous section), the assessment of anhedonia was limited to one or two item(s). For example, it was assessed by one item on the PHQ-9 and one item on the HAMD. Importantly, hedonic function is multifaceted, and includes deficits in consummatory pleasure (i.e., experience of pleasure in response to positive stimuli), and anticipatory pleasure (i.e., "the pleasure that people experience at the thought of a future event") (Strauss, Wilbur, Warren, August, & Gold, 2011). One scale with a limited item coverage cannot adequately assess multiple aspects of anhedonia (Rizvi, Pizzagalli, Sproule, & Kennedy, 2016). Future studies need to incorporate assessment tools that explicitly assess different facets of anhedonia.

Cognitive symptoms: Cognitive impairment, including diminished ability to think or concentrate and indecisiveness, are included in the DSM-5 criteria for the diagnosis of MDD. Most studies relating inflammation to specific symptoms of depression have classified

psychological symptoms of depression (e.g., depressed mood/sadness/helpless, anhedonia, worthlessness, feelings of guilt, and thoughts of death /suicidal ideation) under the cognitive symptom dimension. Some studies did not include any core cognitive elements (i.e., "indecisiveness" or "difficulty concentrating") in their conceptualization of cognitive dimensions of depression. For example, Köhler-Forsberg et al. (2017) reported a positive association between the cognitive dimension and CRP levels; however, the cognitive dimension in this study was defined by the following items: pessimism, loss of interest, anhedonia and reduced activity, but not concentration impairment or indecisiveness. Notably, other cognitive domains can be impaired in depression that are not captured by the aforementioned items.

According to objective neurocognitive testing, patients with MDD may experience cognitive changes in executive functioning, psychomotor speed, attention, visual and verbal memory (Russo, Mahon, & Burdick, 2015). In the majority of the studies examining the association between cognitive symptoms and inflammation, assessment of cognitive dysfunction was limited to one or two questions. For example, core cognitive symptoms are assessed by two items (i.e., indecisiveness and concentration difficulty) on the BDI scale and a single item (i.e., trouble concentrating on things) on the PHQ-9. Hence, these scales likely underrepresent the construct of cognitive impairment, as researchers cannot assess multiple domains of cognitive functioning that might be disturbed in depression by using these scales.

Very few studies have examined inflammation in relation to objective measures of cognitive function in patients with MDD. One study found that poorer executive functioning was associated with higher levels of inflammation (i.e., CRP) in the entire sample of MDD patients

and healthy controls (Krogh et al., 2014). Another study found no association between CRP and attention or executive function in MDD patients (Chang et al., 2012). Additional evidence for the effects of inflammation on cognition is provided by studies that examined altered cognitive functioning following inflammatory challenge (i.e., immune therapy, typhoid vaccination, endotoxin exposure). For example, typhoid vaccination has been associated with impaired spatial memory (Harrison et al., 2014) and IFN therapy in HCV patients was associated with worse performance on working memory and verbal fluency (Lieb et al., 2006). However, some studies reported inconsistent findings; for example, IFN-α treatment was not associated with impairment in executive function, attention or working memory (Amodio et al., 2005; Bender et al., 2000; Capuron et al., 2001; Majer et al., 2008). Overall, further exploration of the associations between objective measures of cognitive functioning (i.e., performance on cognitive tests) and inflammation is needed to clarify whether specific cognitive symptoms of depression have underlying inflammatory etiology. This notion is a key component of the current study.

Psychomotor retardation: Based on the DSM-5 criteria for MDD, manifestations of psychomotor retardation include "slowed speech, thinking, and body movements; increased pauses before answering; speech that is decreased in volume, inflection, amount, or variety of content, or muteness" (American Psychiatric Association, 2013.) In general, psychomotor retardation has two aspects: the motor component and cognitive component. This could possibly explain the inconsistencies in conceptualization of this construct as a neurovegetative symptom or a cognitive symptom across studies. In the present study, psychomotor retardation is discussed as a separate construct from cognitive or neurovegetative symptoms. Interestingly, there are

neuropsychological tasks that assess motor or/and cognitive components (reviewed by Buyukduraa, McClintock, & Croarkina, 2011). For example, the finger-tapping test is a measure of motor function and the digit symbol substitution test can assess both motor and cognitive components (Buyukdura et al., 2011). Two studies have examined the association between inflammation and psychomotor speed among unmedicated MDD patients using multiple neurocognitive assessments. One study employed the reaction time tasks of the Cambridge Neuropsychological Test Automated Battery [CANTAB], Finger Tapping Test [FTT], Digit Symbol Substitution Test [DSST], and Trail Making Test A [TMT-A]) (Goldsmith et al., 2016). All tasks of psychomotor speed were combined to create a single psychomotor factor. Results revealed that higher IL-6 was reliably associated with worse performance on this psychomotor factor. Another study found that higher CRP correlated with motor slowing (measured by the FTT), and marginally correlated with psychomotor speed (measured by the TMT-A) (Felger et al., 2016). Additional support for these findings comes from inflammation-induced models. For example, two studies found that IFN-α treatment was associated with slower reaction time and motor speed (as measured by the reaction time task of the CANTAB) (Capuron, Ravaud, & Dantzer, 2001; Majer et al., 2008). Overall, the association between psychomotor processing and inflammation has repeatedly been shown in the context of inflammation-induced depressive symptoms, however, more studies need to explore this association among patients with MDD. In addition, measurements of both cognitive and motor components are needed to adequately assess the constructs of psychomotor retardation in the context of depression.

Fatigue: Loss of energy or fatigue is one criterion of MDD based on the DSM-5. Fatigue in widely used instruments that measure depressive symptoms is assessed by limited items; for example by two items on the BDI scale, a single item on the HAMD and one item on the PHQ-9. Importantly, it has been shown that fatigue has multiple domains, including behavioral, cognitive, somatic and affective (Stein, Jacobsen, Blanchard, & Thors, 2004). One study among patients with MDD reported a positive association between fatigue as measured by the multidimensional fatigue inventory (MFI) and inflammation (Felger et al., 2018); in this study TNF in cerebrospinal fluid (CSF) was associated with total MFI scores and the reduced motivation subscale of MFI. Additional support comes from inflammation-induced models. A large proportion of patients (up to 80%) developed fatigue symptoms following IFN therapy (Capuron et al., 2002). Increased glucose metabolism in the basal ganglia (i.e., putamen and left nucleus accumbens) following IFN therapy correlated with fatigue symptoms as measured by the "energy" subscale of the Visual Analog Scale of Fatigue (Capuron et al., 2007). Another study found higher scores on all five subscales of the MFI including general fatigue, mental fatigue, physical fatigue, reduced motivation and reduced activity following IFN therapy compared to baseline (Majer et al., 2008). In sum, there appears to be an association between inflammation and fatigue. More studies need to examine the association between inflammation and domains within fatigue in patients with major depressive disorder.

Together, it is obvious that depression includes multiple constructs. In addition, each of these constructs within depression is multifaceted, which further complicates the matter. Given that these facets might differ in their underlying neurobiology, relying on the severity of

depression (total depression score) in the context of etiological research might mask important information. Examining the neurobiological correlates of each construct and multiple facets within each construct could help unravel the complex pathophysiology of depression.

1.8 Current study (*Study 2*)

This study aimed to measure depression-related constructs (e.g., cognition) more accurately and examine how these constructs relate to inflammatory markers in individuals with mild to severe depressive symptoms (reflected by PHQ-9 $\geq$ 5). To accomplish these aims, a battery of questionnaires and laboratory-based tasks were employed to measure depression-related constructs.

Aim 1: To examine the degree to which inflammation is associated with depression severity.

Hypothesis 1. Higher inflammation is associated with higher severity of depressive symptoms.

Aim 2: To examine the degree to which inflammation is associated with various constructs within depression, including cognitive domains (i.e., inhibitory control, working memory and episodic memory), psychomotor processing (i.e., psychomotor speed and motor speed), anhedonia (i.e., anticipatory and consummatory anhedonia) and fatigue (i.e., total fatigue, mental fatigue, physical fatigue, general fatigue, reduced activity, and reduced motivation).

Hypotheses 2.1.-2.3 A priori hypotheses were not made regarding how inflammation and multiple cognitive domains (inhibitory control [*2.1*], working memory [*2.2*], episodic memory [*2.3*]) are related, given the limited evidence in this regard.

Hypotheses 2.4.-2.5. Higher inflammation is associated with slower processing speed (*2.4*) and motor speed (*2.5*).

Hypotheses 2.6.-2.7. Higher inflammation is associated with higher scores on consummatory (*2.6*) and anticipatory (*2.7*) anhedonia.

Hypotheses 2.8.-2.13. Higher inflammation is associated with higher scores on total fatigue (*2.8*). As an exploratory step, the associations between inflammation and each subscale of fatigue (general fatigue [*2.9*], physical fatigue [*2.10*], mental fatigue [*2.11*], reduced activity [*2.12*], reduced motivation [*2.13*]) were examined.

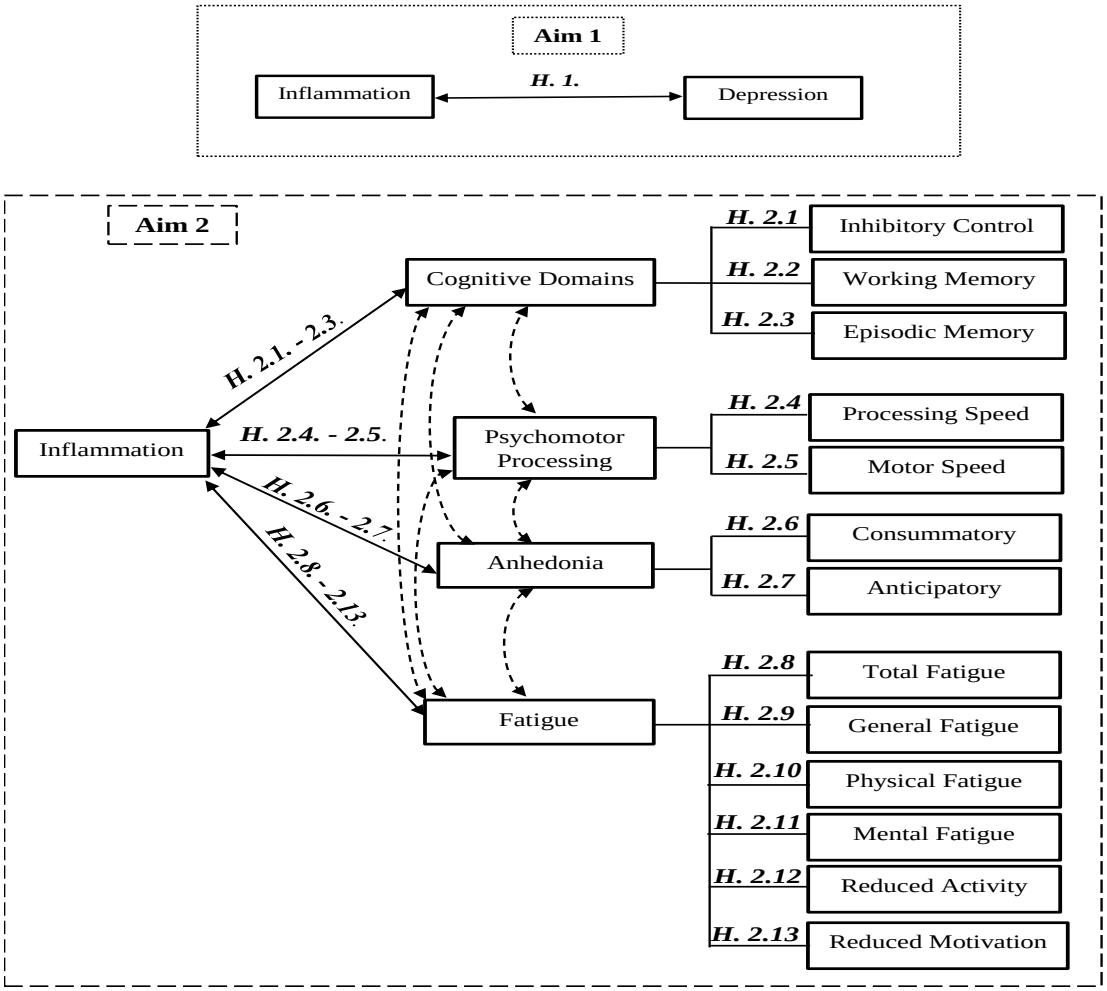

Figure 3. Theoretical model of Study 2 with specific hypotheses.

2. Methods-Study 2

2.1 Overview

This study is a cross-sectional design. Participation in this study involved two parts: 1) initial online screening (10-15 minutes); interested individuals were screened online for initial eligibility. 2) In-lab visit (up to 2h 50min); if participants met the inclusion/exclusion criteria based on the online screening, they were scheduled for an in-lab visit.

2.2 Participants

Approximately 190 interested individuals completed the online survey. Of these, 65 individuals were not eligible to participate. Approximately 44 individuals did not reply to the invitation email and 11 individuals did not show up for the in-lab visit. Of 70 participants who attended the in-lab visit, one was excluded because of the presence of Hashimoto's disease which is an inflammatory-related disorder. Given that 94% of participants were below 35 years of age, the present sample was not representative of an older age range (around 45 to 50 years). Thus, one participant with an age of 50 who was recruited at the beginning of data collection was excluded from analyses.

Inclusion criteria included men and women between the ages of 18 - 50 years, fluent in English with mild to severe depression as reflected by a Patient Health Questionnaire (PHQ-9) score of 5 or greater. Subjects were required to be stable on a current dose of antidepressants, or free from antidepressants - both for a minimum of 8 weeks prior to the study.

Subjects were excluded if they met any of the following criteria: active suicidal ideation or plan, psychotic disorders or mood disorders with psychotic features, severe eating disorders,

serious medical conditions including stroke, myocardial infarction, cancer, autoimmune disorders or inflammatory disorders, hepatitis B, C or Human Immunodeficiency Virus (HIV), evidence of infectious diseases within one month of screening that required treatment with antibiotics or antiviral agents, taking aspirin, non-steroidal anti-inflammatory agents or statins everyday within the past week, immunosuppressants, immunomodulatory agents (e.g., immunotherapy), antipsychotics, or mood stabilizers. Women who were post-menopausal, pregnant or lactating by self-report were excluded. Post-menopausal women were excluded because inflammatory profiles may differ by menopause status (Sites et al, 2002). In addition, pregnant or lactating individuals were excluded because depressive episodes during pregnancy or postpartum may be associated with various biological and psychological alterations due to reproductive hormones, which were not the focus of this study.

2.3 Procedure

Recruitment. Subjects were recruited from University Park in Centre County, PA. Advertisements via flyers, laboratory websites, the Penn State study finder website, and class announcements were used to recruit subjects. Flyers were distributed across University Park campus such as research labs, counseling and psychological services (CAPS), and the Clinical Research Center (CRC).

Initial online screening for eligibility. Interested individuals were screened online for initial eligibility. During the online screening process, participants were asked to complete: 1) a questionnaire to evaluate if they met inclusion and exclusion criteria (see appendix C), and 2) the patient Health Questionnaire 9-item (PHQ-9) (see appendix B). Subjects were scheduled for an

in-person visit if they met the initial inclusion and exclusion criteria and had a PHQ-9 score ≥5 with the items related to little interest/pleasure or feeling down/depressed/hopeless being scored at least 1 (i.e., several days). A PHQ-9 score of 5 to 9 represents mild depressive symptoms and a score of 10 or greater represents moderate to severe depression (Kroenke, Spitzer, & Williams, 2001). In the case that someone endorsed suicidality during the online screening session (as indicated by choosing "more than half the days" or "nearly every day" on item 9 of the PHQ-9), participants were directed to the contact information for the Penn State Psychological Clinic or Penn State Counseling and Psychological Services (CAPS) to set up an appointment.

In-person visit. This session was scheduled approximately within two weeks after the completion of online survey and took place at the Penn State Clinical Research Center. The structure of the in-person visit consisted of:

1. A detailed description of the study procedure was provided to subjects and explained (*approximately 10 minutes*). Candidates read and signed the informed consent form detailing procedures, compensation, etc.

2. The MINI interview was administered verbally (by M. M.) to screen for major depressive disorder and other mental disorders (*approximately 30-45 minutes*).

3. Body temperature, blood pressure, height, and weight were measured and the in-lab visit form was completed (see appendix D).

4. A blood sample was drawn by a certified nurse at the Clinical Research Center on the non-dominant arm. A single blood sample (10 milliliters) was collected into an EDTA-coated

collection tube to assess inflammatory biomarkers; the samples were kept in a refrigerator until centrifuged and processed.

5. Behavioral assessment: Participants completed the “Beck Depression Inventory”, “Multidimensional Fatigue Inventory” (see appendix E), and “Massachusetts General Hospital Cognitive and Physical Functioning” (see appendix F) questionnaires (*approximately 12 minutes*).

6. Cognitive and psychomotor tasks: Subjects completed neurocognitive tasks (*approximately 40 minutes*) (See appendices K to Q). At the beginning of the cognitive tasks, several demographic questions were completed by participants on an iPad. Specifically, they were asked about their gender, birthdate, race/ethnicity, age, handedness, their education level and their mother’s education. An iPad and a smart phone were provided to participants to complete neurocognitive tasks. Subjects were allowed to take breaks whenever they desired. Each test began with a practice session. The order of tasks was kept constant for all participants and was presented in the following sequence: 1) finger tapping test-one target (FTT1) with the dominant hand, 2) finger tapping test-one target with the nondominant hand, 3) finger tapping test-two targets (FTT2) with the dominant hand, 4) finger tapping test-two targets with the nondominant hand, 5) go/no-go test, 6) trail making test-A, 7) pattern comparison processing test, 8) picture sequence memory test, 9) list sorting memory test, and 10) digit symbol coding.

7. Behavioral assessments: Inventory of Depressive Symptomatology self-report (IDS) was administered to measure depressive symptoms. The Snaith-Hamilton Pleasure Scale (SHAPS) and the Temporal Experience of Pleasure Scale (TEPS), which are self-report

questionnaires, were administered to measure anhedonia (*approximately 22 minutes*) (see appendix G, H, I).

8. Participants were asked to complete a self-report survey (see appendix J) assessing demographic and socioeconomic variables (*approximately 10-15 minutes*).

9. Participants were compensated $50 for completing the study.

2.4 Measures

For a full list of all neuropsychological questionnaires and tasks, see Appendices B to Q. A summary of each construct and related measures is presented in Tables 7 & 8. Internal consistency of all questionnaires was assessed using Cronbach's alpha.

Neuropsychological assessments

Depressive symptoms. Depressive symptoms were assessed as part of the initial online screening using the PHQ-9, which is a self-report assessment tool containing 9 items that correspond to the DSM criteria for diagnosis of MDD (see appendix B) (Manea, Gilbody, & McMillan, 2015). The PHQ-9 showed a Cronbach's α of .77. Respondents answered questions regarding *how often* a symptom has bothered them over the last two weeks. Each item is rated on a 4-point scale, "0 (*not at all)*, 1 (*several days)*, 2 (*more than half the days)*, 3 (*nearly every day)*". Scores 0-4 represent minimal range, scores 5-9 represent mild depression, scores 10-14 represent moderate depression, scores 15-19 represent moderately severe depression, and scores 20-27 represent severe depression (Kroenke et al., 2001).

The MINI international neuropsychiatric interview, version 7.0.2 was administered verbally as part of the in-lab visit to screen for major depressive disorder and other mental

disorders, including suicidality, manic and hypomanic episodes, panic disorder, agoraphobia, social anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder, alcohol use disorder, substance use disorder, psychotic disorders, anorexia nervosa, bulimia nervosa (including binge eating disorder), generalized anxiety disorder, medical, organic or drug causes for all disorders, antisocial personality disorder. The MINI interview is a series of structured diagnostic interviews based on DSM-5 criteria for mental disorders including 17 Axis I disorders, a suicidality module, and one Axis II disorder (Sheehan et al., 1998). Each question has a "yes" or "no" answer. At the end of the MDD module, participants were asked at what age they had first experienced depressive symptoms such that symptoms caused dysfunction.

The Beck Depression Inventory (BDI) and Inventory of Depressive Symptomatology-Self Report (IDS-SR) were used to measure depressive symptoms as part of the "in-lab visit". The BDI is the most widely used depression measure (Beck et al., 1988; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). The BDI is a self-report assessment tool that consists of 21 items. The BDI showed a Cronbach's alpha of 0.90. Respondents answered questions regarding intensity of symptoms (i.e., the way they have been feeling during the past two weeks). Each item is rated on a 4-point scale "0 to 3".

The IDS self-report consists of 30 items (Rush et al., 1996). Each item is rated on a 4-point scale 0-3 (see appendix G). The IDS showed a Cronbach's alpha of 0.85. Respondents answered questions about the frequency of symptoms. Scores 0-14 are considered minimal range, scores 15-26 are considered mild depression, scores 27-37 are considered moderate depression, and scores 38 and over are considered severe depression (Trivedi, et al., 2004).

Fatigue. The Multidimensional Fatigue Symptom Inventory (MFI) was used to measure fatigue (see appendix E) (Smets, Garssen, Bonke, & De Haes, 1995). The MFI consists of 20 items and showed a Cronbach's alpha of 0.89. Each item is rated on a 5-point Likert scale, from (1) *that is true* to (5) *no that is not true*." The MFI includes five subscales, including general fatigue (Cronbach's alpha = 0.70), physical fatigue (Cronbach's alpha = 0.77), reduced motivation (Cronbach's alpha = 0.73), reduced activity (Cronbach's alpha = 0.79), and mental fatigue (Cronbach's alpha = 0.87) (Lin et al., 2009). The MFI subscales are defined as following: General fatigue includes items that capture both physical and psychological aspects of fatigue (e.g., I feel rested). Physical fatigue relates to physical sensations associated with fatigue (e.g., physically I feel only able to do a little). Mental fatigue relates to cognitive functioning (e.g., I can concentrate well). Reduced motivation pertains to lack of motivation to initiate any activity. Reduced activity relates to the effect of physical and psychological factors on the level of activity (e.g., I get little done) (Lin et al., 2009).

Anhedonia. Two self-report measures of anhedonia were used: the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) and the Temporal Experience of Pleasure Scale (TEPS) (Gard, Gard, Kring, & John, 2006). The SHAPS consists of 14 items that mainly focus on consummatory pleasure (i.e., experience of pleasure in response to positive stimuli) (see appendix H). The SHAPS showed a Cronbach's α of 0.87. Each item is rated on a 4-point scale, (1) *definitely agree*, (2) *agree*, (3) *disagree*, (4) *definitely disagree*. Either of the *agree* items scored zero points and the *disagree* items scored one point. The TEPS consists of 18 items with a 6-point Likert scale from (1) *very false for me* to (6) *very true for me* (see appendix J). TEPS has

a two-factor structure with 10 items measuring anticipatory pleasure (i.e., the pleasure that people experience at the thought of a future event) (Strauss et al., 2011) and 8 items measuring consummatory pleasure (Gard et al., 2006). Cronbach's alphas for overall score, anticipatory and consummatory scales were 0.84, 0.79 and 0.67 respectively.

Psychomotor processing. Both motor and cognitive aspects of psychomotor processing were measured. The Finger Tapping Test (FTT) was employed to measure the motor component (see appendix Q) (Buyudura et al., 2011). In this task, subjects were asked to tap a touch screen with their index finger of their dominant and non-dominant hands separately as fast as possible for a restricted time (20 seconds) for three trials. This task consisted of two phases: one-target and two-target phases. During the one-target phase, participants were asked to tap inside a one-circle target as quickly as possible. During the two-target task, participants were asked to tap two circles back and forth as quickly as they can. The means of the three trials for each task were calculated for each hand. A higher score reflects better motor performance. Subjects completed the finger tapping tests using a touch screen phone.

Processing speed was measured by performing three tasks: the Digit Symbol Test (DST), Pattern Comparison Processing (PCP), and Trail Making Test A (TMT-A). The DST included boxes with symbols on the top of each box and numbers on the bottom of each box (Germine et al., 2012). Each symbol was paired with each number (see appendix K). To perform this test, a symbol appeared on the top of screen, and subjects were asked to tap the button with its number corresponded to that symbol. While performing the task, the boxes with paired symbols and numbers were present on the screen, meaning subjects did not need to memorize which numbers

matched which symbols. Both motor and cognitive aspects of psychomotor retardation can be assessed by this test (Buyudura et al., 2011). The number of correct items in 90 seconds were counted.

The TMT-A was administered by using a sheet of paper (see appendix L). Subjects were asked to connect 25 circles that contained numbers in an ascending order as fast as possible without lifting the pencil from the sheet (Buyudura et al., 2011; Strauss et al., 2006). The completion time was recorded.

The pattern comparison processing speed test (PCP) is part of the National Institute of Health (NIH) toolbox cognition battery (see appendix M). Subjects were asked to identify whether two side-by-side pictures on the screen were the *same* or *not the same* as fast as possible by touching a *yes* or *no* button. The number of items answered corrected during 85 seconds were counted (Carlozzi, Beaumont, Tulsky, & Gershon, 2015).

Inhibitory control. The go/no-go test was used to measure the inhibitory control component of executive function (see appendix N). In this task, cues were presented to the participants on the screen and a motor response was requested (i.e., press a button). In this test, letters were flashing quickly on the screen. Participants were asked to tap a button as quickly as possible when they saw a letter, except for "X". The number of incorrect items across 120 trials were recorded. Subjects completed the go/no-go task using a touch screen phone.

Working memory. The list sorting test, which is part of the NIH toolbox cognition battery, was used to measure working memory (see appendix O) (Weintraub et al., 2013). To perform this task, participants were required to recall and repeat a series of stimuli that were

presented visually and orally in order of size, from smallest to largest. Number of correct items across trials were recorded.

Episodic memory. The picture sequence memory, which is part of the NIH toolbox cognition battery, was used to measure episodic memory (see appendix P) (Weintraub et al., 2013). Participants were asked to reproduce a sequence of pictures that were presented on the screen. Pictures appeared in the center of the screen one at a time and then moved into a fixed spatial order. This continued until the entire sequence was presented on the screen. Then, all pictures appeared in the center of the screen in a random manner and participants were asked to move the pictures in the same way they saw them on the screen. Scores were calculated by the cumulative number of adjacent pairs of pictures moved correctly over 3 trials (Weintraub et al., 2013).

Subjective assessment of cognitive function. The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) is a subjective cognitive scale that has been psychometrically validated in patients with MDD (see appendix F) (Fava, Iosifescu, Pedrelli, & Baer, 2009; Lam, 2016). The CPFQ measures both subjective fatigue and cognition and consists of seven items including motivation/interest/enthusiasm, wakefulness/alertness, energy, ability to focus/sustain attention, ability to remember/recall information, ability to find words, and sharpness/mental acuity. The CPFQ showed a Cronbach's alpha of 0.81. Each item is rated on a 6-point Likert scale, "from 1, *greater than normal* to 6, *totally absent*".

Inflammatory biomarkers

Blood samples were drawn between 9 AM and 5 PM by a certified phlebotomist. In the present study, blood was drawn before cognitive tasks. Several reasons favor the notion that it is better to draw blood at the beginning of the study (i.e., before cognitive tasks). First, it is consistent with practice from the existing literature. In studies of this kind, blood samples were drawn before cognitive tasks. Second, the primary aim of this study involves measuring baseline/resting inflammation, not stress-induced inflammation. Given that cognitive tasks may serve as a stressor, quantifying cytokines in blood samples by the end of the study may be reflective of an acute inflammatory response due to stress. Indeed, measures of cognitive control, such as the Stroop test, have been employed as a psychosocial stress task in prior studies (reviewed by Steptoe et al., 2007).

Whole blood was centrifuged at 3000rpm, 1500g for 15 minutes at room temperature. The supernatants were aliquoted and stored at -80°C. High sensitivity C-reactive protein (CRP), and pro- (IL-6, IL-17, TNF-α) and anti- inflammatory cytokines (IL-10) were quantified via multiplex arrays using commercial assay kits (Meso Scale Discovery, Rockville, MD). Multiplex array technology has several advantages compared to traditional enzyme linked immunosorbent assay (ELISA); it allows simultaneous measurement of interrelated cytokines in the same sample, less sample is required, and it saves time and cost (Zhou et al., 2010). For CRP, the minimum detection limit ranges from 0.69 to 19.8 pg/ml, intra-assay CVs range from 2.2 to 4.1% and inter- assay CVs range from 6.7 to 9.9%. For cytokines, the minimum detection limit ranges from 0.01 to 0.55 pg/ml for each analyte, inter- assay CVs are below 12%, and intra- assay CVs

are below 11%. All samples were run in duplicate. One participant had adverse reactions from blood collection, thus no blood was drawn from this subject. One sample had a higher than 15% coefficient of variation for CRP, thus this sample was excluded from the current analyses. To minimize the influence of outliers, values greater than 3 *SD* above the mean were winsorized to 3 *SD* for each inflammatory marker.

2.5 Covariates

Given that both inflammation and depression have been linked with age and gender (O'Connor et al., 2009), analyses were controlled for these variables. The analyses were further statistically controlled for antidepressant use and BMI. Given that all participants had at least some college education and that the sample was predominantly White, neither education or race/ethnicity were included as covariates. Additional adjustment for time of blood draw (AM versus PM) as a covariate did not change the results; thus, this factor was not included in the final analyses. Three participants had a diagnosis of attention deficit disorder and were stable on their current dose of stimulants for at least three months. Removing this subsample did not change the results, therefore they were retained in the final analyses. Only 6% of participants reported that they were smokers, thus tobacco use was not included in the models.

2.6 Statistical analyses

Data analyses were conducted using SAS software, Version 9.4 (SAS Institute Inc., Cary, North Carolina), and IBM SPSS Statistics, Version 22.0 (Armonk, NY). A value of $p < 0.05$ was considered statistically significant. Demographic and clinical characteristics and inflammatory values were reported by using means and standard deviations for continuous variables and

percentages for categorical variables. Independent-samples t-tests were conducted to compare continuous variables across men and women and antidepressant use groups. In addition, Chi square tests were used to compare these groups in terms of categorical variables. Multiple linear regression analyses were conducted to determine the relationship between inflammatory markers and total depression score, anhedonia, fatigue, psychomotor processing, and cognitive functioning. Standardized beta estimates and 95% confidence intervals are reported for each association. In addition, partial eta-squared is reported as the estimate of effect size; partial eta-squared is the proportion of variance in the dependent variable that is explained by a given variable (Brown, 2008). The values of 0.01, 0.06 and 0.14 for partial eta-squared have been suggested to represent small, medium, and large effect sizes, respectively (Draper, 2002). Log-10 transformation of inflammatory data was conducted prior to analyses to normalize the data. Given the limited data currently available on the associations between specific symptoms of depression and various inflammatory cytokines, we decided to report the results for each cytokine separately and not to calculate an inflammatory composite. This approach may help elucidate the role of each cytokine with respect to specific depressive symptoms. For example, this approach would allow us to explore which cytokine(s) is/are more strongly associated with fatigue. This decision was supported by the results of principal component analysis (PCA). We used PCA with varimax rotation (i.e., orthogonal rotation) to determine whether all cytokines form a single cluster (factor loadings are shown in Table 9). The Kaiser-Meyer Olkin (KMO) value, an index of sampling adequacy for a factor analysis, was 0.493. A KMO value of less than 0.5 indicates that the data are not acceptable for using PCA (Kaiser, 1974). Hence, the results of

PCA did not support the use of an inflammatory composite. Therefore, in the main-effect models, each inflammatory marker was entered as a predictor variable and the score for each psychological/cognitive measure was entered as an outcome variable (all predictors and outcomes are shown in Table 10). Covariates were sequentially added to the regression models as follows: 1) age, gender, and antidepressant use (model 1); 2) BMI (model 2). The present study examined 20 outcome variables, therefore, the sequential entry method was employed to gain a better understanding of which covariates impact the relationship between inflammation and the dependent variable. Importantly, given that prior studies suggest that heightened BMI (e.g., obesity) is a potential pathway linking specific symptoms of depression with elevated inflammation (e.g., Case and Stewart, 2014; Duivis et al., 2013), the sequential entry of covariates can help better inform whether BMI explained the association between specific symptoms of depression and inflammation. Moreover, if the association between a predictor and an outcome became significant after adding a covariate to regression models, an interaction between the predictor and covariate was examined in an exploratory step. Because the present study might have been underpowered to detect interaction effects, even when the interaction terms were non-significant (e.g., interaction of CRP × antidepressants on general fatigue score) follow-up regression analyses were performed to explore the association between the predictor and outcome at different levels of the covariate (e.g., those who are taking antidepressants versus not). These findings are reported in the unadjusted and adjusted models. It should be noted that these latter analyses were exploratory. As an exploratory step, subjects were categorized into high inflammation (CRP>3mg/L) and low to medium inflammation (CRP≤3 mg/L) groups and

independent-samples t-tests were conducted to examine whether depressive symptoms and cognitive performance differ across these two groups (for more information on CRP cutoff scores see Miller et al., 2013).

2.7 Power analysis

Statistical power is defined as the probability of detecting an effect (i.e., rejecting the null hypothesis) when there is an effect to be detected (i.e., the null hypothesis is false). The power value of 0.80 or higher is recommended as a general rule (80% chance of detecting a real effect) (Cohen et al., 1992). Power analyses were conducted using a range of parameter values according to prior studies. Based on a meta-analysis, effect sizes (*d)* for the associations between total depression score and inflammatory biomarkers were 0.22 for CRP and 0.25 for IL-6 (Howren et al., 2009). In addition, based on prior research, correlation coefficients for the associations between inflammatory markers and specific symptoms of depression (i.e., as measured by self-report questionnaires or neurocognitive tasks) ranged from 0.20 to 0.58 (more details in Table 11). For the proposed study, the following specifications were used to estimate the sample size (anticipated effect size: $r = 0.30$, desired power = 0.80, alpha = 0.05), which yielded 85 participants. With a sample size of 68, the power of detecting an association for a correlation coefficient of 0.30 is approximately 0.70.

3. Results-Study 2

3.1 Sociodemographic characteristics

Subject characteristics are shown in Table 12. Sixty-eight subjects with a mean age of 23.5 ± 5.7 years (78% women) were included in the analysis. The racial composition of the sample was 75% White, 19% Asian and 6% Black/African-American. All participants completed high school. Approximately 74% were college students and 26% had completed a Bachelor's degree or higher. No differences were observed between men and women in demographic characteristics (all *p's* > .3).

3.2 Clinical characteristics

Table 13 summarizes the clinical characteristics of the sample. The mean depression score (as measured by the IDS) was 29.9 ± 10.7, reflecting moderate severity of depressive symptoms. Approximately 65% of participants reported that they had been diagnosed with depression by a health care professional in their lifetime. Based on the MINI interview, 55% of the subjects met DSM-5 criteria for a current major depressive episode and 96% for a past major depressive episode. According to subjects' self-report, the mean age at onset of depression was 16.1 ± 4.6 years. On average, participants reported eight depressive episodes in their lifetime. A family history of unipolar depression was reported by 48% of the subjects. Sixteen percent of the subjects reported prior suicide attempts. Based on the MINI interview, approximately 16% had substance use disorder (i.e., marijuana use) and 22% had alcohol use disorder. The most comorbid condition was generalized anxiety disorder (35%). Women reported higher severity of depressive symptoms, as measured by the IDS, compared with men (t =2.39, p = .02). No

differences were observed between men and women in other clinical characteristics. Three subjects had comorbid attention deficit/hyperactivity disorder; these subjects were stable on a dose of stimulant for at least three months. Total depression score was not significantly correlated with BMI (r = .09, p = .46) or age (r = -.007, p = .96). Correlations between total depression score and other subjective measures of depressive symptoms (i.e., anhedonia, pleasure, fatigue, cognition) are presented in Supplemental Table 6 [S6].

Twenty-six participants were taking antidepressants. Of these, 23% (n = 6) were in remission (a score of ≤14 on the IDS). Clinical characteristics by antidepressant use are shown in Table 14. No differences were observed between these two groups with respect to severity of depressive symptoms. However, subjects who were taking antidepressants reported a greater number of previous depressive episodes than those who were free from antidepressants (t = -2.35, p = .02). It is important to note that the reported number of previous depressive episodes are subject to recall bias. Substance use disorder was found to be higher in those who were not taking antidepressants compared with those who were taking antidepressants (24% versus 4%, respectively; $\chi 2$ (1) = 5.61, p = .02). In addition, the antidepressant group reported greater scores on pleasure (t = -2.34, p = .02), lower levels of anhedonia (t = 1.96, p = .05) and lower scores on a subjective assessment of cognitive impairment (t = 2.22, p = .03) compared to the antidepressant-free group. No differences were observed between these two groups with respect to BMI (t = 1.47, p = 0.15).

3.3 Neurocognitive assessments

Descriptive data on neurocognitive tests are provided in Table 15. Average performance on psychomotor processing speed tests as measured by the trail making test-A (17.9 ± 4.21), digit symbol test (54.7 ± 5.9), and finger tapping test-one target (dominant hand: 124 ± 15, nondominant hand: 107 ± 13) was above normative standards (see Table 16 for normative data on these tests). In addition, the average score on the pattern comparison processing speed test (129 ± 16) was 2 *SD* above the NIH normative mean of 100 (*SD* = 15) and the average score on episodic memory (117 ± 14) was 1 *SD* above the NIH normative mean of 100 (*SD* = 15). The mean score on working memory test (109 ± 9) was close to the NIH normative mean. Men exhibited a higher frequency of the finger tapping test-one target for the dominant hand (i.e., motor speed) compared with women (t = -1.98, p = .05). No differences were observed in other neurocognitive tests across gender. No significant correlations were observed between total depression score and any of the cognitive measures (see Table S7). Correlations between cognitive measures and subjective measures of depressive symptoms (i.e., fatigue, pleasure, anhedonia) are presented in Table S7. In addition, correlations between objective cognitive measures are presented in Table S8.

3.4 Inflammatory biomarkers

Non-log transformed levels of CRP and basal cytokines are shown in Table 17. CRP significantly correlated with IL-6 (r = 0.56, p < .001) and TNF-α (r = .25, p = .04) (see Table 18). Significant correlations were observed between IL-6 and TNF-α (r = .37, p = .002), and IL-10 and TNF-α (r = .27, p = .02). No significant correlations were observed between IL-17 and

other inflammatory markers (*r's* ≤ .1, *p's* > .3). BMI was significantly associated with CRP (*r* = .58, *p* < .001), IL-6 (*r* = .74, *p* < .001) and TNFα (*r* = .34, *p* < .05).

No differences were observed between men and women in levels of inflammatory biomarkers (see Table 17-A). Approximately 42% of the subject had *low* inflammation levels [i.e., plasma CRP concentrations <1mg/L], 37% had *high* inflammation [CRP >3mg/L] and 18% had *medium* levels of inflammation [1 ≤CRP≤ 3 mg/L] (see Table 17-B) (for more information on CRP cutoff scores see Miller et al., 2013). Regarding the categorical measure of inflammation, men were more likely to exhibit low levels of inflammation than women (CRP <1mg/L; 60% versus 37%, respectively) ($\chi 2$ (2) = 7.20, *p* = .03). Participants who were taking antidepressants had higher levels of CRP (*t* = 3.63, *p* = .001) and IL-17 (*t* = 2.39, *p* = .02) than those who were not taking antidepressants (see Table 14). No differences were observed with respect to inflammatory markers between those who met criteria for a current major depressive episode and those who did not (all *p's* >.3). Similarly, no association was observed between inflammation and the number of previous episodes of depression. However, lower TNF-α was associated with a greater number of years affected by depression (*r* = -.26, *p* =.04). A follow-up analysis showed that this negative association was only evident in the antidepressant-free group (*r* = -.48, *p* =.003), but not in the antidepressant group (*r* = .05, *p* =.81). In addition, a negative association between IL-10 and number of years affected by depression was observed in the antidepressant-free group (*r* = -.34 *p* =.04).

3.5 Aim 1 results

3.5.1 Total severity of depression

To examine the degree to which inflammation is associated with depression severity (i.e., total depression score).

Results of unadjusted and fully adjusted analyses (i.e., standardized *beta* coefficients, *SE*, 95% confidence intervals, partial eta-squared, *p* values) are presented in Table 19. Regression analysis revealed no significant main effects of CRP or cytokine levels on total depression score in both the unadjusted and fully adjusted (i.e., controlling for age, gender, antidepressant use and BMI) models, with the exception of TNF-α (see Table 19). Higher levels of TNF-α was associated with lower severity of depression in the fully adjusted model (*beta* = -.30, *p* = .02), but not in the unadjusted model (*beta* = -.19, *p* = .12). An exploratory step was conducted to examine which covariate changed this association. When BMI was added to the model, the association between TNF-α and total depression score became significant (*beta* = -.29, *p* = .03). Exploratory analyses revealed a marginally significant interaction of TNF-α × BMI on total depression score (*beta* = -.25, *p* = .05). As an exploratory step, separate regression analyses were conducted to explore the associations between TNF-α and total depression score by BMI categories. In individuals with BMI ≥ 25 (*n* = 32), higher TNF-α was associated with lower severity of depression (*beta* = -.39, *p* = .03). This association was not evident in individuals of healthy weight (*n* = 36; *beta* = .02, *p* = .91).

3.6 Aim 2 results

Results of unadjusted and fully adjusted analyses (i.e., standardized beta coefficients, SE, 95% confidence intervals, partial eta-squared, *p* values) are presented in Tables 20 to 40.

3.6.1 Cognitive domains

To examine the degree to which inflammation is associated with deficits in cognitive domains including executive function and episodic memory.

Regarding the inhibitory control test, higher levels of CRP (*beta* = .27, *p* = .03), IL-6 (*beta* = .28, *p* = .01) and IL-17 (*beta* = .29, *p* = .01) were significantly associated with worse response inhibition (i.e., higher error rates) in the unadjusted model (see Table 20). Results remained significant after controlling for age, gender, and antidepressants. When BMI was added to the model the associations became marginally significant for CRP (*beta* = .27, *p* = .09) and IL-6 (*beta* = .32, *p* = .07). The results remained significant for IL-17 (*beta* = .32, *p* = .009). An exploratory step was conducted to examine if motivation or fatigue explained the association between response inhibition and inflammation. Results revealed that the association between CRP and worse response inhibition became stronger after controlling for fatigue in model 2 (*beta* = .33, *p* = .02) and remained the same in the unadjusted and fully adjusted models. The associations between IL-6 and IL-17 and worse response inhibition remained the same after adjustment for fatigue in all models. Results did not change after inclusion of anhedonia in any of the models.

There were no significant main effects of CRP or cytokine levels on either episodic memory (see Table 21) or working memory (see Table 22) in either unadjusted or fully adjusted

models (all *p's* > 0.1). With respect to other significant predictors in the model, greater age was associated with worse performance on episodic memory as measured by the picture sequence memory test (*beta* = -.22 to -.29, *p's* < .05).

3.6.2 Psychomotor processing

To examine the degree to which inflammation is associated with psychomotor speed.

There were no significant associations between inflammatory markers and performance on the digit symbol coding test, trail making test-A, or pattern comparison processing speed test with the exception of IL-17 (see Table 23-25). Higher levels of IL-17 were associated with better performance on the trail making test-A in both the unadjusted (*beta* = -.27, *p* = .02) and fully adjusted models (*beta* = -.29 and -.30, *p's* ≤ .05). An exploratory step was conducted to examine if anhedonia or fatigue explained these associations. Results remained the same after adjustment for anhedonia or fatigue. With respect to other predictors in the model, greater age was associated with lower processing speed as measured by the digit symbol coding test.

Regarding motor speed, no significant associations were observed between inflammatory markers and finger tapping test performance, with the exception of IL-17 (See Table 26-29). Analysis of the unadjusted model revealed that higher IL-17 was significantly associated with motor slowing (i.e., lower frequency of tapping) as measured by the finger tapping test-two targets (on non-dominant hand only) (*beta* = -.25, *p* = .04; Table 29). This association became nonsignificant in the model 1 (*beta* = -.21, *p* = .10), and marginally significant in the fully adjusted model (*beta* = -.23, *p* = .08). An exploratory step was conducted to explore which covariate explained this association. When antidepressant use was added to the model, the

association between IL-17 and motor speed became non-significant (*beta* = .21, *p* = .09). Controlling for age, sex and BMI did not change the association between IL-17 and motor speed. Significant additional predictors of the finger tapping test-one target included gender, with men exhibiting a higher frequency of tapping (*beta* = .30, *p* = .02) than women.

An exploratory step was conducted to examine if motivation or fatigue explained the association between slower motor speed and IL-17. Results revealed that this association became stronger after controlling for fatigue in all three models (unadjusted: *beta* = -.29, *p* = .01; model 1: *beta* = -.24, *p* = .05; model 2: *beta* = -.25, *p* = .04). A similar pattern of results was observed after adjusted for anhedonia (unadjusted: *beta* = -.27, *p* = .03; model 1: *beta* = -.23, *p* = .07; model 2: *beta* = -.24, *p* = .06).

3.6.3 Anhedonia and pleasure

To examine the degree to which inflammation is associated with anhedonia.

Anhedonia: Higher TNF-α was associated with lower levels of anhedonia (as measured by the SHAPS) in both the unadjusted (*beta* = -.30, *p* = .01) and fully adjusted models (*beta* = -.32 and -.36, *p's* ≤ .01). No significant associations were observed between other inflammatory markers and anhedonia (see Table 30). Other predictors of anhedonia in the model included antidepressant use, with those who were taking antidepressants reporting lower levels of anhedonia (*beta* = -.25, *p* = .04).

Pleasure: No significant associations were observed between inflammatory markers and total pleasure score (as measured by the TEPS), with the exception of IL-17 (Table 31). Unadjusted model analysis revealed a significant positive association between IL-17 and total

pleasure score (*beta* = .26, *p* = .03). This association became non-significant in the adjusted models (i.e., models 1 and 2). An exploratory step was conducted to explore which covariate explained this association. When antidepressant use was added to the model, the association between IL-17 and pleasure became non-significant (*beta* = .20, *p* = .10). Controlling for age, sex and BMI did not change the association between IL-17 and pleasure. Subscale analyses revealed that the association between IL-17 and total pleasure score was driven by the consummatory pleasure subscale of the TEPS (unadjusted model: *beta* = .29, *p* = .02; fully adjusted model: *beta* = .25, *p* = .048; Table 32), but not the anticipatory pleasure subscale (unadjusted model: *beta* = .20, *p* = .10; fully adjusted model: *beta* = .14, *p* = .26; Table 33). No other significant associations were observed between other inflammatory markers and either anticipatory pleasure or consummatory pleasure.

3.6.4 Fatigue

To examine the degree to which inflammation is associated with fatigue.

Total fatigue: Unadjusted analyses revealed no association between CRP and total fatigue score (*beta* = .19, *p* = .13; see Table 34). This association became significant after controlling for age, gender, antidepressant use (i.e., model 1). Thus, an exploratory step was conducted to explore which covariate changed this association. When antidepressant use, but not age or gender, was added to the unadjusted model, the association between CRP and total fatigue score became significant (*beta* = .31, *p* = .02). When BMI was added to the model 1, this association was no longer significant (*beta* = .27, *p* = .09). Similarly, when BMI was added individually to the unadjusted model, the association between CRP and total fatigue score became

nonsignificant (*beta* = .13, *p* = .38). Another significant predictor of total fatigue in the fully adjusted model was antidepressant use (*beta* = -.34, *p* = .01), with those who were taking antidepressants reporting lower levels of total fatigue. No significant associations were found between other inflammatory markers and total fatigue.

Exploratory analyses revealed no significant interaction of CRP × antidepressants on total fatigue score (*beta* = -.09, *p* = .46). Separate regression analyses were conducted to explore the associations between CRP and total fatigue score by antidepressant use. In the antidepressant-free group, higher CRP was associated with higher total fatigue, controlling for age and sex (*beta* = .42, *p* = .01). When BMI was added to this model, the association between CRP and total fatigue was no longer significant (*beta* = .37, *p* = .12). No significant association was observed in the antidepressant group (*beta* = .21, *p* = .30).

General fatigue: Subscale analyses revealed that higher CRP was associated with greater general fatigue in both the unadjusted model (*beta* = .25, *p* = .046) and model 1 (*beta* = .31, *p* = .02) (See Table 35). When BMI was added to the model 1, this association became non-significant (beta = .21, *p* = .20). In addition, higher IL-6 was marginally associated with greater general fatigue in both the unadjusted model (*beta* = .23, *p* = .06) and model 1 (*beta* = .24, *p* = .05). No significant associations were found between other inflammatory markers and general fatigue score. An additional predictor of general fatigue in the models was BMI (*beta* = .27 to .28, *p's* < .05).

Exploratory analyses revealed a significant interaction of IL-6 × antidepressants on general fatigue score (*beta* = -.24, *p* = .046), and a marginally significant interaction of CRP ×

antidepressants on general fatigue score (*beta* = -.24, *p* = .06). Separate regression analyses were conducted to explore the associations between CRP and IL-6, and general fatigue score by antidepressant use. In the antidepressant-free group, higher CRP (*beta* = .43, *p* = .005) and IL-6 (*beta* = .37, *p* = .01) were associated with higher general fatigue score, controlling for age and sex. When BMI was added to this model, these associations were no longer significant (*for CRP*: *beta* = .26, *p* = .17; *for IL-6*: *beta* = .15, *p* = .43). No significant associations were observed in the antidepressant group (*for CRP*: *beta* = .08, *p* = .70; *for IL-6*: *beta* = .04, *p* = .86).

Physical fatigue: Subscale analyses revealed that higher IL-6 was associated with greater physical fatigue in both the unadjusted model (*beta* = .28, *p* = .02) and model 1 (*beta* = .30, *p* = .02). When BMI was added to the model 1, these results became non-significant (*beta* = .25, *p* = .18) (See Table 36). No significant associations were observed between CRP, IL-10, IL-17 or TNF-α and physical fatigue.

Exploratory analyses revealed no significant interaction of IL-6 × antidepressants on physical fatigue (*beta* = -.07, *p* = .56). Separate regression analyses were conducted to explore the associations between IL-6 and physical fatigue by antidepressant use. In the antidepressant-free group, higher IL-6 was associated with higher physical fatigue, controlling for age and sex (*beta* = .30, *p* = .049). When BMI was added to this model, this association was no longer significant (*beta* = .16, *p* = .43). No significant associations were observed in the antidepressant group (*beta* = .33, *p* = .11).

Mental fatigue: Unadjusted analyses revealed no association between CRP and mental fatigue (*beta* = .18, *p* = .14; Table 37). This association became significant after controlling for

age, gender, and antidepressant use (i.e., model 1; *beta* = .32, *p* = .02). An exploratory step was conducted to explore which covariate changed this association. When antidepressant use, but not age or gender, was added to the unadjusted model, the association between CRP and mental fatigue became significant. When BMI was added to the model 1, it did not change the results (*beta* = .44, *p* = .006). Another significant predictor of mental fatigue in the fully adjusted model was antidepressant use (*beta* = -.35, *p* = .01), with those who were taking antidepressants reporting lower levels of mental fatigue. No significant associations were found between other inflammatory markers (i.e., IL-6, IL-10, IL-17, TNF-α) and mental fatigue score.

Exploratory analyses revealed no significant interaction of CRP × antidepressants on mental fatigue score (*beta* = -.03, *p* = .82). Separate regression analyses were conducted to explore the associations between CRP and mental fatigue score by antidepressant use. In the antidepressant-free group, higher CRP was associated with higher mental fatigue score, controlling for age and sex (beta = .35, *p* = .01). When BMI was added to this model, this association remained significant (beta = .52, *p* = .006). No significant association was observed in the antidepressant group (*beta* = .24, *p* = .25).

Reduced Motivation: No associations were observed between any inflammatory markers and reduced motivation in the both unadjusted and adjusted models (all *p's* > .3; Table 38).

Reduced activity: Unadjusted analyses revealed no association between CRP and reduced activity score (*beta* = .17, *p* = .18; Table 39). This association became significant after controlling for age, gender, and antidepressant use (i.e., model 1; *beta* = .27, *p* = .03). An exploratory step was conducted to explore which covariate changed this association. When

antidepressant use was added to the model, but not age or gender, the association between CRP and reduced activity became significant. When BMI was added to this model this association became marginally significant (*beta* = .29, *p* = .06). An additional predictor of reduced activity in this model was antidepressant use (*beta* = -.30, *p* = .02), with those who were taking antidepressants reporting lower levels of reduced activity. No significant associations were found between other inflammatory markers (i.e., IL-6, IL-10, IL-17, TNF-α) and reduced activity score.

Exploratory analyses revealed no significant interaction of CRP × antidepressants on reduced activity score (*beta* = .06, *p* = 0.61). Separate regression analyses were conducted to explore the associations between CRP and reduced activity score by antidepressant use. In the antidepressant-free group, no association was observed between CRP and reduced activity in the both unadjusted and adjusted models (*beta* = 19, *p* = .24). A marginally significant association was observed between CRP and reduced activity in the antidepressant group, controlling for age and gender (*beta* = .35, *p* = .09). When BMI was added to this model this association was no longer marginally significant (beta = .32, *p* = .16).

3.6.5 Subjective cognitive assessment

To examine the degree to which inflammation is associated with subjective cognitive impairment.

No significant associations were observed between inflammatory markers and subjective reports of cognitive impairment, with the exception of IL-6 (Table 40). Unadjusted analyses revealed no association between IL-6 and subjective reports of cognitive impairment (*beta* = -.12, *p* = .33). This association became significant after controlling for the model 2 (*beta* = -.41, *p* = .02). An exploratory step was conducted to explore which covariate changed this association.

When BMI (but not age, gender or antidepressant use) was added to the unadjusted model, the association between IL-6 and subjective reports of cognitive impairment became significant. Exploratory analyses revealed no significant interaction of IL-6 × BMI on subjective report of cognitive impairment (*beta* = -.05, $p = .63$). As an exploratory step, separate regression analyses were conducted to explore the associations between IL-6 and subjective cognitive impairment by BMI categories. No associations were observed in individuals with BMI ≥ 25 (*beta* = -.18, $p = .32$) or individuals of healthy weight (*beta* = -.08, $p = .77$). Another significant predictor of subjective reports of cognitive impairment in the models was antidepressant use (*beta* =-.26 to -.33, $p < .05$), with those who were taking antidepressants reporting lower levels of cognitive impairment.

3.7 Comparisons across inflammation groups

Based on exploratory analyses, no significant differences were observed between the two inflammation groups with respect to subjective measures of depression (i.e., severity of depression, anhedonia, fatigue). Regarding cognitive domains, individuals in the high inflammation group (CRP>3mg/L) had slower psychomotor speed as measured by the trail making test-A compared to individuals with low to medium inflammation (CRP≤3mg/L) ($t = -2.15$, $p = .03$).

4. Discussion-Study 2

The present study sought to measure various constructs within depression and examine whether these constructs were differentially associated with inflammation. This study primarily consisted of young adults (94% were below 35 years of age) with mild to severe depressive symptoms. Approximately 55% of the sample met DSM-5 criteria for a current major depressive episode. Given that most studies relating depression to inflammation have been conducted among adults with a mean age of 40 years or greater, evidence on the depression-inflammation link among young adults is scarce.

The first aim of this study was to examine the degree to which inflammation was associated with depression severity. The second aim of this study was to examine the degree to which inflammation was associated with cognitive domains (i.e., inhibitory control, working memory and episodic memory), psychomotor processing (i.e., psychomotor speed and motor speed), anhedonia (i.e., anticipatory and consummatory anhedonia) and fatigue (e.g., total fatigue, mental fatigue, physical fatigue, general fatigue).

Of note, due to the multiple number of models that were tested in the present study, a proportion of the observed results might be due to chance. Hence, the strengths of the observed associations (i.e., effect size) are reported in this section to facilitate the interpretation of the results. In addition, we attempted to put more emphasis on CRP given that it is a more stable measure of inflammation than cytokines and has clear clinical cut-offs with implications. Moreover, we tried to emphasize associations that are interpretable in the context of theoretical

concepts and empirical evidence. Further, we highlighted results that were inconsistent with the existing literature which need further investigation.

Total severity of depression

In contrast to our hypothesis, higher depressive symptomatology (as measured by the sum-scores of the IDS-SR) was not associated with higher inflammation. The present study examined inflammation across varying levels of depression severity to explore the magnitude of associations between specific depressive symptoms and inflammation. However, given that the majority of the participants (40%) had moderate depression, this sample may not have included an adequate number of participants across the full spectrum of depression severity. Indeed, one possible reason for the lack of association between total severity of depression and inflammation is that only 55% of the present sample met DSM-5 criteria for a current major depressive episode and the rest had subclinical levels of depression. This possibility is supported by prior meta-analyses reporting a smaller effect size for the depression-inflammation link in individuals with subclinical levels of depression (Hiles et al., 2012a; Howren et al., 2009). In the present sample, although the associations between total depression score and CRP were not significant, the effect sizes for these associations were small (partial eta squared = .01-.05). Hence, a larger sample size may have been needed to detect the depression-inflammation association.

Most of the existing meta-analyses examining the depression-inflammation link have been conducted among studies that examined inflammation in MDD patients in comparison with healthy controls. These meta-analyses found higher levels of CRP (Haapakoski, Mathieu, Ebmeier, Alenius, & Kivimäki, 2015; Hiles et al., 2012a; Howren et al., 2009), IL-6 (Dowlati et

al., 2010; Goldsmith, Rapaport & Miller, 2016; Haapakoski et al., 2015; Hiles et al., 2012a; Howren et al., 2009; Liu et al., 2012), and TNF-α (Dowlati et al., 2010; Goldsmith et al., 2016; Liu, Ho, & Mak, 2012) in MDD patients compared to controls. Only two of these meta-analyses included community samples (Hiles et al., 2012a; Howren et al., 2009). It is possible that the present study would have detected elevated inflammation in individuals with depressive symptoms if we had compared them with a healthy contol group.

In contrast to our hypothesis, a negative association was observed between depression severity and TNF-α. Although the effect size for this association was medium (partial eta squared = .08), the reason behind this observation is not clear. IL-17 showed a similar pattern of results although the results were nonsignificant. Consistent with this finding, Schmidt et al. (2016) found that higher sum scores of the BDI scale correlated with lower TNF-α (r = -.60) in the depressed group. It is possible that increased cortisol in blood was partly responsible for the downregulation of TNF-α (Shelton, Schminkey, & Groer, 2015). This possibility has not been tested in the present study.

Inhibitory control, working memory and episodic memory

No a priori hypotheses were made regarding how multiple cognitive domains relate to inflammation, given the limited evidence in this regard. In the present study, the go/no-go test was employed to measure the inhibitory control component of executive function. We found that higher levels of inflammation (as reflected by greater CRP, IL-6 and IL-17) were associated with worse response inhibition (i.e., higher error rates). The effect sizes associated with these associations were approximately medium to large (partial eta squared = .05 -.10). Of note, the

associations between worse response inhibition and inflammation were not driven by reduced motivation or fatigue. No association was observed between inflammation and either working memory or episodic memory in the present study. Of note, the scores on these two tasks were above the normative standards, which might be expected given that individuals in our sample were more educated than the general public.

Very few studies have examined the association between objective measures of cognition and inflammation in patients with a current major depressive episode. One study measured CRP and IL-6 levels in 112 MDD outpatients and 57 healthy controls (mean age = 40 ± 13 years) (Krogh et al., 2014). A battery of neuropsychological tests was administered to measure cognitive domains including memory (by the Buschke's Selective Reminding Test and Rey's Complex Figure Test), attention (by the Digit Span Test, Serial Sevens and Stroop's Test), language (by the Verbal Fluency Test), executive function (by the Design Fluency Test), and verbal intelligence (by the Dutch Adult Reading Test). Consistent with our results, poorer executive functioning was associated with higher levels of CRP (β = -1.54, p = .001) in the entire sample of MDD patients and healthy controls (Krogh et al., 2014). However, higher IL-6 was associated with higher attention (β = .79, p = .008) in the entire sample. Another study measured CRP in 149 MDD patients (mean age 38.8 ± 12.4 years) and used a battery of neuropsychological tests to measure cognitive function, including attention (by the Continuous Performance Test) and executive function (by the Wisconsin Card Sorting Test) (Chang et al., 2012). No significant association was observed between CRP and either attention or executive function at baseline or at follow-up.

The majority of studies relating inflammation to objective measures of cognition have been conducted in inflammation-induced models of depression. For example, Capuron et al. (2005) examined the neurocognitive effects of low-dose IFN-α on brain activity in patients with hepatitis C virus (HCV). Brain activity was measured using functional magnetic resonance imaging (fMRI) while participants performed a cognitive task (i.e., visuospatial attention). IFN-α treated patients had mild depression (as measured by the Montgomery-Asberg Depression Rating Scale [MADRS]). Compared to controls, IFN-α treated patients exhibited greater activation in the dorsal ACC, which correlated with number of errors in the cognitive task. These data suggest that IFN-α treated patients needed greater cognitive effort to perform the task (Capuron et al., 2005). Another study showed that IL-2 therapy, but not IFN therapy, was associated with impaired spatial working memory and executive function (measured by the Stockings of Cambridge Task) in cancer patients (Capuron, Ravaud, & Dantzer, 2001). Further, IFN therapy in HCV or hepatitis B virus (HBV) patients (n=38) was associated with worse performance on working memory and verbal fluency (respectively, measured by the Auditory Verbal Learning Test and Controlled Oral Word Association Test). Following 12 weeks of IFN therapy, 14% of the sample had mild to moderate depressive symptoms and 5.7% had severe depressive symptoms as measured by the BDI (Lieb et al., 2006). In contrast, some studies did not find cognitive impairment in patients receiving IFN-α after 12 weeks. For example, IFN-α treatment in HCV patients (n=32) was not associated with impairment in executive function (as measured by the Stockings of Cambridge Task on the CANTAB and the Intra/Extra Dimensional Attentional Shift). In addition, performance accuracy of the sustained attention test was not

impaired following IFN therapy. Following 12 weeks of IFN therapy, patients had mild depression as measured by the MADRS (Majer et al., 2008). Similiarly, another study in HCV patients (n=20) found no impairment in executive function, attention and memory (as measured by the TMT-B, Stroop Test, Verbal Fluency Test, Digit Span Test) following IFN therapy (Amodio et al., 2005). Patients did not meet major depressive disorder criteria following 2 or 6 months of treatment. In sum, there appears to be an association between executive function and inflammation. Future studies are needed to focus on exploring the link between inflammation and objective measures of cognition, particularly executive function, in MDD patients to more fully delineate this association.

Due to the cross-sectional nature of this study, the direction of the association between worse inhibitory control and inflammation cannot be examined. However, possible explanations exist based on the literature relating inhibitory control to inflammation. *First*, deficits in inhibitory control associated with depression can lead to maladaptive emotion regulation strategies such as expressive suppression or rumination. As such, individuals with depression may experience difficulty disengaging from negative and distressing thoughts (Joormann & Gotlib, 2010). Hence, these individuals may be more likely to experience heightened and/or prolonged physiological responses to stress, including greater inflammatory responses to perceived and/or actual stressors. Of note, elevated inflammation can further affect emotion regulation. Consistent with this notion, increased activity of the subgenual anterior cingulate cortex (sACC), which plays a key role in emotion regulation, has been found in depression. In a study among healthy males, mood deterioration following typhoid injection was associated with

increased activity within the sACC; brain activity was measured while participants performed a facial emotion recognition task (Harrison et al., 2009a). In addition, decreased connectivity of the sACC to the amygdala, medial prefrontal cortex and nucleus accumbens has been associated with inflammation-associated deterioration in mood, suggesting alterations in processing social/emotional information (Harrison et al., 2009a). In sum, inhibitory control and emotion regulation are interrelated and the involvement of inflammation may potentiate this association.

Second, elevated inflammation may affect brain regions that are implicated in cognitive control and attention. Neuroimaging studies have strengthened this notion. Typhoid injection, but not placebo, enhanced activity within both the dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC) while participants were performing a cognitively demanding incongruent trials of the color word Stroop task (Harrison, et al., 2009b). No differences were found in terms of task performance across groups. This suggests that additional neural resources were needed to maintain an equivalent level of cognitive performance under conditions of inflammation. *Third*, poor inhibition has been linked to maladaptive health behaviors, such as less physical activity (Hall et al., 2008), unhealthy diet (Limbers & Young, 2015) or overeating (Guerrieri, Nederkoorn, & Jansen, 2008), which consequently can result in increased inflammation.

A meta-analysis showed that multiple aspects of executive function including inhibitory control and working memory have been impaired in MDD patients (Snyder, 2013). In this meta-analysis, studies were retained if they included MDD patients with a current major depressive episode or MDD patients in remission at the time of testing. Our preliminary findings support the

notion that an association exists between higher inflammation and disturbances in inhibitory control (i.e., higher error rates). Executive function is a set of higher order cognitive abilities, including inhibitory control, attention, working memory and cognitive flexibility, which plays an important role in goal-directed behavior, evaluating risks and decision making, adapting to varying environmental conditions, reasoning and sustaining attention (Logue & Gould, 2014). Indeed, these skills are essential not only for psychological and mental health, but also for effective social interactions, and academic and occupational achievement. Brain regions that are involved in cognitive control include the dorsolateral prefrontal cortex, anterior cingulate cortex, dorsal parietal cortex and posterior cingulate gyrus (Williams et al., 2018). Importantly, the performance on response inhibition may differ across age groups, given the ongoing brain development throughout adolescence (Stevens, Kiehl, Pearlson, & Calhoun, 2007). One neuroimaging study in healthy participants found that some of the brain networks associated with response inhibition (during a go/no-go task) showed less network engagement and regional connectivity in adolescents (i.e., 11-17 years) compared to adults (i.e., 18-37 years) (Stevens et al., 2007). These differences were associated with a better performance on this task in adults compared to adolescents. Given that our sample primarily consisted of young adults with early-onset depression (i.e., mean age at onset of depression =16 years), an important question can be raised as to whether elevated inflammation associated with depressive symptoms might have interfered with ongoing brain development throughout adolescence, consequently contributing to poorer response inhibition. Further exploration of the association between inflammation and

inhibitory control in adolescents and young adults with MDD, as well as examining the neurobiological mechanisms underlying such associations, are needed in future studies.

Psychomotor processing

Both motor and cognitive aspects of psychomotor processing were measured in the present study. Three tasks were employed to measure psychomotor speed (i.e., the digit symbol coding, pattern comparison processing and trail making test-A). On average, performance on these tasks was above the normative standards, which might be expected given that participants in this study were more educated and younger than the general public.

In contrast to our hypotheses, higher inflammation was not associated with slower processing speed as measured by the aforementioned tasks. A positive association was observed between IL-17 and faster processing speed (i.e., a better performance on the TMT-A) which was unexpected; the effect sizes for this association were medium (partial eta squared = .07-.08). IL-17 is a proinflammatory cytokine that is produced by both innate immune cells and T lymphocytes. It has been shown that IL-17 links T cell-mediated adaptive immunity and the acute inflammatory response (Abbas, Lichtman & Pillai, 2018). Indeed, the involvement of T cells can lead to more severe and prolonged inflammatory responses compared to when only innate immunity is involved (Abbas, 2018). One of the important functions of IL-17 is that it triggers the production of inflammatory mediators (chemokines, other cytokines) that recruit neutrophils to the site of T cell activation (Abbas, 2018). The role of IL-17 has been studied in autoimmune disorders, including psoriasis, rheumatoid arthritis and multiple sclerosis. However, evidence on its role in depression is emerging. To our knowledge, no studies have examined IL-

17 in relation to processing speed in depression. However, some prior findings revealed an association between elevated levels of other inflammatory markers (CRP, IL-6, IL-10) and slower processing speed. One study measured psychomotor processing (by the TMT-A and digit symbol test), and found that higher CRP was associated with slower psychomotor speed in the entire sample of 112 MDD patients and 57 healthy controls (β = 2.42, p =.02) (Krogh et al., 2014). In a study among 93 unmedicated patients with a primary diagnosis of MDD or bipolar disorder who met a current depressive episode, higher IL-10 was associated with a better performance on the DST (*beta* = .28, p =.009) (Goldsmith et al., 2016). Consistent with our findings, no associations were observed between the TMT-A and IL-6, IL-10 or CRP (Goldsmith et al., 2016). Another study in 48 unmedicated patients with a primary diagnosis of MDD or bipolar disorder who met a current depressive episode found that elevated CRP was marginally associated with a slower processing speed (r = .27, p =.07) as measured by the TMT-A (Felger et al., 2016). In both studies, participants had moderate depression as measured by the Hamilton Depression Rating Scale (HAMD). Of note, the completion time of the TMT-A in the aforementioned studies (approximately 32 seconds) was much higher compared to our study (18 seconds), suggesting slower psychomotor speed in those samples.

In the present study, the finger tapping test was employed to measure a motor component of psychomotor processing. The performance on the finger tapping test for one target (FTT-one target) was above the normative standards. Of note, normative data are not currently available for the FTT for two targets (FTT-two targets). Consistent with our hypotheses, higher IL-17 (but not other inflammatory markers) was associated with slower motor speed. The effect size for this

association was medium (partial eta squared = .06). This association was evident only on the FTT with two targets on the non-dominant hand, which might be explained by the more demanding nature of this task compared to either the FTT-one target, or FTT-two targets with the dominant hand. It should be noted that because this test was the last FTT test in terms of order, performance on this test may have captured fatigue and/or motivation effects. This possibility is supported by the observation that both higher fatigue and reduced motivation correlated marginally with performance on the FTT-two targets, but not with FTT-one target. Of note, including fatigue and anhedonia in the regression model strengthened the association between the FTT-two targets and IL-17.

Other studies among unmedicated patients with a current major depressive episode support the link between higher inflammation and slower motor speed. Two studies found that higher CRP was associated with slower motor processing speed as measured by the FTT (r =-.*58* and -.29, $p < .05$ for the dominant hand) (Chang et al., 2012; Felger et al., 2016). One study among 93 unmedicated MDD patients used two tasks to measure motor speed: the simple and five-choice reaction time task of the CANTAB, and the FTT (Goldsmith et al., 2016). Higher IL-6 was associated with slower movement times. In addition, lower soluble tumor necrosis factor receptor (sTNFR)-2 (*beta* = .27, p = .03) and higher monocyte chemoattractant protein (MCP)-1 (*beta* = -.26, p = .02), but not IL-6, TNF-α or IL-1β, were associated with a slower motor speed. In these three studies, participants had moderate depression on average as measured by the HAMD. Of note, the frequency of tapping (i.e., motor speed) in the aforementioned studies was much lower compared to our study, suggesting slower motor speed in those samples. Overall,

some possible reasons for the slower psychomotor processing speed that has been reported in the aforementioned studies compared to our findings include: 1) the present sample was more educated and younger than those samples, 2) those samples only consisted of unmedicated patients with a current major depressive episode.

Additional support for the link between inflammation and objective measures of psychomotor processing comes from inflammation-induced models of depression. Following IFN-α treatment, HCV patients showed slower reaction time and motor speed (as measured by the simple and five-choice reaction time task of the CANTAB) (Capuron et al., 2001; Majer et al., 2008). In addition, slower performance speed in a task of sustained attention (i.e., the Rapid Visual Information Processing Task) was evident (Majer et al., 2008). Finally, another study found that higher IL-6 levels were associated with slower reaction time (as measured by the Stroop Task) in those who received typhoid vaccination (Brydon et al., 2008). In contrast, at least two studies found no changes in psychomotor processing as measure by the TMT-A following IFN therapy (Bender et al., 2000; Lieb et al., 2006).

Overall, the association between psychomotor processing and inflammation has been relatively consistent in the context of inflammation-induced depressive symptoms, however, future studies need to more fully delineate this association among MDD patients.

Anhedonia and pleasure

In contrast to our hypothesis, higher anhedonia (as measured by the SHAPS) was not associated with higher inflammation. Specifically, we did not expect to see that higher inflammation (as reflected by higher TNF-α) was associated with lower anhedonia (effect sizes

associated with this association were large: partial eta squared = .09-.11). Consistently, higher inflammation (as reflected by higher IL-17) was associated with higher consummatory pleasure on the TEPS scale. This association was partly explained by antidepressant use. It is possible that we found a positive association between IL-17 and consummatory pleasure due to the higher levels of IL-17, as well as higher levels of pleasure, observed in the antidepressant group compared to the antidepressant-free group. It is not clear why a negative association was observed between TNF-α and anhedonia in the present study.

In contrast to the present findings, three studies have found an association between inflammation and anhedonia in nonpsychotic MDD patients. One study found that greater severity of anhedonia (as measured by three items of the IDS scale) was associated with higher levels of IL-17, Th1-cytokines (IFN-γ, TNF-α), Th2-cytokines (IL-4, IL-5, IL-9, IL-13), and non-T cell cytokines (IL-1β, IL-1ra, IL-6, IL-8) (Jha, Miller, Minhajuddin, & Trivedi, 2018). Of note, the association between IL-17 and anhedonia was only evident in men (n = 49), not in women (n = 117). In this study, participants met the DSM-IV criteria for either chronic or recurrent major depression with at least moderate severity of depressive symptoms (Jha et al., 2018). Another study measured inflammation in the cerebrospinal fluid (CSF) of MDD patients and found a positive correlation between IL-6 soluble receptor and anhedonia (as measured by the IDS items) (Felger et al., 2018). Another study from this group found that higher CRP correlated marginally with higher anhedonia (as measured by the SHAPS) (r = .26, p = .07) (Felger et al., 2016). Of note, individuals in the latter study, which were unmedicated MDD patients, reported higher levels of anhedonia (mean = 5.6 ± 3.0) compared to our study (mean =

3.2 ± 2.7). This could be explained by the clinical characteristics of the present sample, which did not solely consist of individuals with a current depressive episode. Because of the low mean value of anhedonia in our sample, there may have not been enough variation in the anhedonia score (specifically toward the high end of the spectrum) to detect a positive association with inflammation.

Further support for the inflammation-anhedonia link comes from neuroimaging studies. Higher CRP was associated with reduced connectivity within the corticostriatal reward network (i.e., between the ventral striatum and ventromedial prefrontal cortex), and higher glutamate in the basal ganglia, which both correlated with anhedonia in unmedicated patients diagnosed with MDD or bipolar disorder (depressed type) (Felger et al., 2016; Haroon et al., 2016). Patients in these studies had moderate levels of depressive symptoms as measured by the HAMD. Additional support on this topic has been provided in the context of inflammation-induced depression. Reduced activity in the ventral striatum during the win versus lose condition of a gambling task has been shown following 4 to 6 weeks of IFN therapy in HCV patients (Capuron et al., 2012). In line with this, endotoxin challenge in healthy subjects was associated with reduced ventral striatum activity during reward anticipation, which correlated with depressed mood (Eisenberger et al., 2010). In another study, inflammatory challenge (via typhoid vaccination) was associated with increased sensitivity to punishment (i.e., subjective value of punishment) compared to reward. In addition, exposure to vaccination was associated with reduced encoding of reward prediction error in the ventral striatum and increased encoding of punishment prediction error in the right insula region (Harrison et al., 2016).

Altogether, there appears to be an association between anhedonia and inflammation based on prior studies. However, relatively few studies on this topic have been conducted in MDD patients. Future exploration of the anhedonia-inflammation link is needed to elucidate this association in the context of MDD patients.

Fatigue

Consistent with our hypothesis, higher inflammation (as reflected by CRP) was associated with higher severity of fatigue (i.e., total fatigue score); this association was evident after adjustment for antidepressant use. Exploratory analyses examining how different subscales of fatigue relate to inflammation revealed that higher CRP was associated with higher general fatigue, mental fatigue and reduced activity. In addition, higher IL-6 was associated with higher physical fatigue. The effect sizes associated with these associations ranged from medium to large. Moreover, the associations between inflammation and total fatigue, general fatigue, physical fatigue or reduced activity were largely explained by BMI. Of note, the associations between inflammation and total fatigue as well as general fatigue, physical fatigue and mental fatigue were only evident in individuals who were not taking antidepressants. Given that we did not have a priori hypotheses for the modifying effect of antidepressants on the association between fatigue and inflammation, these findings are exploratory and need to be replicated before any definite conclusions can be drawn.

Our findings regarding the inflammation-fatigue link are consistent with existing literature. One study used the MFI scale to measure fatigue in MDD patients and revealed a positive association between inflammation and total fatigue score ($r = .27$, $p = .03$) as well as the

reduced motivation subscale of MFI (r = .24, p = .04) (Felger et al. 2018). In addition, several cross-sectional studies (Case & Stewart, 2014; Jokela, Virtanen, Batty, & Kivimäki, 2016; White, Kivimäki, Jokela, & Batty, 2017) and longitudinal studies (Chu et al., 2019; Deverts et al., 2010; Niles et al., 2018; Stewart et al., 2009) found that neurovegetative symptoms of depression were associated with higher inflammation. One limitation of these studies was that total severity for the neurovegetative dimension was quantified with sum-scores from individual questionnaire items which were typically related to sleep disturbance, fatigue, changes in appetite and psychomotor disturbance. Hence, it is unclear which symptom(s) explained the observed association. Only three of the aforementioned studies examined inflammation in relation to the individual item of fatigue; these studies reported a positive association (Chu et al., 2019; Jokela et al., 2016; White et al., 2017). Of these, two studies found that this association existed independent of BMI (Chu et al., 2019; White et al., 2017) and one did not control for BMI (Jokela et al., 2016). Of note, utilizing only one or two questionnaire items to measure fatigue in these studies is an inadequate assessment of the fatigue construct, and does not provide information about different facets of fatigue. This is an important limitation that needs to be addressed in future studies. Further support for the fatigue-inflammation link comes from studies that examined inflammation-induced depression. For example, fatigue is commonly reported following IFN therapy (Capuron et al., 2007, 2005, 2002; Majer et al., 2008; Raison et al., 2014).

In the present study, adjustment for BMI partly explained the associations between inflammation and total fatigue, general fatigue, physical fatigue or reduced activity. Of note, the three subscales of general fatigue, physical fatigue and reduced activity consisted of items that

capture the physical aspects of fatigue. Prior evidence suggests that higher BMI is a potential risk factor for developing physical fatigue (Lim, Hong, Nelesen, & Dimsdale, 2005). In line with this, we found that the association between mental fatigue and inflammation was evident over and above of BMI. Although prior studies have not examined the role of BMI on the link between inflammation and different facets of fatigue, there is some evidence showing that the association between neurovegetative symptoms of depression and inflammation is explained by higher BMI (e.g., Case and Stewart, 2014; Duivis et al., 2013). As noted earlier, it is not clear from these studies which depressive symptom(s) within the neurovegetative dimension was/were responsible for driving this effect. One possible reason for the observation that higher BMI contributes to the association of inflammation with physical aspects of fatigue is that feelings of physical fatigue might lead to a more sedentary lifestyle, consequently resulting in increased obesity and inflammation (Khambaty, Stewart, Muldoon, & Kamarck, 2014). It should be noted that the relationship between fatigue and inflammation can be bidirectional. Indeed, increases in general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity scores have been reported following a 4-week IFN therapy (Haroon et al., 2014; Majer et al., 2008). Altogether, future studies are needed to examine the multidimensional nature of the fatigue construct in relation to inflammation in the context of MDD.

The associations between inflammation and total fatigue as well as general fatigue, physical fatigue and mental fatigue were only evident in the antidepressant-free group. This is in line with prior findings from a community sample that the associations between inflammation and fatigue or low energy were significant only in those who were not taking antidepressants (N

= 5281) (White et al., 2017). Of note, in the White and colleagues' study, the association between inflammation and sleep disturbance was significant in both groups. These findings suggest that antidepressants may moderate the association between fatigue and inflammation. It should be noted that our results may be explained by the observation that the antidepressant group reported lower total fatigue, mental fatigue and reduced activity compared to the antidepressant-free group. Therefore, the strength of associations for the fatigue-inflammation link was smaller in those who were taking antidepressants compared to the antidepressant-free group. It is possible that we were underpowered to detect an association in the antidepressant group given the small number of individuals in this group (N = 25). Future studies with larger sample sizes are needed to delineate the moderating role of antidepressants on the inflammation-fatigue link.

Subjective cognitive impairment

Given that subjective and objective measures of cognitive dysfunction do not always correlate among MDD patients (Mohn & Rund, 2016; Russo et al., 2015), we employed a subjective measure of cognition (i.e., the Massachusetts General Hospital Cognitive and Physical Functioning questionnaire [CPFQ]) in addition to objective measures. Consistent with the existing literature, we found no correlations between this scale and objective measures of cognition. In addition, we found that higher inflammation was not associated with higher subjective reports of cognition. Overall, our findings suggest that the mental fatigue subscale of MFI was more sensitive than the CPFQ scale to capture subjective fatigue associated with

inflammation given that a positive relationship was found between inflammation and mental fatigue as measured by the MFI.

Antidepressant use

In the present sample, individuals who were taking antidepressants exhibited higher levels of inflammation (reflected by increased CRP and IL-17) compared to those who were not taking antidepressants. These two groups did not differ in terms of severity of depressive symptoms, but the reported number of previous episodes were greater in the antidepressant group. These findings suggest that a greater number of previous episodes of depression in the antidepressant-group may have contributed to the increased levels of inflammation observed in these individuals. This is consistent with the concept of neuroinflammatory sensitization, which posits that recurrent depressive episodes and/or exposure to early life stress can potentiate the stress response via the sympathetic nervous system and the hypothalamus pituitary adrenal axis, such that the threshold or magnitude of psychological distress that elicits inflammation may be lowered over time (Slavich & Irwin, 2014). As a result, a state of low-level systemic inflammation may become chronic in individuals with a greater number of previous episodes of depression, which can further contribute to the progression of depression. Examining this possibility is an important question for future studies.

The current literature regarding the effect of antidepressants on inflammation is inconsistent. A meta-analysis of short-term studies that measured changes in cytokine levels over the course of antidepressant treatment found that selective serotonin reuptake inhibitors (SSRIs) may reduce IL-6 (Hannestad, DellaGioia, & Bloch, 2011). Another meta-analysis showed a

marginally significant reduction in CRP and a significant reduction in IL-6 after antidepressant treatment (Hiles, Baker, de Malmanche, & Attia, 2012b). In contrast, a population-based study found that use of tricyclic antidepressants (TCAs), but not SSRIs, was associated with greater CRP levels independent of confounding factors (Hamer, Batty, Marmot, Singh-manoux, & Kivimäki, 2011). In another study, use of serotonin–norepinephrine reuptake inhibitors (SNRIs), tetracyclic antidepressants and TCAs was associated with elevated CRP levels (Vogelzangs et al., 2012). Given the small number of individuals in the present study, we were not powered to stratify based on class of antidepressant and examine if the elavated inflammation is specific to any subgroups. Of note, elevated inflmmation in the present sample might be due to some other features of depression that have not been examined. Future exploration of differential effects of antidepressants on inflammation in larger sample sizes would be important in this line of research.

Limitations

The present study findings should be interpreted in the context of some methodological limitations.

Type I and type II errors. Due to the presence of multiple tests, there was a high probability of making type I error in this study. One way to deal with this issue was to modify *alpha* using the Bonferroni correction (i.e., dividing *alpha* by *K* which is the number of statistical tests on given data) (Nakagawa, 2004). However, using the Bonferroni correction increases type II error. Nakagawa (2004) proposed reporting effect sizes as an alternative way to using the Bonferroni correction. In the current study, due to the small sample there is already a high

probability of making type II error. To address this issue in the present study, the strengths of the observed associations (i.e., effect size), which are less sensitive to sample size, were reported in addition to *p* values to facilitate the interpretation of results. In sum, both null findings and significant findings from this study need to be interpreted with caution. The present results need to be replicated in future studies before any definite conclusions can be drawn.

Generalizability. The sample characteristic of this study is unique, such that it primarily consisted of college students at the Penn State University. As such, participants in this study were more educated and younger than the general public. In addition, these students were more likely to be from affluent families. Thus, the generalizability of our findings is limited. Moreover, individuals with comorbid physical illness were excluded from this study, thus these findings are not generalizable to samples with comorbid physical conditions. Future research is needed to replicate these findings.

Objective neurocognitive testing in a controlled environment. Although participants with mild to severe depressive symptoms were included in this study, the mean cognitive performance was above normative standards. One reason could be that some of the neurocognitive tasks that we used may have not been difficult enough to identify more subtle cognitive impairment in young educated adults with depressive symptoms. In addition, objective cognitive assessments were conducted in a controlled laboratory environment, therefore the performance on these tests may not be reflective of participants' cognitive functioning in the real-world conditions, such as stressful situations at school. In addition, given that cognitive

assessment was conducted at a single timepoint, these data may not be generalizable to longer periods of time (Lam, 2016).

Selection bias. One of the methodological limitations of this study is the probability of selection bias. Recruitment in this study was by self-selection. The majority of participants were recruited via class announcements. Given that our study sample was not chosen randomly, it may not be representative of the target population.

Correlational study design and unmeasured variables. Due to the cross-sectional nature of this study, causal inferences regarding the associations between depressive symptoms and inflammation cannot be drawn. In addition, the observed relationships between two variables could have happened because of (or moderated by) other variables that we did not measure or consider in the analyses such as early exposure to life stress or rumination. For instance, exposure to early life stress might have contributed to the observed elevated inflammation in the present sample, however, we did not measure this variable to test this possibility.

Time of day. Due to logistics and time constraints, we were not able to limit the time of blood draw to mornings to control for circadian variations in inflammatory markers. Similarly, neurocognitive testing was conducted both in the morning and afternoon. To address this issue partly, time of day was examined as a covariate in the analyses, which did not change any of the reported results.

Implications and future directions

The present study supports the notion that disaggregating multidimensional constructs such as depression into more homogenous constructs and exploring the various correlates (e.g.,

biological) of each construct could provide insight into the underlying pathophysiology. In the present study, higher inflammation *was not* associated with total depression score. However, higher inflammation *was* associated with specific symptoms of depression, including fatigue and worse inhibitory control. Our preliminary findings support the claim that important information might be missed by only examining total depression score. This might be particularly important in the context of etiological research.

As discussed in detail earlier, most evidence linking depression and inflammation comes from studies of patients who received interferon therapy. Interferon is a potent inducer of the inflammatory response. Hence, it is reasonable to assume that the association between inflammation and depressive symptoms may emerge at higher levels of inflammation. As an exploratory step, we used the categorical measure of inflammation to examine depressive symptomatology in subjects with high levels of inflammation (CRP>3mg/L) versus those with low to moderate levels of inflammation (CRP≤3mg/L). No differences were observed across these groups with the exception of psychomotor speed; participants with CRP>3mg/L had slower psychomotor speed compared to participants with CRP≤3mg/L. It is possible that the effects of inflammation on symptom profiles of depression are most evident at levels of inflammation which are even higher than the threshold value of CRP>3mg/L.

As expected, only a subset of individuals in our sample exhibited elevated inflammation (as reflected by *1 ≤CRP≤ 3mg/L* [18%] & *CRP>3mg/L* [37%]), which highlights the notion that depression as a whole is not driven by inflammation (Raison & Miller, 2011). Importantly, our preliminary results found that elevated inflammation was detectable in young individuals with

varying depressive symptoms in the absence of any comorbid physical conditions, suggesting that the depression-inflammation link is not solely explained by comorbid physical conditions. Given that inflammatory markers were quantified at a single timepoint, we cannot determine for how long elevated inflammation, as reflected by higher CRP, was maintained or which factor(s) caused the inflammation. Future longitudinal studies are needed to identify clinical, biological and psychosocial predictors that increase the risk of developing and/or maintaining low-grade chronic inflammation in young adults with MDD. Importantly, exposure to early life stress or adversity needs to be examined as a potential factor contributing to elevated inflammation in these individuals. Consistent with this notion, prior longitudinal studies found that only among female adolescents with higher levels of childhood adversity, developing a recent major depressive episode (i.e., over the past 6 months) was associated with elevated levels of CRP and IL-6 compared to when participants were euthymic (Miller & Cole, 2012). Similarly, another study found that individuals (at age 32) with current major depression and a history of childhood maltreatment, but not MDD patients without history of maltreatment, were more likely to have elevated levels of CRP. In another longitudinal study, participants were assessed at ages 9, 16, 19 and 21. Cumulative depressive episodes predicted higher levels of CRP after adjustment for all covariates (Copeland et al., 2012). Given that depressed individuals with a history of childhood adversity may develop early onset depression and more depressive episodes (Danese et al., 2008), the cumulative effects of early life stress and/or multiple depressive episodes (combination of duration and intensity of symptoms) on physiological processes may predispose young adults to have elevated levels of inflammation.

There is some evidence suggesting that age at onset of depression may be associated with differences in neurocognitive test performance. Previous studies have shown that patients with early-onset depression exhibited more impaired episodic memory, whereas those with late-life depression (i.e., age of onset: 50 to 65 years) exhibited more pronounced impairment in executive function (e.g., working memory, selective attention, set shifting) and psychomotor speed (Hasselbalch et al., 2011; Herrmann, Goodwin & Ebmeier, 2007). In the present study, which primarily consisted of young individuals with early-onset depression, higher inflammation was associated with worse performance in inhibitory control, but not episodic memory. If replicated, these findings raise an important question as to whether the presence of inflammation in early-onset depression affects the cognitive phenotypes of depression, such that patients with inflammation-associated depression would be more likely to exhibit impairment in executive function compared to their peers who do not show elevated levels of inflammation. In addition, future neuroimaging studies are needed to compare the neural networks of executive function in MDD patients with and without elevated inflammation. This domain of research will provide insights into brain structure/function that are involved in inflammation-associated depression. Given that much of the existing studies in this regard have focused on experimental models of inflammation-induced depression, evidence on this topic among MDD patients is relatively scarce. Finally, studies that examined the association between inflammation and objective cognitive impairment have employed varying neurocognitive tests. As such, these tests can vary in terms of cognitive domains they tapped into, as well as in their sensitivity to capture cognitive impairment in inflammation-associated depression. Standardizing the methods to measure

cognitive functioning in MDD would allow for better comparisons and conclusions drawn across studies.

If replicated, these findings can inform future work on designing more effective, individualized pharmacological and behavioral interventions. Pretreatment CRP levels have been shown to predict differential response to antidepressants. Uher et al. (2014) found that MDD patients with CRP levels ≥1 mg/L had a better response to nortriptyline (a TCA), whereas those with low levels of CRP (<1 mg/L) had a better response to escitalopram (a SSRI). Another study found that MDD patients with higher baseline levels of CRP (≥1 mg/L) exhibited better outcomes with bupropion (a norepinephrine-dopamine reuptake inhibitor) plus escitalopram (a SSRI), whereas those with lower levels of CRP exhibited better outcomes with escitalopram plus placebo (Jha et al., 2017). Determining whether improvement in depressive symptoms was particularly evident on specific symptoms or clusters would be an important next step in this line of research. The findings from those studies could be explained by distinct pharmacological actions of the medications used; bupropion increases the neurotransmission of both dopamine and norepinephrine, nortriptyline increases the neurotransmission of both norepinephrine and serotonin, and escitalopram which is a highly selective serotonin reuptake inhibitor increases the neurotransmission of serotonin. It has been recommended that CRP levels be used for the selection of antidepressants, such that SSRIs may be most appropriate for MDD patients with low CRP levels, whereas those with elevated CRP may benefit more from medications that target dopamine (Miller, Trivedi, & Jha, 2017).

Stimulants and stimulant-like drugs (e.g., modafinil) have been used as an adjunctive therapy in MDD, particularly in the context of late-life depression and treatment-resistant depression (Nierenberg, 2019). They have been shown to alleviate specific depressive symptoms such as fatigue, impaired concentration, hypersomnia, anergia and fatigue (Nierenberg, 2019). Indeed, there is value in using stimulants or modafinil in combination with SSRIs or SNRIs to treat depression (based on presenting symptoms), given that altered dopamine is associated with specific symptoms of depression and neither SSRIs nor SNRIs increase dopaminergic transmission (Nierenberg, 2019). Of note, a meta-analysis showed that modafinil augmentation therapy was associated with a significant improvement in total depression scores in MDD patients (Goss, Kaser, Costafreda, Sahakian, & Fu, 2013). In addition, modafinil has been found to improve inhibitory control in different samples, including healthy volunteers (Randall, Fleck, Shneerson, & File, 2004; Turner et al., 2003) or individuals with ADHD (e.g., Aron, Dowson, Sahakian, & Robbins, 2003). Moreover, animal studies suggest that modafinil can reduce neuroinflammation (Wadhwa, Chauhan, Roy, Sahu, & Deep, 2018). Given our findings suggesting that higher inflammation related to worse inhibitory control, it would be interesting to examine the therapeutic effects of modafinil as well as stimulants as an augmentation therapy in patients with inflammation-associated depression who present with impairment in inhibitory control. In addition, it is important to explore whether pretreatment levels of CRP moderate the therapeutic effect of modafinil or stimulants on inhibitory control. Investigating the therapeutic effects of modafinil or stimulants using neurocognitive testing in inflammation-associated depression would be an interesting avenue of future research.

The present study provides preliminary findings that the inflammation-fatigue association was driven by both physical and mental aspects of fatigue. Little research has focused on parsing the heterogeneity of fatigue and examining the inflammatory correlates in MDD patients. As noted earlier in the introduction, prior evidence has shown that depressed patients with symptoms of fatigue/low energy were more likely to benefit from augmentation of SSRIs with bupropion. Similarly, the beneficial effect of modafinil on fatigue has been shown in MDD patients (Goss et al., 2013). To our knowledge, no studies to date have examined the therapeutic effect of bupropion or modafinil on different facets of fatigue in MDD patients. This is an important gap in this domain of research that needs to be addressed by future research. Given that mental fatigue and physical fatigue have been linked with distinct pathophysiological mechanisms, they may respond differentially to treatments (see chapter 1 section 1.3.1 for details). No correlation was found between mental fatigue and physical fatigue in our sample, which may support the notion that they reflect distinct constructs. In sum, it would be interesting to explore whether CRP levels before treatment moderate the therapeutic effect of modafinil or bupropion on different facets of fatigue.

With respect to behavioral interventions, techniques such as mindfulness meditation may be helpful for improving attention control and emotion regulation (Tang & Leve, 2016). Interestingly, mindfulness meditation has been found to improve the connectivity within brain regions that are involved in self-regulation (e.g., ACC, striatum) (Tang & Leve, 2016). In addition, medication may reduce the physiological markers of stress including inflammation (a meta-analysis by Pascoe, Thompson, Jenkins, & Ski, 2017). Therefore, individuals with higher

inflammation and impairment in inhibitory control may benefit from mindfulness-based interventions. In addition, we found that the associations between inflammation and total fatigue, general fatigue, physical fatigue or reduced activity were largely explained by BMI. Individuals with both higher physical fatigue and inflammation may benefit from interventions that increase self-efficacy towards maintaining a healthy lifestyle, including regular engagement in physical activity as well as adopting a healthy diet. Of note, these types of interventions have been studied in the context of comorbid depression and obesity (Ma et al., 2015). It would be interesting to examine the beneficial effects of these types of interventions in combination with pharmacological interventions on fatigue, particularly physical fatigue, in MDD patients with elevated inflammation.

Summary of key findings

The present study examined the associations between various depressive symptoms and inflammatory markers (CRP, IL-6, IL-10, IL-17, TNF-α). In line with our expectation, higher CRP was associated with lower response inhibition. A similar pattern of associations was observed with respect to IL-6 and IL-17. The strength of these associations ranged from medium to large. In addition, higher CRP was associated with total fatigue as well as multiple facets within fatigue (i.e., general fatigue, mental fatigue and reduced activity); the strength of these associations ranged from medium to large. Moreover, higher IL-6 was associated with physical fatigue and the strength of this association was medium. These results regarding IL-6 are supported by prior evidence indicating that high BMI (i.e., obesity) is a potential risk factor for developing physical fatigue and that IL-6 is the main inflammatory marker produced by adipose

tissue (Lim et al., 2005; O'Connor et al., 2009). Of note, in the present study BMI largely explained the associations between inflammation and general and physical fatigue. Overall, these findings suggest that CRP and IL-6 are two biomarkers that may play a role in the underlying biology of fatigue symptoms.

In contrast to our expectation, higher TNF-α was associated with lower severity of depression and anhedonia. In addition, higher IL-17 was associated with faster processing speed and higher levels of pleasure. The strength of these associations was medium to large. The reason behind these observations is not clear. Although IL-17 is considered a proinflammatory cytokine, it did not correlate with either CRP or other proinflammatory cytokines in the present study. Based on principal component analysis, IL-17 tended to cluster with IL-10 which is an anti-inflammatory cytokine. Hence, it is not clear what inflammatory characteristics IL-17 represents in the present sample. Given that evidence regarding the role of IL-17 in depression is scarce, future studies are needed to elucidate this association.

Finally, it should be noted that the mean cognitive performance on psychomotor processing, working memory and episodic memory was above normative standards, therefore this sample did not exhibit the full spectrum of severity in cognitive impairment which limited our ability to explore the associations between inflammation and performance on these cognitive domains. Similarly, because of the low mean value of anhedonia in our sample, there may have not been enough variation in anhedonia scores (specifically toward the high end of the spectrum) to detect a positive association with inflammation. Thus, the anhedonia-inflammation link needs to be clarified in a MDD sample that exhibits the full spectrum of anhedonia severity.

Conclusion

The results of this study provide further evidence that elevated inflammation is evident in a subset of individuals with depressive symptoms. Importantly, this subset of young individuals with varying levels of depressive symptoms exhibited elevated inflammation in the absence of any comorbid physical conditions. In this study, higher inflammation was not associated with total severity of depression (as reflected by the sum-score of depressive symptoms), which may be explained by the small sample size as well as the sample characteristics (i.e., this sample may not represent the full spectrum of depression severity). In an effort to address the multidimensional nature of depression, we employed a battery of questionnaires and neurocognitive testing to assess depressive symptoms more accurately. Our preliminary findings suggest that an association exists between inflammation and specific symptoms of depression, including different facets of fatigue (e.g., mental fatigue and physical fatigue), and worse inhibitory control in a sample of young adults with mild to severe depressive symptoms. Taken together, these data indicate that examining the biological correlates of each construct within depression and multiple domains within each construct may provide valuable information regarding the neurobiology of depression, beyond what can be learned from focusing on the overall severity of depression. This approach may be of critical importance by informing future work on designing more effective and personalized treatment strategies.

Tables-Study 2

Table 7
Summary of Self-Report Measures

Construct	Measure	Domains/subscales	Administration Time	Measurement time point
Depression	PHQ-9		2 min	Initial Screening
Depression	IDS		15 min	In-lab visit
Depression	BDI		6 min	In-lab visit
Fatigue	MFI	-General fatigue -Physical fatigue -Reduced motivation -Reduced activity -Mental fatigue	3 min	In-lab visit
Anhedonia	SHAPS	Consummatory	3 min	In-lab visit
Pleasure	TEPS	-Anticipatory -Consummatory	4 min	In-lab visit
Subjective cognition	CPFQ		2 min	In-lab visit
Total estimated time = 35 min				

Table 8
Summary of Psychomotor and Cognitive tasks

Construct	Measure	Equipment	Administration Time	Measurement time point
Psychomotor speed	Digit Symbol Coding	iPad	5 min	In-lab visit
Psychomotor speed	Pattern Comparison Processing	iPad	3 min	In-lab visit
Psychomotor speed	Trail Making Test A	Paper and Pencil	2 min	In-lab visit
Motor speed	Finger Tapping Test	Smart phone	10 min	In-lab visit
Inhibitory control	Go/No-Go Test	Smart phone	4 min	In-lab visit
Working memory	List Sorting Working Memory	iPad	7 min	In-lab visit
Episodic memory	Picture Sequence Memory	iPad	10 min	In-lab visit
Total estimated time = 41 min				

Table 9
Principle components analysis with varimax rotation for inflammatory biomarkers

	Loadings	
Inflammatory Biomarker	Component 1*	Component 2*
TNF-α	**.793**	.269
IL-6	**.779**	-.263
IL-17	-.191	**.785**
IL-10	.401	**.622**

*Component 1: Eigenvalue = 1.47; accounted for 36.72% of total variance.

*Component 2: Eigenvalue = 1.10; accounted for 27.73% of total variance.

Table 10
Overview of predictors and outcomes in regression analyses

To examine the degree to which inflammation is associated with depression severity					
Predictors ⟶	**CRP**	**IL-6**	**TNF**	**IL17**	**IL10**
⬇Outcomes					
Depression (IDS-total)					
To examine the degree to which inflammation is associated with deficits in cognitive domains including executive function					
	CRP	**IL-6**	**TNF**	**IL17**	**IL10**
Episodic memory (PSM)					
Working memory (LSM)					
Inhibitory control (GoNoGo)					
To examine the degree to which inflammation is associated with psychomotor speed					
	CRP	**IL-6**	**TNF**	**IL17**	**IL10**
Processing speed (DST)					
Processing speed (TMT-A)					
Processing speed (PCP)					
Motor speed (FTT1)					
Motor speed (FTT2)					
To examine the degree to which inflammation is associated with anhedonia					
	CRP	**IL-6**	**TNF**	**IL17**	**IL10**
Total anhedonia (SHAPS)					
Total Pleasure (TEPS)					
Consummatory (TEPS)					
Anticipatory (TEPS)					
To examine the degree to which inflammation is associated with fatigue					
	CRP	**IL-6**	**TNF**	**IL17**	**IL10**
Total fatigue (MFI)					
General fatigue (MFI)					
Physical fatigue (MFI)					
Reduced motivation (MFI)					
Reduced activity (MFI)					
Mental fatigue (MFI)					
To examine the degree to which inflammation is associated with subjective cognitive functioning					
Subjective cognition (CPFQ)					

Table 11
Reported effect sizes for the associations between specific symptoms of depression and inflammatory biomarkers in patients with MDD from prior studies.

	Psychomotor speed (measured by TMT-A)	**Motor speed (measured by FTT or SMT/CMT)**	**Executive function (measured by WCST)**	**Psychomotor speed (measured by DSST)**	**Anhedonia**	**Fatigue (measured by MFI)**
CRP	r = .27[a], p = .06 (Felger et al., 2016);	r = -.58[a], p < .001 (Chang et al., 2012); r = - .29[a], p = .049 (Felger et al., 2016)	r[b] = .23 (p = .057 (Chang et al., 2012)		**(measured by SHAPS)** r = .26, p = .07 (Felger et al., 2016)	
IL-6		SMT: r = .25[a], p < .05; CMT: r = .24[a], p < .05 (Goldsmith et al., 2016)				
IL-10				r[c] = .28, p < .01 (Goldsmith et al., 2016)		
TNF-α						r = .26, p = .03 (Felger et al., 2018)
IL-17					**(measured by three items on the IDS)** r = .18, p =.02	

CMT= Five Choice Movement Time; DST= Digit Symbol Substitution Test; FTT= Finger Tapping Test; IDS= Inventory of Depressive Symptomatology, MFI= Multidimensional Fatigue Inventory; SHAPS= Snaith-Hamilton Pleasure Scale; SMT= Simple Choice Movement time; TMT-A= Trail Making Test A; WCST= Wisconsin Card-Sorting Test

[a]higher inflammation was associated with slower psychomotor speed

[b]higher inflammation was marginally associated with poorer executive function

[c]higher IL-10 was associated with faster psychomotor speed

Table 12
Subject characteristics for total sample and by gender.

	Total sample	Women	Men
N (%)	68	53 (78)	15 (22)
Age [years]: Mean (SD) Range	23.5 (5.7) 18-42	23.5 (6.0) 18-42	23.4 (4.7) 18-33
BMI [kg/m^2]: Mean (SD) Range	26.2 (6.3) 17.2-45.9	25.6 (6.4) 17.2-45.9	25.6 (6.4) 17.9-40.0
Race: N (%) White Black/African-American Asian	 51 (75) 4 (6) 13 (19)	 39 (73) 4 (8) 10 (19)	 12 (80) 0 (0) 3 (20)
Ethnicity: N (%) Not Hispanic or Latino Hispanic or Latino	 65 (96) 3 (4)	 50 (94) 3 (6)	 15 (100) 0 (0)
Household income: N (%) ≥ $40,000 < $40,000 Missing	 45 (66) 10 (14) 13 (20)	 33 (62) 7 (13) 13 (25)	 12 (80) 3 (20) 0 (0)
Education: N (%) Bachelor's degree or higher College students (completed high school with some college)	 18 (26) 50 (74)	 16 (30) 37 (70)	 2 (13) 13 (87)
Smoking status: N (%) Smokers Non-smokers	 4 (6) 64 (94)	 2 (4) 51 (96)	 2 (13) 13 (87)

Table 13
Clinical characteristics for total sample and by gender.

	Total sample	Women	Men
N (%)	68	53 (78)	15 (22)
Depressive scores: Mean (SD) IDS-SR Total Score BDI Total Score	 29.9 (10.7) 21.4 (10.0)	 30.9 (11.7) 21.9 (10.9)	 26.3 (4.4) 20.2 (6.3)
IDS-SR depression cutoff scores: N (%) None/Remission threshold: [14 and less] Mild depression: [15 – 25] Moderate depression: [26 – 38] Severe depression: [39 and over]	 7 (10) 19 (28) 27 (40) 15 (22)	 7 (13) 10 (19) 21 (40) 15 (28)	 0 (0) 9 (60) 6 (40) 0 (0)
Anhedonia scores: Mean (SD) Range	3.2 (2.7) 0-9	3.1 (2.8) 0-9	3.3 (2.7) 0-9
Pleasure scores: Mean (SD) Range	69.2 (13.4) 39-108	69.0 (14.7) 39-108	69.6 (7.1) 57-79
Fatigue scores: Mean (SD) Range	67.5 (13.4) 37-95	68.4 (14.2) 37-95	64.1 (9.7) 49-79
Subjective report of cognitive impairment: Mean (SD)	23.3 (5.2) 13-34	23.2 (5.5) 13-34	23.8 (4.2) 17-31
Current major depressive episode[1]: N (%)	37 (55)	28 (53)	9 (60)
Past major depressive episode[1]: N (%)	65 (96)	51 (96)	14 (93)
Recurrent MDD*[1]: N (%)	40 (60)	30 (58)	10 (67)
History of MDD diagnosed by a health care provider	44 (65)	36 (68)	8 (53)
Age at onset of depression [Years]: Mean (SD)	16.1 (4.6)	15.8 (4.5)	17.1 (5.1)
Duration of depression [Years]: Mean (SD)	7.2 (5.2)	7.1 (4.8)	6.2 (5.3)
No. of major depressive episodes: Mean (SD)	8 (7)	8 (8)	7 (6)
History of at least one suicide attempt[1]: N (%)	11 (16)	10 (19)	1 (7)

Suicidal thoughts/plans in the past month[1]: N (%)	38 (56)	32 (60)	6 (40)
Family history of MDD: N (%)	32 (48)	26 (50)	6 (40)
Alcohol use disorder[1]: N (%)	15 (22)	12 (23)	3 (20)
Substance use disorder[1]: N (%) (marijuana use) Note: two were in early remission	11 (16)	8 (15)	3 (20)
Comorbidity with other mental disorders[1]: N (%)			
Generalized anxiety disorder	24 (35)	19 (36)	5 (33)
Panic disorder	14 (21)	10 (19)	4 (27)
Agoraphobia	12 (18)	9 (17)	3 (20)
Post-traumatic stress disorder	10 (15)	10 (19)	0 (0)
Social anxiety disorder	9 (13)	8 (15)	1 (7)
Obsessive-compulsive disorder	7 (10)	7 (13.5)	0 (0)
Binge eating disorder	4 (6)	4 (8)	0 (0)
Medication use: N			
Antidepressants	26	23	3
Bupropion	8	6	2
Escitalopram	7	7	0
Sertraline	5	4	1
Fluoxetine	4	3	1
Venlafaxine	4	3	1
Duloxetine	2	2	0
Trazodone	2	2	0
Citalopram	1	1	0
Buspirone	1	1	0
OCPs[*]	17	17	0

*MDD=Major Depressive Disorder, OCPs= Oral Contraceptives
[1]Accoring to the MINI interview

Table 14
Clinical characteristics by antidepressant use.

	Current antidepressant use	
	Yes	No
N (%)	26 (38)	42 (62)
Age [years]: Mean (SD)	23.8 (6.6)	23.3 (5.2)
BMI [kg/m^2]: Mean (SD)	27.5 (6.6)	25.2 (6.1)
Gender: N (%) Women Men	 23 (88.5) 3 (11.5)	 30 (71) 12 (29)
Depressive scores: Mean (SD) IDS Total Score BDI Total Score	 28.6 (13.4) 19.1 (12.0)	 30.73 (8.8) 22.9 (8.3)
IDS depression cutoff scores: N (%) None/Remission threshold: [14 and less] Mild depression: [15 – 25] Moderate depression: [26 – 38] Severe depression: [39 and over]	 6 (23) 4 (15) 9 (35) 7 (27)	 1 (2.5) 11 (26) 22 (52.5) 8 (19)
Current major depressive episode: N (%)	11 (44)	26 (62)
Past major depressive episode: N (%)	26 (100)	39 (93)
Recurrent MDD: N (%)	16 (62)	24 (57)
Age at onset of depression [Years]: Mean (SD)	15.9 (4.3)	16.3 (4.9)
Duration of MDD [Years]: Mean (SD)	8.1 (5.4)	6.5 (5.1)
No. of major depressive episodes: Mean (SD)	10.7 (9.7)	5.6 (4.3)
History of at least one suicide attempt: N (%)	7 (27)	4 (10)
Suicidal thoughts/plans in the past month: N (%)	18 (69)	20 (48)
Family history of MDD: N (%)	13 (50)	19 (45)
Alcohol use disorder: N (%)	7 (27)	8 (19)
Substance use disorder: N (%) (marijuana use)	1 (4)	10 (24)
Non-log transformed levels of inflammatory markers: CRP (mg/L) IL-6 (pg/ml) IL-10 (pg/ml) IL-17 (pg/ml) TNF-α (pg/ml)	 5.648 (1.122) 0.529 (0.075) 0.211 (0.024) 0.894 (0.076) 1.227 (0.062)	 2.058 (0.422) 0.462 (0.043) 0.189 (0.016) 0.681 (0.058) 1.235 (0.053)

Table 15
Descriptive data on neurocognitive tests for total sample and by gender, mean (SD).

	Total sample	Women	Men
N (%)	68	53 (78)	15 (22)
Trail Making Test-A [mean no. of seconds to complete the task]	17.9 (04.21)	17.9 (04.6)	17.8 (02.5)
Digit Symbol Coding [mean no. of correct responses in a minute and half]	54.7 (5.9)	54.8 (5.9)	54.4 (6.2)
Pattern Comparison Processing Speed Test [mean no. of items answered correctly in 85 sec]			
Raw scores	57.8 (7.9)	58.5 (7.5)	55.5 (9.3)
Uncorrected Standard Scores[1]	129.3 (16.5)	130.6 (15.6)	124.8 (19.5)
Fully corrected T-Score[2]	62.6 (11.5)	63.8 (10.7)	58.6 (13.6)
Picture Sequence Memory Test [mean no. of adjacent pairs placed correctly for each of trials]			
Raw score	21.1 (7.5)	21.6 (7.3)	19.3 (8.1)
Uncorrected Standard Score[1]	117.0 (13.9)	117.9 (13.3)	114.1 (15.7)
Fully corrected T-Score[2]	55.8 (12.4)	55.6 (12.02)	56.9 (14.02)
List Sorting Working Memory Test [mean total no. of items correctly recalled and sequenced]			
Raw scores	19.1 (2.3)	18.9 (2.3)	19.9 (2.5)
Uncorrected Standard Scores[1]	109.4 (9.02)	108.6 (8.7)	112.3 (9.9)
Fully corrected T-Score[2]	49.2 (8.4)	48.3 (8.1)	52.1 (9.4)
Go No Go Test [mean no. of errors for go and no-go responses]	3.4 (2.6)	3.5 (2.6)	3.1 (2.3)
Finger Tapping Test – One Target [mean no. of taps per 20 sec]			
Dominant hand	124 (15)	122 (14)	131 (17)
Non-dominant hand	107 (13)	105 (10)	114 (19)
Finger Tapping Test – Two Targets [mean no. of taps per 20 sec]			
Dominant hand	104 (12)	104 (13)	102 (8)
Non-dominant hand	86 (11)	85 (12)	87 (7)

[1] This score uses a standard score metric (normative mean = 100, SD = 15). It compares the performance of the test-taker to those in the entire NIH Toolbox nationally representative normative sample, regardless of age or any other variable.
[2] This score (which has a mean of 50 and an SD of 10) compares the score of the test-taker to those in the NIH Toolbox nationally representative normative sample, while adjusting for key demographic variables collected during the NIH Toolbox national norming study. These variables include age, gender, race/ethnicity (white/Asian, black, Hispanic, multiracial), and educational attainment.

Table 16
Normative data for the Trail Making Test-A, Digit Symbol Test and Finger Tapping Tests.

Trail Making Test A [mean no. of seconds to complete the task] (Yeudall et al., 1987)	Age 15-20	24.75 ± 8.19
	Age 21-25	24.53 ± 7.93
	Age 26-30	24.49 ± 7.22
	Age 31-40	25.74 ± 7.53
	Age 15-40	24.81 ± 7.75
Digit Symbol Coding [mean no. of correct responses in a minute and half] (Germine et al., 2012)	46.93 to 47.78	
Finger Tapping Test-One Target [Dominant hand for intervals of 10 seconds] (Yeudall et al., 1987)	Age 15-20	46.59 ± 6.60
	Age 21-25	47.28 ± 8.13
	Age 26-30	50.47 ± 7.28
	Age 31-40	50.52 ± 8.37
	Age 15-40	48.38 ± 7.76
Finger Tapping Test-One Target [Non-Dominant hand for intervals of 10 seconds] (Yeudall et al., 1987)	Age 15-20	42.51 ± 5.81
	Age 21-25	44.38 ± 7.20
	Age 26-30	45.64 ± 6.68
	Age 31-40	46.54 ± 6.75
	Age 15-40	44.54 ± 6.76

Table 17

A. Non-log transformed levels of C-reactive protein and basal cytokines, Mean (SEM).

	Total sample	Women	Men
CRP (mg/L)	3.418 (0.539)	3.589 (0.648)	2.837 (0.897)
IL-6 (pg/ml)	0.487 (0.039)	0.492 (0.045)	0.473 (0.080)
IL-10* (pg/ml)	0.197 (0.014)	0.185 (0.013)	0.240 (0.042)
IL-17 (pg/ml)	0.764 (0.048)	0.756 (0.048)	0.789 (0.137)
TNF-α (pg/ml)	1.232 (0.040)	1.244 (0.045)	1.188 (0.094)

*Anti-inflammatory cytokine

B. C-reactive protein cutoff scores: N (%)

	Total sample	Women	Men
CRP < 1mg/L	29 (42)	20 (37)	9 (60)
1 ≤CRP≤ 3 mg/L	12 (18)	11 (21)	1 (7)
CRP > 3mg/L	25 (37)	20 (38)	5 (33)
Missing	2 (3)	2 (4)	0 (0)

Table 18
Correlation coefficients between inflammatory markers in the entire sample

	CRP	IL-6	TNF-α	IL-10	IL-17
CRP	1.00	**.56*** **	**.25***	-.05	.12
IL-6		1.00	**.37***	.04	-.08
TNF-α			1.00	**.27***	.06
IL-10				1.00	.09
IL-17					1.00

***<.001, **<.01, *<.05

Table 19
Multiple regression using CRP and basal cytokine levels to predict **total depression score**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 1: Outcome: Total Depression score						
		b[1] (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.09 (.12)	-.16	.34	.008	.47
Model 1[a]	CRP	.16 (.13)	-.11	.43	.02	.25
Model 2[b]	CRP	.14 (.16)	-.19	.47	.01	.40
IL-6						
Unadjusted Model	IL-6	.06 (.12)	-.18	.31	.004	.62
Model 1[a]	IL-6	.07 (.12)	-.18	.31	.005	.58
Model 2[b]	IL-6	-.02 (.19)	-.40	.36	.0002	.91
IL-10						
Unadjusted Model	IL-10	-.14 (.12)	-.39	.09	.02	.24
Model 1[a]	IL-10	-.10 (.13)	-.35	.15	.01	.43
Model 2[b]	IL-10	-.10 (.13)	-.35	.16	.01	.43
IL-17						
Unadjusted Model	IL-17	-.21 (.12)	-.46	.03	.05	.08[†]
Model 1[a]	IL-17	-.19 (.13)	-.45	.06	.04	.13
Model 2[b]	IL-17	-.19 (.13)	-.44	.06	.03	.15
TNF-α						
Unadjusted Model	TNF-α	-.19 (.12)	-.43	.05	.04	.12
Model 1[a]	TNF-α	-.22 (.12)	-.47	.03	.05	**.08**[†]
Model 2[b]	TNF-α	-.30 (.13)	-.57	-.04	.08	**.02***

[**] $p < 0.01$, [*] $p < 0.05$, [†] $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 20
Multiple regression using CRP and basal cytokine levels to predict **inhibitory control**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 2: Outcome: Inhibitory Control						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.27 (.11)	.02	.49	.07	**.03***
Model 1[a]	CRP	.30 (.13)	.03	.55	.08	**.02***
Model 2[b]	CRP	.27 (.16)	-.04	.58	.05	**.09**†
IL-6						
Unadjusted Model	IL-6	.28 (.11)	.05	.50	.09	**.01***
Model 1[a]	IL-6	.28 (.12)	.04	.51	.08	**.02***
Model 2[b]	IL-6	.32 (.18)	-.03	.67	.05	**.07**†
IL-10						
Unadjusted Model	IL-10	-.14 (.12)	-.37	.10	.02	.25
Model 1[a]	IL-10	-.15 (.13)	-.39	.10	.02	.24
Model 2[b]	IL-10	-.15 (.12)	-.39	.10	.02	.24
IL-17						
Unadjusted Model	IL-17	.29 (.11)	.06	.51	.09	**.01***
Model 1[a]	IL-17	.30 (.12)	.06	.54	.09	**.01***
Model 2[b]	IL-17	.32 (.12)	.08	.55	.10	**.009***
TNF-α						
Unadjusted Model	TNF-α	.13 (.12)	-.11	.35	.02	.30
Model 1[a]	TNF-α	.11 (.12)	-.13	.36	.01	.37
Model 2[b]	TNF-α	.05 (.13)	-.21	.31	.002	.71

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 21
Multiple regression using CRP and basal cytokine levels to predict **episodic memory**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 2: Outcome: Episodic Memory						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.17 (.13)	-.08	.44	.03	.18
Model 1[a]	CRP	.17 (.13)	-.10	.44	.02	.22
Model 2[b]	CRP	.05 (.17)	-.28	.38	.001	.78
IL-6						
Unadjusted Model	IL-6	.11 (.12)	-.14	.35	.01	.39
Model 1[a]	IL-6	.07 (.12)	-.17	.31	.005	.57
Model 2[b]	IL-6	-.22 (.18)	-.58	.14	.02	.22
IL-10						
Unadjusted Model	IL-10	.15 (.12)	-.09	.40	.02	.22
Model 1[a]	IL-10	.15 (.13)	-.17	.33	.02	.25
Model 2[b]	IL-10	.15 (.12)	-.10	.39	.02	.24
IL-17						
Unadjusted Model	IL-17	-.07 (.13)	-.33	.18	.005	.57
Model 1[a]	IL-17	-.11 (.13)	-.37	.15	.01	.38
Model 2[b]	IL-17	-.10 (.13)	-.35	.16	.009	.45
TNF-α						
Unadjusted Model	TNF-α	.19 (.12)	-.05	.43	.03	.13
Model 1[a]	TNF-α	.13 (.12)	-.12	.39	.02	.29
Model 2[b]	TNF-α	.05 (.13)	-.21	.32	.003	.66

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 22
Multiple regression using CRP and basal cytokine levels to predict **working memory**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 2: Outcome: Working Memory						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.02 (.13)	-.23	.28	.0006	.84
Model 1[a]	CRP	-.04 (.14)	-.32	.24	.002	.76
Model 2[b]	CRP	-.19 (.17)	-.52	.15	.02	.26
IL-6						
Unadjusted Model	IL-6	.07 (.12)	-.17	.31	.005	.56
Model 1[a]	IL-6	.06 (.12)	-.18	.30	.004	.61
Model 2[b]	IL-6	-.09 (.19)	-.46	.28	.004	.62
IL-10						
Unadjusted Model	IL-10	.17 (.12)	-.07	.42	.03	.16
Model 1[a]	IL-10	.12 (.13)	-.13	.37	.01	.37
Model 2[b]	IL-10	.11 (.13)	-.13	.37	.01	.37
IL-17						
Unadjusted Model	IL-17	.002 (.13)	-.25	.26	.00	.99
Model 1[a]	IL-17	-.06 (.13)	-.32	.19	.003	.62
Model 2[b]	IL-17	.05 (.13)	-.31	.21	.002	.68
TNF-α						
Unadjusted Model	TNF-α	-.03 (.12)	-.28	.21	.001	.80
Model 1[a]	TNF-α	-.005 (.13)	-.25	.24	.00	.97
Model 2[b]	TNF-α	-.07 (.14)	-.33	.20	.003	.63

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 23
Multiple regression using CRP and basal cytokine levels to predict **processing speed**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 3: Outcome: Processing Speed-Digit Symbol Coding						
		b[1] (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	-.04 (.12)	-.28	.21	.001	.78
Model 1[a]	CRP	-.03 (.13)	-.30	.23	.001	.79
Model 2[b]	CRP	-.02 (.16)	-.34	.30	.0002	.91
IL-6						
Unadjusted Model	IL-6	-.03 (.12)	-.27	.21	.001	.80
Model 1[a]	IL-6	-.07 (.12)	-.31	.17	.006	.56
Model 2[b]	IL-6	-.10 (.18)	-.47	.26	.005	.58
IL-10						
Unadjusted Model	IL-10	.11 (.12)	-.13	.35	.01	.37
Model 1[a]	IL-10	.09 (.12)	-.15	.33	.008	.47
Model 2[b]	IL-10	.09 (.12)	-.15	.34	.008	.47
IL-17						
Unadjusted Model	IL-17	.002 (.12)	-.24	.24	.00	.98
Model 1[a]	IL-17	-.02 (.13)	-.27	.23	.0003	.88
Model 2[b]	IL-17	-.02 (.13)	-.27	.23	.0004	.87
TNF-α						
Unadjusted Model	TNF-α	.04 (.12)	-.20	.28	.002	.74
Model 1[a]	TNF-α	-.04 (.12)	-.28	.21	.001	.76
Model 2[b]	TNF-α	-.03 (.13)	-.29	.24	.0007	.83

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 24
Multiple regression using CRP and basal cytokine levels to predict **processing speed**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 3: Outcome: Processing Speed-Trail Making Test A						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.18 (.12)	-.06	.42	.03	.15
Model 1[a]	CRP	.20 (.14)	-.06	.48	.04	.14
Model 2[b]	CRP	.16 (.17)	-.17	.49	.01	.35
IL-6						
Unadjusted Model	IL-6	.15 (.12)	-.09	.40	.02	.21
Model 1[a]	IL-6	.17 (.13)	-.08	.42	.03	.19
Model 2[b]	IL-6	.12 (.19)	-.26	.50	.006	.55
IL-10						
Unadjusted Model	IL-10	-.13 (.12)	-.38	.11	.02	.28
Model 1[a]	IL-10	-.15 (.13)	-.40	.11	.02	.25
Model 2[b]	IL-10	-.15 (.13)	-.40	.11	.02	.25
IL-17						
Unadjusted Model	IL-17	-.27 (.12)	-.51	-.03	.07	**.02***
Model 1[a]	IL-17	-.30 (.13)	-.55	-.04	.08	**.02***
Model 2[b]	IL-17	-.29 (.13)	-.54	-.03	.08	**.03***
TNF-α						
Unadjusted Model	TNF-α	.10 (.12)	-.14	.34	.01	.41
Model 1[a]	TNF-α	.14 (.13)	-.12	.39	.02	.29
Model 2[b]	TNF-α	.09 (.14)	-.18	.37	.007	.52

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 25
Multiple regression using CRP and basal cytokine levels to predict **processing speed**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 3: Outcome: Processing Speed-Pattern Comparison Processing						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.02 (.13)	-.23	.28	.0006	.85
Model 1[a]	CRP	.02 (.14)	-.26	.30	.0005	.86
Model 2[b]	CRP	.16 (.17)	-.18	.50	.01	.36
IL-6						
Unadjusted Model	IL-6	-.11 (.12)	-.35	.13	.01	.38
Model 1[a]	IL-6	-.12 (.12)	-.37	.12	.01	.32
Model 2[b]	IL-6	-.07 (.19)	-.44	.31	.002	.72
IL-10						
Unadjusted Model	IL-10	.03 (.12)	-.22	.27	.0008	.82
Model 1[a]	IL-10	.05 (.13)	-.21	.30	.002	.71
Model 2[b]	IL-10	.05 (.13)	-.21	.30	.002	.71
IL-17						
Unadjusted Model	IL-17	.07 (.13)	-.18	.32	.005	.57
Model 1[a]	IL-17	.08 (.13)	-.18	.34	.006	.56
Model 2[b]	IL-17	.07 (.13)	-.19	.33	.004	.60
TNF-α						
Unadjusted Model	TNF-α	.08 (.12)	-.16	.32	.007	.51
Model 1[a]	TNF-α	.05 (.13)	-.20	.30	.003	.69
Model 2[b]	TNF-α	.12 (.14)	-.16	.39	.01	.41

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 26
Multiple regression using CRP and basal cytokine levels to predict **motor speed**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 3: Outcome: Motor Speed-Finger Tapping Test, One Target, Dominant Hand						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.01 (.12)	-.23	.26	.0001	.92
Model 1[a]	CRP	-.06 (.13)	-.32	.20	.003	.66
Model 2[b]	CRP	-.09 (.16)	-.41	.23	.005	.57
IL-6						
Unadjusted Model	IL-6	.02 (.12)	-.22	.27	.0006	.84
Model 1[a]	IL-6	.01 (.12)	-.22	.25	.0002	.92
Model 2[b]	IL-6	.01 (.18)	-.35	.38	.0001	.95
IL-10						
Unadjusted Model	IL-10	.09 (.12)	-.15	.33	.008	.48
Model 1[a]	IL-10	.008 (.12)	-.23	.25	.0001	.94
Model 2[b]	IL-10	.008 (.12)	-.24	.25	.0001	.94
IL-17						
Unadjusted Model	IL-17	.18 (.12)	-.06	.42	.03	.14
Model 1[a]	IL-17	.14 (.12)	-.12	.37	.02	.32
Model 2[b]	IL-17	.13 (.13)	-.12	.37	.02	.32
TNF-α						
Unadjusted Model	TNF-α	-.13 (.12)	-.38	.10	.02	.27
Model 1[a]	TNF-α	-.12 (.12)	-.36	.12	.01	.34
Model 2[b]	TNF-α	-.14 (.13)	-.40	.12	.02	.29

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 27
Multiple regression using CRP and basal cytokine levels to predict **motor speed**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 3: Outcome: Motor Speed-Finger Tapping Test, One Target, Non-Dominant Hand						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.13 (.12)	-.11	.38	.02	.29
Model 1[a]	CRP	.11 (.12)	-.15	.37	.01	.34
Model 2[b]	CRP	.13 (.16)	-.19	.45	.01	.45
IL-6						
Unadjusted Model	IL-6	.10 (.12)	-.14	.35	.01	.40
Model 1[a]	IL-6	.12 (.12)	-.12	.35	.01	.31
Model 2[b]	IL-6	.19 (.18)	-.17	.56	.02	.29
IL-10						
Unadjusted Model	IL-10	.06 (.12)	-.18	.31	.004	.61
Model 1[a]	IL-10	-.006 (.12)	-.25	.24	.00	.96
Model 2[b]	IL-10	-.005 (.12)	-.25	.24	.00	.96
IL-17						
Unadjusted Model	IL-17	.06 (.12)	-.19	.30	.003	.64
Model 1[a]	IL-17	.01 (.12)	-.23	.26	.0002	.91
Model 2[b]	IL-17	.02 (.13)	-.23	.27	.0003	.89
TNF-α						
Unadjusted Model	TNF-α	-.09 (.12)	-.34	.15	.009	.45
Model 1[a]	TNF-α	-.04 (.12)	-.28	.20	.001	.73
Model 2[b]	TNF-α	-.07 (.13)	-.33	.20	.004	.62

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 28
Multiple regression using CRP and basal cytokine levels to predict **motor speed**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 3: Outcome: Motor Speed-Finger Tapping Test, Two Targets, Dominant Hand						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.03 (.12)	-.21	.28	.001	.78
Model 1[a]	CRP	.02 (.14)	-.25	.30	.0005	.85
Model 2[b]	CRP	.17 (.17)	-.16	.50	.02	.31
IL-6						
Unadjusted Model	IL-6	-.03 (.12)	-.28	.21	.001	.77
Model 1[a]	IL-6	-.02 (.13)	-.27	.23	.0005	.86
Model 2[b]	IL-6	.21 (.19)	-.16	.58	.02	.27
IL-10						
Unadjusted Model	IL-10	-.10 (.12)	-.35	.13	.01	.37
Model 1[a]	IL-10	-.09 (.13)	-.34	.16	.007	.49
Model 2[b]	IL-10	-.09 (.13)	-.34	.16	.008	.49
IL-17						
Unadjusted Model	IL-17	-.07 (.12)	-.31	.17	.004	.59
Model 1[a]	IL-17	-.07 (.13)	-.32	.19	.004	.61
Model 2[b]	IL-17	-.08 (.13)	-.33	.18	.006	.55
TNF-α						
Unadjusted Model	TNF-α	-.01 (.12)	-.25	.22	.0001	.92
Model 1[a]	TNF-α	.01 (.13)	-.24	.27	.0002	.91
Model 2[b]	TNF-α	.08 (.14)	-.19	.35	.006	.55

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 29
Multiple regression using CRP and basal cytokine levels to predict **motor speed**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 3: Outcome: Motor Speed-Finger Tapping Test, Two Targets, Non-Dominant Hand						
		b[1] (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	-.08 (.13)	-.32	.17	.009	.54
Model 1[a]	CRP	-.006 (.14)	-.28	.27	.00	.96
Model 2[b]	CRP	.13 (.17)	-.20	.46	.01	.43
IL-6						
Unadjusted Model	IL-6	-.08 (.12)	-.33	.15	.008	.47
Model 1[a]	IL-6	-.07 (.13)	-.32	.18	.005	.59
Model 2[b]	IL-6	.11 (.19)	-.26	.49	.005	.55
IL-10						
Unadjusted Model	IL-10	-.05 (.12)	-.29	.19	.003	.68
Model 1[a]	IL-10	-.03 (.13)	-.29	.22	.001	.80
Model 2[b]	IL-10	-.03 (.13)	-.29	.22	.001	.80
IL-17						
Unadjusted Model	IL-17	-.25 (.12)	-.49	-.009	.06	**.04**†
Model 1[a]	IL-17	-.21 (.13)	-.47	.04	.04	.10
Model 2[b]	IL-17	-.23 (.13)	-.48	.02	.05	**.08**†
TNF-α						
Unadjusted Model	TNF-α	.02 (.12)	-.22	.27	.0005	.86
Model 1[a]	TNF-α	.04 (.13)	-.21	.30	.002	.74
Model 2[b]	TNF-α	.12 (.14)	-.15	.39	.01	.39

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 30
Multiple regression using CRP and basal cytokine levels to predict **anhedonia**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 4: Outcome: Anhedonia-Snaith Hamilton Pleasure Scale						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	-.08 (.12)	-.32	.17	.006	.54
Model 1[a]	CRP	.03 (.14)	-.24	.29	.0006	.85
Model 2[b]	CRP	.07 (.16)	-.26	.40	.003	.66
IL-6						
Unadjusted Model	IL-6	-.08 (.12)	-.32	.16	.008	.49
Model 1[a]	IL-6	-.06 (.12)	-.31	.18	.004	.61
Model 2[b]	IL-6	-.09 (.19)	-.47	.29	.004	.63
IL-10						
Unadjusted Model	IL-10	-.03 (.12)	-.28	.21	.001	.79
Model 1[a]	IL-10	-.005 (.13)	-.25	.24	.00	.96
Model 2[b]	IL-10	-.006 (.13)	-.26	.25	.00	.96
IL-17						
Unadjusted Model	IL-17	-.15 (.12)	-.39	.09	.02	.22
Model 1[a]	IL-17	-.09 (.13)	-.34	.16	.009	.47
Model 2[b]	IL-17	-.10 (.13)	-.35	.16	.009	.46
TNF-α						
Unadjusted Model	TNF-α	-.30 (.12)	-.53	-.07	.09	**.01***
Model 1[a]	TNF-α	-.32 (.12)	-.56	-.08	.10	**.009***
Model 2[b]	TNF-α	-.36 (.13)	-.61	-.09	.11	**.008***

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 31
Multiple regression using CRP and basal cytokine levels to predict **pleasure**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 4: Outcome: Pleasure-Temporal Experience of Pleasure Scale (total)						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.20 (.12)	-.04	.44	.04	.10
Model 1[a]	CRP	.11 (.13)	-.15	.37	.01	.42
Model 2[b]	CRP	-.01 (.16)	-.33	.30	.0001	.92
IL-6						
Unadjusted Model	IL-6	.17 (.12)	-.08	.40	.03	.18
Model 1[a]	IL-6	.13 (.12)	-.10	.37	.02	.28
Model 2[b]	IL-6	-.01 (.18)	-.37	.35	.0001	.95
IL-10						
Unadjusted Model	IL-10	.05 (.12)	-.19	.29	.003	.68
Model 1[a]	IL-10	-.001 (.12)	-.25	.24	.00	.99
Model 2[b]	IL-10	-.001 (.12)	-.24	.24	.00	.99
IL-17						
Unadjusted Model	IL-17	.26 (.12)	.02	.50	.07	**.03***
Model 1[a]	IL-17	.19 (.12)	-.05	.44	.04	.12
Model 2[b]	IL-17	.21 (.12)	-.03	.45	.04	.10
TNF-α						
Unadjusted Model	TNF-α	.19 (.12)	-.05	.43	.04	.12
Model 1[a]	TNF-α	.18 (.12)	-.06	.42	.03	.15
Model 2[b]	TNF-α	.13 (.13)	-.13	.39	.01	.33

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 32
Multiple regression using CRP and basal cytokine levels to predict **consummatory pleasure**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 4: Outcome: Consummatory Pleasure Subscale						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.15 (.12)	-.10	.39	.02	.24
Model 1[a]	CRP	.07 (.14)	-.20	.33	.004	.62
Model 2[b]	CRP	-.07 (.16)	-.39	.25	.003	.68
IL-6						
Unadjusted Model	IL-6	.07 (.12)	-.17	.31	.005	.55
Model 1[a]	IL-6	.05 (.12)	-.19	.29	.003	.68
Model 2[b]	IL-6	-.19 (.18)	-.56	.17	.02	.29
IL-10						
Unadjusted Model	IL-10	.12 (.12)	-.12	.36	.01	.34
Model 1[a]	IL-10	.08 (.13)	-.17	.32	.006	.54
Model 2[b]	IL-10	.08 (.13)	-.17	.32	.006	.54
IL-17						
Unadjusted Model	IL-17	.29 (.12)	.04	.51	.08	**.02***
Model 1[a]	IL-17	.23 (.12)	-.01	.48	.05	**.06**†
Model 2[b]	IL-17	.25 (.12)	.002	.49	.06	**.048***
TNF-α						
Unadjusted Model	TNF-α	.19 (.12)	-.05	.42	.04	.12
Model 1[a]	TNF-α	.20 (.12)	-.04	.44	.04	.11
Model 2[b]	TNF-α	.15 (.13)	-.11	.41	.02	.26

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 33
Multiple regression using CRP and basal cytokine levels to predict **anticipatory pleasure**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 4: Outcome: Anticipatory Pleasure Subscale						
		b[1] (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.21 (.12)	-.03	.45	.04	.09†
Model 1[a]	CRP	.12 (.13)	-.14	.38	.01	.38
Model 2[b]	CRP	.03 (.16)	-.29	.34	.0005	.87
IL-6						
Unadjusted Model	IL-6	.20 (.12)	-.03	.45	.04	.09†
Model 1[a]	IL-6	.17 (.12)	-.07	.41	.03	.16
Model 2[b]	IL-6	.12 (.18)	-.24	.49	.007	.50
IL-10						
Unadjusted Model	IL-10	-.007 (.12)	-.25	.24	.00	.95
Model 1[a]	IL-10	-.06 (.12)	-.31	.19	.003	.64
Model 2[b]	IL-10	-.06 (.12)	-.30	.19	.004	.64
IL-17						
Unadjusted Model	IL-17	.20 (.12)	-.04	.44	.04	.10
Model 1[a]	IL-17	.13 (.13)	-.12	.38	.02	.30
Model 2[b]	IL-17	.14 (.12)	-.10	.39	.02	.26
TNF-α						
Unadjusted Model	TNF-α	.16 (.12)	-.08	.40	.02	.19
Model 1[a]	TNF-α	.14 (.12)	-.11	.38	.02	.27
Model 2[b]	TNF-α	.09 (.13)	-.17	.35	.007	.50

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 34
Multiple regression using CRP and basal cytokine levels to predict **total fatigue**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 5: Outcome: Total Fatigue Score						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.19 (.12)	-.05	.43	.03	.13
Model 1[a]	CRP	.31 (.13)	.05	.57	.08	**.02***
Model 2[b]	CRP	.27 (.16)	-.04	.59	.05	**.09**†
IL-6						
Unadjusted Model	IL-6	.16 (.12)	-.08	.40	.02	.20
Model 1[a]	IL-6	.18 (.12)	-.06	.42	.03	.14
Model 2[b]	IL-6	.07 (.19)	-.30	.43	.002	.72
IL-10						
Unadjusted Model	IL-10	-.05 (.12)	-.29	.19	.003	.68
Model 1[a]	IL-10	.01 (.13)	-.24	.26	.0001	.94
Model 2[b]	IL-10	.01 (.13)	-.24	.26	.0001	.93
IL-17						
Unadjusted Model	IL-17	-.16 (.12)	-.41	.08	.03	.18
Model 1[a]	IL-17	-.11 (.13)	-.36	.14	.01	.40
Model 2[b]	IL-17	-.09 (.13)	-.34	.15	.009	.46
TNF-α						
Unadjusted Model	TNF-α	.04 (.12)	-.20	.29	.002	.71
Model 1[a]	TNF-α	.04 (.13)	-.28	.29	.001	.77
Model 2[b]	TNF-α	-.05 (.13)	-.31	.22	.002	.73

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 35
Multiple regression using CRP and basal cytokine levels to predict **general fatigue**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 5: Outcome: General Fatigue Score						
		b[1] (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.25 (.12)	.004	.49	.06	**.046***
Model 1[a]	CRP	.31 (.13)	.04	.57	.08	**.02***
Model 2[b]	CRP	.21 (.16)	-.11	.52	.03	.20
IL-6						
Unadjusted Model	IL-6	.23 (.12)	-.01	.47	.05	**.06**†
Model 1[a]	IL-6	.24 (.12)	-.001	.48	.06	**.05**†
Model 2[b]	IL-6	.08 (.18)	-.28	.44	.003	.67
IL-10						
Unadjusted Model	IL-10	.01 (.12)	-.23	.26	.0002	.91
Model 1[a]	IL-10	.08 (.13)	-.17	.33	.006	.55
Model 2[b]	IL-10	.08 (.12)	-.16	.32	.006	.53
IL-17						
Unadjusted Model	IL-17	-.12 (.12)	-.37	.12	.01	.31
Model 1[a]	IL-17	-.10 (.13)	-.36	.15	.01	.42
Model 2[b]	IL-17	-.08 (.12)	-.33	.16	.008	.50
TNF-α						
Unadjusted Model	TNF-α	.13 (.12)	-.11	.37	.02	.30
Model 1[a]	TNF-α	.12 (.13)	-.12	.38	.01	.33
Model 2[b]	TNF-α	.02 (.13)	-.24	.29	.0005	.86

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 36
Multiple regression using CRP and basal cytokine levels to predict **physical fatigue**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 5: Outcome: Physical Fatigue Score						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.09 (.12)	-.15	.36	.009	.46
Model 1[a]	CRP	.17 (.14)	-.09	.44	.02	.21
Model 2[b]	CRP	.02 (.16)	-.30	.34	.0003	.89
IL-6						
Unadjusted Model	IL-6	.28 (.12)	.04	.51	.08	**.02***
Model 1[a]	IL-6	.30 (.12)	.05	.53	.09	**.02***
Model 2[b]	IL-6	.25 (.18)	-.12	.61	.03	.18
IL-10						
Unadjusted Model	IL-10	.06 (.12)	-.18	.31	.004	.62
Model 1[a]	IL-10	.11 (.13)	-.14	.37	.01	.38
Model 2[b]	IL-10	.11 (.12)	-.13	.36	.01	.37
IL-17						
Unadjusted Model	IL-17	-.21 (.12)	-.46	.02	.05	.08†
Model 1[a]	IL-17	-.18 (.13)	-.44	.07	.03	.16
Model 2[b]	IL-17	-.16 (.13)	-.41	.08	.03	.20
TNF-α						
Unadjusted Model	TNF-α	.19 (.12)	-.05	.43	.04	.12
Model 1[a]	TNF-α	.19 (.13)	-.06	.44	.03	.14
Model 2[b]	TNF-α	.11 (.13)	-.16	.38	.01	.42

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 37
Multiple regression using CRP and basal cytokine levels to predict **mental fatigue**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 5: Outcome: Mental Fatigue Score						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.18 (.12)	-.06	.43	.03	.14
Model 1[a]	CRP	.32 (.13)	.06	.57	.09	**.02***
Model 2[b]	CRP	.44 (.16)	.13	.75	.12	**.006***
IL-6						
Unadjusted Model	IL-6	.002 (.12)	-.24	.25	.00	.98
Model 1[a]	IL-6	.003 (.12)	-.24	.25	.00	.98
Model 2[b]	IL-6	-.05 (.19)	-.43	.32	.001	.78
IL-10						
Unadjusted Model	IL-10	-.13 (.12)	-.38	.11	.02	.28
Model 1[a]	IL-10	-.10 (.13)	-.35	.15	.009	.44
Model 2[b]	IL-10	-.10 (.13)	-.35	.15	.009	.45
IL-17						
Unadjusted Model	IL-17	.03 (.12)	-.21	.28	.001	.77
Model 1[a]	IL-17	.10 (.13)	-.16	.35	.009	.45
Model 2[b]	IL-17	.10 (.13)	-.16	.35	.009	.45
TNF-α						
Unadjusted Model	TNF-α	.009 (.12)	-.23	.25	.0001	.94
Model 1[a]	TNF-α	-.03 (.13)	-.28	.22	.001	.79
Model 2[b]	TNF-α	-.05 (.14)	-.33	.22	.002	.69

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 38
Multiple regression using CRP and basal cytokine levels to predict **reduced motivation**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 5: Outcome: Reduced Motivation						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.02 (.12)	-.23	.26	.0004	.87
Model 1[a]	CRP	.08 (.14)	-.19	.35	.005	.57
Model 2[b]	CRP	.02 (.17)	-.31	.36	.0003	.90
IL-6						
Unadjusted Model	IL-6	-.004 (.12)	-.25	.24	.00	.98
Model 1[a]	IL-6	.01 (.13)	-.24	.26	.0001	.93
Model 2[b]	IL-6	-.16 (.19)	-.54	.22	.01	.40
IL-10						
Unadjusted Model	IL-10	.02 (.12)	-.23	.26	.0003	.88
Model 1[a]	IL-10	.05 (.13)	-.20	.31	.003	.67
Model 2[b]	IL-10	.05 (.13)	-.20	.31	.003	.67
IL-17						
Unadjusted Model	IL-17	-.14 (.12)	-.38	.10	.02	.26
Model 1[a]	IL-17	-.11 (.13)	-.37	.15	.01	.40
Model 2[b]	IL-17	-.10 (.13)	-.36	.15	.01	.43
TNF-α						
Unadjusted Model	TNF-α	-.12 (.12)	-.37	.12	.01	.31
Model 1[a]	TNF-α	-.13 (.13)	-.38	.13	.01	.33
Model 2[b]	TNF-α	-.19 (.14)	-.47	.08	.03	.16

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 39
Multiple regression using CRP and basal cytokine levels to predict **reduced activity**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 5: Outcome: Reduced Activity						
		b[1] (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.17 (.12)	-.07	.39	.03	.18
Model 1[a]	CRP	.27 (.13)	.01	.52	.07	**.03***
Model 2[b]	CRP	.29 (.15)	-.01	.60	.06	**.06**[†]
IL-6						
Unadjusted Model	IL-6	.10 (.12)	-.14	.34	.01	.41
Model 1[a]	IL-6	.13 (.12)	-.10	.37	.02	.27
Model 2[b]	IL-6	.13 (.18)	-.24	.49	.008	.49
IL-10						
Unadjusted Model	IL-10	-.13 (.12)	-.37	.11	.02	.30
Model 1[a]	IL-10	-.08 (.12)	-.33	.16	.007	.49
Model 2[b]	IL-10	-.08 (.12)	-.33	.16	.008	.50
IL-17						
Unadjusted Model	IL-17	-.17 (.12)	-.41	.07	.03	.16
Model 1[a]	IL-17	-.11 (.13)	-.36	14	.01	.38
Model 2[b]	IL-17	-.10 (.13)	-.35	.15	.01	.42
TNF-α						
Unadjusted Model	TNF-α	-.02 (.12)	-.26	.21	.0006	.84
Model 1[a]	TNF-α	-.007 (.12)	-.25	.24	.0001	.95
Model 2[b]	TNF-α	-.05 (.13)	-.32	.21	.003	.69

[**] $p < 0.01$, [*] $p < 0.05$, [†] $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Table 40
Multiple regression using CRP and basal cytokine levels to predict **subjective cognitive impairment**, Beta, SE, confidence intervals, partial eta-square, and *p* values.

Aim 5: Outcome: Subjective Cognitive Impairment						
		b^1 (SE)	95% Confidence Intervals		Partial Eta-Square	*P* value
CRP						
Unadjusted Model	CRP	.02 (.12)	-.22	.27	.0006	.84
Model 1[a]	CRP	.16 (.13)	-.10	.43	.02	.22
Model 2[b]	CRP	.14 (.16)	-.18	.47	.01	.38
IL-6						
Unadjusted Model	IL-6	-.12 (.12)	-.36	.12	.01	.33
Model 1[a]	IL-6	-.09 (.12)	-.33	.14	.01	.44
Model 2[b]	IL-6	-.41 (.18)	-.76	-.05	.08	**.02***
IL-10						
Unadjusted Model	IL-10	-.20 (.12)	-.44	.03	.04	.09†
Model 1[a]	IL-10	-.19 (.12)	-.43	.05	.03	.13
Model 2[b]	IL-10	-.19 (.12)	-.43	.06	.04	.13
IL-17						
Unadjusted Model	IL-17	-.05 (.12)	-.29	.19	.003	.68
Model 1[a]	IL-17	.03 (.13)	-.22	.28	.0009	.81
Model 2[b]	IL-17	.04 (.13)	-.21	.29	.001	.77
TNF-α						
Unadjusted Model	TNF-α	-.03 (.12)	-.27	.21	.0009	.81
Model 1[a]	TNF-α	-.02 (.12)	-.27	.22	.0005	.86
Model 2[b]	TNF-α	-.07 (.13)	-.34	.19	.005	.58

** $p < 0.01$, * $p < 0.05$, † $p < 0.1$.

[1] *b* denotes standardized *beta*.

[a] Model 1 includes age, gender, antidepressant use as covariates.

[b] Model 2 includes age, gender, antidepressant use and BMI as covariates.

Supplementary Tables-Study 2

Table S6
Correlation coefficients between total depression score and other subjective measures of depressive symptoms, *r*'s and *p* values.

	IDS-To	SHAPS-To	TEPS-Tot	TEPS-Con	TEPS-Ant	MFI-To	MFI-GenFa	MFI-PhyFa	MFI-MenFa	MFI-RedMot	MFI-RedAct	CPFQ
IDS-To	1.00	**.52*** <.0001**	**-.26* .03**	-.18 .13	**-.27* .02**	**.45*** <.0001**	**.34** .004**	**.25* .04**	**.28* .02**	**.44*** <.0001**	**.37** .002**	**.30* .01**
SHAPS-To		1.00	**-.64*** <.0001**	**-.52** <.0001**	**-.63*** <.0001**	**.50*** <.0001**	**.37** .002**	**.329** .006**	**.25* .04**	**.52*** <.0001**	**.38** .001**	**.30* .01**
TEPS-To			1.00	**.87*** <.0001**	**.93*** <.0001**	**-.28* .02**	-.20 .10	-.08 .47	-.13 .27	**-.33** .005**	**-.29* .01**	-.15 .19
TEPS-Con				1.00	**.62*** <.0001**	-.18 .12	-.15 .20	-.01 .92	-.12 .29	**-.22† .07**	-.18 .12	-.05 .62
TEPS-Ant					1.00	**-.30* .01**	-.20 .10	-.13 .29	-.11 .34	**-.36** .002**	**-.32** .008**	**-.20† .09**
MFI-To						1.00	**.78*** <.0001**	**.73*** <.0001**	**.63*** <.0001**	**.79*** <.0001**	**.77*** <.0001**	**.56*** <.0001**
MFI-GenFa							1.00	**.62*** <.0001**	**.39** .001**	**.51*** <.0001**	**.45*** <.0001**	**.36** .002**
MFI-PhyFa								1.00	.19 .11	**.44*** .0002**	**.45*** .0001**	**.30* .01**
MFI-MenFa									1.00	**.38** .001**	**.33** .006**	**.45*** .0001**
MFI-RedMot										1.00	**.58*** <.0001**	**.46*** <.0001**
MFI-RedAct											1.00	**.49*** <.0001**
CPFQ												1.00

***** <.001, **<.01, *<.05, †<.1**

CPFQ= Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, IDS-To= Inventory of Depressive Symptomatology-Total score, SHAPS-To= Snaith Hamilton Pleasure Scale-Total score, TEPS= Temporal Experience of Pleasure Scale, TEPS-Ant= TEPS-Anticipatory Subscale, TEPS-Con= TEPS-Consummatory Subscale, MFI-To= Multidimensional Fatigue Inventory-Total score, MFI-GenFa= MFI-General Fatigue Subscale, MFI-MenFa= MFI-Mental Fatigue Subscale, MFI-PhyFa= MFI-Physical Fatigue Subscale, MFI-ReMot= MFI-Reduced Motivation, MFI-RedAct = MFI-Reduced Activity

Table S7
Correlation coefficients between total depression score and objective measures of cognition, *r*'s and *p* values.

	PSM	LSM	GoNoGo	DST	TMT-A	PCP	FT1-D	FT1-ND	FT2-D	FT2-ND
IDS-Total	-.05 .64	-.18 .12	.02 .85	-.13 .26	.02 .84	.03 .79	-.20 .10	-.19 .11	-.07 .55	-.11 .34
MFI-Total	-.22 .95	-.19 .10	-.03 .79	**-.23†** **.05**	.10 .40	-.13 .28	**-.25*** **.04**	-.17 .14	-.19 .10	**-.23†** **.06**
MFI-General fatigue	.06 .60	**-.22†** **.07**	.00 .99	-.17 .14	-.09 .43	-.04 .69	-.11 .36	-.001 .99	.041 .74	-.05 .66
MFI-Mental fatigue	.01 .91	-.09 .42	-.03 .77	.07 .53	.10 .40	-.04 .70	-.08 .48	.08 .51	**-.22†** **.07**	**-.23†** **.06**
MFI-Physical fatigue	.06 .61	-.09 .44	.02 .82	**-.26*** **.03**	.04 .72	**-.22†** **.08**	**-.23†** **.06**	**-.21†** **.08**	-.06 .60	-.18 .12
MFI-Reduced activity	-.14 .25	**-.27*** **.03**	-.01 .90	**-.35**** **.003**	**.24†** **.05**	-.17 .15	**-.32**** **.008**	-.20 .10	**-.23†** **.06**	-.14 .23
MFI-Reduced motivation	-.00 .96	-.04 .71	-.095 .4	-.14 .22	.04 .70	.01 .91	-.16 .19	-.13 .25	**-.22†** **.07**	**-.22†** **.07**
SHAPS-Total	-.01 .93	-.10 .41	-.01 .89	-.04 .70	-.02 .82	.15 .20	**-.27*** **.02**	-.18 .14	-.14 .24	-.10 .41
TEPS-Total	.008 .94	.08 .47	.00 .96	.08 .48	.004 .97	-.12 .31	**.24*** **.04**	.17 .15	.02 .85	.004 .97
TEPS-Consummatory	-.03 .77	.05 .64	.0 .81	-.08 .50	-.0007 .99	-.10 .38	.14 .24	.13 .28	-.009 .94	-.04 .73
TEPS-Anticipatory	.03 .74	.09 .42	-.01 .92	.19 .10	.006 .95	-.11 .35	**.28*** **.02**	.17 .15	.04 .72	.03 .75
CPFQ-Total	-.12 .29	-.05 .68	-.03 .80	.04 .71	-.02 .86	.09 .45	-.02 .82	-.11 .34	-.05 .68	-.04 .72

***** <.001, **<.01, *<.05, †<.1**

CPFQ= Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, DST= Digit Symbol Coding, FT1-D= Finger Tapping Test for one target with dominant hand, FT1-ND= Finger Tapping Test for one target with nondominant hand, FT2-D= Finger Tapping Test for two targets with dominant hand, FT2-ND= Finger Tapping Test for two targets with nondominant hand, GoNoGo=Go/No-Go Test, IDS= Inventory of Depressive Symptomatology-Total score, SHAPS= Snaith Hamilton Pleasure Scale-Total score, LSM= List Sorting Memory Working Memory, MFI= Multidimensional Fatigue Inventory, PCP= Pattern Comparison Processing Test, PSM= Picture Sequence Memory Test, TEPS= Temporal Experience of Pleasure Scale, TMT-A= Trail Making Test A

Table S8
Correlation coefficients between objective measures of cognition, *r*'s and *p* values.

	PSM	**LSM**	**GoNoGo**	**DST**	**TMT-A**	**PCP**	**FT1-D**	**FT1-ND**	**FT2-D**	**FT2-ND**
PSM	1:00	.19 .11	-.04 .71	.17 .15	-.16 .16	.02 .82	.006 .95	.10 .41	-.03 .81	.09 .42
LSM		1:00	.12 .31	**.32***** **.009**	-.15 .20	.03 .78	**.22†** **.07**	**.26*** **.03**	.02 .85	.07 .55
GoNoGo			1:00	-.070 .572	-.16 .18	.17 .14	.10 .40	.18 .13	.12 .29	.08 .49
DST				1:00	**-.42***** **.0003**	**.49***** **<.0001**	**.32**** **.006**	**.23†** **.06**	**.26*** **.03**	**.28*** **.02**
TMT-A					1:00	**-.29*** **.02**	**-.31*** **.01**	**-.26*** **.03**	**-.37**** **.002**	**-.25*** **.04**
PCP						1:00	**.23†** **.06**	**.23†** **.06**	**.42***** **.0003**	**.44***** **.0002**
FT1-D							1:00	**.78***** **<.0001**	**.44***** **.0001**	**.34**** **.004**
FT1-ND								1:00	**.49***** **<.0001**	**.56***** **<.0001**
FT2-D									1:00	**.76***** **<.0001**
FT2-ND										1:00

***** <.001, **< .01, *<.05,** †**<.1**

DST= Digit Symbol Coding Test, FT1-D= Finger Tapping Test for one target with dominant hand, FT1-ND= Finger Tapping Test for one target with nondominant hand, FT2-D= Finger Tapping Test for two targets with dominant hand, FT2-ND= Finger Tapping Test for two targets with nondominant hand, GoNoGo=Go/No-Go Test, LSM= List Sorting Memory Working Memory, PCP= Pattern Comparison Processing Test, PSM= Picture Sequence Memory Test, TMT-A= Trail Making Test A

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CHAPTER 4: Conclusion

Depression is the leading cause of disability worldwide (World Health Organization, 2018). Patients with depression show a wide range of clinical symptomatology including affective symptoms (e.g., depressed mood), cognitive symptoms (e.g., concentration difficulty), and neurovegetative symptoms (e.g., fatigue). These constructs may differ in their underlying etiology, prognoses, medical comorbidities as well as in responsiveness to treatment. Therefore, there has been a call to identify more homogenous constructs within depressive symptomatology rather than only relying on a single score of a multidimensional construct (Smith et al., 2009). This concept is the overarching theme of the present dissertation, which consisted of two studies. A brief overview of each study and the findings are discussed below.

4.1 Summary

Study 1. The presentation of depression varies significantly across patients. Comorbidity of depression with other conditions may account for such variation. Obesity is one example of these conditions. In spite of the high comorbidity of depression with obesity, little research has focused on the relationship between obesity and symptom profiles of depression. Understanding depressive symptomology in the context of obesity will provide insight into more comprehensive assessment tools that capture the heterogeneity of depression. Both the depression symptom checklist 20-item (SCL-20) and the patient health questionnaire 9-item (PHQ-9) are widely used tools for screening depression; however, no studies have examined the factor structure of these scales in patients with comorbid depression and obesity. In ***Study 1***, we determined the factor structure of depressive symptomatology using exploratory factor analysis (EFA) in 409 patients

with comorbid depression and obesity. Results from ***Study 1*** suggest that both the SCL-20 and PHQ-9 scales capture the "negative affect" construct in these patients. However, the SCL-20 seems more sensitive than the PHQ-9 to capture other depression-related constructs (i.e., anhedonia, sleep disturbance). Some possible reasons include: 1) differences in number of scale items, and 2) differences in the aspects of depression they tap into; the SCL-20 measures the severity of symptoms, whereas the PHQ-9 measures the frequency of symptoms. Overall, we found that neurovegetative symptoms of depression may be more prevalent and/or severe compared to affective/cognitive symptoms in patients with comorbid obesity. A comprehensive assessment tool that measures various aspects of depression, particularly cognitive symptoms (via objective neurocognitive testing), fatigue, anhedonia, sleep, and overeating, in addition to negative emotions/affect, may be needed to better characterize the nature of depression in patients with comorbid obesity.

Study 2. There is evidence that inflammation contributes to the pathophysiology of depression. Most studies examining the depression-inflammation link have used a sum-score as a proxy for total severity of depression. Relatively few studies have examined markers of inflammation in relation to specific symptoms of depression, and the majority of these studies limited the assessment of underlying constructs to one or two subjective questions, which does not allow for a full representation of each measured construct. ***Study 2*** attempted to address this important gap in the literature by providing information regarding the association between inflammation and specific symptoms of depression (as measured by a battery of questionnaires and neurocognitive testing). Due to the presence of multiple tests, it is possible that some of our

findings might be due to chance. We attempted to put more emphasis on CRP given that it is a more stable measure of inflammation compared to cytokines and has clear clinical implications. In addition, the effect sizes were reported to help interpret the results (see figures 4 to 8). In line with our expectation, higher CRP was associated with lower response inhibition. A similar pattern of associations was observed with respect to IL-6 and IL-17. In addition, higher CRP was associated with total fatigue as well as multiple facets within fatigue (i.e., general fatigue, mental fatigue and reduced activity). Moreover, higher IL-6 was associated with physical fatigue. These findings suggest that CRP and IL-6 are two biomarkers that may play a role in the underlying biology of fatigue symptoms.

In contrast to our expectation, higher TNF-α was associated with lower severity of depression and anhedonia. In addition, higher IL-17 was associated with faster processing speed and higher levels of pleasure. Although the strength of these associations was medium to large, the reason behind these observations is not clear. Because of the low mean value of anhedonia in our sample, there may have not been enough variation in the anhedonia score (specifically toward the high end of the spectrum) to detect a positive association with inflammation. In addition, the mean cognitive performance on psychomotor processing, working memory and episodic memory was above normative standards, therefore this sample did not represent the full spectrum of severity in cognitive impairment which limited our ability to explore the associations between inflammation and performance on these cognitive domains.

In sum, our preliminary findings from **Study 2** suggest that an association exists between inflammation and specific symptoms of depression, including fatigue and inhibitory control in a sample of young adults with depressive symptoms.

4.2 Implications

There is general consensus that depression is a heterogenous disorder and the use of total depression scores (i.e., the sum of depressive symptoms) may mask important information. Yet, a critical question is whether this line of information (i.e., parsing the heterogeneity of depression) has clinical applicability? To answer this question, some background information is provided as follow:

The diagnosis of mental disorders is defined by a constellation of signs and symptoms that is described in the diagnostic and statistical manual of mental disorders (DSM). Currently, there are no reliable objective biomarkers with sufficient specificity and sensitivity for the diagnosis of depression. One possible explanation is that most studies that have explored the underlying pathophysiology of depression have defined depression as a broad syndrome (based on signs and symptoms) with an assumption that all constructs within depression have the same underlying cause. This notion has been challenged by emerging evidence suggesting that specific depressive symptoms differ in their underlying neurobiology and responsiveness to treatment (see chapter 1 for more detail). In addition, a concern has been raised by experts in the field that advances in biobehavioral sciences and neuroscience did not contribute to any progress in the DSM diagnostic framework (Cuthbert, 2014). To address this issue, the National Institute of Mental Health has launched a new way of classifying mental disorders for research purposes

based on proximal neurobiological mechanisms, which is entitled the Research Domain Criteria (RDoC) framework (Etkin & Cuthbert, 2014). Based on this approach, studies with a RDoC design should include participants with a wide spectrum of functioning (i.e., from normal to impaired) with respect to the constructs of interest (Etkin & Cuthbert, 2014); these constructs (e.g., negative valence, positive valence, cognitive systems) can be assessed using various units of analysis (e.g., physiology, behavior, self-reports). According to the RDoC framework, researchers do not need to limit their samples to those who meet the criteria for a particular mental disorder, given that this type of categorization based on clinical criteria is somewhat arbitrary (National Institute of Mental Health, 2020). Participants who meet the criteria for a disorder may share qualitative similarities with those who did not meet the cutoff for diagnosis because of less severity and/or frequency of symptoms (Etkin & Cuthbert, 2014). Importantly, exclusion of the latter participants may mask important information with respect to psychopathology, which is to understand the full range of functioning from "normal" to "pathological/abnormal" for a particular characteristic (National Institute of Mental Health, 2020). One aim of this approach is to relate these abnormalities to relevant symptoms, rather than a specific disorder (Etkin & Cuthbert, 2014). This information may help identify specific symptoms or cluster of symptoms as targets for treatment strategies. Current pharmacotherapy guidelines for MDD patients are mainly based on treating depression as a whole, whereas individuals with the same diagnosis may overlap on only a limited number of symptoms. This practice may partly explain the observation that less than 40% of patients achieve remission following the initial course of treatment (Rush et al., 2006). As such, measuring the efficacy and

effectiveness of antidepressants only by using the sum-scores of depression needs to be re-examined. In sum, this background information shows that the field of psychiatry has been going through a major shift in how it conducts research on psychopathology.

Consistent with what is discussed above, both ***Study 1*** and ***Study 2*** of this dissertation aimed to parse the heterogeneity of depression. In ***Study 1***, we used baseline data from a randomized clinical trial in comorbid depression and obesity to examine the factor structure of depression. The results of ***Study 1*** will add to our overall understanding of the components of depression that are measured by two depression rating scales, the SCL-20 and PHQ-9, in individuals with comorbid depression and obesity. In addition, these findings can help identify those constructs that are more central to the concept of depression in patients with comorbid depression and obesity, which will provide insight into designing more comprehensive assessment tools that capture the heterogeneity of depression. Moreover, this information has implications in efficacy and effectiveness studies given that components of depression may respond differentially to treatment. Ultimately, these data may help tailor treatment to individuals based on presenting symptoms and could improve treatment outcomes. This notion is in line with precision medicine approaches that aim to improve outcomes for patients. As a follow up to ***Study 1***, we will examine the efficacy of the intervention in the RAINBOW trial on different factors that emerged from this study to explore whether various factors within depression respond differentially to treatment.

Study 2 integrated both behavioral and biological components to better understand the underlying pathophysiology of depression in participants with varying levels of depressive

symptoms, which is consistent with the notion of RDoC. Identifying homogenous constructs within depression with a particular biosignature is an important step in advancing translational research. An increased understanding of the neurobiological correlates of depressive symptoms would better enable the development of novel therapeutic targets and effective treatments.

In both studies, we discuss the need to move towards using more comprehensive assessment tools that capture different aspects of depressive symptoms rather than only relying on a single depression scale with a few items. Given that most depression rating scales were designed and developed from a broader pool of symptoms (i.e., with a larger set of items), one could argue that why we need to go backwards by including more items in depression rating scales. In addition, using a battery of questionnaires and objective measures to assess various aspects of depression may be very time-consuming, thus, may not be practical in routine clinical practice. These questions can be answered in the context of a major shift in psychiatry research (discussed above). Indeed, the RDoC framework seeks to move beyond defining signs and symptoms based on the DSM and introduces several functional constructs or domains (e.g., positive valence, cognitive systems). These constructs need to be measured more accurately at various units of analysis (e.g., physiology, behavior). Using a single depression rating scale with limited items cannot adequately measure any related construct. For example, in ***Study 1*** we found that two widely used depression scales are limited in the aspects of depression they tap into among patients with comorbid depression and obesity. Therefore, more specific instruments are needed to assess symptoms/constructs that are more prevalent in this population. Overall, this line of research will eventually help identify the key elements of depression-related constructs

which will help optimize the assessment of each construct. From a clinical perspective, a critical challenge is the lack of validated assessment tools with an adequate sensitivity, specificity and reproducibility to objectively assess different constructs of depression (such as cognition and anhedonia). Although the use of multiple testing (e.g., neuropsychological assessment) is time-consuming and increases the burden for patients, it should not be considered as an impractical approach in clinical settings. Given that individuals with depression show a wide range of symptoms, there could be an initial screening in routine clinical care to determine which symptoms are among the chief complaints of patients and then more specific diagnostic tests could be run to subclassify their symptoms. In sum, the field of psychiatry would benefit from research studies that parse the heterogeneity of mental disorders because this line of research would help clarify the nature of mental illness and inform both diagnostic tools (e.g., biomarkers, neuropsychological assessment) and targeted treatment.

4.3 Future directions

In ***Study 1***, we found that low energy/fatigue was among the most endorsed symptoms in patients with comorbid depression and obesity. Given that three questionnaire items (two items on the SCL-20 and one on the PHQ-9) were used to measure fatigue in this study, we were not able to determine which facets of fatigue are most relevant to the concept of depression in this sample. In addition, in ***Study 2***, we found that higher inflammation was associated with higher fatigue. Indeed, our findings suggest that this association may be more robust for some aspects of fatigue, including physical fatigue, mental fatigue and reduced activity. Given that obesity is characterized by low-grade inflammation (Shelton & Miller, 2010), it would be important to use

multidimensional fatigue measures to determine which facets of fatigue are associated with inflammation in patients with comorbid depression and obesity. Moreover, as discussed in chapter 2, we found that the loss-of-interest item on the SCL-20 shared the same latent factor as loss of energy and fatigue symptoms (i.e., loaded on the same factor). Evidence suggests that inflammation can alter dopamine in the basal ganglia, resulting in anhedonia, fatigue and psychomotor retardation (reviewed by Felger & Miller, 2012). Hence, we speculated that loss of energy, fatigue and loss of interest lumped together partly because they are interrelated in an inflammatory network. Future studies are needed to utilize more comprehensive assessment tools to measure anhedonia, fatigue and psychomotor processing speed (via objective measures) in patients with comorbid depression and obesity. In addition, neuroimaging studies are needed to examine neural substrates of the aforementioned symptoms in this specific population and determine whether elevated inflammation correlate with altered activity in the basal ganglia. Finally, in ***Study 2*** we found that higher inflammation was associated with less response inhibition as measured by objective neurocognitive testing. Given that cognitive control has been implicated in both depression and obesity (Williams et al., 2018), examining the association between inflammation and response inhibition will be an important research question in the context of depression and obesity.

4.4 Closing remarks

Both ***Study 1*** and ***Study 2*** of the current dissertation were conducted in an attempt to address the multidimensionality of depression. The results of both studies support the idea that depression is not a unidimensional construct and relying only on depression sum-scores (i.e. total

score) may mask important information. Taken together, breaking down depression into homogenous constructs can help elucidate the distinct neurobiological correlates of depressive symptoms and may help clinicians use more targeted treatment strategies that correspond to each clusters' underlying biological mechanisms (Stahl, 2003). Identifying the biological and behavioral correlates of various constructs within depression may be of critical importance to inform future work on designing more effective and personalized treatments.

Figures-Chapter 4

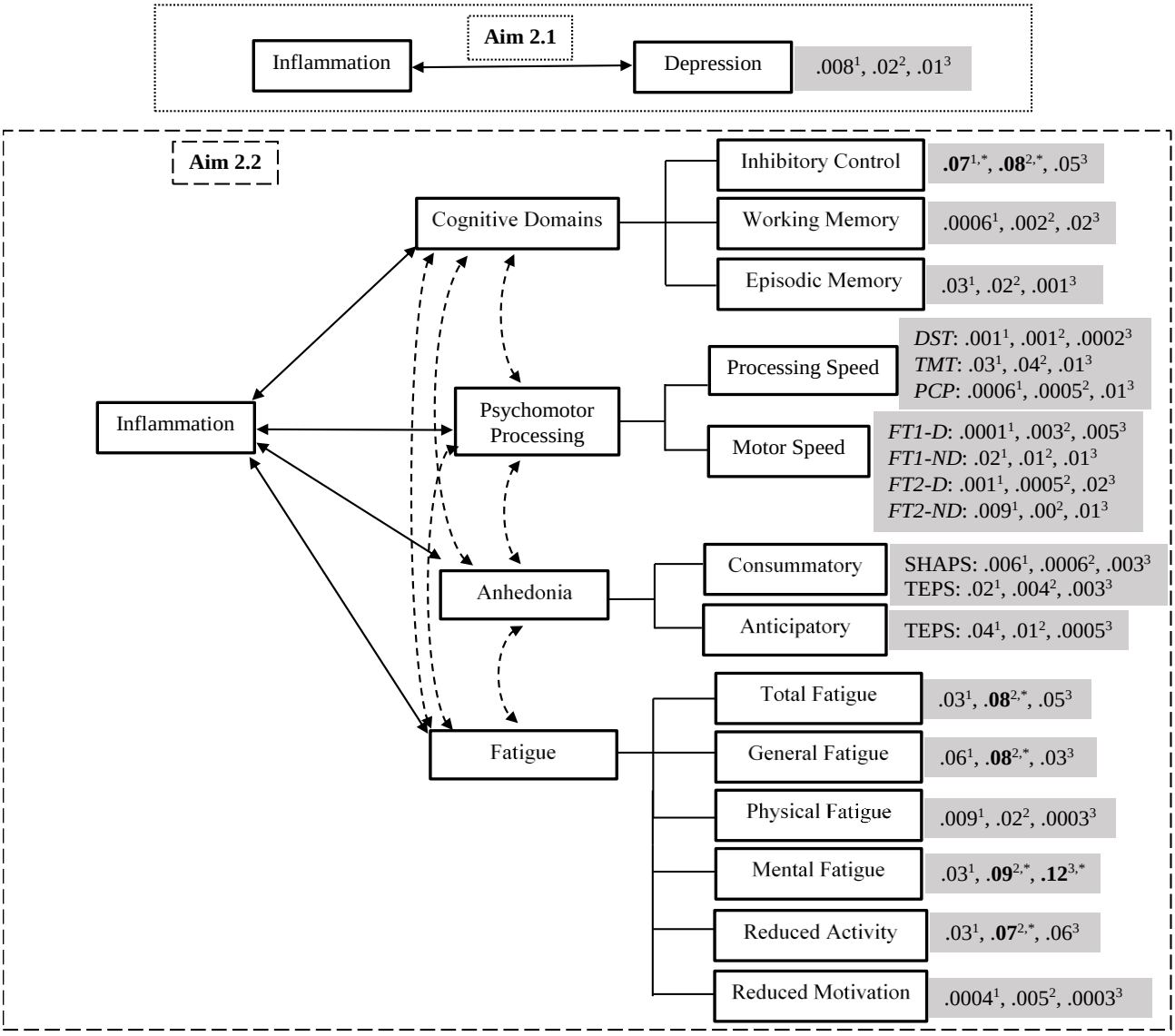

Figure 4. Effect sizes (i.e., partial eta-square) for the associations between ***CRP*** and depressive symptoms
**p* <.05. The values of *0.01, 0.06* and *0.14* for partial eta-squared represent small, medium, and large effect sizes.
[1]Unadjusted Model, [2]Model 1 (includes age, gender, antidepressant use as covariates), [3]Model 2 (includes age, gender, antidepressant use and BMI as covariates)
DST= Digit Symbol Coding, FT1-D= Finger Tapping Test-one target with dominant hand, FT1-ND= Finger Tapping Test-one target with nondominant hand, FT2-D= Finger Tapping Test-two targets with dominant hand, FT2-ND= Finger Tapping Test-two targets with nondominant hand; PCP= Pattern Comparison Processing, SHAPS= Snaith Hamilton Pleasure Scale; TEPS= Temporal Experience of Pleasure Scale; TMT-A= Trail Making Test A

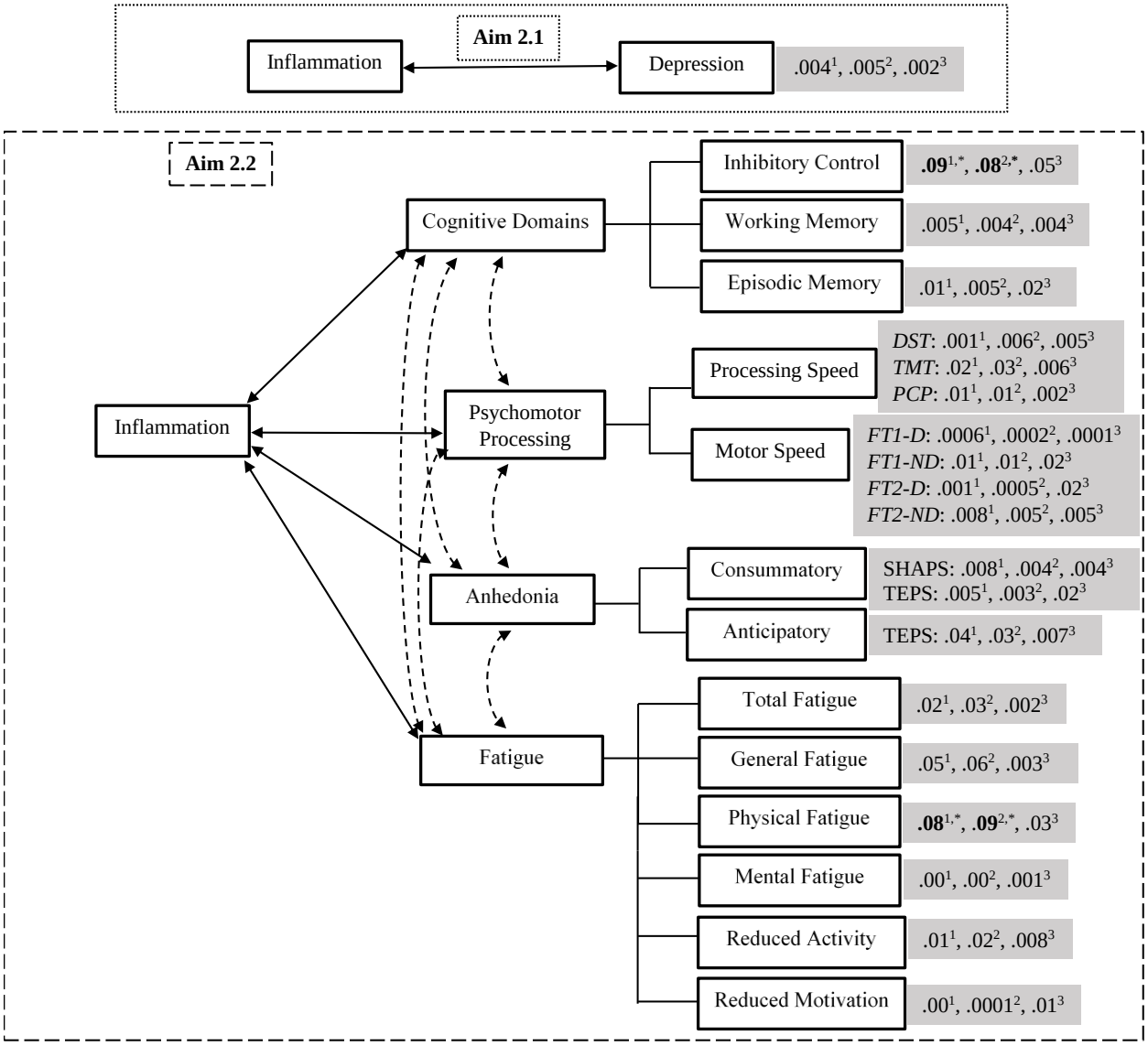

Figure 5. Effect sizes (i.e., partial eta-square) for the associations between ***IL-6*** and depressive symptoms
*p <.05. The values of *0.01*, *0.06* and *0.14* for partial eta-squared represent small, medium, and large effect sizes.
[1]Unadjusted Model, [2]Model 1 (includes age, gender, antidepressant use as covariates), [3]Model 2 (includes age, gender, antidepressant use and BMI as covariates)
DST= Digit Symbol Coding, FT1-D= Finger Tapping Test-one target with dominant hand, FT1-ND= Finger Tapping Test-one target with nondominant hand, FT2-D= Finger Tapping Test-two targets with dominant hand, FT2-ND= Finger Tapping Test-two targets with nondominant hand; PCP= Pattern Comparison Processing, SHAPS= Snaith Hamilton Pleasure Scale; TEPS= Temporal Experience of Pleasure Scale; TMT-A= Trail Making Test A

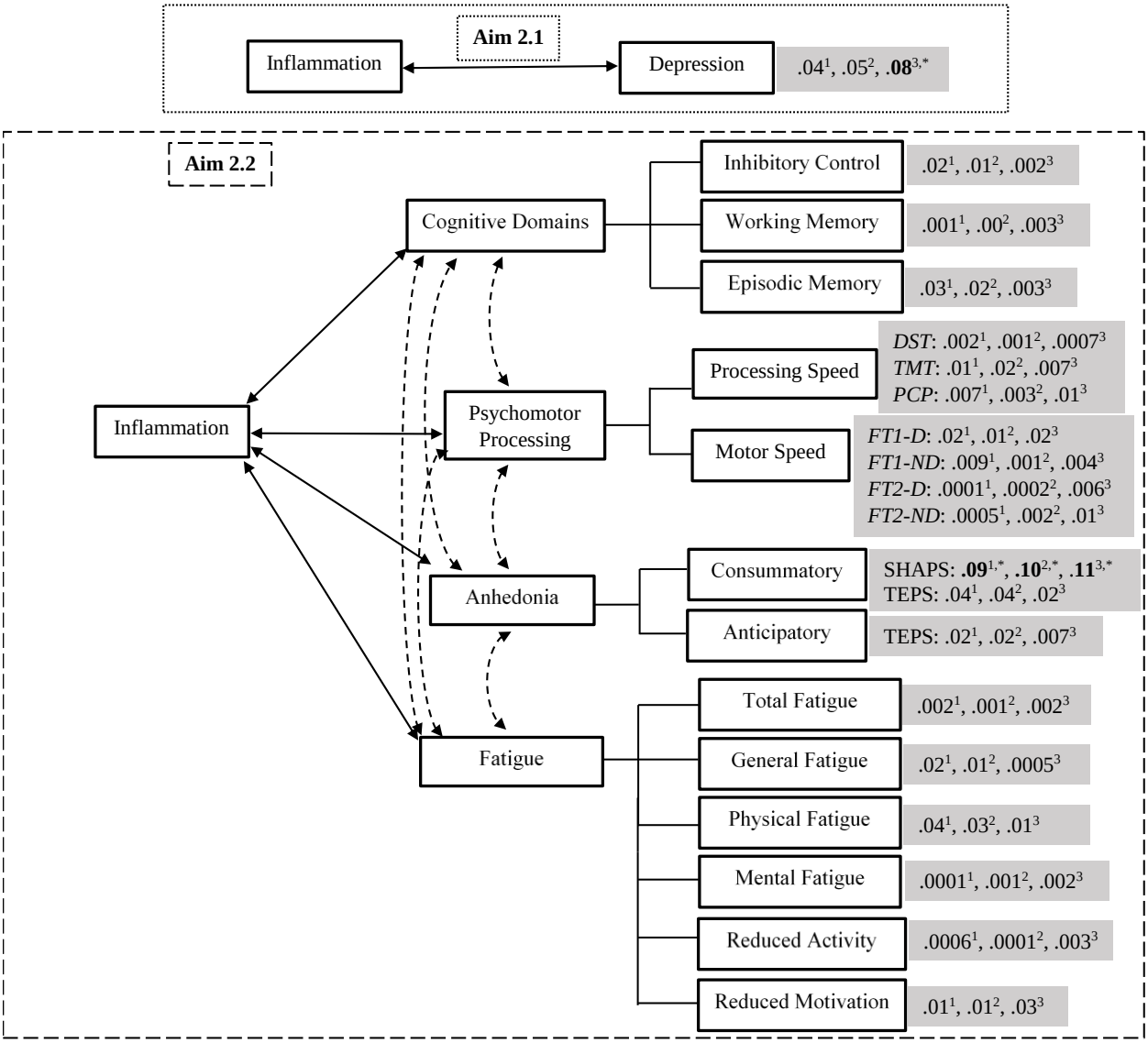

Figure 6. Effect sizes (i.e., partial eta-square) for the associations between ***TNF-α*** and depressive symptoms
**p* <.05. The values of *0.01*, *0.06* and *0.14* for partial eta-squared represent small, medium, and large effect sizes.
[1]Unadjusted Model, [2]Model 1 (includes age, gender, antidepressant use as covariates), [3]Model 2 (includes age, gender, antidepressant use and BMI as covariates)
DST= Digit Symbol Coding, FT1-D= Finger Tapping Test-one target with dominant hand, FT1-ND= Finger Tapping Test-one target with nondominant hand, FT2-D= Finger Tapping Test-two targets with dominant hand, FT2-ND= Finger Tapping Test-two targets with nondominant hand; PCP= Pattern Comparison Processing, SHAPS= Snaith Hamilton Pleasure Scale; TEPS= Temporal Experience of Pleasure Scale; TMT-A= Trail Making Test A

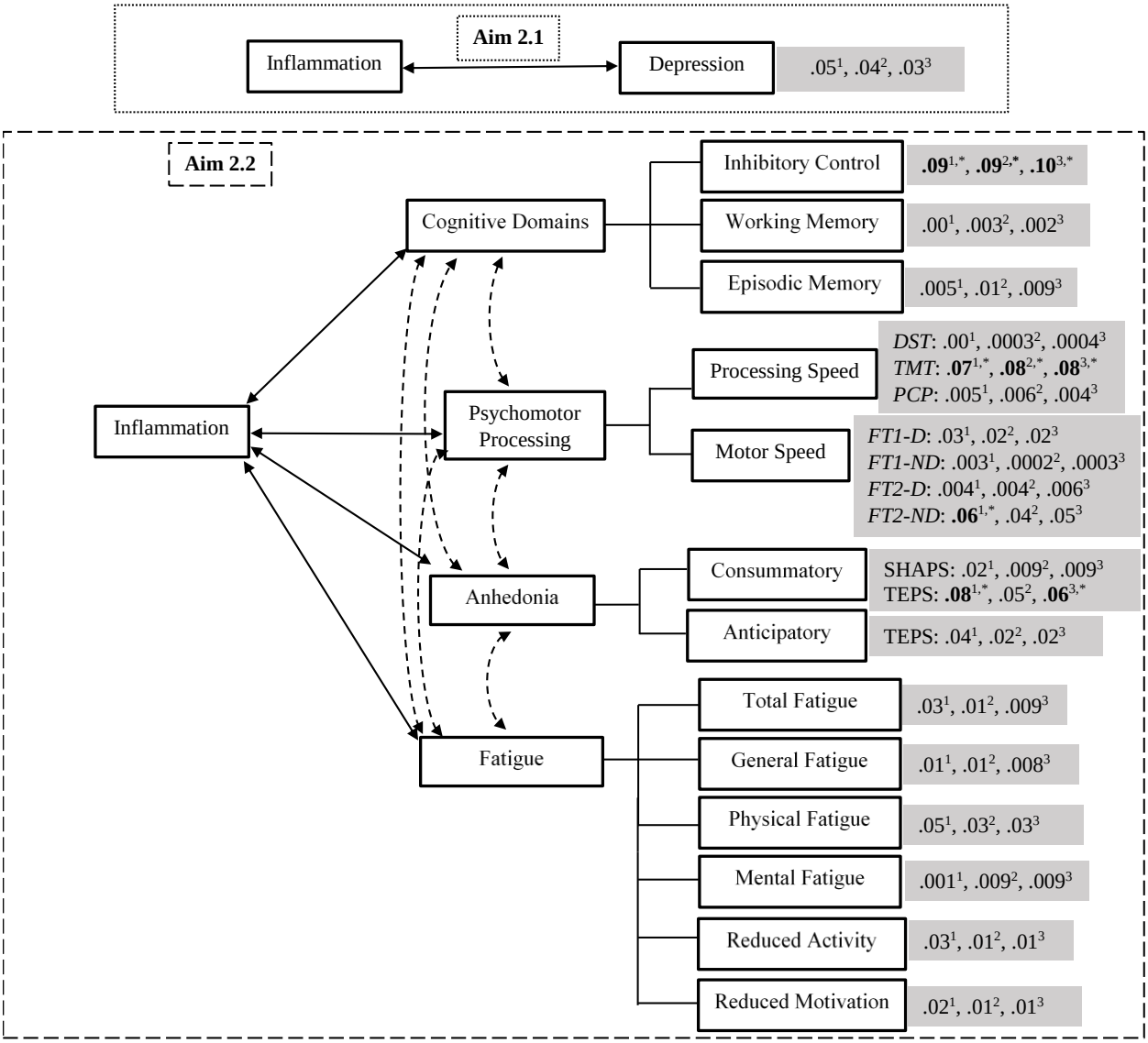

Figure 7. Effect sizes (i.e., partial eta-square) for the associations between ***IL-17*** and depressive symptoms
*p <.05. The values of *0.01*, *0.06* and *0.14* for partial eta-squared represent small, medium, and large effect sizes.
[1]Unadjusted Model, [2]Model 1 (includes age, gender, antidepressant use as covariates), [3]Model 2 (includes age, gender, antidepressant use and BMI as covariates)
DST= Digit Symbol Coding, FT1-D= Finger Tapping Test-one target with dominant hand, FT1-ND= Finger Tapping Test-one target with nondominant hand, FT2-D= Finger Tapping Test-two targets with dominant hand, FT2-ND= Finger Tapping Test-two targets with nondominant hand; PCP= Pattern Comparison Processing, SHAPS= Snaith Hamilton Pleasure Scale; TEPS= Temporal Experience of Pleasure Scale; TMT-A= Trail Making Test A

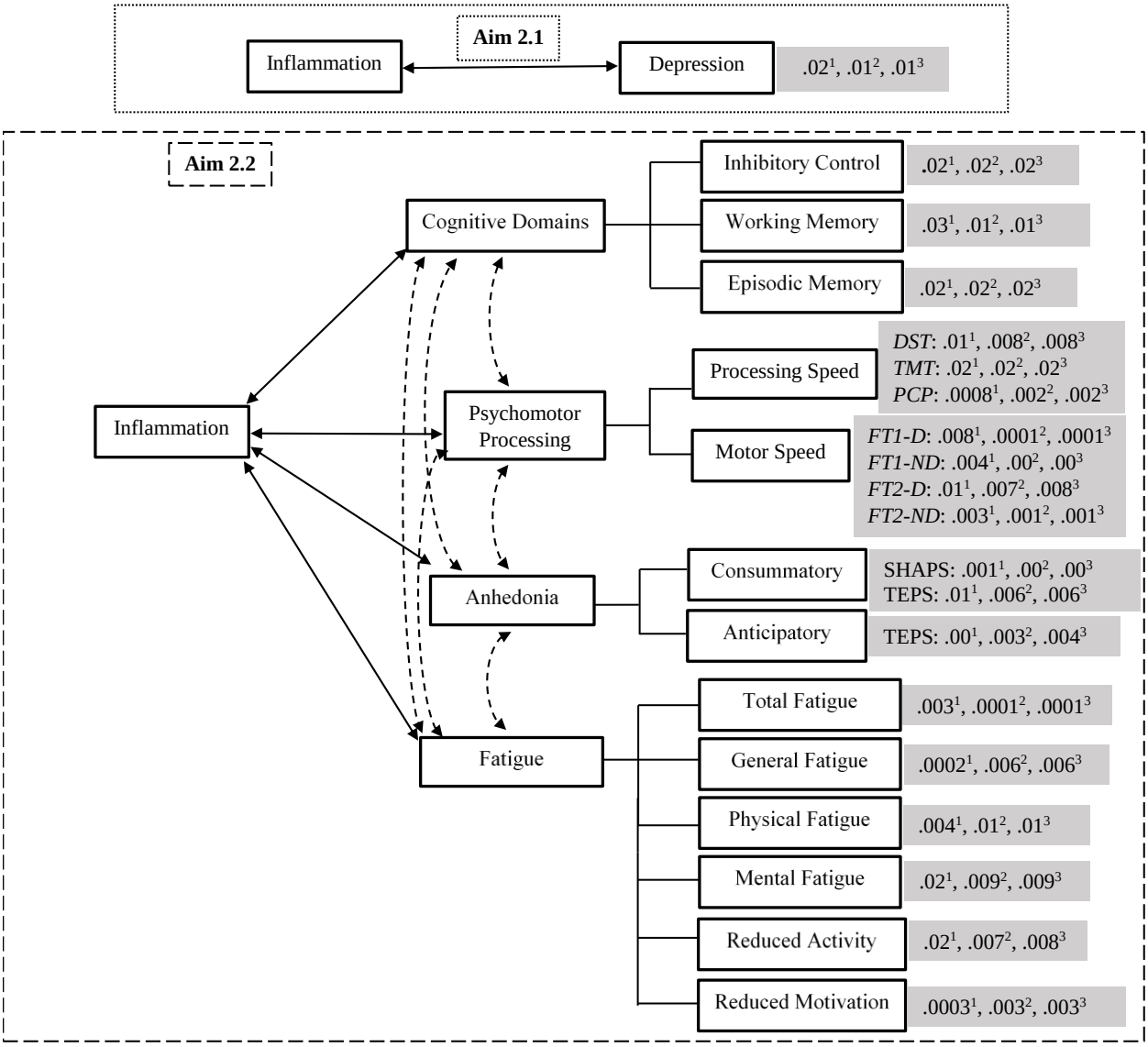

Figure 8. Effect sizes (i.e., partial eta-square) for the associations between ***IL-10*** and depressive symptoms
*p <.05. The values of *0.01*, *0.06* and *0.14* for partial eta-squared represent small, medium, and large effect sizes.
[1]Unadjusted Model, [2]Model 1 (includes age, gender, antidepressant use as covariates), [3]Model 2 (includes age, gender, antidepressant use and BMI as covariates)
DST= Digit Symbol Coding, FT1-D= Finger Tapping Test-one target with dominant hand, FT1-ND= Finger Tapping Test-one target with nondominant hand, FT2-D= Finger Tapping Test-two targets with dominant hand, FT2-ND= Finger Tapping Test-two targets with nondominant hand; PCP= Pattern Comparison Processing, SHAPS= Snaith Hamilton Pleasure Scale; TEPS= Temporal Experience of Pleasure Scale; TMT-A= Trail Making Test

References-Chapter 4

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Appendices

Appendix A: Depression Symptom Checklist (SCL-20)

Instructions: Below is a list of problems and complaints that people sometimes have. Read each one carefully and CIRCLE THE NUMBER that best describes how much discomfort that problem has caused you during the past 2 weeks, including today.

EXAMPLE

HOW MUCH WERE YOU DISTRESSED BY:

	Not at all	A little bit	Moderately	Quite a bit	Extremely
0 Backache	0	1	2	(3)	4

DURING THE PAST 2 WEEKS, HOW MUCH WERE YOU DISTRESSED BY:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Feeling low in energy or slowed down	0	1	2	3	4
2. Thoughts of ending your life	0	1	2	3	4
3. Poor appetite	0	1	2	3	4
4. Crying easily	0	1	2	3	4
5. Feeling of being caught or trapped	0	1	2	3	4
6. Blaming yourself for things	0	1	2	3	4
7. Feeling lonely	0	1	2	3	4
8. Feeling blue	0	1	2	3	4
9. Worrying too much about things	0	1	2	3	4
10. Feeling no interest in things	0	1	2	3	4
11. Loss of sexual interest or pleasure	0	1	2	3	4
12. Trouble falling asleep	0	1	2	3	4
13. Feeling hopeless about the future	0	1	2	3	4
14. Thoughts of death or dying	0	1	2	3	4

15. Overeating	0	1	2	3	4
16. Awakening early in the morning	0	1	2	3	4
17. Sleep that is restless or disturbed	0	1	2	3	4
18. Feeling everything is an effort	0	1	2	3	4
19. Feelings of worthlessness	0	1	2	3	4
20. Feelings of guilt	0	1	2	3	4

(Derogatis et al., 1974)

Appendix B: Patient Health Questionnaire (PHQ-9)

Instruction: over the last 2 weeks, how often have you been bothered by any of the following problems? Please circle the number in front of each statement.

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

(Kroenke et al., 2001)

Appendix C: Online screening form

Thanks for your interest in our study, the Depressive Symptomatology and Inflammation Study. Please note that completion of this survey neither guarantees nor requires your participation in this study. To determine initial eligibility for this study, please answer the following questions using the scale provided by filling information in the blanks provided.

Please enter your study ID number	
Your age	
Gender	**Female** **Male** **Transgender** **Other**
What country were you born in?	
Is English your first language?	Yes No
If English is not your first language, do you consider yourself fluent in English?	Yes No
How long have you lived in the United States?	( ) years
Have you ever been diagnosed with depression by a health care provider?	Yes No
Are you currently taking antidepressants?	Yes No
If yes, for how long?	
Have you ever been prescribed antidepressants?	Yes No
Do you currently have an active eating disorder?	Yes No
Have you ever been diagnosed with a mental disorder other than depression such as bipolar disorder, post-traumatic stress disorder (PTSD), anxiety disorders, an eating disorder, etc.?	Yes No If yes, Please describe here.
Have you had any infection within the last month that required treatment with antibiotics or antiviral agents?	Yes No
Do you have any of these health conditions? If yes, circle which one(s).	Cancer Hepatitis B Hepatitis C Serious kidney or liver disease Autoimmune disorders or inflammatory disorders

	such as rheumatoid arthritis (RA), lupus, HIV/AIDS, multiple sclerosis (MS), scleroderma, or others? Other: please describe here:
How often do you consume alcoholic beverages (e.g., wine, beer, hard alcohol)?	□ Everyday □ Nearly everyday □ 3-4 times a week □ 2 times a week □ 1 time a week □ 2-3 times a month □ 1 time a month □ 7-11 times a year □ 3-6 times a year □ 1-2 times a year □ Never
If female: Are you currently pregnant? Are you currently breastfeeding? Are you:	 Yes No Yes No Pre-menopausal Post- menopausal Other: please describe: ----------
Please list all prescription and over the counter (e.g., Advil) medications that you are currently taking.	***Medication 1*** Name: Reason for taking: How much (dose): How often (frequency): For how long have you used this medication? ***Medication 2*** Name: Reason for taking: How much (dose): How often (frequency): For how long have you used this medication? ***Medication 3*** Name: Reason for taking: How much (dose): How often (frequency): For how long have you used this medication?

Please list all prescription and over the counter (e.g., Advil) medications that you have taken within the last 2 months (even if not currently taking).	***Medication 1*** Name: Reason for taking: How much (dose): How often (frequency): For how long have you used this medication? ***Medication 2*** Name: Reason for taking: How much (dose): How often (frequency): For how long have you used this medication? ***Medication 3*** Name: Reason for taking: How much (dose): How often (frequency): For how long have you used this medication?

Appendix D: In-lab visit form

Instruction: This form should be completed by a research assistant.

Date	
SID	
What time did you wake up this morning?	
What time did you go to sleep last night?	
Weight (kg)	
Height (cm)	
Blood pressure	
Pulse rate	
Body temperature	
Time of blood draw	

Appendix E: Multidimensional Fatigue Inventory (MFI)

SID: _____ **DATE _____**

Instructions: By means of the following statement we would like to get an idea of how you have been feeling lately. There is, for example, the statement: "I feel relaxed"
If you think that this is **entirely true,** that indeed you have been feeling relaxed lately, please place an **X** in the extreme left box like:

Yes, that is true 1 2 3 4 5 **No, that is not true**

The more you disagree with the statement, the more you can place an X in the direction of "no", that is "not true".

		Yes, that is true						**No, that is not true**
1	I feel fit.		1	2	3	4	5	
2	Physically, I feel only able to do a little.		1	2	3	4	5	
3	I feel very active.		1	2	3	4	5	
4	I feel like doing all sorts of nice things.		1	2	3	4	5	
5	I feel tired.		1	2	3	4	5	
6	I think I do a lot in a day.		1	2	3	4	5	
7	When I am doing something, I can keep my thoughts on it.		1	2	3	4	5	
8	Physically I can take on a lot.		1	2	3	4	5	
9	I dread having to do things.		1	2	3	4	5	
10	I think I do very little in a day.		1	2	3	4	5	
11	I can concentrate well.		1	2	3	4	5	
12	I am rested.		1	2	3	4	5	
13	It takes a lot of effort to concentrate on things.		1	2	3	4	5	
14	Physically I feel I am in a bad condition.		1	2	3	4	5	
15	I have a lot of plans.		1	2	3	4	5	

16	I tire easily.		1	2	3	4	5	
17	I get little done.		1	2	3	4	5	
18	I don’t feel like doing anything.		1	2	3	4	5	
19	My thoughts easily wander.		1	2	3	4	5	
20	Physically I feel I am in an excellent condition.		1	2	3	4	5	

(Lin et al., 2009; Smets et al., 1995)

Appendix F: Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

Instruction: Please answer these questions by *circling* the *correct answer* or the answer which seems the most *appropriate* to you (consider 'normal' the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning).

		Greater than normal	Normal	Minimally diminished	Moderately diminished	Markedly diminished	Totally absent
1	How has your motivation/interest/enthusiasm been over the past month?	1	2	3	4	5	6
2	How has your wakefulness/alertness been over the past month?	1	2	3	4	5	6
3	How has your energy been over the past month?	1	2	3	4	5	6
4	How has your ability to focus/sustain attention been over the past month?	1	2	3	4	5	6
5	How has your ability to remember/recall information been over the past month?	1	2	3	4	5	6
6	How has your ability to find words been over the past month?	1	2	3	4	5	6
7	How has your sharpness/mental acuity been over the past month?	1	2	3	4	5	6

(Fava et al., 2009)

Appendix G: Inventory of Depressive Symptomatology-Self report (IDS-SR)

Instruction: please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:
0 I never take longer than 30 minutes to fall asleep.
1 I take at least 30 minutes to fall asleep, less than half the time.
2 I take at least 30 minutes to fall asleep, more than half the time.
3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:
0 I do not wake up at night.
1 I have a restless, light sleep with a few brief awakenings each night.
2 I wake up at least once a night, but I go back to sleep easily
3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:
0 Most of the time, I awaken no more than 30 minutes before I need to get up.
1 More than half the time, I awaken more than 30 minutes before I need to get up.
2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:
0 I sleep no longer than 7-8 hours/night, without napping during the day.
1 I sleep no longer than 10 hours in a 24-hour period including naps.
2 I sleep no longer than 12 hours in a 24-hour period including naps.
3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:
0 I do not feel sad.
1 I feel sad less than half the time.
2 I feel sad more than half the time.
3 I feel sad nearly all of the time.

6. Feeling Irritable:
0 I do not feel irritable.
1 I feel irritable less than half the time.
2 I feel irritable more than half the time.

3 I feel extremely irritable nearly all of the time.

7. Feeling Anxious or Tense:
0 I do not feel anxious or tense.
1 I feel anxious (tense) less than half the time.
2 I feel anxious (tense) more than half the time.
3 I feel extremely anxious (tense) nearly all of the time.

8. Response of Your Mood to Good or Desired Events:
0 My mood brightens to a normal level which lasts for several hours when good events occur.
1 My mood brightens but I do not feel like my normal self when good events occur.
2 My mood brightens only somewhat to a rather limited range of desired events.
3 My mood does not brighten at all, even when very good or desired events occur in my life.

9. Mood in Relation to the Time of Day:
0 There is no regular relationship between my mood and the time of day.
1 My mood often relates to the time of day because of environmental events (e.g., being alone, working).
2 In general, my mood is more related to the time of day than to environmental events.
3 My mood is clearly and predictably better or worse at a particular time each day.

9A. Is your mood typically worse in the morning, afternoon or night? (circle one)
Yes
No

9B. Is your mood variation attributed to the environment? (circle one)
Yes
No

10. The Quality of Your Mood:
0 The mood (internal feelings) that I experience is very much a normal mood.
1 My mood is sad, but this sadness is pretty much like the sad mood I would feel if someone close to me died or left.
2 My mood is sad, but this sadness has a rather different quality to it than the sadness I would feel if someone close to me died or left.
3 My mood is sad, but this sadness is different from the type of sadness associated with grief or loss.

11. Decreased Appetite:
0 There is no change in my usual appetite.
1 I eat somewhat less often or lesser amounts of food than usual.
2 I eat much less than usual and only with personal effort.
3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

12. Increased Appetite:
0 There is no change from my usual appetite.
1 I feel a need to eat more frequently than usual.
2 I regularly eat more often and/or greater amounts of food than usual.
3 I feel driven to overeat both at mealtime and between meals.

Please complete either 13 or 14 (not both)

13. Decreased Weight (Within the Last Two Weeks):
0 I have not had a change in my weight.
1 I feel as if I've had a slight weight loss.
2 I have lost 2 pounds or more.
3 I have lost 5 pounds or more.

14. Increased Weight (Within the Last Two Weeks):
0 I have not had a change in my weight.
1 I feel as if I've had a slight weight gain.
2 I have gained 2 pounds or more.
3 I have gained 5 pounds or more.

15. Concentration/Decision Making:
0 There is no change in my usual capacity to concentrate or make decisions.
1 I occasionally feel indecisive or find that my attention wanders.
2 Most of the time, I struggle to focus my attention or to make decisions.
3 I cannot concentrate well enough to read or cannot make even minor decisions.

16. View of Myself:
0 I see myself as equally worthwhile and deserving as other people.
1 I am more self-blaming than usual.

2 I largely believe that I cause problems for others.
3 I think almost constantly about major and minor defects in myself.

17. View of My Future:
0 I have an optimistic view of my future.
1 I am occasionally pessimistic about my future, but for the most part I believe things will get better.
2 I'm pretty certain that my immediate future (1-2 months) does not hold much promise of good things for me.
3 I see no hope of anything good happening to me anytime in the future.

18. Thoughts of Death or Suicide:
0 I do not think of suicide or death.
1 I feel that life is empty or wonder if it's worth living.
2 I think of suicide or death several times a week for several minutes.
3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

19. General Interest:
0 There is no change from usual in how interested I am in other people or activities.
1 I notice that I am less interested in people or activities.
2 I find I have interest in only one or two of my formerly pursued activities.
3 I have virtually no interest in formerly pursued activities.

20. Energy Level:
0 There is no change in my usual level of energy.
1 I get tired more easily than usual.
2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

21. Capacity for Pleasure or Enjoyment (excluding sex):
0 I enjoy pleasurable activities just as much as usual.
1 I do not feel my usual sense of enjoyment from pleasurable activities.
2 I rarely get a feeling of pleasure from any activity.
3 I am unable to get any pleasure or enjoyment from anything.

22. Interest in Sex (Please Rate Interest, not Activity):

0 I'm just as interested in sex as usual.
1 My interest in sex is somewhat less than usual or I do not get the same pleasure from sex as I used to.
2 I have little desire for or rarely derive pleasure from sex.
3 I have absolutely no interest in or derive no pleasure from sex.

23. Feeling slowed down:

0 I think, speak, and move at my usual rate of speed.
1 I find that my thinking is slowed down or my voice sounds dull or flat.
2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
3 I am often unable to respond to questions without extreme effort.

24. Feeling restless:

0 I do not feel restless.
1 I'm often fidgety, wring my hands, or need to shift how I am sitting.
2 I have impulses to move about and am quite restless.
3 At times, I am unable to stay seated and need to pace around.

25. Aches and pains:

0 I don't have any feeling of heaviness in my arms or legs and don't have any aches or pains.
1 Sometimes I get headaches or pains in my stomach, back or joints but these pains are only sometime present and they don't stop me from doing what I need to do.
2 I have these sorts of pains most of the time.
3 These pains are so bad they force me to stop what I am doing.

26. Other bodily symptoms:

0 I don't have any of these symptoms: heart pounding fast, blurred vision, sweating, hot and cold flashes, chest pain, heart turning over in my chest, ringing in my ears, or shaking.
1 I have some of these symptoms but they are mild and are present only sometimes.
2 I have several of these symptoms and they bother me quite a bit.
3 I have several of these symptoms and when they occur I have to stop doing whatever I am doing.

27. Panic/Phobic symptoms:

0 I have no spells of panic or specific fears (phobia) (such as animals or heights).
1 I have mild panic episodes or fears that do not usually change my behavior or stop me from functioning.
2 I have significant panic episodes or fears that force me to change my behavior but do not stop me from functioning.
3 I have panic episodes at least once a week or severe fears that stop me from carrying on my daily activities.

28. Constipation/diarrhea:

0 There is no change in my usual bowel habits.
1 I have intermittent constipation or diarrhea which is mild.
2 I have diarrhea or constipation most of the time but it does not interfere with my day-to-day functioning.
3 I have constipation or diarrhea for which I take medicine or which interferes with my day-to-day activities.

29. Interpersonal Sensitivity:

0 I have not felt easily rejected, slighted, criticized or hurt by others at all.
1 I have occasionally felt rejected, slighted, criticized or hurt by others.
2 I have often felt rejected, slighted, criticized or hurt by others, but these feelings have had only slight effects on my relationships or work.
3 I have often felt rejected, slighted, criticized or hurt by others and these feelings have impaired my relationships and work.

30. Leaden Paralysis/Physical Energy:

0 I have not experienced the physical sensation of feeling weighted down and without physical energy.
1 I have occasionally experienced periods of feeling physically weighted down and without physical energy, but without a negative effect on work, school, or activity level.
2 I feel physically weighted down (without physical energy) more than half the time.
3 I feel physically weighted down (without physical energy) most of the time, several hours per day, several days per week.

(Rush et al., 1996)

Appendix H: Snaith-Hamilton Pleasure Scale-self report (SHAPS)

Instructions: This questionnaire is designed to measure your ability to experience pleasure in the last few days. It is important to read each statement very carefully. Tick one of the boxes [ ] to indicate how much you agree or disagree with each statement.

		Definitely agree	**agree**	**Disagree**	**Strongly disagree**
1	I would enjoy my favorite television or radio programme	1	2	3	4
2	I would enjoy being with my family or close friends	1	2	3	4
3	I would find pleasure in my hobbies and pastimes	1	2	3	4
4	I would be able to enjoy my favorite meal	1	2	3	4
5	I would enjoy a warm bath or refreshing shower:	1	2	3	4
6	I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread	1	2	3	4
7	I would enjoy seeing other people's smiling faces	1	2	3	4
8	I would enjoy looking smart when I have made an effort with my appearance:	1	2	3	4
9	I would enjoy reading a book, magazine or newspaper:	1	2	3	4
10	1 would enjoy a cup of tea or coffee or my favorite drink	1	2	3	4
11	I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend	1	2	3	4
12	I would be able to enjoy a beautiful landscape or view	1	2	3	4
13	I would get pleasure from helping others:	1	2	3	4
14	I would feel pleasure when I receive praise from other people	1	2	3	4

(Snaith et al., 1995)

Appendix I: Temporal Experience of Pleasure Scale (TEPS)

Instructions: Please read each statement carefully and decide how true that statement is for you in general. Please respond to *all item*s. In the rare case where you have ***never*** had the experience described, think about the most similar experience you've had and make your response. Do *not* leave any blank. Choose only *one* response to each statement. Don't worry about being consistent in your responses. Choose from the following 6 response options and **CIRCLE** your response to the right of the item.

Very false for me	Moderately false for me	Slightly false for me	Slightly true for me	Moderately true for me	Very true for me
1	2	3	4	5	6

1. When I hear about a new movie starring my favorite actor, I can't wait to see it.	1	2	3	4	5	6
2. I enjoy taking a deep breath of fresh air when I walk outside.	1	2	3	4	5	6
3. The smell of freshly cut grass is enjoyable to me.	1	2	3	4	5	6
4. I look forward to a lot of things in my life.	1	2	3	4	5	6
5. I love it when people play with my hair.	1	2	3	4	5	6
6. Looking forward to a pleasurable experience is in itself pleasurable.	1	2	3	4	5	6
7. A hot cup of coffee or tea on a cold morning is very satisfying to me.	1	2	3	4	5	6
8. When I think of something tasty, like a chocolate chip cookie, I have to have one.	1	2	3	4	5	6
9. I appreciate the beauty of a fresh snowfall.	1	2	3	4	5	6
10. I get so excited the night before a major holiday I can hardly sleep.	1	2	3	4	5	6
11. When I'm on my way to an amusement park, I can hardly wait to ride the roller coasters.	1	2	3	4	5	6
12. I really enjoy the feeling of a good yawn.	1	2	3	4	5	6
13. I don't look forward to things like eating out at restaurants.	1	2	3	4	5	6
14. I love the sound of rain on the windows when I'm lying in my warm bed.	1	2	3	4	5	6
15. When I think about eating my favorite food, I can almost taste how good it is.	1	2	3	4	5	6
16. When ordering something off the menu, I imagine how good it will taste.	1	2	3	4	5	6
17. The sound of crackling wood in the fireplace is very relaxing.	1	2	3	4	5	6
18. When something exciting is coming up in my life, I really look forward to it.	1	2	3	4	5	6

(Gard et al., 2006)

Appendix J: Demographic survey

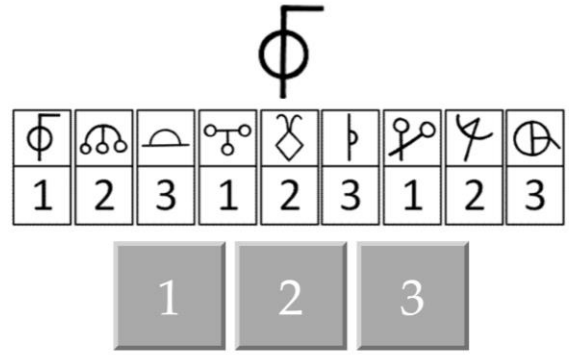
Instructions: Please answer the following questions using the scale provided by circling or filling information in the blanks provided.

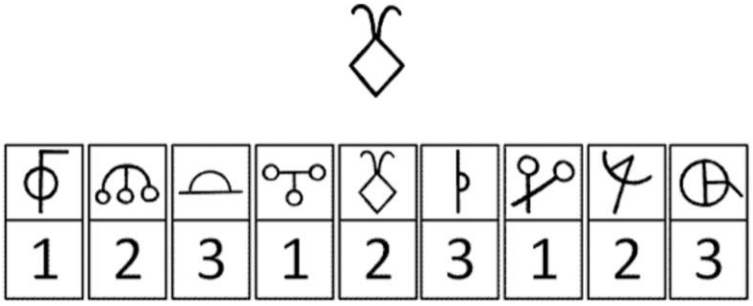
SID	
Which range best describes your total income during the past 12 months? (If married or in domestic partnership, your household income)	□ Less than 4,999 □ 5,000-19,999 □ 20,000-39,999 □ 40,000-59,999 □ 60,000-79,999 □ 80,000-99,999 □ 100,000-149,999 □ 150,000 or more □ Don't know □ Don't wish to answer
What is your mother's occupation?	
What is your father's occupation?	
What is the highest degree your father **earned**?	□ None □ Preschool □ Kindergarten □ 1st grade to 5th grade □ 6th grade to 11th grade □ High school diploma or equivalency (GED) □ Some college credit but less than 1 year □ One or more years of college at a 2-year program, no degree □ One to three year(s) of college at a 4-year program, no degree □ Three years or more of college at a 4-year program, no degree □ Associates degree (junior college) □ Bachelor's degree □ Master's degree □ Professional (MD, JD, DDS, etc.) □ Doctorate degree (e.g., PhD, EdD) □ Don't know □ Don't wish to answer
What is the highest degree your mother **earned**?	□ None □ Preschool

	□ Kindergarten
	□ 1st grade to 5th grade
	□ 6th grade to 11th grade
	□ High school diploma or equivalency (GED)
	□ Some college credit but less than 1 year
	□ One or more years of college at a 2-year program, no degree
	□ One to three year(s) of college at a 4-year program, no degree
	□ Three years or more of college at a 4-year program, no degree
	□ Associates degree (junior college)
	□ Bachelor's degree
	□ Master's degree
	□ Professional (MD, JD, DDS, etc.)
	□ Doctorate degree (e.g., PhD, EdD)
	□ Don't know
	□ Don't wish to answer
Relationship Status	□ Single □ In a relationship □ Married □ Divorced □ Separated □ Widowed □ Domestic Partnership (living together but not married)
What is your best estimate of your parent's household income per year? (If you switch between households, please estimate the household income of your *primary* residence or average the incomes of the two households)	□ Less than 4,999 □ 5,000-19,999 □ 20,000-39,999 □ 40,000-59,999 □ 60,000-79,999 □ 80,000-99,999 □ 100,000-149,999 □ 150,000 or more □ Don't know □ Don't wish to answer
Do you have any of these health conditions?	□ Frequent headaches (including migraines) □ Overactive or underactive thyroid □ Diabetes □ Epilepsy □ Kidney problems

	□ Liver problems □ Allergies or hay fever □ Asthma or other respiratory problems □ Coronary heart/artery disease □ High blood pressure □ History of stroke □ History of myocardial infarction □ Hemophilia, or any other blood-related problems
	□ any serious gynecological problems
Do you currently have any other health problems not listed above? **If yes, please describe:**	
Do you currently smoke cigarettes, cigars, a pipe, or chew tobacco?	Yes No
If yes: How many cigarettes per day do you smoke?	□ 10 or less cigarettes □ 11-20 cigarettes □ 21-30 cigarettes □ 31 or more cigarettes
If female: What is your menstrual status? Are you currently using hormonal birth control?	 Pre-menopausal: Start date of last period:____/____/_____ Post-menopausal: Month and year of last period: _____/_____ Other: Please describe:_____ Yes No If yes, please describe (oral pill, IUD, etc.):_____ _____

Appendix K: Digit Symbol Test (DST)

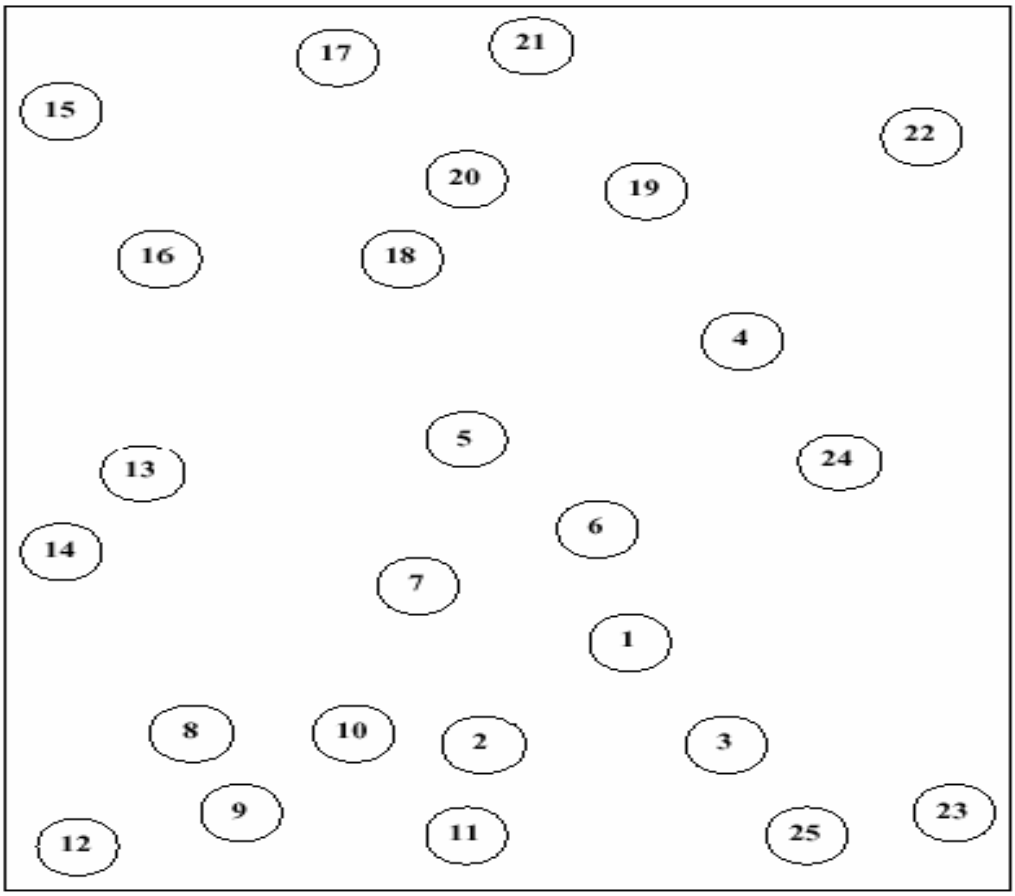




(Germine et al., 2012)

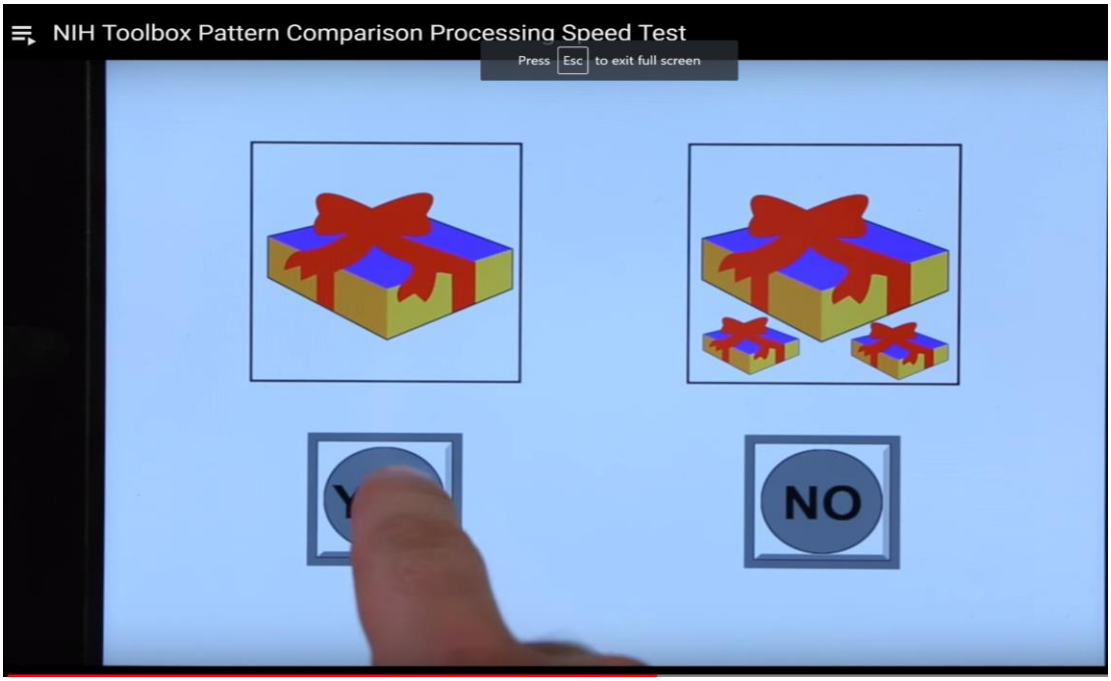
Appendix L: Trail Making Test Part A (TMT-A)

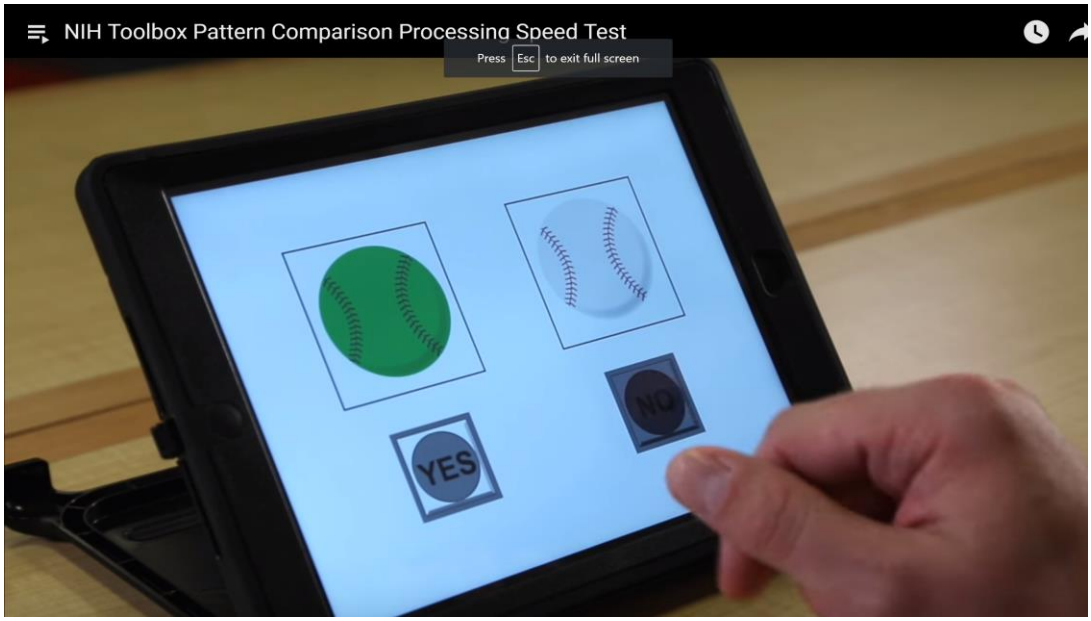
Please draw lines to connect the numbers in ascending order as fast as possible without lifting the pen from the sheet.



(Strauss et al., 2006)

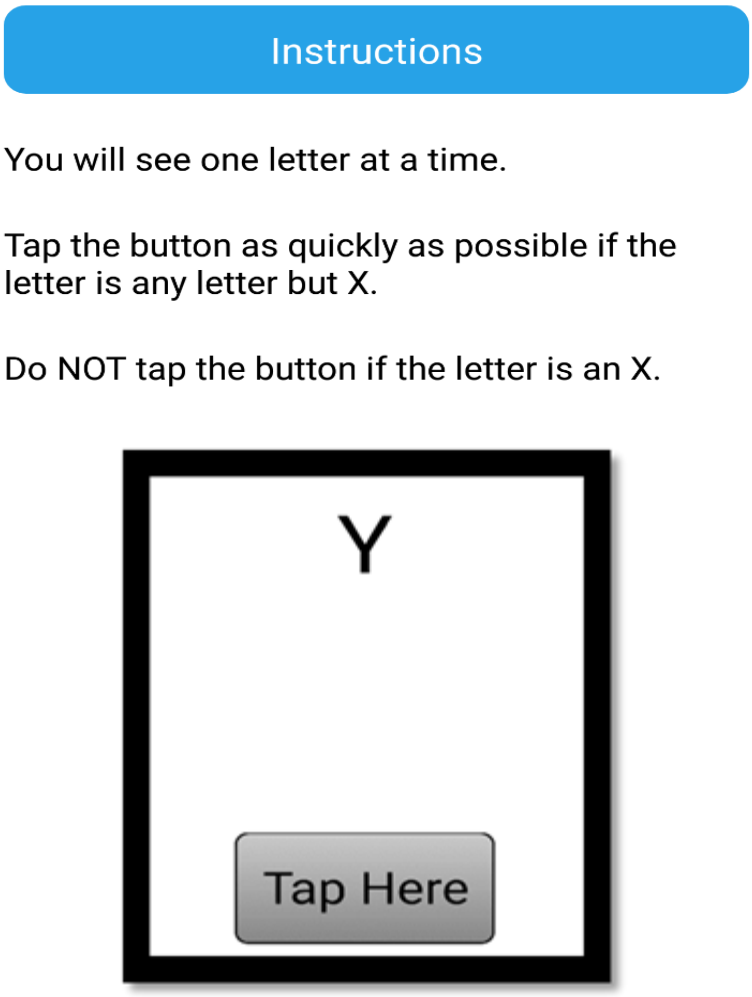
Appendix M: Pattern Comparison Processing (PCP)



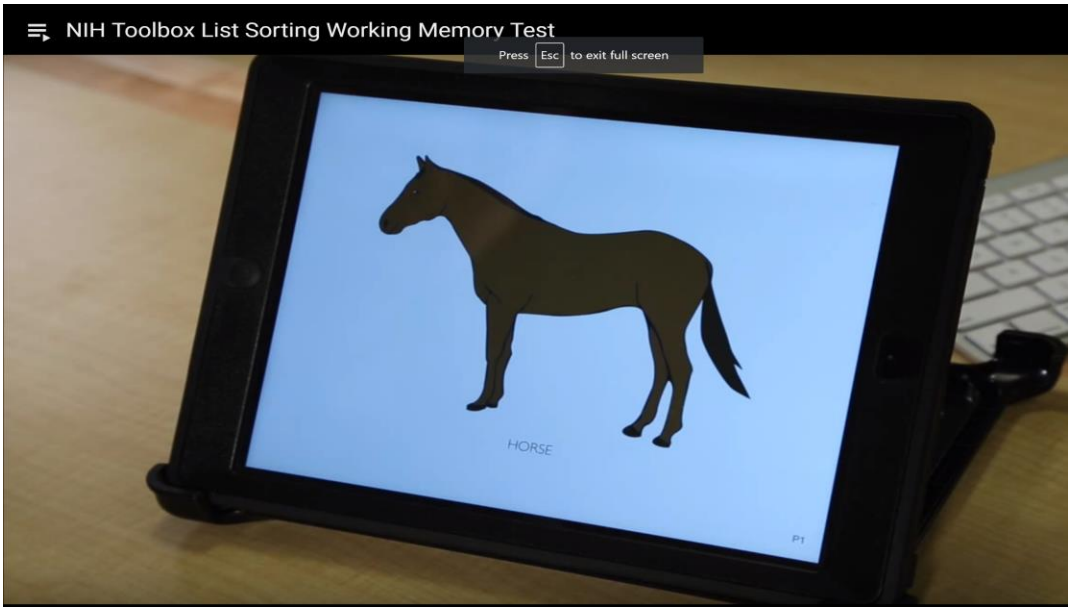


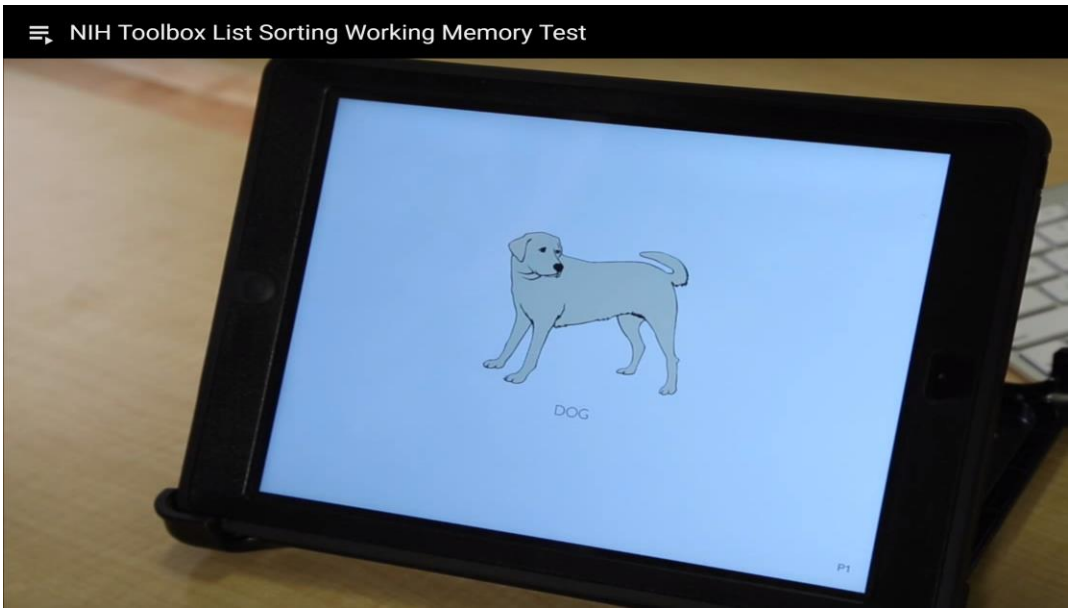
(Weintraub et al., 2013)

Appendix N: Go/No-Go Test



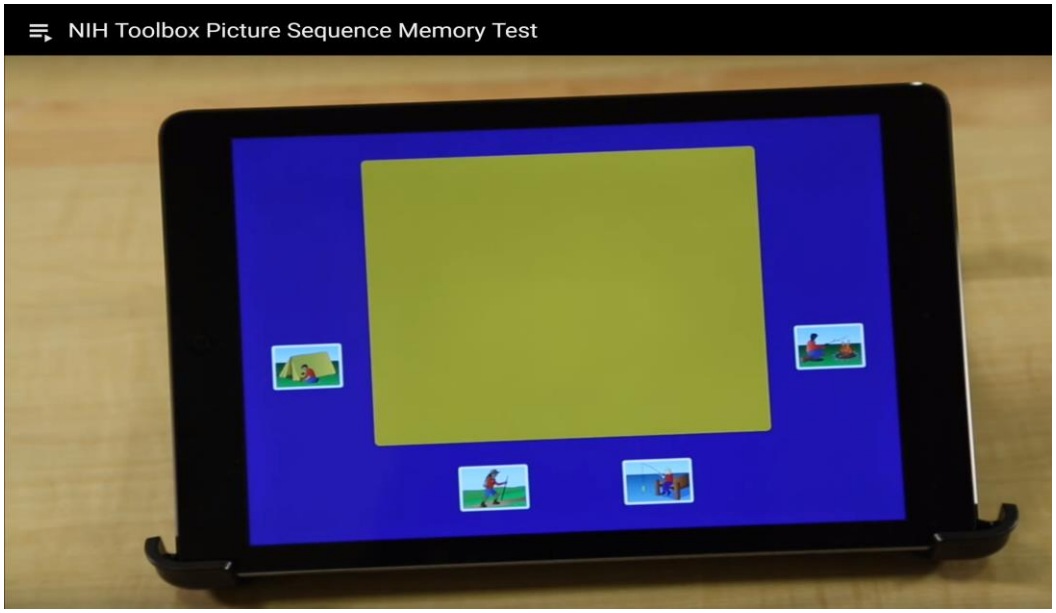
Appendix O: Working Memory; List Sorting Test (LST)

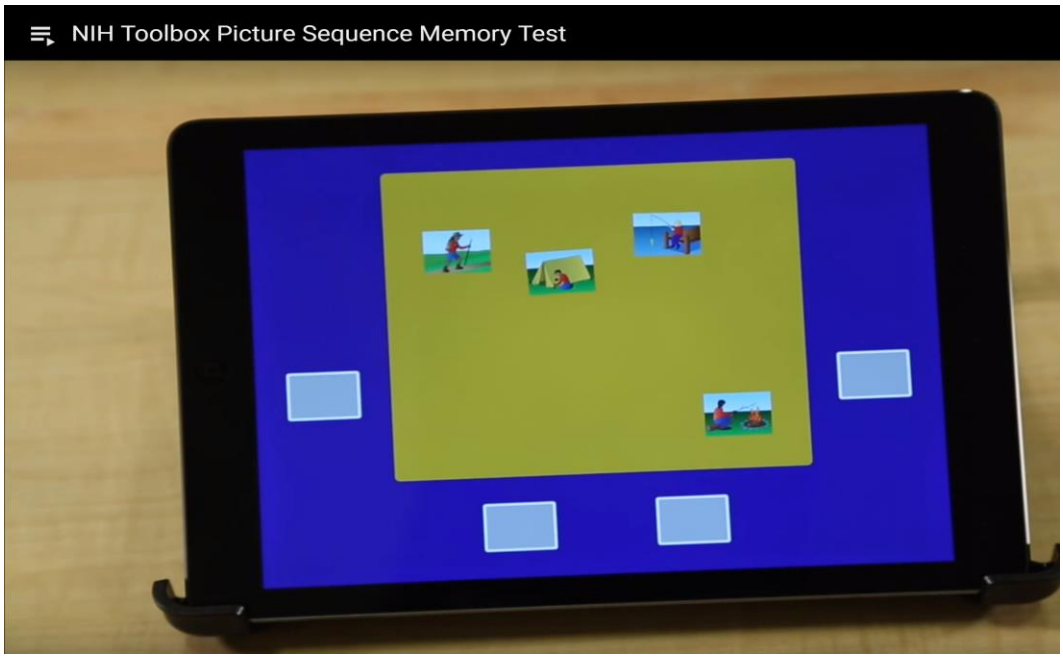




(Weintraub et al., 2013)

Appendix P: Episodic memory; Picture Sequence Memory (PSM)

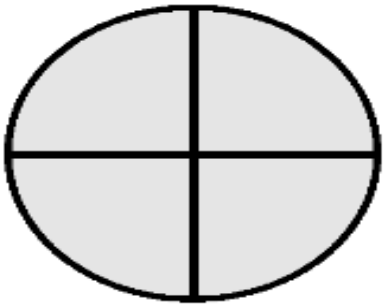




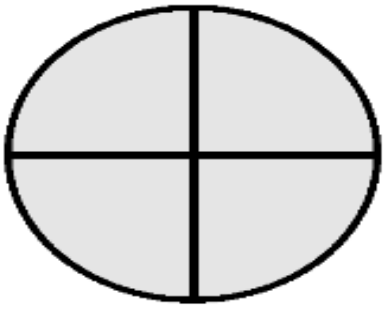
(Weintraub et al., 2013)

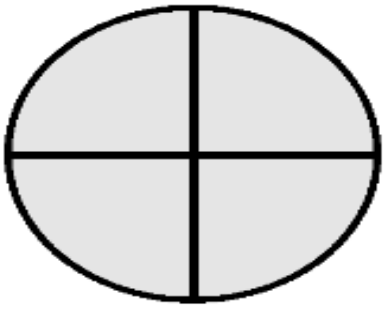
Appendix Q: Finger Tapping Test

One Target



Two Targets





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Education

2014-present Biobehavioral Health, The Pennsylvania State University

2004-2010 Doctor of Pharmacy, Azad University–Pharmaceutical Sciences Branch, Tehran, Iran.

Honors and Awards

2020 The Alumni Association Dissertation Award, Penn State

2019 College of Health and Human Development Endowed Fund for Dissertation Research

2018 College of Health and Human Development Endowed Fund for Dissertation Research

2018 Gerald E. McClearn Graduate Student Award, Penn State

Peer-Reviewed Publications

N Lv, L Xiao, **M Majd**, PW Lavori, JM Smyth, LG Rosas, EM Venditti, MB Snowden, MA Lewis, E Ward, L Lesser, LM Williams, KMJ Azar, J Ma. 2020. Variability in engagement and progress in efficacious integrated collaborative care for primary care patients with obesity and depression: within-treatment analysis in the RAINBOW trial. *PLoS one*, 15 (4), e0231743.

E Knight, **M Majd**, J Graham-Engeland, J Smyth, M Sliwinski, C Engeland. 2020. Gender differences in the link between depressive symptoms and *ex vivo* stimulated cytokine responses are dependent on levels of endotoxin in blood. *Brain, Behavior, and Immunity – Health, 100013.*

M Majd, E Saunders, C Engeland. 2020. Inflammation and the Dimensions of Depression: A review. *Frontiers in Neuroendocrinology, 56, 100800.*

M Majd, J Graham-Engeland, J Smyth, M Sliwinski, R Lipton, M Katz, C Engeland. Distinct inflammatory response patterns are evident among men and women with higher depressive symptoms. *Physiology & Behavior*, 2018, 184: 108-115.

Selected Conference Presentations

2019 Poster presentation: **M Majd***, E Saunders, C Engeland. Inflammation and the dimensions of depression. American Society of Clinical Psychopharmacology Annual Meeting, Scottsdale, Arizona.

2018 Poster presentation: **M Majd***, J Greaney, E Saunders, C Engeland. Inflammatory correlates of specific symptoms of depression. American Society of Clinical Psychopharmacology Annual Meeting, Miami, Florida

2017 Poster presentation: **M Majd***, J Greaney, E Saunders, C Engeland. Ex vivo inflammatory response patterns among non-medicated depressed patients. American Society of Clinical Psychopharmacology Annual Meeting, Miami, Florida