Differential Impact of Psychological and Physiological Health Outcomes on Long-Term Associative Recognition

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ABSTRACT

Evidence suggests that lifestyle and environmental factors may contribute to later life cognitive decline and dementia. Although there is a large amount of evidence linking psychological and physiological factors to general memory performance, little focus has been given to specific memory systems. The present study was designed to investigate relationships between psychophysiological health predictors and recollection and familiarity processes of recognition memory. We hypothesized that these recognition processes may be differentially impacted by the included health variables. The present study involved 96 relatively healthy young adults between 17 and 25 years old. Health measures included visceral obesity (waist-to-hip ratio), heart rate variability (root mean square of the successive differences in heart beats), inflammation (serum interleukin 6 levels), stress and anxiety (Perceived Stress Scale and the State-Trait Anxiety Inventory), and depression symptoms (Center for Epidemiological Studies Depression Scale-Revised). The results showed that state and trait anxiety were related to recollection, but not familiarity. High trait anxiety was related to better recollection, whereas high state anxiety was related to poorer recollection. We also found that heightened levels of inflammation and depression symptoms were related to worse recollection, but better familiarity. Furthermore, we showed that trait anxiety, inflammation, and depression served as suppressor variables for each other. These findings suggested that trait anxiety was beneficial for recollection, especially when inflammation and depression were controlled, and that inflammation and depression shifted recognition processes from recollection toward a greater dependence on familiarity. These findings are important because they demonstrate that depression and inflammation are impacting recognition processes in young, relatively healthy adults, suggesting a need for health interventions early in life to help prevent late life cognitive decline and dementia.

Differential Impact of Psychological and Physiological Health Outcomes on Long-Term Associative Recognition

Associative memory decline often occurs with aging, and there is now strong theoretical evidence suggesting that many psychological and physiological health factors may differentially impact the underlying brain regions supporting associative memory. Associative recognition can be accomplished through the two recognition processes recollection and familiarity, with the latter being less susceptible to age-related memory decline (Bastin et al., 2013). Although a great deal of research has associated many psychological and physiological health factors with general memory decline (Sapolsky, 2003; Yates, Sweat, Yau, Turchiano, & Convit, 2012), research investigating their specific impact on recollection and familiarity processes is lacking. Therefore, factors leading to this differential memory loss with aging remain somewhat unknown. The current proposal seeks to add to this area of research by relating recollection and familiarity abilities to the following health predictors: visceral obesity, inflammation, heart rate variability, stress, anxiety, and depression.

Over the past several decades, scientists around the world have been working to prevent memory loss associated with aging and dementia. A large amount of evidence has accumulated from this field of research demonstrating that several modifiable environmental and lifestyle factors likely contribute to memory decline, including physiological conditions such as obesity, inflammation, and cardiovascular health (Yates et al., 2012) and psychological conditions such as chronic stress and depression (Sapolsky, 2003). However, progress in this area of research has been sluggish because memory processes may be differentially impacted by the varying physiological mechanisms associated with each health factor. Currently, there is still much to be learned about the complex relationships between these health predictors and memory.

Another problem with the current state of the literature is a lack of consistency between memory tests employed and a lack of specificity associated with many of these tests. Although It is now

generally accepted that the brain possesses multiple memory systems (Squire, 2004), many frequently used memory tests were originally developed many years ago and often do not adequately reflect our current understanding of human memory systems. For example, the Wechsler Memory Scale was first introduced in the 1940s, and is still one of the most frequently used memory tests today. Although the scale has improved through revisions over the years, it is still not strongly grounded in our current understanding of the neuroanatomy of human memory (Kent, 2013). Because of this, it is difficult to make predictions about how negative health predictors may impact memory performance measured by this scale. Therefore, there is a need for more specific tests of memory function that have theoretical groundings in the neuroanatomy of human memory.

One such memory test is of long-term associative recognition. Associative recognition procedures have been widely used in the field of cognitive neuroscience to investigate the neural mechanisms of human episodic memory, and numerous examples from neuroimaging and lesion studies have demonstrated that associative memory is strongly dependent on the hippocampus (Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012). Tests of associative memory can involve memory for an item and its context (e.g. a background color) or memory of two items paired together. On these memory tests, subjects are asked to study and recognize paired items (e.g. two words, two pictures, a word with a picture, a word with a colored background, or a picture with a colored background). Through careful experimental design, variations of these procedures can be used to specifically test the construct of episodic memory. Episodic memory can be broken down into two underlying components: recollection and familiarity (see Table 1). Importantly, these two subcomponents have been shown to involve different memory systems in the brain (Yonelinas, 2001). For instance, recognition through recollection processes is thought to largely depend on the hippocampus, whereas recognition through familiarity processes can be accomplished using other medial temporal lobe structures (Eichenbaum et al., 2012).

Eichenbaum et al. (2007) propose a model describing how the medial temporal lobe structures accomplish these recognition processes. Structures included in the model are the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex. Eichenbaum et al. propose that item information projects down from neocortex to perirhinal cortex and through to the lateral entorhinal cortex before it reaches the hippocampus, whereas context information projects down from neocortex to parahippocampal cortex and through to medial entorhinal cortex before reaching the hippocampus. The hippocampus then binds together the item and its associated context together in memory. Eichenbaum et al.'s (2007) model also suggests that familiarity-based recognition can occur through medial temporal lobe structures at the pre-hippocampal level (via perirhinal cortex), whereas recollection-based recognition occurs at the level of the hippocampus where both items and contexts are bound together.

One method for testing recollection and familiarity processes is through recognition of word pairs. Numerous functional neuroimaging studies have demonstrated that word pair recognition relies on recollection processes involving the hippocampus (Jackson & Schacter, 2004; Park & Rugg, 2008; Sullivan Giovanello, Schnyer, & Verfaellie, 2004). Further, Park & Rugg (2011) even compared recognition of associations between word pairs, picture pairs, and word-picture pairs, and did not find differences between them in hippocampal activation. Therefore, it appears that the hippocampus is involved in associative memory regardless of stimulus modality. Word pairs have also been shown to differentiate recollection and familiarity processes by varying the degree of unitization between word pairs (Zheng, Li, Xiao, Broster, & Jiang, 2015). When two words form a unitized pair (e.g. paper-towel), an association between the pairs already exists. However, if two words are unrelated (e.g. bottle-trout), an association needs to be formed and retrieved at recognition. Therefore, recognition of unitized word pairs can be accomplished through familiarity processes (not dependent on newly formed associations), whereas recognition of unrelated word pairs requires recollection (of the newly formed association).

Based on Eichenbaum et al.'s model (Figure 1), medial temporal lobe regions involved in recognition of unitized and unrelated word pairs can be predicted. Because perirhinal cortex is sufficient for recognition through familiarity processes, recognition of unitized word pairs can be accomplished at the pre-hippocampal level. On the other hand, because the hippocampus is required for recognition through recollection, recognition of unrelated word pairs requires the hippocampus.

The importance of dissociating recollection from familiarity processes becomes apparent when examining the differential effects many negative health predictors have on the brain. Specifically, evidence suggests that the hippocampus is particularly vulnerable. For example, the aberrant levels of circulating glucocorticoids associated with chronic stress and depression are particularly damaging to the hippocampus relative to other brain areas (Kim & Diamond, 2002). Similarly, evidence suggests that the effects of inflammatory cytokines associated with metabolic conditions particularly affect the blood brain barrier of the hippocampus (Freeman & Granholm, 2012; Freeman, Haley-Zitlin, Rosenberger, & Granholm, 2014). Likewise, the function of the hippocampus partly depends on insulin signaling, which can become disrupted in metabolic conditions related to obesity (De Felice, Lourenco, & Ferreira, 2014). Further, memory loss associated with Alzheimer's disease is believed to be a direct result of deterioration of the hippocampus and other medial temporal lobe structures (Jack et al., 1998).

Differentiation of recollection and familiarity memory processes has been observed in clinical settings as well. For instance, evidence has shown that memory decline related to both healthy aging and amnesia is less pronounced for familiarity-based recognition than recollection-based recognition (Ahmad, Fernandes, & Hockley, 2015; Bastin et al., 2013; Quamme, Yonelinas, & Norman, 2007; Ryan, Moses, Barense, & Rosenbaum, 2013; Zheng et al., 2015). Therefore, it appears that hippocampal damage is impacting recollection processes more strongly than familiarity processes. Because many negative health predictors related to stress, obesity, and inflammation seem to preferentially impact the

hippocampus, the impact of these variables on memory function should be most pronounced in tests of recollection.

Obesity/Fat Deposition

Considerable research has linked obesity to cognitive decline, and this relationship is apparent across many age groups including adolescents (Verdejo-García et al., 2010) as well as adults (Gunstad, Lhotsky, Wendell, Ferrucci, & Zonderman, 2010). Further, there is now convincing evidence that midlife obesity contributes to the development of dementia and cognitive decline later in life (Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005).

Additionally, neurological evidence links obesity to hippocampal and memory decline. For instance, human neuroimaging studies have shown hippocampal atrophy in obese relative to control subjects (Mueller et al., 2012; Raji et al., 2010) and controlled animal experiments that have induced obesity have observed that obesity caused hippocampal atrophy and reduced memory performance (Stranahan et al., 2008; Winocur et al., 2005); also, see Kanoski and Davidson (2011) for a review. Because of these relationships between obesity and the hippocampus, it is likely that obesity will more greatly affect recollection processes compared to familiarity.

Theoretically, obesity could affect memory in a number of ways. For instance, obesity could affect brain health via its effects on metabolic and cardiovascular functions (Grundy, 2004). For instance, Kivipelto et al. (2005) showed that obesity and related cardiovascular risk factors at midlife increased the likelihood of developing dementia later in life. Likewise, in a review, Yates et al. (2012) outline many studies linking obesity and metabolic dysfunction to cognitive dysfunction in both adults and adolescents. Further, others have shown that diet-induced insulin resistance negatively impacts hippocampal synaptic plasticity (Stranahan et al., 2008). Therefore, obesity-related insulin resistance may impact memory function as well.

Obesity may also increase the amount of circulating inflammatory cytokines. Adipose cells in obesity become hypertrophied and induce a low grade inflammatory state (Gregor & Hotamisligil, 2011). These inflammatory cytokines can then travel to the brain and cause damage (Freeman et al., 2014). Further, Freeman et al. (2011) showed that inflammation may particularly impact the blood brain barrier around the hippocampus. Therefore, obesity may impact memory through modulation of the hippocampal blood brain barrier via obesity-induced inflammation. Adipose tissue that is most inflammatory is that in the visceral cavity (and referred to as visceral or central obesity; Tchernof & Després, 2013). Therefore, many relationships between obesity and negative health outcomes are linked more strongly with measures of visceral adiposity, such as waist-to-hip ratio (WHR), than measures of overall body weight (e.g. body mass index). This suggests that inflammation may be a key contributor to memory deficits associated with obesity.

Inflammation

The negative impact of excessive inflammation on brain health has recently gained much attention, and there is now a large amount of evidence linking inflammation to Alzheimer's disease (Holmes, 2013; McNaull, Todd, McGuinness, & Passmore, 2010; Wyss-Coray & Rogers, 2012). Further, increased inflammation has been linked to other psychological and physiological illnesses also thought to influence brain health, such as chronic stress and depression (Miller & Blackwell, 2006), and metabolic syndrome and cardiovascular disease (Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000).

Much animal research has demonstrated causal links between inflammation and memory impairment. For instance, evidence has shown that inflammation inhibits hippocampal neurogenesis in the rat (Ekdahl, Claasen, Bonde, Kokaia, & Lindvall, 2003; Monje, Toda, & Palmer, 2003). Similar evidence linking inflammation to the hippocampus has been corroborated with humans using neuroimaging. For example, Marsland et al. (2008) showed that plasma interleukin-6 (IL-6) levels were negatively related to hippocampal grey matter volume, even when controlling for total grey matter

volume, suggesting that the hippocampus is particularly affected by inflammation. Further, inflammation appears to particularly damage the blood brain barrier surrounding the hippocampus (Freeman et al., 2011). Therefore, memory functions that are dependent on the hippocampus (i.e., recollection processes) are likely to be compromised by excessive inflammation.

Inflammation may also be linked to other measures that could impact memory. For example, evidence suggests that increases in inflammation could be an indication of altered autonomic nervous system activity (Nance & Sanders, 2007). It has been proposed that the acetylcholine released by the vagus nerve of the parasympathetic nervous system activates cholinergic anti-inflammatory mechanisms that reduce the production of pro-inflammatory cytokines (Huston & Tracey, 2011). Therefore, alterations in parasympathetic activity may be partially responsible for increases in inflammation.

Heart Rate Variability

Heart rate variability (HRV) refers to changes in heart rate across time and reflects the activity of the parasympathetic nervous system (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Further, HRV has been shown to be negatively associated with inflammation (Lampert et al., 2008). Thayer (2009) proposed that reductions in HRV result in reductions in cholinergic anti-inflammatory mechanisms initiated by the vagus nerve. Therefore, alterations in in parasympathetic nervous system activity, assessed by HRV, may reflect other mechanisms of inflammation that could impact the brain and influence memory.

Further, research suggests that HRV relates to overall psychological and physiological health, linking low HRV to cardiovascular disease, diabetes, obesity, inflammation, depression, and anxiety (Kemp & Quintana, 2013), all of which have been linked to cognitive dysfunction. Further, HRV is also theorized to directly relate to cognitive function. Thayer et al. (2009) propose that the Neurovisceral Integration Model explains relationships between HRV and cognitive function. According to this model, projections from the prefrontal cortex influence brainstem nuclei that control the vagus nerve, and

heart rate is coordinated with cognitive functions through these mechanisms. Therefore, HRV reflects the integrity of these systems; greater variability relates to better performance on cognitively-mediated goal-directed tasks.

Further, psychological factors may also contribute to alterations in the autonomic nervous system that are reflected in HRV. For instance, both stress and depression have been associated with reduced HRV (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012 and Kemp et al., 2010, respectively). Importantly, both stress and depression have been linked to memory deficits (Burt, Zembar, & Niederehe, 1995; Kim & Diamond, 2002). Therefore, there are strong theoretical reasons to believe that HRV will be related to hippocampal-dependent memory performance, and therefore will be associated with deficits in recollection memory.

Stress, Anxiety, and Depression

Stress, anxiety, and depression may impact memory function through a number of mechanisms. For instance, stress, anxiety, and depression are each related to inflammation. Miller et al. (2002) showed that chronic stress is associated with a reduced ability to terminate inflammatory responses. Cohen et al. (2012) propose that chronic high levels of circulating glucocorticoids associated with chronic stress eventually result in glucocorticoid resistance. Glucocorticoid resistance disrupts mechanisms important for down-regulating inflammatory responses. Further, like inflammation, research has also linked heightened levels of glucocorticoids to hippocampal damage (McEwen, 1999, 2001). Therefore, stress may impact the hippocampus through increases in both glucocorticoids and pro-inflammatory cytokines. There is now a multitude of studies demonstrating a link between stress, hippocampal dysfunction, and memory deficits (Kim & Diamond, 2002; Sapolsky, 2003). Therefore, stress likely negatively affects hippocampal-dependent memory.

Evidence has suggested that chronic stress can lead to depression (Sapolsky, 2003), and other research has suggested that increases in pro-inflammatory cytokines in the brain can further increase

depressive symptoms through their effects on many of the physiological processes associated with depression including neurotransmitter metabolism, neuroendocrine function, and neural plasticity (Miller, Maletic, & Raison, 2009). Meta-analyses of human studies have linked depression with increased inflammation (Valkanova, Ebmeier, & Allan, 2013), reduced memory performance (Burt et al., 1995), and reduced hippocampal volume (Videbech & Ravnkilde, 2004). In addition, recent research has even shown that anti-inflammatory medications may be an effective treatment for depression, implicating a causal role of inflammation in depression (Miller, Maletic, & Raison, 2009).

Like chronic stress, anxiety disorders have also been linked to inflammation (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017), suggesting that they share physiological mechanisms. Furthermore, there is evidence that altered attentional processes may influence memory in both clinical and subclinical anxiety (Herrera, Montorio, Cabrera, & Botella, 2017). Also, other research has suggested that anxiety disorders are often comorbid with depression (Brady & Kendall, 1992; Mineka, Watson, & Clark, 1998). Therefore, chronic stress, anxiety, and depression are all closely related. Memory deficits may arise from these conditions through increases in circulating levels of glucocorticoids and pro-inflammatory cytokines, each of which has been shown to negatively impact the hippocampus. Therefore, it is expected that stress, anxiety, and depression will negatively impact recollection memory processes.

Inflammation as a Mediating Variable

Obesity, HRV, stress, anxiety, and depression all relate to inflammation, and inflammation is believed to damage the hippocampus. Therefore, inflammation appears to be an important underlying factor linking these predictors to memory dysfunction. In obesity, adipose cells become hypertrophied which affects macrophage infiltration and results in an increase in pro-inflammatory cytokine release from adipose tissue (Gregor & Hotamisligil, 2011). HRV reflects the activity of the parasympathetic nervous system, where low parasympathetic activity (i.e. low HRV) results in reduced

parasympathetically-mediated anti-inflammatory mechanisms (Huston & Tracey, 2011). Stress increases the number of circulating glucocorticoids, which over time results in chronic inflammation (S. Cohen et al., 2012). Further, longitudinal studies have shown that depressive symptoms often precede inflammation (Copeland, Shanahan, Worthman, Angold, & Costello, 2012; Stewart, Rand, Muldoon, & Kamarck, 2009). Therefore, inflammation may mediate individual relationships that obesity, HRV, stress, and depression have with memory performance.

Interrelatedness of Variables and Brain Function

Relationships among the abovementioned variables are complex and many share similar mechanisms. As outlined previously, obesity, HRV, stress, anxiety, and depression are all linked to inflammation. Given that inflammation may particularly impact the hippocampus, these predictors may share variance related to hippocampal dysfunction through inflammation. Further, all predictors (including inflammation) also relate to cardiovascular disease (Rocha & Libby, 2009; Rumsfeld & Ho, 2005; Shively, Register, & Clarkson, 2009; Thayer, Yamamoto, & Brosschot, 2010), which could have a widespread effect on brain activity through disruptions in cortical processing. Because the brain is vascularized from the outside-in, blood vessels that penetrate deep into the white matter tissue of the cerebrum are particularly thin and vulnerable (Iadecola, 2013). Therefore, any cognitive process that requires cortical processing could potentially be affected, meaning that cognitive dysfunction associated with cardiovascular disease could be widespread and non-specific. This is reflected in a recent meta-analysis; Yates et al. (2012) observed that a wide variety of cognitive tasks have been shown to relate to cardiovascular disease risk factors including executive functioning, working memory, long-term memory, processing speed, and visuospatial abilities.

However, the variables included in this study were chosen because of their unique mechanisms through which they may influence brain function in addition to widespread inflammatory or cardiovascular-related dysfunction. For instance, obesity-related insulin resistance may impact

hippocampal insulin signaling and result in hippocampal dysfunction (Stranahan et al., 2008), HRV reflects the activity of the parasympathetic nervous system and also reflects the overall ability to integrate our cognitive processes with the rest of our body (Thayer, Hansen, Saus-Rose, & Johnsen, 2009), stress-related chronically high levels of circulating glucocorticoids damage the hippocampus (Sapolsky, 2003), anxiety may affect attentional processes that impact memory (Herrera et al., 2017), and depression has been linked to reduced hippocampal neurotrophin levels which impacts health and function of hippocampal cells (Castren, Voikar, & Rantamaki, 2007). Thus, although these predictors share mechanistic ways in which they may affect memory function, they all may do so in other independent ways. Therefore, it is important to include all variables when investigating memory function.

In sum, all predictors likely relate to general cognitive decline, which would include memory. However, because these effects on cortex are widespread and fairly non-specific, they may affect recollection and familiarity processes equally. Therefore, one must look beyond these widespread effects to differentiate recollection from familiarity. As argued above, the hippocampus appears to be an area of the brain that is both highly vulnerable to the negative effects of these health predictors (showing deficits above and beyond those attributable to general widespread damage attributable to cardiovascular disease) and differentially involved in recollection and familiarity processes. Therefore, an experimental paradigm designed to measure hippocampal function may be used to differentiate these memory processes.

The proposed experimental design was able to differentiate recollection and familiarity despite their reliance on shared neurological mechanisms outside of the hippocampus. The experiment had two conditions: recognition of unrelated word pairs and recognition of unitized word pairs. Recognition of unrelated word pairs required recollection (and therefore, required the hippocampus), whereas recognition of unitized word pairs was accomplished through familiarity (and therefore, was less

dependent on the hippocampus). Importantly, these two conditions were under tight experimental control; they differed only on a single dimension: word pair relatedness (i.e. unrelated vs. unitized). Otherwise, the two conditions were the same: they were visually identical (font, size, and color), they were presented for the same amount of time, they were studied using the same study task, they were presented for recognition in the same way, the trial numbers were the same, and the lures (i.e. rearranged pairs) were created in the same way. Therefore, shared neurological mechanisms that dictate cognitive functions associated with many extraneous factors (such as visual processing, language processing, attention, etc.) were controlled for by the experimental paradigm. The only difference between conditions was the manipulation of word pair relatedness, and therefore the cause of performance differences between conditions could be attributed to word pair relatedness. For successful recognition of unrelated word pairs, an association between the words needed to be formed, whereas the association already existed for unitized pairs. Therefore, because the hippocampus was responsible for creating associations, it was predicted that hippocampal deficits would be reflected in recognition performance of unrelated word pairs (i.e. recollection) but not in recognition performance of unitized pairs (i.e. familiarity). Further, because experimental conditions were identical in every other way apart from word pair associations, deficits related to cognitive functions outside of associative processes would be equally represented in each condition (including many shared mechanisms associated with widespread non-specific cognitive deficits associated with cardiovascular disease).

Therefore, although both recollection and familiarity could have been broadly impacted due to deficits associated with basic information processing in the cerebral cortex, it was predicted that recollection would be impacted above and beyond this broad impact because of its dependence on the hippocampus, as many of the variables chosen for this study were expected to differentially impact the hippocampus above and beyond effects attributable to widespread cardiovascular-related deficits.

Therefore, it was predicted that this greater impact on the hippocampus would be reflected as greater memory deficits in recollection compared to familiarity.

Further, although recollection and familiarity processes shared some overlapping brain mechanisms, the relationship between these memory processes was only moderate. Previous unpublished research conducted in the laboratory of Dr. Heekyeong Park showed a correlation between recollection and familiarity memory performance of $r = .49$, indicating only 24% variance overlap between these memory processes. Therefore, 76% of the variance was still unaccounted for and may have been explained by the abovementioned health predictors.

HYPOTHESES

The purpose of this dissertation was to demonstrate the impact of psychological and physiological health predictors on specific subdivisions of episodic memory (i.e. recollection and familiarity), with a specific focus on the damaging effects of inflammation.

Based on the relationships between the health variables and memory functions, it was expected that these variables included together in a model would predict memory function (Hypotheses 1). Therefore, for Hypothesis 1a, it was predicted that together, the psychological and physiological variables (i.e. stress, anxiety, depression symptoms, inflammation, WHR, and HRV) would significantly predict memory function for both recollection and familiarity (Figure 2a). Because of the unique mechanisms through which these health variables may contribute to neurological dysfunction, it was important to assess their unique contribution to memory function. Therefore, for Hypothesis 1b, it was expected that each predictor would independently predict memory function while controlling for the other predictors (Figure 2b). Specifically, it was expected that stress, anxiety, depression, inflammation, and WHR would show negative relationships with both recollection and familiarity, whereas HRV would show positive relationships with recollection and familiarity.

Further, because recollection and familiarity were believed to be supported by different neurological memory systems, it was predicted that they would be differentially impacted by these health predictors. Because of its dependence on the hippocampus, it was expected that recollection processes would be more greatly impacted than familiarity. Therefore, for Hypothesis 2, it was predicted that these health variables would show their same relationships with recollection that they did for Hypothesis 1 after accounting for their relationships with familiarity (Figure 3).

Finally, because inflammation relates to obesity, HRV, stress, anxiety, and depression, it was expected that inflammation may be a primary underlying mechanism of reduced recollection memory performance. Therefore, for Hypothesis 3, it was expected that each predictor would be indirectly associated with recollection through the inflammatory marker interleukin-6 (IL-6; Figure 4).

METHOD

Participants

Participants were recruited as part of a larger study investigating the relationships among social media use, cognitive function, and psychological and physiological health. However, social media use was not investigated in the present study. Participants were recruited either through UT Arlington's participant recruitment system (SONA) or through flyers posted around campus; participants could either earn course credit or a $30 gift card for participation. Inclusion criteria required participants to be between 17 and 25 years old, fluent in written and spoken English, and healthy. Participants were excluded for the following reasons: medication for psychological diagnoses, pregnancy, tobacco use, taking anabolic steroids or anti-inflammatory medication, taking opioids, a recent experience of head trauma (last 6 months) or physical injury, surgery, chemotherapy, or radiation therapy (last two weeks), deafness or tinnitus, seizure disorder, cancer, a history of significant coronary events, high blood pressure, high cholesterol, diabetes, hepatitis C or viral cirrhotic hepatic disease, active infection, severe anemia, connective tissue disease, or any illness not controlled by a stable therapeutic regimen.

Procedures

Participants underwent a blood draw, rested quietly for 5 minutes for heart rate data collection, completed an associative memory test on a computer, and completed a number of surveys on a computer (including those for stress, anxiety, and depression symptoms). All experimental procedures occurred in the afternoon, and all blood draws occurred between 2:00 p.m. and 4:00 p.m. to reduce variability attributable to circadian fluctuations in inflammatory marker levels.

Independent Measures. Obesity was assessed by measuring WHR. Negative health outcomes associated with overweight and obesity have been shown to be correlated more strongly with measures of visceral obesity (i.e., WHR) than with measures of general weight (e.g. body mass index; (Shuster, Patlas, Pinthus, & Mourtzakis, 2012). Waist-to-hip ratio was determined by measuring around the waist midway between the lowest rib and the iliac crest and around the hip at the level of the greater trochanters (lateral portion of the top of the femur), as in (Onat et al., 2004). Waist circumference was divided by hip circumference, so smaller values represented lower amounts of visceral obesity.

Inflammation was measured by assessing levels of the plasma inflammatory marker interleukin 6 (IL-6) taken from a blood draw. IL-6 was chosen for a number of reasons. First, the hippocampus possesses a relatively high density of IL-6 receptors (Freeman et al., 2014). Second, serum IL-6 levels have shown a negative relationship with cognitive functioning in humans (Wright et al., 2006). Finally, IL-6 has been shown to be negatively correlated with human hippocampal volume while controlling for total brain volume (Marsland et al., 2008). Blood samples were collected in 10-mL serum separator tubes by venipuncture, centrifuged, and temporarily frozen in a -80° F freezer. Interleukin 6 levels were measured in the serum using the sandwich enzyme-linked immunosorbent assay (ELISA) technique. Samples were run in duplicate; duplicate samples with coefficients of variance below 15% were averaged and used in the analysis.

Heart rate variability was assessed through electrocardiogram (ECG) recordings using a Zephyr™ Bioharness placed around the chest. Recordings occurred during a 5-minute baseline prior to performing the associative memory task and at least 20 minutes after the blood draw. Heart rate variability was investigated in the time domain, by using the root mean square of the successive differences (RMSSD) of heart beats. This measure was used to reflect parasympathetic activity (Laborde, Mosley, & Thayer, 2017). Kubios software was used to process heart rate data. Previously published recommendations have suggested to exclude samples with more than 5% missing data (Quintana, Alvares, & Heathers, 2016); we employed this cutoff as well.

Depression symptoms, stress, and anxiety were measured using the following self-report scales: The Center for Epidemiologic Studies Depression Scale Revised (CESD-R, Appendix A), the Perceived Stress Scale (PSS, Appendix B), and the State-Trait Anxiety inventory (STAI, copyrighted but can obtained from the publisher Mind Garden). The CESD-R was designed to reflect diagnostic criteria for major depression, and consists of 20 items (Eaton, Smith, Ybarra, Muntaner, & Tien, 2004; Van Dam & Earleywine, 2011). The PSS measures perceptions of stress rather than actual stressful events, and it consists of 10 items reflective of perceived stress that occurred over the past month (Sheldon Cohen, Kamarck, & Mermelstein, 1983). The STAI was designed to assess both state and trait anxiety, where state anxiety refers to acute anxiety attributable to situational factors and trait anxiety refers to a personality characteristic or tendency toward experiencing greater amounts of state anxiety in stress-inducing situations (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1977). The STAI state scale assessed how participants felt right then, at the present moment. The STAI trait assessed how participants generally feel, with no specific timeframe mentioned. Each scale is widely used and has been shown to be valid and reliable (Barnes, Harp, & Jung, 2002; Roberti, Harrington, & Storch, 2006; Van Dam & Earleywine, 2011).

Dependent Measures. Recollection and familiarity were assessed by measuring recognition of unrelated and unitized word pairs (see Table 2). Unrelated pairs were comprised of unrelated words (e.g., toast-pool, volcano-hamster, mirror-lantern) and unitized pairs were comprised of two words that created a single unitized concept/item (e.g., face-mask, fork-lift, side-walk). During test, rearranged pairs of each type (e.g., from above, for unrelated: toast-hamster, for unitized: face-lift) and new pairs were intermixed for participants to differentiate from memory. Word pairs were taken from previously published research (Dalton, Tu, Hornberger, Hodges, & Piguet, 2014; Schaeffer et al., 2014). Research has demonstrated that recognition of unrelated pairs involves recollection-based memory processes whereas recognition of unitized pairs can be accomplished through familiarity-based memory processes (Eichenbaum et al., 2012). Therefore, the difference between memory performance for each pair type will indicate the degree to which our psychophysiological measures differentially impact recollection and familiarity.

For the associative memory procedure, participants completed a study phase and a test phase. During the study phase, word pairs were presented on a computer screen one at a time, and participants made a pleasantness judgment about each word; they responded either “pleasant” or “not pleasant” using the keyboard. Each word pair remained on screen for 2 seconds. The purpose of this study phase was to simply get participants to read and process each word pair. Therefore, subjective pleasantness ratings were irrelevant and were not included in the analysis. During the test phase, word pairs were presented again and participants made recognition judgments about each pair. Each word pair remained on screen for 3 seconds or until a response was made. Test word pairs were either intact (a pair presented during study), rearranged (words presented during study, but paired differently) or new (a word pair comprised of two unstudied words). Participants responded “intact,” “rearranged,” or “new” to each test pair. See Figure 5 for a diagram of the procedure.

During study, participants were presented with 120 word pairs: 60 unrelated and 60 unitized. During test, participants responded to 120 word pairs: 20 intact unrelated, 20 rearranged unrelated, 20 new unrelated, 20 intact unitized, 20 rearranged unitized, and 20 new unitized. Word pair presentation order was randomized for each participant in both study and test phases.

Associative memory was assessed by comparing hits ("intact" responses to intact pairs) to false alarms ("intact" responses to rearranged pairs) with *d'*, a measure of discrimination used in signal process theory (MacMillan & Creelman, 2005). The *d'* value was calculated by subtracting the proportion of false alarms from the proportion of hits using values from the *z*-distribution [*d'* = *z*(Hit) - *z*(False Alarm)]. For the present study, *d'* was calculated by comparing the proportion of correct "intact" (hit) responses to intact pairs relative to the total number of intact pairs to the proportion of incorrect "intact" (false alarm) responses to rearranged pairs relative to the total number of rearranged pairs. Therefore, *d'* values reflect participants' ability to discriminate intact studied word pairs from rearranged lures for both types of word pairs; *d'* values for unrelated pairs reflect recollection and *d'* values for unitized pairs reflect familiarity.

ANALYSES

To test Hypotheses 1a and 1b, two regression analyses were conducted. The first used recollection-based memory performance (i.e. *d'* for unrelated word pairs) as the dependent variable, gender, PSS scores, STAI state scores, STAI trait scores, CESD-R scores, IL-6 values, WHR, and HRV as predictors; the second used the same predictors with familiarity-based memory performance as the dependent variable (i.e., *d'* for unitized word pairs). For all regression models, gender was added as a covariate because gender differences have been shown to explain some of the relationships between these predictors and health risk (Després & Lemieux, 2006; Keyes, 2004; Regitz-Zagrosek, Lehmkuhl, & Mahmoodzadeh, 2007). T-tests of regression weights, zero-order correlation coefficients, and semi-partial correlation coefficients were used to determine the strength and direction of each predictor.

Further, relative weight analysis was also employed to help determine the importance of predictors. Relative weights analysis was conducted using the methods outlined in (Johnson, 2000), where a set of orthogonal predictor variables that were highly correlated with the true predictors were created and used to estimate the relative weights of the true predictors.

To test Hypothesis 2, a hierarchical regression was conducted with recollection-based memory performance as the dependent variable, familiarity-based memory performance entered into the first step, and gender, PSS scores, STAI state scores, STAI trait scores, CESD-R scores, IL-6 values, WHR, and HRV entered into the second step. R^2-change was examined to determine if the variables predicted recollection memory above and beyond their relationships with familiarity. Next, a second hierarchical regression was conducted with familiarity-based memory performance as the dependent variable, recollection-based memory performance entered into the first step, and gender PSS scores, STAI state scores, STAI trait scores, CESD-r scores, IL-6 values, WHR, and HRV entered into the second step. For each regression, follow-up analyses for this hypothesis consisted of interpreting *t*-tests of regression weights, zero-order correlation coefficients, semi-partial correlation coefficients, and relative weights of each predictor variable.

Finally, because it was hypothesized that inflammation may explain relationships between stress, anxiety, depression, WHR, and HRV with memory function, regression analyses where conducted with and without IL-6 added to the model and investigated whether or not IL-6 could be considered a mediating variable. Indirect effects from mediation analysis were investigated when mediation was suspected, as depicted in Figure 4.

RESULTS

Data

In total, data were collected from 136 participants. Data were not available for all measures for all participants due to the following reasons: did not complete memory task (*n* = 2), did not provide

waist-to-hip ratio measurements (*n* = 1), electrocardiography equipment failure (*n* = 19), unreliable IL-6 from blood serum (*n* = 10), blood serum not obtained (n=17), did not complete STAI (n=1). Some participants had multiple sources of missing data. For all measures included in the regression analyses (i.e., memory scores, WHR, PSS scores, STAI State scores, STAI Trait scores, CESD-R scores, HRV values, and IL-6 levels), data were available for a total of 96 participants. Data distributions were examined for all variables. CESD-R scores, STAI state scores, STAI trait scores, HRV values, and IL-6 values were positively skewed. CESD-R scores were square root transformed, and STAI State scores, STAI Trait scores, HRV values, and IL-6 levels were log transformed to achieve normality.

Descriptive Statistics and Correlations

Response proportions for each type of memory task are presented in Table 3. These proportions demonstrate that correct responses were made most often for each stimulus type. Cronbach's alpha was used to assess scale reliability for STAI state (α = .84), for STAI trait (α = .91), for PSS (α = .83), and for CESD-R (α = .89), demonstrating strong internal consistency. Descriptive statistics for each predictor variable are presented in Table 4, and the correlation matrix for all predictor variables is presented in Table 5.

Regression analyses

To test hypothesis 1, two regressions were conducted. The first, with recollection-based memory performance as the criterion and gender, PSS, STAI state, STAI trait, CESD-R, WHR, HRV, and IL-6 as predictor variables was significant, R^2 = .19, $F(8, 87) = 2.58$, p = .014. STAI state and STAI trait were each significant predictors of recollection memory, where higher state anxiety predicted poorer performance (p = .016) and higher trait anxiety predicted better performance (p = .001). Gender was a marginal predictor, in which being male predicted poorer performance (p = .091); no other predictors were significant. Relative weights analysis confirmed these findings, where STAI trait had the largest relative weight followed by STAI state. Interestingly, PSS had the third largest relative weight, ahead of

gender. The trend for PSS was in the same direction as STA trait. Beta weights, semi-partial correlation coefficients, and relative weights for these predictors are presented in Table 6.

The second regression, with familiarity-based recognition memory performance as the criterion, and gender, PSS, STAI state, STAI trait, CESD-R, WHR, HRV, and IL-6 as predictor variables was only marginally significant, $R^2 = .14$, $F(8, 87) = 1.81$, $p = .086$. Together, these analyses suggest that hypothesis 1 was partially supported. STAI state and STAI trait significantly predicted recollection memory, although the direction of STAI Trait was opposite of what was predicted. However, familiarity-based recognition memory was not significantly predicted by any variable.

To test hypothesis 2, first, a hierarchical regression was run with recollection-based recognition memory performance as the criterion, familiarity-based recognition memory performance entered into step 1, and gender, PSS, STAI state, STAI trait, CESD-R, WHR, HRV, and IL-6 entered into step 2. The regression showed that Step 2 added significant predictive power, $\Delta R^2 = .19$, $\Delta F(8, 86) = 3.58$, $p = .001$, indicating that these health variables significantly predicted recollection-based memory performance above and beyond what was predicted by familiarity-based memory performance. Higher STAI trait predicted better performance ($p < .001$), whereas higher IL-6 ($p = .014$) and CESD-R scores ($p = .010$) predicted poorer performance. Additionally, higher STAI state marginally predicted poorer performance as well ($p = .070$); other predictors were not significant (Table 6). Next, a second hierarchical regression was run with familiarity- based recognition memory performance as the criterion, recollection-based recognition memory performance entered into step 1, and gender, PSS, STAI state, STAI trait, CESD-R, WHR, HRV, and IL-6 entered into step 2. This regression also showed that Step 2 added significant predictive power, $\Delta R^2 = .15$, $\Delta F(8, 86) = 2.76$, $p = .009$, indicating that these variables also significantly predicted familiarity above and beyond recollection. Higher IL-6 ($p = .014$) and CESD-R ($p = .014$) scores predicted greater familiarity. Additionally, higher STAI trait marginally predicted poorer performance ($p = .087$). Other predictors were not significant (Table 6).

Interestingly, comparisons of zero-order to semi-partial correlation coefficients for these predictors suggested suppression. When predicting recollection while controlling for familiarity, semi-partial correlations where higher than zero-order correlations for IL-6, CESD-R, and STAI trait. When predicting familiarity while controlling for recollection, semi-partial correlations were higher than zero-order correlations for CESD-R scores. Therefore, relationships between these significant predictors and recollection were strengthened by the addition of each other. Further, this suggested that IL-6 was not a mediating variable. Hierarchical regression analyses were used to confirm this conclusion and further investigate these suppression effects. While predicting recollection-based memory performance, each predictor was entered with familiarity-based memory performance and gender in step one, all other predictors except for IL-6 were entered into step 2, and IL-6 was entered into step 3. Changes in semi-partial correlation coefficients were observed across each step. While predicting familiarity-based memory performance, each predictor was entered with recollection-based memory performance and gender in step one, all other predictors except for IL-6 were entered into step 2, and IL-6 was entered into step 3. Changes in semi-partial correlation coefficients were observed across each step. These results are presented in Table 7.

While predicting recollection, all semi-partial correlation coefficients were lowest in step 1 and not reduced by the addition of IL-6 in step 3. Although PSS was reduced in the end, this reduction occurred in step 2 prior to the addition of IL-6 because of its shared variance with STAI, not because the relationship was mediated by IL-6. However, while predicting familiarity, the results suggested that IL-6 may have been mediating the relationship between WHR and familiarity. The indirect effect from mediation analysis using 5000 bootstrapped samples with familiarity as the criterion, WHR as the predictor, IL-6 as the mediator, and recollection and gender as covariates was investigated. Waist-to-hip ratio was significantly related to IL-6 (B = 1.78, SE = 0.65, p = .007) and IL-6 was significantly related to familiarity (B = 0.52, SE = 0.22, p = .021). Without IL-6 added to the model, WHR was significantly

related to familiarity (*B* = 2.98, *SE* = 1.40, *p* = .036), but when IL-6 was included, WHR was no longer significantly related to familiarity (*B* = 2.06, *SE* = 1.43, *p* = .152). However, the indirect effect was not significant, 95% CI [-0.001 2.13], suggesting that IL-6 was not significantly explaining the relationship between WHR and familiarity. Therefore, Hypothesis 3 was not supported; IL-6 was not mediating any of the relationships. Rather, IL-6 increased the predictive power of STAI scores on recollection through suppression.

DISCUSSION

The results showed that the hypotheses were partially supported. When predicting recollection, STAI trait and STAI state were significant predictors. Higher STAI state scores were related to poorer recollection, whereas higher STAI trait scores were related to greater recollection. When predicting recollection while controlling for familiarity, STAI trait, IL-6 levels, and CESD-R scores were all significant predictors; higher STAI trait scores were related to greater recollection, whereas higher IL-6 levels and CESD-R scores were related to poorer recollection. When predicting familiarity, no health variable was a significant predictor. However, when predicting familiarity while controlling for recollection, IL-6 levels and CESD-R scores were significant predictors; higher IL-6 levels and CESD-R scores were related to greater familiarity. Although IL-6 levels were predicted to mediate relationships between health variables and recognition memory, IL-6 levels instead served as a suppressor variable. These findings are interpreted below.

Predicting Familiarity

Although it was hypothesized that stress, anxiety, depression, visceral obesity, HRV, and inflammation would significantly predict familiarity-based recognition performance without controlling for recollection performance, this was not really the case. Although 14% of the variance in familiarity-based recognition performance was accounted for, it was only marginally significant. Therefore, familiarity was not strongly related to any of the health variables in the present study. Although we had

hypothesized that the health variables would negatively impact familiarity, we suspected that this effect would be much larger for recollection. Therefore, this null finding was not surprising.

Predicting Familiarity Above and Beyond Recollection

However, when predicting familiarity while controlling for recollection, we observed that both IL-6 levels and CESD-R scores were significant positive predictors, suggesting that higher levels of inflammation and depression were related to better familiarity-based recognition performance. Research has shown that recollection and familiarity differentially change with age. In a recent meta-analysis, Koen and Yonelinas (2014) showed that healthy aging was accompanied by moderate-to-large impairments in recollection, whereas familiarity showed little or no impairment with age. Furthermore, some evidence suggests that age-related decline in recognition memory can be reduced by encouraging familiarity-based encoding strategies. For example, Zheng, Li, Xiao, Ren, & He (2016) tested recognition of source information in older adults, by first asking older adults to study images presented on colored backgrounds and later testing their recognition for these images and their ability to correctly report the studied background color. Older adults who were instructed to study images using a unitization strategy were better able to remember the correct background color for studied items. This unitization strategy involved imagining that each image was the color of the background (e.g., a black umbrella presented with a red background would be imagined as a red umbrella). Therefore, participants did not have to remember the association between the color "red" and the image "umbrella." Instead they just had to remember a red umbrella. However, encouraging familiarity-based recognition could come with some problems, as evidence suggests that familiarity-based recognition is more susceptible to false alarms (Yonelinas, 2002).

Tibon & Henson (2015) provided an interesting interpretation of recollection and familiarity processes that may help to explain these and the present findings. They suggest that these two recognition processes may interact, where changes in recollection may affect familiarity and vice versa.

Our findings showed that higher levels of inflammation and depression were related to poorer recollection but better familiarity. This can be interpreted in the following way. High levels of inflammation and depression may have been hindering recollection processes for a long enough time in these participants that recognition memory had shifted toward favoring familiarity-based processes. Therefore, participants with high levels of inflammation and depression may have performed better on familiarity-based recognition and worse on recollection-based recognition because this has become their typical pattern of recognition memory in everyday life.

Predicting Recollection

It was hypothesized that stress, anxiety, depression, visceral obesity, HRV, and inflammation would predict recollection memory without controlling for familiarity. This hypothesis was partially supported; together, these variables accounted for 19% of the variance in recollection memory. However, the strength and direction of some of the predictors did not meet expectations; only state and trait anxiety were significant, and higher trait anxiety was related to better recollection. Upon closer investigation of semi-partial and zero-order correlations, it was clear that suppression occurred. Similar relationships and patterns of suppression were also observed when predicting recollection while controlling for familiarity. These findings are discussed together and in more detail below.

Predicting Recollection Above and Beyond Familiarity

It was hypothesized that stress, anxiety, depression, visceral obesity, HRV, and inflammation would predict recollection-based recognition performance when controlling for familiarity. This hypothesis was partially supported. Together, these predictors accounted for an additional 19% of the variance in recollection beyond what was already accounted for by familiarity. In this model, three predictors were significant: STAI trait anxiety, CESD-R depression scores, and IL-6 levels. Higher trait anxiety related to better recollection, and higher CESD-R scores and IL-6 levels related to poorer recollection.

All three significant predictors showed evidence of suppression; when controlling for each other, trait anxiety, CESD-R scores, and IL-6 levels all become better predictors. This is important for the following reasons. First, although we had expected that the variance accounted for by each predictor would largely overlap, it is clear that each variable is accounting for unique variance in recollection performance, and that these relationships are dependent on the suppressive effects of each other. This highlights the importance of including these variables together in the same model when predicting recollection. This point is most clearly demonstrated when examining the relationships between recollection and CESD-R scores. The zero-order correlation between CESD-R scores and recollection was very low, and without trait anxiety entered into the model, depression would not have been interpreted as an important predictor of recollection.

Second, the suppression effects of IL-6 and CESD-R on trait anxiety can help explain why trait anxiety was such a strong positive predictor of recollection. Correlations between IL-6, CESD-R scores, and trait anxiety scores showed that they are all positively related to each other, as one increases the others do as well (Table 5), and regression analyses show that both higher IL-6 levels and depression scores were related to poorer recollection. Yet, higher trait anxiety predicted better recollection. These relationships suggested that trait anxiety may have been beneficial for recollection, especially when the negative health outcomes associated with trait anxiety were controlled. Therefore, when we controlled for inflammation and depression, higher trait anxiety became a stronger predictor of better recollection.

Recollection vs. Familiarity

The present findings provide further support for the dual-process model of recognition memory by suggesting that recollection and familiarity are qualitatively different recognition processes. Trait anxiety, depression scores, and inflammation were able to predict variance in recollection that was not accounted for by familiarity, and inflammation and depression scores were able to predict variance in familiarity that was not accounted for by recollection. Further, trait anxiety showed a fairly strong

positive relationship with recollection while displaying a nonsignificant negative relationship with familiarity, and both inflammation and depression scores showed significant differential relationships with recollection and familiarity. Together, these observations suggest that the mechanisms underlying each memory process are differentially affected by these health variables, implying differences in their underlying physiological mechanisms.

Health Variables

Although it was hypothesized that all health predictors would relate to memory performance, only state and trait anxiety, inflammation, and depression were significant predictors in any of the regression analyses. Explanations and interpretations of these findings are provided below.

Waist-to-hip Ratio. Although visceral obesity has been shown to be negatively related to health (Tchernof & Després, 2013), WHR did not show this relationship in the present study. One interpretation for this null finding is that visceral obesity was not well represented in our sample. For females, WHR ranged from 0.70 to 0.91, and for males, WHR ranged from 0.76 to 0.95. The World Health Organization suggested a cutoff for WHR-related health risk at 0.85 for females and 0.90 for males (World Health Organization, 2011). Based on these values, only 11 female and 8 male participants in our study had levels of visceral obesity to put them at a health risk. Therefore, WHR in the present study, may not have been negatively impacting health for the majority of our participants. This was also reflected in the correlation matrix presented in table 5. Waist-to-hip ratio was not significantly correlated with any other health measure.

Heart Rate Variability. Waist-to-hip ratio has been linked to cognitive processes in many studies. However, a recent large meta-analysis consisting of 123 studies demonstrated that HRV and cognitive control/regulation shared a small relationship, with *r's* somewhere between .10 and .15 for the age range of our participants (Holzman & Bridgett, 2017). The relationship that we observed in the present study between HRV and recollection was within this range as well. Therefore, if similar

neurological mechanisms underlie the relationships between HRV and memory performance, then the present study was simply underpowered; a much larger sample size would be needed to detect this small effect. Future HRV researchers should keep this in mind when investigating relationships between HRV and memory. Further, as with the relationships with WHR, HRV did not show strong relationships with any other health measure, suggesting that it may not be reflective of poor health in the present sample.

Inflammation. The present study demonstrated that inflammation predicted recollection when familiarity was controlled; higher levels of IL-6 related to poorer recollection. Yet, inflammation also predicted familiarity when recollection was controlled; higher levels of IL-6 related to greater familiarity. This suggested that inflammation is differentially impacting these two recognition processes. Some evidence has suggested that the hippocampus is particularly vulnerable to inflammation, compared to some other brain areas (Freeman et al., 2011; Marsland et al., 2008), and others have demonstrated that inflammation can inhibit hippocampal neurogenesis (Ekdahl et al., 2003; Monje et al., 2003), providing a causal link between inflammation and hippocampal dysfunction. This fit with the dual-process theory of recollection, which suggested that recollection is dependent on the hippocampus (Eichenbaum et al., 2012). If this was truly the case, then the negative relationship between IL-6 and recollection-based recognition observed in the present study may have been the result of hippocampal dysfunction through inflammation. This interpretation could also be applied to the positive relationship between inflammation and familiarity; decreased recollective ability may have shifted recognition to favor familiarity processes. However, future neuroimaging research is needed to confirm the neurological underpinnings of the effects of inflammation on recollection.

Depression. There has been a long history of research confirming a link between depression and memory dysfunction (Burt et al., 1995). In the present study, we showed that higher depression scores related to poorer recollection, when familiarity was controlled. This suggested that depression

may particularly impact recollection processes. Evidence of hippocampal dysfunction has often been reported in individuals with depression (Videbech & Ravnkilde, 2004). Therefore, the present findings on depression were also in line with the dual-process theory of recognition (Eichenbaum et al., 2012). Furthermore, like inflammation, depression also showed a positive relationship with familiarity, which also suggested that depression symptoms had shifted recognition memory to favor familiarity-based processes.

Some proposed mechanisms liking depression to hippocampal and memory dysfunction involve chronic stress (Sapolsky, 2003) and inflammation (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). However, depression still showed a significant relationship with recollection even when stress, anxiety, and inflammation were controlled. Therefore, depression must be accompanied by a unique psychophysiological state that hinders recollection. One limitation to the present study was that cortisol levels were not measured. Cortisol has had both relatively rapid (minutes) and long-term effects (days to years) on cellular function, including cells of the hippocampus (McEwen et al., 2015), and depression has been associated with both abnormal cortisol levels and cortisol reactivity (Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011). It may be that cortisol was the missing piece to this puzzle. Future research should consider measuring cortisol levels together with these variables to get a better understanding of the nature of the relationship between depression and recollection.

Stress. The present findings on stress are enlightening. Over the years, research has demonstrated that the relationship between stress and memory is highly complex, and that stress can be either beneficial or detrimental, depending on the timing and duration of stress and the amount of stress hormones and their epigenetic and nongenomic actions on cells in the hippocampus, as well as other brain areas (McEwen et al., 2015). So far, only a few studies have investigated the effects of stress on recollection and familiarity processes. In an acute stress model, (McCullough & Yonelinas, 2013) found that acute stress experimentally administered after encoding differentially impacted recollection

and familiarity. Further, (McCullough, Ritchey, Ranganath, & Yonelinas, 2015) showed that heightened cortisol levels prior to encoding related to poorer performance for both recollection and familiarity. These two findings are comparable to those of the present study. We too dissociated recollection and familiarity but with anxiety, and we also showed that greater state anxiety was related to poorer recollection.

We also used the PSS to measure stress. However, the correlation matrix (Table 5) suggests that PSS was highly related to both state and trait anxiety. Because both trait and state anxiety were such stronger predictors, their influence in the model was greater than that of the PSS. Therefore, PSS scores did not show a strong relationship with recollection in the end because of its shared variance with the STAI.

Anxiety. State and trait anxiety were found to be predictive of recollection, but not familiarity, and we also observed that each measure differentially impacted recollection; higher state anxiety was related to poorer recollection, whereas higher trait anxiety was related to greater recollection. Higher state anxiety and poorer recollection was consistent with previous findings (McCullough et al., 2015), as mentioned above. However, the relationship between trait anxiety and recollection was a new finding. We were unaware of any other research that has attempted to differentiate recollection from familiarity based on trait anxiety. However, many researchers have investigated relationships between recognition memory and trait anxiety. Two meta-analyses have shown findings to be incredibly mixed (Herrera et al., 2017; Mitte, 2008); research has shown both positive and negative relationships between anxiety and recognition memory. Therefore, the present findings may be used to explain these previous mixed results. First, we broke down recognition memory into its two component processes (recollection and familiarity) and showed differential effects; high trait anxiety was related to greater recollection, but showed a trend toward worse familiarity. Therefore, the amount to which recognition tests required recollection versus familiarity may have influenced the outcome. This interpretation was also proposed

by both Mitte (2008) and Herrera et al. (2017) in their meta-analyses. Second, we also measured comorbid conditions (i.e., inflammation and depression), which have often been linked to anxiety (Michopoulos et al., 2017; Mineka et al., 1998). These conditions differentially affected recollection and familiarity processes. Therefore, it is also important to consider the effects other conditions related to anxiety may have on recognition performance as well.

Furthermore, higher trait anxiety was a predictor of better recollection even when controlling for state anxiety. This suggests that an underlying individual difference- a tendency toward anxiety, rather than situational anxiety, benefitted recollection. Research has suggested that high anxiety may be associated with hypervigilance (Richards, Benson, Donnelly, & Hadwin, 2014) and a narrowing of the focus of attention (Harmon-Jones, Gable, & Price, 2013). Others have proposed that high arousal causes perceptual competition that favors memory consolidation for goal-related perceptual stimuli (Mather & Sutherland, 2011), and that norepinephrine, released during heightened states of arousal, may benefit hippocampal-dependent memory (Mather et al., 2016). Furthermore, others have shown that attention has a greater impact on recollection than familiarity (Yonelinas, 2002), and that highly arousing stimuli were more likely to be remembered with recollective- than familiarity-based processes (Ochsner, 2000). Taken together, this evidence seems to suggest that our participants who showed higher levels of trait anxiety may have been operating at a heightened state of arousal during our memory task, which could have narrowed their focus of attention and increased recollection-based recognition through enhanced hippocampal memory function via norepinephrine. Because the memory task was not specifically designed to be stress-inducing, the experience of heightened arousal during the memory task may not have been interpreted or reported as state anxiety by our participants, which could explain why state anxiety was not also a positive predictor.

Although it is now often recognized that state anxiety and memory function show a quadratic, inverted-U relationship, where small to moderate amounts of stress are beneficial and high levels of

stress are detrimental (McEwen et al., 2015), this relationship was not observed in the present study. One explanation for this could be that our sample was comprised by relatively healthy participants, and we had excluded participants with psychological disorders. It may be that clinical levels of trait anxiety will not show a beneficial relationship with recollection.

Furthermore, the relationship between state anxiety and recollection became stronger when also controlling for inflammation and depression. This suggested that although higher trait anxiety predicted better recollection, other health factors related to trait anxiety (e.g. inflammation and depression) negatively impacted recollection. When inflammation and depression were controlled, higher trait anxiety became more strongly predictive of better recollection. Evidence has suggested that depression and inflammation are related to cognitive decline and dementia in older age (Leonard & Myint, 2006). Therefore, although our results suggested that trait anxiety benefited recollection, other negative health consequences associated with trait anxiety may be detrimental to recollection in the long run. Future research investigating these relationships in middle-age and elderly populations are needed to assess short- and long-term consequences of trait anxiety on recollection and familiarity processes. Longitudinal investigations would be ideal, because would be better able to capture changes over time associated with these mechanisms.

Neurological Underpinnings

Although the hypotheses in this study were based on the theoretical effects of the included health variables on medial temporal lobe structures, more research is needed to clarify the relationships between these health variables and brain function. Current neuroimaging evidence suggests that the hippocampus is just one part of a network of recognition memory, which has been shown to involve coordinated activity in other brain regions as well, including prefrontal (Scalici, Caltagirone, & Carlesimo, 2017) and parietal cortex (Sestieri, Shulman, & Corbetta, 2017). Furthermore, although we provided theoretical reasons that implicate the hippocampus as a primary area of interest, all of the health

variables included in the present study also relate to cardiovascular disease (Eckel, Grudy, & Zimmet, 2005; G. E. Miller & Blackwell, 2006; Julian F. Thayer et al., 2010) and could potentially relate to widespread brain changes due to damage to cerebrovasculature. Therefore, the observed effects may be the result of altered processing in the hippocampus, other specific brain regions, or network interactions between brain regions supportive of recollection.

CONCLUSION

The present study provides evidence that health variables relate to recollection memory beyond their relationships with familiarity. Specifically, higher trait anxiety was related to better recollection, whereas higher depression scores and inflammation levels were related to poorer recollection. These findings suggested that higher trait anxiety benefited recollection, but also may lead to negative health outcomes that are detrimental to recollection (e.g. inflammation and depression). The negative effects of inflammation and depression on recognition may suggest that the hippocampus is particularly impacted by these health variables, although future neuroimaging research is needed to confirm this interpretation. We also showed that inflammation and depression each showed positive relationships with familiarity-based recognition when recollection was controlled. This suggested that these negative health variables may have shifted recognition memory to favor familiarity-based processes over recollection.

Furthermore, although depression and inflammation have been associated with cognitive decline and dementia later in life, the present study showed negative effects of inflammation and depression on recollection in relatively healthy, young adults between 17 and 25 years old. Therefore, negative effects of inflammation and depression on memory are already apparent early in life, implying a need for early-life interventions to help reduce incidence of cognitive decline in old age. Further, interesting relationships were observed between trait anxiety, inflammation, and depression, where these variables were serving as suppressors for each other. This suggests that relationships between

any one predictor and memory function may not provide sufficient information about the nature of relationships between health predictors and memory. Therefore, it is important to consider multiple related variables when investigating their effects on memory function.

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Table 1. Components of Episodic Memory: Recognition Processes

Recollection	Familiarity

• Involves recollection of details of an event
• Ability declines more with age than familiarity
• Thought to be largely dependent on the hippocampus
• Can be tested through recognition of unrelated word pairs
  • E.g. lamp-computer, violin-crab, cloth-soup
	• Involves a feeling of familiarity without memory of specific details
	• Ability declines less with age than recollection
	• Thought to be dependent on multiple brain areas including other medial temporal lobe and cortical structures
	• Can be tested through recognition of unitized word pairs
	  • E.g. paper-towel, back-bone, market-place

Table 2. Associative Memory and Unitization

Associative Memory for Unrelated Items	**Associative Memory for Unitized Items**
Associative memory can be examined by testing recognition of word pairs. Evidence of recognition of a word pair is apparent with discrimination between correct pairs and lures (i.e. rearranged word pairs). For example, consider these word pairs: "cake-trumpet" and "trout-sky." Recognition of the association would mean that participants could discriminate intact pairs during test (e.g. "cake-trumpet") from rearranged pairs during test (e.g. "cake-sky). Therefore, associative recognition requires participants to not only remember the words in the pair, but also must remember the correct pairing (i.e. the association).	Unitization involves situations where two independent items are remembered as one item. Take for example, the word pair "paint-brush." Because paintbrush is already a known item, it can be remembered as a single unitary item (i.e. "paintbrush"), rather than as two items paired together (i.e. "paint" and "brush"). Here, the association between the two items is already known and therefore does not need to be remembered in the same way as if the words were unrelated (such as with "cake-trumpet")

Table 3. Recognition Response Proportions for Unitized and Unrelated Word Pairs

	Unitized Word Pairs			Unrelated Word Pairs		
	Intact Response	*Rearranged Response*	*New Response*	*Intact Response*	*Rearranged Response*	*New Response*
Intact Pair	**.87**	.08	.05	**.65**	.25	.09
Rearranged Pair	.31	**.42**	.25	.26	**.52**	.20
New Pair	.15	.27	**.56**	.05	.28	**.66**

Note. Correct responses were made most often for each pair type

Table 4. Descriptive Statistics for All Measures by Gender as Mean (SD)

	All	Female (n = 63)	Male (n = 33)
*WHR**	0.82 (0.06)	0.80 (0.05)	0.86 (0.06)
HRV	49.03 (23.68)	47.77 (21.65)	51.45 (27.33)
*PSS**	17.01 (6.02)	17.94 (5.90)	15.24 (5.93)
STAI Trait	39.44 (9.75)	40.65 (10.43)	37.12 (7.96)
STAI State	34.39 (7.64)	35.46 (8.23)	32.33 (5.94)
CESD-R	10.21 (8.74)	10.92 (9.17)	8.85 (7.82)
IL-6	1.11 (0.82)	1.16 (0.87)	1.01 (0.72)

Note: WHR = waist-to-hip ratio, HRV = Heart Rate Variability, PSS = Perceived Stress Scale, STAI Trait = State-Trait Anxiety Inventory: Trait Measure, STAIT State = State-Trait Anxiety Inventory: State Measure, CESD-R = Center for Epidemiological Studies Depression Scale Revised, IL-6 = Interleukin 6. HRV, STAI scores, CESD-R scores, and IL-6 levels were transformed for the analyses. Raw scores are presented here.

* Variables showing a gender difference, where $p < .05$

Table 5. Correlation Matrix for Predictor Variables

	Familiarity	WHR	HRV	PSS	STAI Trait	STAI State	CESDr	IL-6
Recollection	.51	.04	.07	.17	.28	-.01	.07	.01
Familiarity		.23*	-.03	.06	.09	-.10	.20*	.24*
WHR			.08	.01	-.03	-.03	.12	.20*
HRV				-.10	-.10	-.09	.01	.04
PSS					.75*	.52*	.54*	.27*
STAI Trait						.61*	.61*	.30*
STAI State							.36*	.08
CESD-R								.25*

Note: WHR = waist-to-hip ratio, HRV = Heart Rate Variability, PSS = Perceived Stress Scale, STAI Trait = State-Trait Anxiety Inventory: Trait Measure, STAIT State = State-Trait Anxiety Inventory: State Measure, CESD-R = Center for Epidemiological Studies Depression Scale Revised, IL-6 = Interleukin 6. * $p < .05$

Table 6. Unstandardized Regression Coefficients with Standard Error, Semi-Partial Correlation Coefficients, and Relative Weights from the Regression Analyses

Criterion	Predictors	B	SE	*sr*	Relative Weight
Recollection	*Gender*	-0.28	0.16	-.17	10.79
R2 = .19	*WHR*	1.53	1.33	.11	3.96
	HRV	0.16	0.14	.11	4.78
	IL-6	-0.29	0.21	-.13	3.17
	CESDr	-0.09	0.07	-.14	5.83
	PSS	-0.002	0.02	-.01	11.83
	STAI State	-0.97*	0.39	-.24	12.98
	STAI Trait	1.71*	0.49	.34	46.67
Familiarity	*Gender*	-0.13	0.21	-.06	2.59
R2 = .14	*WHR*	2.86	1.67	.17	29.47
	HRV	-0.05	0.18	-.03	0.24
	IL-6	0.37	0.27	.14	24.15
	CESDr	0.12	0.08	.15	20.43
	PSS	-0.01	0.02	-.03	2.66
	STAI State	-0.81	0.49	-.16	14.9
	STAI Trait	0.25	0.61	.04	5.56
Recollection	*Familiarity*	0.44	0.07	.50	57.39
ΔP2 = .19	*Gender*	-0.22	0.14	-.13	3.86
	WHR	0.27	1.13	.02	1.21
	HRV	0.19	0.12	.13	2.32
	IL-6	-0.45*	0.18	-.20	3.64
	CESDr	-0.14*	0.06	-.21	3.95
	PSS	0.001	0.01	.01	5.03
	STAI State	-0.61	0.33	-.15	3.82
	STAI Trait	1.60*	0.41	.32	18.77
Familiarity	*Recollection*	0.70	0.113	.52	63.36
ΔP2 = .15	*Gender*	0.062	0.175	.03	0.10
	WHR	1.784	1.407	.11	8.06
	HRV	-0.166	0.152	-.09	1.17
	IL-6	0.576*	0.229	.21	11.14
	CESDr	0.184*	0.069	.22	9.30
	PSS	-0.005	0.018	-.03	1.17
	STAI State	-0.132	0.428	-.03	2.44
	STAI Trait	-0.95	0.548	-.14	2.99

Note: WHR = waist-to-hip ratio, HRV = Heart Rate Variability, PSS = Perceived Stress Scale, STAI Trait = State-Trait Anxiety Inventory: Trait Measure, STAIT State = State-Trait Anxiety Inventory: State Measure, CESDr = Center for Epidemiological Studies Depression Scale Revised, IL-6 = Interleukin 6.* $p < .05$

Table 7. Semi-Partial Correlation Coefficients from Hierarchical Regressions Predicting Recollection: Evidence of Suppression

	Step 1:	Step 2:	Step 3:
Predicting Recollection	Familiarity + Gender	Familiarity + Gender + (All Others)	Familiarity + Gender + (All Others) + IL-6
WHR	-.01	-.02	.02
HRV	.09	.13	.13
PSS	.11	.01	-.01
STAI State	.02	-.12	-.15
STAI Trait	.21	.29	.32
CESD-R	-.05	-.22	-.21
IL-6	-.13	-.20	

	Step 1:	Step 2:	Step 3:
Predicting Familiarity	Recollection + Gender	Recollection + Gender + (All Others)	Recollection + Gender + (All Others) + IL-6
WHR	.19	.16	.11
HRV	-.05	-.09	-.09
PSS	-.01	-.01	-.03
STAI State	-.08	-.06	-.03
STAI Trait	-.04	-.11	-.14
CESD-R	.18	.23	.22
IL-6	.24	.21	

Note: "All Others" refers to all other predictors excluding IL-6 (i.e. WHR, HRV, PSS, STAI state, STAI trait, and CESD-R)

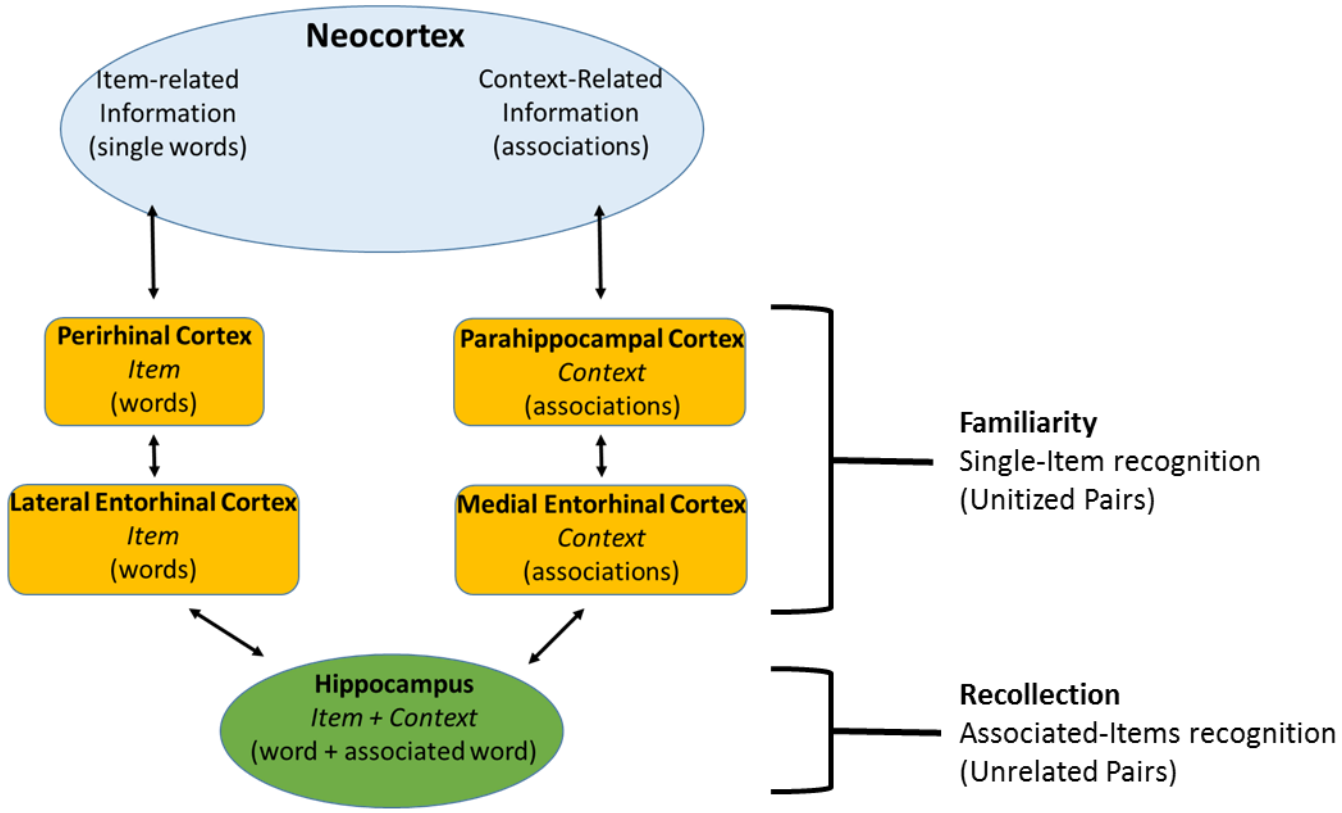
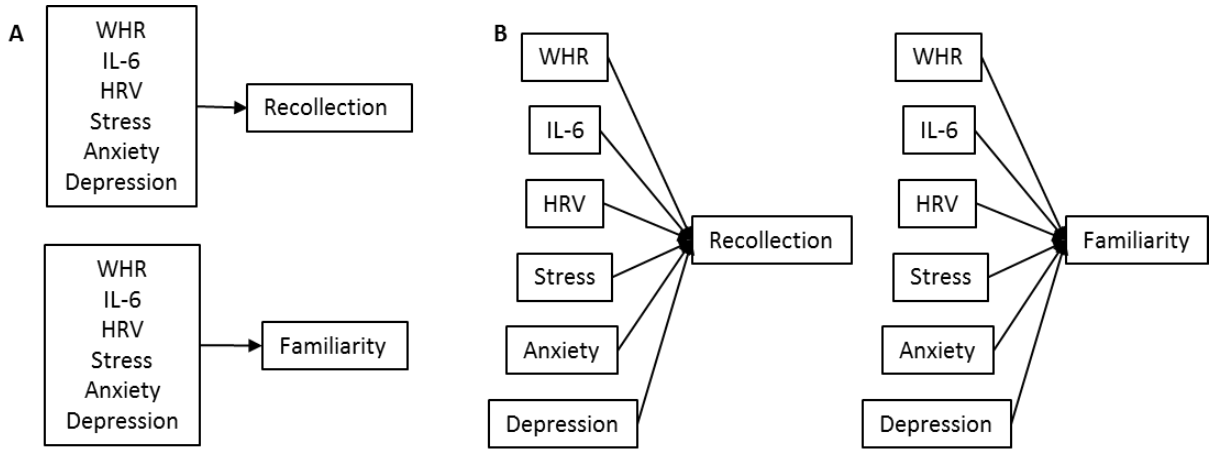
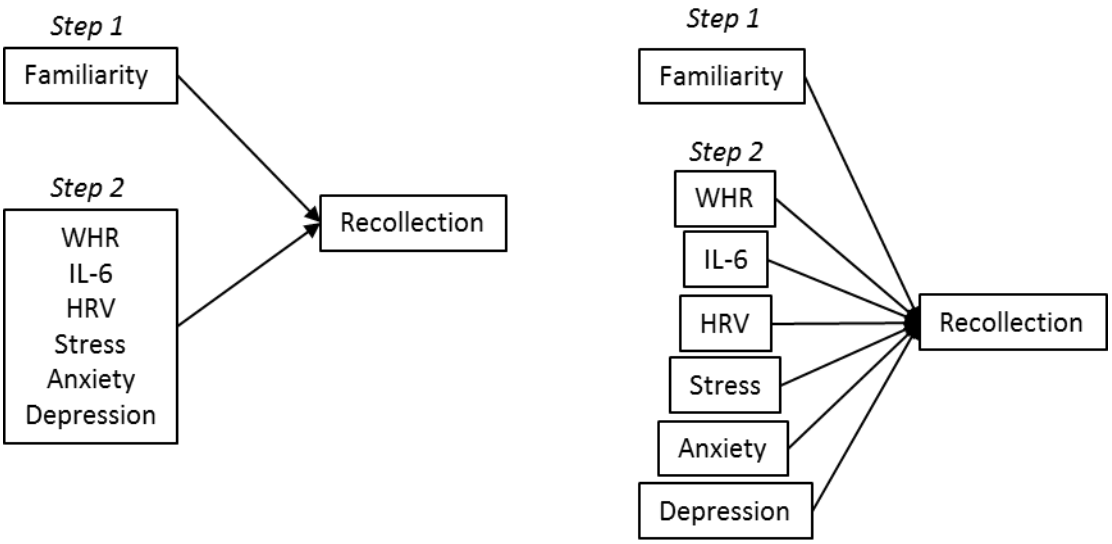


Figure 1. Associative Memory in the medial temporal lobe, modeled after theories proposed in Eichenbaum et al. (2007). Recognition through familiarity processes can be accomplished at the pre-hippocampal level (orange). Recognition through recollection requires the hippocampus (green).



Note: WHR = waist-to-hip ratio, HRV = Heart Rate Variability, IL-6 = Interleukin 6.

Figure 2. A) Model of Hypothesis 1a. B) Model of Hypothesis 1b.



Note: WHR = waist-to-hip ratio, HRV = Heart Rate Variability, IL-6 = Interleukin 6.

Figure 3. Model of Hypothesis 2, which predicts that the health variables will predict recollection when controlling for familiarity.

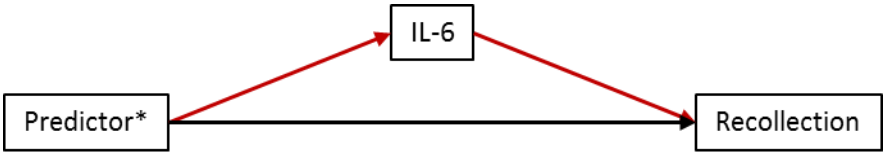


Figure 4. Model of Hypothesis 3 which predicted that IL-6 would have a mediating relationship between heart rate variability, waist-to-hip ratio, stress, anxiety, and depression symptoms.
* waist-to-hip ratio, heart rate variability, stress, anxiety, or depression

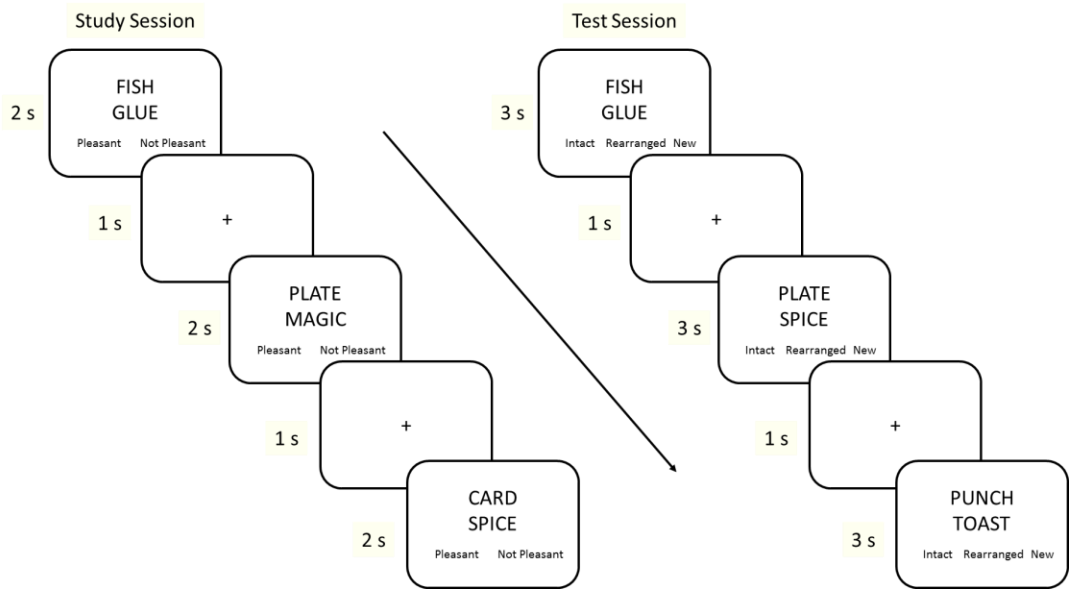


Figure 5. A diagram of the associative memory paradigm.

Appendix A

The Center for Epidemiological Studies Depression Scale – Revised (Eaton et al., 2004)

Below is a list of the ways you might have felt or behaved. Please check the boxes to tell me how often you have felt this way in the past week or so.	Last Week				Nearly every day for 2 weeks
	Not at all *or* Less than 1 day	1 - 2 days	3 - 4 days	5 - 7 days	
My appetite was poor.	0	1	2	3	4
I could not shake off the blues.	0	1	2	3	4
I had trouble keeping my mind on what I was doing.	0	1	2	3	4
I felt depressed.	0	1	2	3	4
My sleep was restless.	0	1	2	3	4
I felt sad.	0	1	2	3	4
I could not get going.	0	1	2	3	4
Nothing made me happy.	0	1	2	3	4
I felt like a bad person.	0	1	2	3	4
I lost interest in my usual activities.	0	1	2	3	4
I slept much more than usual.	0	1	2	3	4
I felt like I was moving too slowly.	0	1	2	3	4
I felt fidgety.	0	1	2	3	4
I wished I were dead.	0	1	2	3	4
I wanted to hurt myself.	0	1	2	3	4
I was tired all the time.	0	1	2	3	4
I did not like myself.	0	1	2	3	4
I lost a lot of weight without trying to.	0	1	2	3	4
I had a lot of trouble getting to sleep.	0	1	2	3	4
I could not focus on the important things.	0	1	2	3	4

Appendix B

The Perceived Stress Scale (Cohen et al., 1983)

Perceived Stress Scale (PSS)

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

	Never	Almost never	Some-times	Fairly often	Very often
1. In the last month, how often have you been upset because of something that happened unexpectedly?	☐	☐	☐	☐	☐
2. In the last month, how often have you felt that you were unable to control the important things in your life?	☐	☐	☐	☐	☐
3. In the last month, how often have you felt nervous and "stressed"?	☐	☐	☐	☐	☐
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	☐	☐	☐	☐	☐
5. In the last month, how often have you felt that things were going you way?	☐	☐	☐	☐	☐
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	☐	☐	☐	☐	☐
7. In the last month, how often have you been able to control irritations in your life?	☐	☐	☐	☐	☐
8. In the last month, how often have you felt that you were on top of things?	☐	☐	☐	☐	☐
9. In the last month how often have you been angered because of things that were outside of your control?	☐	☐	☐	☐	☐
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	☐	☐	☐	☐	☐