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Mood and Cardiovascular Reactivity in Response to Interpersonal Conflict: The Effects of Acute Tryptophan Depletion on High and Low Hostile Individuals

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Abstract

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Erwin Neumark

The present study investigated the influence that trait hostility and serotonin may have on individuals' mood and cardiovascular responses to stress. Sixty high and low hostile males and females participated in an either an acute tryptophan depletion, a procedure that lowers brain serotonin levels, or a sham tryptophan depletion, that leaves serotonin levels unchanged, and the four resulting groups (Low Hostile–Non-Depleted, High Hostile–Non-Depleted, Low Hostile–Depleted, High Hostile–Depleted) were subsequently exposed to an interpersonal conflict. High and low hostile participants in the tryptophan depleted group reported increases in hostility-related affect following the 5.5 hour waiting phase, a period of time necessary for the full effects of the tryptophan manipulation to take effect. This finding partially supports previous research reports. There were no mood differences as a function of hostility status during this waiting period. Overall participants, regardless of grouping, exhibited a cardiovascular change pattern that is generally associated with a more relaxed state, a result that is incongruent with the increased negative affect in the tryptophan depleted groups. High hostile individuals showed a slightly less relaxed pattern during this period without any tryptophan-related differences. All participants exhibited heightened cardiovascular responses to the interpersonal conflict, as well as reduced positive affect and increased negative affect,

including hostility/anger-related mood changes. Contrary to expectations, there were no differential effects of trait hostility status nor tryptophan condition. Possible reasons for these findings are explored.

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Mood and Cardiovascular Reactivity in Response to Interpersonal Conflict: The Effects of Acute Tryptophan Depletion on High and Low Hostile Individuals

Cardiovascular disease (CVD) includes hypertension, stroke, and chronic diseases of the heart muscles or membranes, as well as coronary heart diseases (CHD), such as angina pectoris and myocardial infarction, which are characterized by an inadequate supply of oxygen to the heart (Houston, 1988). CVD is the leading cause of death in developed countries (Allen, 2000; Dembroski & Costa, 1987; Ferrari & Bianchi, 2000) and continues to be the primary cause of death in North America for both men and women (Frolkis, 1999), regardless of ethnicity and race. In the United States, approximately 40% of all deaths are caused by CVD (American Heart Association, 2001), in Canada the rate is just under 36% (Statistics Canada, 1999).

CVD is a multifactorial disease (Frolkis, 1999; Statistics Canada, 1999; Wimbush & Peters, 2000) with traditional medical risk factors, such as high blood pressure, elevated serum cholesterol, diabetes, habitual cigarette smoking, physical inactivity, and obesity, accounting for only approximately 50% of CHD cases (Brand, Rosenman, Sholtz, & Friedman, 1976; Jenkins, 1971, 1978; Thom, Epstein, Feldman, & Leaverton, 1985). The etiology of the remaining cases continues to be a focus of investigation, with the potential influence of psychological factors hypothesized to be a mediating factor (Dembroski, Macdougall, Costa, & Grandits, 1989; Kaplan, Manuck, Williams, & Strawn, 1993). Psychosocial factors have an impact comparable to other risk factors and can increase risk two to four fold (Frolkis, 1999). Psychological stress has been posited as a mediating factor in CVD, both in its role as a factor in the etiologically non-identified cases as well

as in relation to high blood pressure or hypertension. Individuals vary in their reaction to psychological stressors and research suggests that psychological stress may only confer additional risk on individuals who are susceptible either physically or mentally to the development of the disease (Brody et al., 1987).

Psychological Mediators of CHD: The Role of Type A Behavior Pattern

Early research identified a constellation of behaviors that were linked to the onset of CHD. Friedman and Rosenman (1974) labeled their particular behavioral style construct "Type A Behavior Pattern" (TABP), which included success oriented behavior (such as hard-driving job involvement, intense ambition and competitiveness, impatience, and schedule inflexibility), hostility, and aggression (Friedman & Rosenman). Prior research, and findings of the next decade were almost unanimously positive in upholding the epidemiological validity of TABP. Individuals with TABP had markedly increased prevalence of clinical CHD over those individuals ("Type B") that did not demonstrate these behaviors (Friedman & Rosenman, 1959). Type A behavior was assessed using the Structured Interview (SI), which challenged participants in a confrontational manner that "relied more on the presence of empathetic and vigorous voice stylistics than it does as on the content of responses as the major criteria" (Williams & Barefoot, 1988). A major prospective study utilizing this paradigm was conducted by Rosenman and his colleagues (Rosenman et al., 1964), the Western Collaborative Group Study (WCGS), that followed more than 3,000 men between the ages of 30 and 59 for a period of 8-1/2 years. Type A participants, on follow-up, had CHD or its symptoms at twice the prevalence rate of the

Type B's (Rosenman et al., 1964, 1975), even after controlling for traditional risk factors and, therefore, being a Type A individual was viewed as an independent risk factor. Additional studies on related CVDs and their symptoms, supported the hypothesis that TABP was a significant factor in the endpoint development of CVD, as did studies on patients undergoing coronary angiography (e.g. Blumenthal, Williams, Kong, Schanberg & Thompson, 1978; Frank, Heller, Kornfeld, Sporn, & Weiss, 1978; Zyzanski, Jenkins, Ryan, Flessas, & Everist, 1976). In the late 1970s, given the strong evidence, scientific review panels of the National Institute of Health (Siegman, 1989) and in 1981, the National Heart, Lung, and Blood Institute (Dembroski & Williams, 1989; Houston, 1988) concluded that TABP was an independent risk factor for CHD, comparable to traditional risk factors.

In the decade that followed, however, new and re-analyzed data began to contradict the findings of the previous 25 years, both in terms of prospective epidemiological studies and in cross-sectional studies on patients undergoing coronary angiography (Williams & Barefoot, 1988). In a re-analysis of the WCGS data with appropriate statistical controls, many of the predictive findings were no longer supported (Brand, 1978). One study showed that Type A individuals were actually at less risk for CHD mortality if their initial diagnosis was symptomatic myocardial infarction (Ragland, & Brand, 1988). Angiographic studies, as well, failed to support the link (Dembroski & Williams, 1989; Dimsdale, Hackett & Hutter, 1979; Siegman, Feldstein, Tommaso, Ringel, & Lating, 1987). The most damaging evidence came from the Multiple Risk Factor Intervention Trial (MRFIT), a major prospective study, which failed to replicate

the findings of the WCGS though it used the same protocol and included more than 3.000 participants in the subset that specifically addressed this issue (Siegman, 1989).

Psychological Mediators of CHD: The Role of Anger and Hostility

TABP in itself was mostly a constellation of behaviors, rather than a psychological construct, and its multi-dimensionality led researchers to look at underlying factors or components of TABP that might better explain both the positive and negative findings. The role of anger and the construct of hostility began to be investigated as mediators or risk factors in CHD (Dembroski & Williams, 1989; Diamond, 1982) and have continued to be intensively studied over the past three decades. Hostility and anger "form the toxic core of the TABP", according to Williams (1989, p. 196). In a review paper on hostility and health, Smith (1992) noted that this research suffers from ambiguity and a lack of consensus concerning the basic concepts, with the least amount of agreement regarding hostility. Hostility is considered a stable personality trait that may lead to angry affect, in combination with behavioral aggression, in diverse situations (DiGiuseppe, Eckhardt, Tafrate & Robin, 1994). A similar definition, of a tendency to feel anger towards others and the desire to inflict harm on others, is offered by Chaplin (as cited in Smith). Others have defined hostility as a pervasive, complex set of feelings, negative attitudes, beliefs, and appraisals, concerning other individuals, which motivate aggressive behavior (Spielberger, Reheiser & Sydeman, 1995). A hostile attribution bias results in individuals viewing others as threatening and tends to produce reactive aggression (Dodge & Coie, 1987), as well as a belief that others are generally unworthy and not to be trusted (Smith).

One of the most widely used measures of hostility (Barefoot, 1992; Smith, 1992) is the Cook and Medley Hostility (Ho) scale (Cook & Medley, 1954), a 50-item true-false questionnaire derived from the Minnesota Multiphasic Personality Inventory. Although the scale includes items that ostensibly measure both hostility and the admission that the respondent may act aggressively or view aggression as an appropriate instrumental tool, it is purported to tap into the cognitive component of hostility (Barefoot) and is relevant to interpersonal processes (Kamarck, Manuck, & Jennings, 1990).

In 1976 researchers at Duke University began to use the Ho as an evaluative measure, alongside the SI and other psychosocial measures, with patients that were to undergo coronary angiography. Williams and his colleagues (Williams, et al., 1980) found that patients with high Ho scores were 1.5 times more likely to have clinically significant arterial occlusion that those with low Ho scores. Several other prospective studies found that the Ho scale predicted CHD and mortality rates (Barefoot, Dahlstrom & Williams, 1983; Barefoot, Williams, Dahlstrom & Dodge, 1987; Shekelle, Gale, Ostfeld, & Paul, 1983). One 25-year follow-up study of almost 500 physicians who completed the MMPI prior to medical school admission, failed to predict CHD or mortality rates (McCranie, Watkins, Brandsma, & Sisson, 1986). Barefoot and Williams (1988) argue that the fact that the MMPI profile was to be used as part of the admissions process, makes it likely that applicants answered in a socially desirable way, thus under-reporting their hostility levels. Based on the accumulated data, Williams and Barefoot (1988) concluded, in their review of the Ho scale, that, as a valid measure in assessing adverse health outcomes, "the Ho scale must be considered a robust indicator of coronary-prone as well as of "mortality-

prone behavior" (p. 198). Several studies have supported the construct validity of the scale (Barefoot, Dodge, Peterson, Dahlstrom & Williams, 1989; Pope, Smith & Rhodewalt, 1990; Smith, & Frohm, 1985). Subsequent to Barefoot and Williams' (1988) review, at least two other studies failed to support an association between Ho and CHD. Hearn, Murray, and Luepker (1989) failed to find a predictive link for CHD mortality, CHD morbidity, or total mortality in a retrospective study of more than 1,300 university students who had completed the MMPI more than 30 years earlier and a study by Leon, Finn, Murray, and Bailey (1988) arrived at a similar conclusion, based on 30-year data from close to 300 men.

Cardiovascular Reactivity: The Link Between Stress and CVD

Stress – Reactivity Component

Cardiovascular reactivity or 'hyperreactivity', has been posited as a link between stress and CVD, as well as between hostility, and its related components, and CVD. Blascovich and Katkin (1993) reviewed the stress-reactivity-disease model and point out that, although the stress-reactivity component of the model has been well studied, the reactivity-disease component has received less attention.

Animal and human studies have provided much evidence for a stress – reactivity link. In the laboratory, physical stressors elicit increased cardiovascular responses. One such stressor, the cold pressor test, in which a limb is immersed in ice water, results in relatively large increases in both systolic and diastolic blood pressure, as well greatly increased peripheral resistance, with lesser increases in heart rate (DeQuattro & De-Ping

Lee. 1989). Psychological stressors. such as public speaking tasks. mental arithmetic tasks. competitive games. and interpersonal conflict. also result in varying patterns of increased cardiovascular responding. Manuck. Kasprowicz. Monroe. Larkin. and Kaplan (1989) give an excellent review of studies utilizing both physical and psychological stressors.

Stressors exert variable cardioreactivity influences. as a function of personality characteristics. Hostility in particular appears to moderate the cardiovascular responses to stress. In a natural hospital setting. researchers found that high hostile ambulatory paramedics were more reactive in interpersonal conflict situations than their low hostile co-workers. A fairly large number of laboratory studies have looked at the hostility – stress interaction. A deception paradigm study. in which participants were told that unsolvable anagrams were easy to solve. found increased cardiovascular reactivity in high hostile women and men. with few differences between the sexes (Weidner. Friend. Ficarrotto. & Mendell. 1989). In our own laboratory. competitive games. mental arithmetic. and mental arithmetic with harassment - an interpersonal conflict - have clearly shown increased cardiovascular reactivity to psychological stressors. especially amongst individuals who are high on trait hostility (Miller. Dolgoy. Friese.& Sita. 1996. 1998: Miller et al.. 1998). Other researchers have studied the effects of interpersonal challenge or conflict on cardiovascular reactivity of individuals with high trait hostility and have shown increased reactivity in that group (Davis. Matthews. & McGrath. 2000: Smith. & Allred. 1989: Suarez. Kuhn. Schanberg. Williams. & Zimmerman. 1998); not all studies have supported this finding. In a study utilizing an interpersonal conflict. Allred and Smith (1991) found that there was no association between level of Ho scores and cardiovascular

reactivity. A similar finding was reported by Smith and Houston (1987). Suls and Wan (1993) used a meta-analytic approach to review 28 research reports and concluded that the Ho scale was predictive of at least some cardiovascular reactivity components and, furthermore, that interpersonal stressors were more likely to result in cardiovascular reactivity than other forms of psychological stress.

Reactivity – Disease Component

With regard to the reactivity – disease component of the model, there has been considerable research as well. Animal research has shown links from stress to cardiovascular reactivity to disease endpoint. In a series of studies with cynomologous macaques, Kaplan et al. (1993) demonstrated that manipulation of psychosocial stress was associated with degree of atherosclerosis. Kaplan et al. posit that the primate model is relevant to humans and argue that, in fact, humans face even greater numbers and types of psychosocial stressors. In a study looking at a common daily event, Spitzer, Llabre, Ironson, Gellman, and Schneiderman (1992) found that simply meeting strangers in social situations resulted in increased cardiovascular reactivity as compared to social situations with family members. Rodent models of hypertension are reviewed in Saab and Schneiderman (1993) and the authors conclude that the development of hypertension in rats is facilitated by the interplay between stress and cardiovascular reactivity. Humans who respond to stress with increased total peripheral resistance (one of the cardiovascular reactivity mechanisms) are at greater risk for hypertension (Girdler, Turner, Sherwood, & Light, 1990; Light & Sherwood, 1989). While the exact mechanisms leading from

cardiovascular hyperreactivity to CHD are not certain. various pathways are posited. Animal studies provide evidence that recurrent pharmacologically induced or behaviorally induced (utilizing various physical and social stressors) sympathetic activation leads to transient elevations in blood pressure and the development of endothelial damage. similar to that found in early atherosclerosis (Kaplan et al.. 1993).

Stress induced reactivity is also related to morphological changes. such as the narrowing of the arterial lumen (tubular cavity) in both coronary and peripheral arteries. hence increased vascular resistance (Blascovich & Katkin. 1993). This vasoconstriction is thought to occur partially due to arterial muscle hypertrophy and results in chronic blood pressure elevations and increased hemodynamic turbulence during reactive episodes (e.g. stressful encounter). leading to atherosclerotic lesions (Blascovich & Katkin). High cardiovascular reactivity in response to both physical and psychological laboratory stress challenges predict hypertension in later life (Light. Dolan. Davis. & Sherwood. 1992: Light. Sherwood. & Turner. 1992) supporting the line of reactivity to disease endpoint. In addition to blood pressure. increased heart rate has also been shown to cause similar type of damage (Clarkson. Manuck. & Kaplan. 1986). While the exact mechanism of even this small portion of the physiology of CVD is not known. Julius (1987) has emphasized the contribution of the central nervous system. Other pathways including neuroendocrine systems are likely involved as well. with the possibility that short term cardiovascular reactivity to stress may mediate longer term neuroendocrine responses (Larson. Ader. & Moynihan. 2001).

Hostile individuals are likely to exhibit cardiovascular hyperreactivity

(Engebretson. & Matthews. 1992: Williams. Barefoot. & Shekelle. 1985). especially in situations that elicit an anger response to an interpersonal conflict (Hardy & Smith. 1988: Lai & Linden. 1992: Miller. Dolgoy. Friese.& Sita. 1996. 1998: Miller et al.. 1998: Smith & Allred. 1989) and this may be the pathway by which hostility confers additional risk for CVD. Studies that focused on the cardiovascular responses of women found that their greatest cardiovascular response was to anger eliciting stressors (Powch & Houston. 1996: Suarez. Harlan. Peoples. & Williams. 1993). Suarez and Williams (1990) argue that the experience of anger is. in fact. essential in eliciting a hyper cardiovascular response. Studies. such as those by Smith and Houston (1987). that did not elicit anger fail to show such responses.

Serotonin: Psychological and Behavioral Effects

Serotonin (5-hydroxytryptamine; 5-HT) has been associated with the regulation of mood in both normal (Ellenbogen. Young. Dean. Palmour. & Benkelfat. 1996: Knott. Howson. Perugini. Ravindran. & Young. 1999: Ravindran. Griffiths. Merali. Knott. & Anisman. 1999: Smith. Pihl. Young. & Ervin. 1987: Young. Smith. Pihl. & Ervin. 1985) and clinical (Delgado et al.. 1990. 1994: Leyton et al.. 1997. 2000) or at risk populations (Benkelfat. Ellenbogen. Dean. Palmour. & Young. 1994: Ellenbogen. Young. Dean. Palmour. & Benkelfat. 1999: Quintin et al.. 2001). Approximately half of the studies on healthy adults demonstrated a lowering of mood or depression-like affect (Young & Leyton. 2001). while the findings in both the clinical and at risk populations reported mixed findings. with a greater number of at risk studies demonstrating a mood lowering

effect and most clinical studies reporting lowered mood (Bell, Abrams, & Nutt, 2001; Young & Leyton, 2001). Van der Does (2001) examined several of the mood studies and suggested that the negative findings may be an artifact of incomplete manipulatory reduction of 5-HT levels.

Impulsivity and disinhibition, also, have been linked to 5-HT function in similar populations as described above, both in laboratory settings (LeMarquand et al., 1998) and in natural settings (Dolan, Anderson, & Deakin, 2001). Aggression is the most frequently studied behavior in relation to 5-HT dysfunction (Young & Leyton, 2001). As with mood and impulsivity, the association between 5-HT and aggression has been studied in diverse populations both in the laboratory (e.g. Bjork, Dougherty, Moeller, & Swann, 2000; Cleare & Bond, 1995, 1997, 2000; Dougherty, Bjork, Huckabee, Moeller, & Swann, 1999) and natural settings (Brown et al., 1982, Dolan, Anderson, & Deakin; Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). Animal studies have shown that vervet monkeys with experimentally manipulated (lowered) levels of 5-HT exhibit increased levels of aggression (Chamberlain, Ervin, Pihl, & Young, 1987). Rat studies demonstrate 5-HT-deficit-induced increases in muricide (mouse killing behavior), filicidal (pup-killing) behavior, as well as other aggressive behaviors; similar effects are found with felines, effects which can be reversed through restoration of 5-HT function (Eichelman, 1979).

An inverse relationship between aggression and 5-HT levels in humans is the most frequently reported finding. The findings related to laboratory induced aggression have been mixed and it is important to understand the 5-HT manipulation paradigms and elicitor tasks used. Correlational studies have most often assessed the level of 5-HT

through the analysis of the major 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid, obtained through a lumbar puncture. Golden et al. (1991) reviewed the literature relating to suicide, aggression, and 5-HT and reported that almost all studies of individuals who have attempted suicide and postmortem studies on successful suicides have revealed low 5-HIAA levels. Repeat violent offenders have lower levels of 5-HIAA than those who have committed a single violent crime (Golden et al.) and a study by Virkkunen et al. (1987) revealed that arsonists had lower levels that normal controls.

Studying Brain Serotonin Levels

There is no easy way to directly study brain 5-HT levels and the relation between central 5-HT and 5-HIAA is not always clear (Golden et al., 1991). Nishizawa et al. (1997) point out that there is spinal cord metabolism of 5-HT, catabolism rates of 5-HT vary, and there is transport of 5-HIAA into and out of the CSF. They conclude that "CSF 5-HIAA levels are a poor index of dynamic changes in 5-HT synthesis in brain tissue" (Nishizawa et al., pp. 5310-5311). Carpenter et al. (1998) state that 5-HIAA in lumbar CSF only approximates central 5-HT release and utilization. Questions about 5-HIAA aside, Dougherty, Bjork, Marsh, and Moeller (1999, pp. 227-228) claim that "dysfunctional serotonin (5-HT) neurotransmission has been correlated with aggressive acts towards self and others and this is the most replicated finding in the neurobiology of aggression."

In experimental studies, pharmacological challenges that either increase or decrease the availability of 5-HT have been used. The 5-HT agonist *d*-fenfluramine has

been shown to be associated with decreases in aggression in a non-clinical population (Manuck, et al., 1998). This study utilized a point/money subtraction provocation (The Point Subtraction Aggression Paradigm – Cherek at al. 1996, 1997a, 1997b, 1997c) and measured the number of retaliatory subtractions made by the participant against the purported competitor who had caused money to be subtracted from the participant and compared a control group with a pharmacologically challenged group. Another *d*-fenfluramine study by Cleare and Bond (1997) that did not include any confrontational component, using only self report questionnaires assessing hostility and aggression, demonstrated the inverse relationship between 5-HT and aggression as well.

Acute Tryptophan Depletion and 5-HT Reduction

Tryptophan (Trp), a large amino acid, is one of the ten essential amino acids and is the precursor to 5-HT, being first converted by the enzyme tryptophan hydroxylase into 5-hydroxytryptophan (5-HTP) and into 5-HT by the decarboxylizing action of the enzyme L-aromatic acid decarboxylase. As the enzyme tryptophan hydroxylase is, under normal physiological conditions, only approximately half saturated by its substrate, the rate of 5-HT synthesis is dependent on the availability of free plasma Trp. Most of the Trp in the blood stream is in an albumin-bound form that is unable to cross the blood-brain barrier; hence, it is not available for synthesis into brain 5-HT. Unbound, or free plasma Trp, competes with the five of the other amino acids (isoleucine, leucine, phenylalanine, tyrosine & valine) in crossing the blood brain barrier, sharing a common transport system (Bell, Abrams, & Nutt, 2001;Young, Smith, Pihl, & Ervin, 1985). Once it enters the brain

it is available to be acted upon by tryptophan hydroxylase. Tryptophan, in addition to being the precursor to 5-HT, is a rate limiter of all protein synthesis. The combination of these two properties provides a unique way to manipulate brain 5-HT levels.

Protein synthesis by the liver is a continual activity and requires a steady supply of amino acids including, Trp. Subsequent to an amino acid deprivation (through dietary restrictions, for example) the liver is primed to resume protein synthesis. In laboratory studies, participants are typically put on a 24-hour protein-Trp-restricted regimen. Following the 24-hour diet, the consumption of a balanced amino acid challenge will result in the resumption of normal protein synthesis. If, however, the post-diet challenge of amino acids lacks Trp, several events occur. The liver begins to synthesize protein and, in so doing, quickly scavenges any remaining Trp from the blood pool and tissues, incorporating it into new proteins. This prevents Trp from, potentially, crossing the blood-brain barrier. Additionally, the presence of a large quantity of amino acids competing with Trp for transport across the blood-brain barrier further reduces the chance that any Trp will become available in the brain for conversion into 5-HT (Olendorf, 1973). Approximately 5 hours after the ingestion of a Trp deficient amino acid challenge, free and total plasma Trp levels will have declined by approximately 80-90% (Bell, Abrams, & Nutt, 2001; Carpenter et al., 1998; Delgado et al., 1990; Reilly, McTavish, & Young, 1997; Williams et al., 1999). Following this reduction there is a marked decline in brain 5-HT synthesis (Nishizawa et al., 1997; Young, 2002). Many studies have utilized a Trp augmented challenge, in addition to the depletion and control, with findings that suggest inverse effects of the depletion paradigm (i.e. reduced aggression and impulsivity as well

as mood enhancement).

Effectiveness and Specificity of Acute Tryptophan Depletion

Evidence that acute tryptophan depletion (ATD) reduces 5-HT levels comes from various sources. Nishizawa et al. (1997) measured 5-HT synthesis in the human brain using positron emission tomography imaging that demonstrated a marked lowering of 5-HT synthesis in all brain regions following an ATD. Carpenter et al. (1998) utilized a continuous sampling of CSF and found that Trp depletion does robustly lower central Trp levels, but "only modestly lowers central 5-HIAA levels and may reduce general 5-HT function" (pp. 33). Williams, Shoaf, Hommer, Rawlings, and Linnoila (1999), sampled CSF and plasma levels of free and bound Trp as well as 5-HIAA during a Trp depletion protocol. Plasma levels of Trp began to decrease 2 hours post depletion and reached a nadir 4 hours later. CSF Trp began to decrease at 2.5 hours after depletion followed by 5-HIAA 1.5 hours later. CSF Trp reached its lowest point 8 hours post depletion and 5-HIAA at approximately 14 hours after the depletion. Animal studies have shown that an ATD can lower central nervous system levels of Trp, 5-HT, and 5-HIAA in the CSF (Williams et al.). That an ATD lowers CSF Trp and 5-HIAA levels in vervet monkeys as well as being specific in its actions, in that it did not lower metabolites of other amino acids, was demonstrated by Young, Ervin, Pihl, and Finn (1989). More recently, Klaassen, Riedel, Deutz, Van Someren, and Van Praag (1999) showed that a lysine depletion did not result in the same mood and memory differences found in ATD, supporting the hypothesis that ATD effects brain 5-HT metabolism and not protein metabolism in general. Moore et

al. (2000) point out that while there has been limited investigation of changes in other Trp containing regulatory proteins such as neurotransmitter receptors, ion channels, and enzymes that are involved in neurotransmitter synthesis and breakdown. 5-HT remains the "most parsimonious TRP "metabolite" capable of producing the spectrum of RTD effects" (Moore et al., pp. 618).

Acute Tryptophan Depletion and Aggression Studies

Smith, Pihl, Young, and Ervin (1986) used a modified Buss (1961) paradigm (shock delivery to a nonexistent partner), in conjunction with depletion and augmentation, and found no effect of Trp manipulation on aggressive behavior. LeMarquand, Benkelfat, Phil, Palmour, and Young (1999) reported no effects of depletion on aggression in healthy males without a positive family history of alcoholism who were engaged in a modified Taylor aggression task, similar to the Buss paradigm described above. Participants with a positive family history displayed more aggressive behavior, especially early in the task. They also reported evidence of increased impulsivity and decreased mood in all of the participants. A possible limitation of this study is the small sample size (N=36). Previously, Pihl et al. (1995) used a similar paradigm in combination with the administration of alcohol to look at aggression in normal human males and found that both the depletion and alcohol ingestion increased aggressive responding. Using a point/money subtraction paradigm, such as that described above, in combination with depletion and augmentation, Marsh, Dougherty, Moeller, Swann, and Spiga (2002) studied aggressive behavior in women and found that aggressive behavior increased with depletion and decreased with

augmentation.

Studies have been conducted that explicitly examined the possible interaction between trait hostility or aggressivity and 5-HT levels in producing increased or decreased aggressive responding and related disinhibition or impulsivity. LeMarquand et al. (1998) reported an ATD disinhibition effect in non-aggressive adolescent males, however they found no effect in the aggressive group, possibly due to a ceiling effect. In a study by Cleare and Bond (1995), Trp depletion and augmentation caused a marked rise and fall, respectively, in subjective feelings of aggression, as well overt behaviors, in the high trait aggression group. The findings from the low trait aggression group were less consistent, with little effect on subjective feelings of aggression and variable results on the measures of actual aggressive behavior. In a study with negative results, Saloman, Mazure, Delgado, Mendia, and Charney (1994) failed to find ATD related changes of self-reported hostility in a group of aggressive patients. The authors point out that their sample size was small (N=14) and there was no provocational aspect to the study, with participants merely being observed for spontaneous acts of hostility in a "neutral, clinically sterile environment" (Saloman et al., pp. 571).

Two studies looked at the effects of Trp on aggression in hostile and non-hostile participants and supported the inverse aggression – 5-HT relation. Finn, Young, Pihl, and Ervin (1998) reported that ATD resulted in higher hostile mood on the Multiple Affect Adjective Checklist (Zuckerman & Lubin, 1965) in participants with both low and high trait hostility as assessed by the Ho scale. The increase, however, was greater for those high in trait hostility. High hostiles demonstrated decreases in hostile mood in the balanced

condition. an unexpected finding that the authors attribute to the increase in Trp levels following the Trp loading which resulted from a balanced amino acid challenge. They hypothesize that individuals who are high on antisocial and hostile traits may be susceptible towards Trp induced changes in hostility. These results may not be generalizable to high hostiles in the population at large. as many of study participants had MMPI profiles indicative of a personality disorder and may form a distinct subgroup. Dougherty. Bjork. Marsh. and Moeller (1999) induced laboratory aggression using the Point Subtraction Aggression Paradigm described above. The eight male participants were classified as high or low hostile based on a median split of scores on the Buss-Perry Aggression Questionnaire (Buss & Perry. 1992). In a repeated measures 3-condition plus baseline design: baseline. depletion. augmentation. and a food restricted control day. high hostiles exhibited elevated aggression in the depletion condition.

Serotonin. Tryptophan Depletion. and Cardiovascular Effects

Serotonin's role in regulation of the cardiovascular system is extremely complex. In the early 1990s the number of positively identified main 5-HT receptor families had reached three and all appeared to mediate cardiovascular activity. with the proposed fourth type playing a hypothesized myocardial stimulation role as well (Saxena & Villalon. 1990). At last count. there were seven main 5-HT receptor types with almost 20 subtypes identified (Hamel. 1999). The modulating and mediating effects of both central and peripheral serotonergic systems. directly and indirectly through their effects on other physiological systems. is yet to be fully unraveled.

5-HT acting directly on the vasculature can cause both vasoconstriction (Chester, et al., 1990; Conner, Fenuik, & Humphrey, 1989; Dahm et al., 1996) and vasodilation (McFadden et al., 1991). In healthy individuals, direct infusion of 5-HT into coronary arteries results in vasodilation, whereas infusion in arterioscelrotic coronary arteries results in severe vasoconstriction (McFadden et al.); slow intravenous infusion of 5-HT will elicit tachycardia prior to any changes in blood pressure (Saxena & Villalon, 1990). Heart rate and blood pressure can be reduced through the administration of selective 5-HT_{1A} receptor agonists, however, 5-HT_3 receptors on the vagal nerve endings in the heart can lower heart rate by inducing a short duration hypotension. This reduction in heart rate is reversed when the bradycardia reflex is suppressed, as in deep anesthesia, for example, and tachycardia ensues. The blood pressure response to 5-HT generally follows a three step sequence: an initial short duration fall in blood pressure (hypotension), a longer duration rise (hypertension), followed by a longer lasting hypotension. The initial hypotensive response is the result of a rapid bradycardia and subsequent decrease in cardiac output following the stimulation of 5-HT_3 receptors located on the afferent cardiac vagal nerve. The middle hypertensive phase, or pressor phase, results from 5-HT_2 mediated vasoconstriction. These receptors are located directly on blood vessels in certain species (e.g. rat and cat) and on the adrenal medulla in others (e.g. dog). The third phase, hypotensive effect or depressor effect, is caused by activation of CNS of 5-HT_1 receptors, that decrease sympathetic activity and stimulate vagal nerve activity, reduced transmitter release of sympathetic nerve terminals, vasodilatation (expansion of the smooth muscles of the vasculature system), and the release of a relaxant factor in the walls (the endothelium)

of the vasculature system (Saxena & Villalon). Blood pressure increase in rats is presumed to be mediated by the activation of a particular central receptor subtype, 5-$HT_{2\,1C}$, which then causes the release of vasopressin (Pergola, Sved, Voogt, & Alper, 1993).

5-HT injected directly into the CNS results in depressor, pressor, and biphasic responses. The particular effect depends on many factors including the dosage, the site, and the physiological state of the animal. For example, opposite effects can be observed depending on whether the animal is conscious or not, normotensive or hypertensive, etc. Distinct receptor subtypes in particular brain sites, such as the dorsal and median raphe, anterior hypothalamus, and ventrolateral medullary raphe, produce mainly pressor effects, while other subtypes, located in the midline medullary raphe nuclei, can produce pressor or depressor effects, depending on which subtypes are activated. CNS 5-HT stimulation of particular serotonergic pathways and receptor subtypes results in an integrated cascade of neuroendocrine and autonomic responses. The opposing effects which can occur simultaneously within a singular brain structure may also be observed in the vasculature. Whether constriction or dilation occurs depends, again, on many factors, such as the relative density of particular subtypes located in the same blood vessel areas, the dose of 5-HT, as well as the pre-administration vessel tone (Saxena & Villalon, 1990).

Across many species, the main effect of 5-HT administration is a rapid, short-lived, deep bradycardia (Saxena & Villalon, 1990). In human beings, an increase in CNS 5-HT, usually as a result of drugs aimed as boosting 5-HT function such as SSRI's, can lead to Serotonin Syndrome. This condition, though usually mild, can in extreme cases lead to death. Symptoms include tachycardia and, paradoxically, either hyper or hypo tension,

with the former being more prevalent (Nolan & Scoggin, 1988). A possible explanation for the two opposing symptoms may be as described above, with each effect resulting from a different phase of the three phase process.

5-HT is also stored within the blood platelets and its release, possibly during ischemic (reduced blood-flow) periods, stimulates thrombus formation (similar to a blood clot) and platelet aggregation. Selective serotonin reuptake inhibitors (SSRIs) reduce the level of platelet stored 5-HT and possibly have an anti-aggregation effect (Krishnan & Clary, 2000). Transient hemodynamic turbulence in severely stenosed canine arteries with endothelial injury can be eliminated with a 5-HT receptor antagonist and recreated through the administration of 5-HT. It is argued that similar effects can be created in humans and, therefore, may be involved in certain ischemic syndromes (Van den Berg et al., 1989). The contraction of the muscular coat of the blood vessels, vasospasm or angiospasm, is thought to be caused by increased concentrations of 5-HT at the site of the coronary arterial stenosis (narrowing) in both animal models and humans (Ashton et al., 1986; Schmitz, Apprill, Buja, Willerson, & Campbell, 1985).

The autonomic activity modulated by the pattern of central nervous activity of stimulated 5-HT_1 receptors, described above, decreased sympathetic activity, an increase in parasympathetic function, and vagal nerve activity, can be induced through 5-HT loading, agonist administration, as well as through Trp supplementation (Saxena & Villalon, 1990). This pattern of autonomic activity is seen in low hostile individuals and the converse pattern of increased sympathetic and decreased parasympathetic activity seen in high hostile individuals may thus be associated with serotonergic dysfunction. Reduced

autonomic arousal and lower heart rate is associated with disinhibited temperament, socialized aggression, as well early adulthood criminal and violent behavior, whereas heightened levels of autonomic arousal and reactivity may confer a protection from criminal activity (Raine, 1997).

Acute Tryptophan Depletion Induced Cardiovascular Changes

There have been two studies that have reported cardiovascular changes induced by ATD. In a study utilizing a cholecystkinin-tetrapeptide (CCK-4) challenge. In these studies researchers looked at the possible interaction between this drug (CCK-4) and 5-HT. CCK-4 is known to cause panic attack like symptoms and is thought to be associated with an interaction between the CCK-4 and 5-HT systems. Although they do not report pre-depletion cardiovascular measures, they report that there was no statistically significant cardiovascular effect of the ATD (Koszycki, Zacharko, Le-Melledo, Young, & Bradwejn, 1996). Williams et al. (2001), in a correlational type study (measurement of natural levels of 5-HIAA as opposed to 5-HT manipulation), collected cardiovascular measures during a 45-minute mental stress protocol and carried out CSF 5-HIAA sampling. They analyzed their cardiovascular data using a two-way repeated-measures ANOVA and used a median split to assign participants into high or low 5-HIAA groups, comparing baseline to stress period cardiovascular changes. Based on the literature described above, they expected to find increased reactivity in the depleted group. "The greater CV responses exhibited by persons with high CSF 5HIAA levels were surprising to us in light of our expectation that decreased CNS 5-HT function (ie, *low* 5HIAA) would be associated with increased

biological reactivity. Because our results are quite robust statistically and internally consistent, it is unlikely they are due to chance" (Williams et al., pp. 304).

Hypotheses

Given the research described above, that trait hostility may play a moderating role in the cardiovascular and neuroendocrine responses to interpersonal stress, with high hostile individuals generally being more reactive, and that 5-HT may have a modulatory effect on hostile and aggressive mood, especially in individuals that may be predisposed to hostile reactions by virtue of being relatively high on trait hostility, it was hypothesized that when exposed to an interpersonal conflict:

a) High hostile (HiHo) participants in the acute Trp depleted (T-) group would exhibit the greatest increases in self-reported hostile mood as well as anger, relative to the low hostile (LoHo) participants in the non-depleted control group (B) group, with the participants of the remaining two groups showing intermediate level responses.

b) HiHo participants in the T- group would show the greatest cardiovascular responses to an interpersonal conflict and that LoHo participants in the B would show the least reactivity, with the participants of the remaining two groups showing intermediate level responses.

Methods

Participant Selection

Thirty-eight males and 22 females, aged 18-40, with sufficient command of English or French were recruited from Concordia University and McGill University. The stated purpose of the study was to look at the relation between 5-HT, cognition, and cardiovascular function. Pre-screening at the recruitment table was conducted using the Cook-Medley Hostility Inventory (Ho: Cook & Medley, 1954) (see Appendix A), Prime MD Clinician Evaluation Guide DSM-IV Version – Revised (1995), and the General Health Questionnaire (see Appendix B), developed in our laboratory and used in previous studies. Potential participants who did not report a systemic medical condition, were not smokers or recent drug users and, if female, were not using oral or injectable contraceptives, were invited to visit the laboratory for a more comprehensive interview. Potential participants who reported using Ecstasy (3-4 methylenedioxymethamphetamine, MDMA) on more than three occasions were excluded, due to Ecstasy's serotonergic effects.

Measures and Apparatus

Psychological and Medical Screening

During the comprehensive interview, potential participants underwent a Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-patient edition (SCID -I/NP: First, Spitzer, Gibbon, & Williams, 1996). Applicants who met the criteria for a psychiatric disorder, including alcohol or substance abuse/dependence, were

excluded. Potential participants who had completed the SCID successfully were referred to a physician for a medical examination and health history. The examination included blood pressure measurement which, along with the health history, served to ensure that only normotensive participants were included. An electrocardiogram was obtained and evaluated by the physician. A urine analysis was conducted to determine the presence or absence of proteins or blood and verify pH levels. The physician recommended inclusion or exclusion in the study based on clinical judgement and exclusion criteria (see Appendix C) and completed a medical report (see Appendix D).

Assignment and Demographic Measures

The Cook-Medley Hostility Inventory (Ho) (Cook & Medley, 1954), a 50-item true and false questionnaire derived from the Minnesota Multiphasic Personality Inventory, has been demonstrated to have relatively high levels of internal consistency, with an average Chronbach's alpha of approximately .80 (Smith & Frohm, 1985). Spielberger's Trait Anxiety Inventory- Form Y-2 (STAI) (Spielberger, Gorusch, & Lushene, 1970) was used to assess homogeneity and the possible confounding influence of anxiety (see Appendix G). The STAI correlates with the Taylor Manifest Anxiety Scale, at .80 and the IPAT Anxiety Scale at .75. Test-Retest reliabilities range from .86 at 4 hours to .65 at 104 days. The Beck Depression Index (Beck, 1987), a 21-item self-report rating inventory measuring characteristic attitudes and symptoms of depression, was administered as part of the comprehensive interview during the screening process (see Appendix H). The BDI demonstrates high internal consistency, with average alpha

coefficients of .86 (Devilly, 2001).

Outcome Measures

State Affect Measures

State affect during the test period was assessed using the Bipolar Profile of Mood States - POMS (McNair, Lorr, & Droppleman, 1988) as well as with the Visual Analog Mood Scale - VAMS (see Appendices I & J respectively). The POMS is composed of 72 questions scored on a 4-point scale split into six bipolar scales such as agreeable–hostile, composed–anxious, etc. There are various versions of this scale and, in general, they appear to be internally consistent with a relatively stable factor structure. The VAMS is similar to an analog affect scale, used previously in by Miller et al. (1998), which assesses changes in affective state. Participants indicate their present mood state on each of 13 affective variables, such as happiness, anger, irritation etc., by making a perpendicular mark, as instructed by the experimenter, along a continuous 120 mm, horizontal line, representing the bipolar dimension of each mood state, e.g., Not at all Angry – Very Angry. The POMS and VAMS were administered in the morning – pre-ingestion of the amino acid mixture, 5.5 hours post-ingestion – prior to participating in the stressor phase, and immediately following the stressor phase. Both scales are considered highly sensitive to nonclinical changes in affective state.

Cardiovascular Measurements

Systolic blood pressure (SBP) is the arterial pressure during the contraction phase

of the ventricles and diastolic blood pressure (DBP) is the arterial pressure during the relaxed phase of the ventricles. Measurements of SBP and DBP (in mm Hg) were obtained at one minute intervals using the IBS Automated Blood Pressure and Pulse Rate Monitor SD- 700 A (IBS Corporation, Waltham, Mass, USA) and a blood pressure cuff placed on the participant's non-dominant arm. The blood pressure monitor uses a ruggedized sensor to detect arterial wall motion and audible as well as inaudible Korotkoff vibrations. A special filter identifies specific vibrations associated with obstructed blood flow between the systolic and diastolic pressure range. The filtered signals correlate closely with those obtained by standard ausculatory methods using a stethoscope (Matthews et al., 1986, 1987).

Additional cardiovascular measures include heart rate (HR: in bpm), stroke volume (SV: in ml), cardiac output (CO: in l/min.), pre-ejection period (PEP: in msec), left ventricular ejection time (LVET: in msec), Heather Index (HI: ohms/sec/sec), and total peripheral resistance (TPR: in dyne-sec.cm $^{-5}$). HR is the number of heart beats each minute. SV is the quantity of blood ejected by the heart during a single cardiac cycle. CO is the total volume of blood ejected by the heart during a period of time, typically, as is the case in the present study, one minute. PEP is the time interval from the beginning of electrical stimulation of the ventricles to the opening of the aortic valve. LVET is the time interval from the opening to the closing of the aortic valve. HI is an estimate of myocardial contractility and TPR is the resistance to blood flow throughout the entire cardiovasculature. Values for these measures were obtained through non-invasive means using a Minnesota Impedance Cardiograph (Model 304A, Instrumentation for Medicine,

Greenwich, Conn, USA), an IBM compatible personal computer, EKG spot electrodes, and the Cardiac Output Program (C.O.P. Version 2.1, Bio-impedance Technology, Chapel Hill, North Carolina, USA). The impedance cardiography utilized a tetrapolar electrode-band configuration. The inner two recording electrode-bands were placed around the base of the participant's neck and around the thorax over the tip of the xiphoid process. The outer two electrode-bands were placed around the neck and the thorax at least 3 cm apart from each of the inner electrode bands.

The ECG signal was recorded independently using three spot electrodes. Two electrodes were placed on opposite sides of the rib cage at approximately the level of the seventh rib. The ground electrode was placed on the right hip bone. The ECG signal was filtered through a Coulbourn Instruments bandpass filter (Coulbourn Instruments, Allentown, Penn, USA) and then routed to the Minnesota Impedance Cardiograph. This bandpass filter is configured for optimal filtering of the EKG signal (low cutoff: 1 Hz, high cutoff: 150 Hz).Within every measurement minute 55 seconds of recordings were obtained and processed by the C. O. P. system, yielding ensemble averaged values for HR, SV, CO, PEP, LVET, HI, and TPR.

Experimental Procedure

Overview

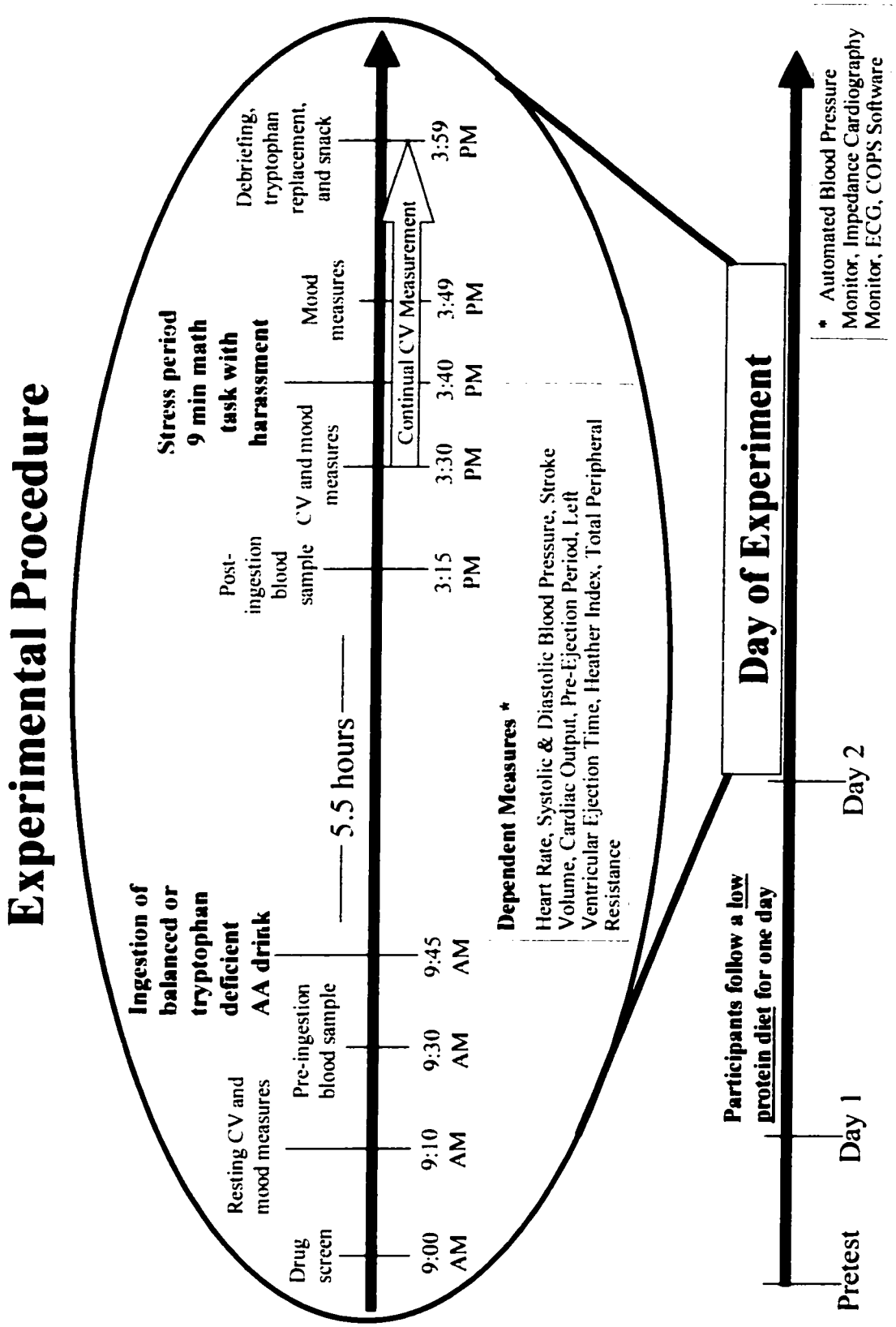
The experiment was a double-blind, placebo controlled study. The test period consisted of a preparatory day followed, 24 hours later, by the test day. The preparatory session was conducted outside of the laboratory, during which participants consumed a

low protein diet and abstained from caffeinated coffee, cigarette smoking, alcohol, and drug consumption. The second session, the testing day, was conducted in the laboratory. Participants were divided into two groups, based on a median split of the Ho scores of the first 50 potential participants screened (LoHo < 17), and randomly assigned to either the amino acid balanced control condition (B) or to the Trp deficient amino acid experimental condition (T-). All participants participated in a deception paradigm that consisted of a nine-minute math task stressor and harassment by a confederate, five and a half hours after ingestion of the amino acid mixtures. Venous blood samples were obtained prior to ingestion and five hours after ingestion. Cardiovascular measurements were obtained prior to ingestion, five hours post ingestion and during the nine-minute stress period at five and a half hours post ingestion. A diagram of the study protocol is presented in Figure 1.

Details of the Procedure

On the day (preparatory day) prior to the laboratory session, participants consumed a low protein diet (see Appendix E) which included prepacked, pre-cooked meals. These meals were similar to those used in previous ATD studies (Benkelfat, Ellenbogen Dean, Palmour, and Young, 1994; Delgado, et al., 1990; Ellenbogen, Young, Dean, Palmour, and Benkelfat, 1996). The meals provided adequate protein (22.6 g/24 hours) and caloric content (2212 kcal/24 hours), with minimal Trp content (160 mg/24 hours). The purpose of the low protein diet was two-fold: firstly, to ensure as much as possible similar dietary intake prior to the test day, secondly, to prime the participant to synthesize protein on the test day. Participants in both conditions were provided with the

Figure 1. Experimental Procedure



same diet in order to maintain the double blind aspect of the study. Participants were encouraged to eat at regular hours and were allowed water ad libitum. Participants were instructed to fast from midnight until their arrival at the laboratory at 9:00 a.m (see Appendix F).

Upon their arrival at the laboratory participants were screened for a broad range of drugs of abuse (including, phencyclidine, cocaine, amphetamines, tetrahydrocannabinol, and opiates). Urine samples were obtained and tested with a mouse monoclonal antibody competitive binding immunoassay based disposable test kit (Express Test® 5 Test Drug Panel, Biosite Diagnostics, San Diego California). Females were screened for possible pregnancy using a human chorionic gonadotropin (hCG) urine level detecting kit (ABBOTT Test Pack® +Plus hCG Urine, ABBOTT Laboratories Ltd., Mississauga, Ontario). Human chorionic gonadotropin is a hormone secreted by the developing placenta shortly after fertilization and can indicate pregnancy within 72-96 hours after implantation.

Accepted participants (two males and one female were rejected due to THC or amphetamine positive test results) were instrumented for cardiovascular measurements and 10 minutes of measurements were obtained. After the cardiovascular measurements recordings, participants provided a venous blood sample of approximately 15 millilitres for measurement of baseline total and free (non-albumin-bound) plasma Trp. Each participant was then given either a Trp-free amino acid drink or a balanced amino acid drink, both containing the same amino acids, with Trp added to the balanced drink. For the next five hours, participants remained in the test room and were monitored by video camera. They

were not allowed to sleep, but were allowed to read affectively neutral material (EnRoute magazines) and watch affectively neutral videos (e.g. National Geographic: Titanic, Egypt, Gorillas of the Rainforest). Water, but not food, was available ad libitum.

After a delay of five hours, participants provided a second venous blood sample and, after a 15-minute wait, baseline cardiovascular measurements were obtained. Immediately following the baseline measurements recording, participants underwent a nine-minute math task stressor with harassment. The harassment procedure was a variation of a protocol developed by Suarez and Williams (1989) and is described in greater detail below. During this stressor period, cardiovascular measures were obtained and the participants were videotaped. At the completion of the math, task there was a 10-minute recovery period during which cardiovascular measurements and videotaping were continued. Following the recovery period, participants were debriefed and provided with a snack and given a 1-g L-tryptophan tablet. This tablet served as a tryptophan replacement for those participants in the depleted, experimental condition and acted to maintain the double blind status of the study by being given to the non-depleted control participants as well. The tryptophan preparation is available by prescription in Canada and has not been associated with any cases of eosinophilia myalgia syndrome (Wilkins, 1990). As a means of ascertaining any negative sequellae from the test procedures, telephone contact was maintained during the evening and morning following the test session.

Amino Acid Drinks

The amino acid mixtures are the same as those used by Young, Smith, Pihl, &

Ervin (1985) previously in men, except that lysine monohydrochloride was used instead of lysine, to increase palatability, and the drinks to be given to females are adapted for the lower body weight of women (Ellenbogen et al., 1996). The AA mixture for males consists of L-alanine, 5.5 g; L-arginine 4.9 g, cysteine, 2.7 g; glycine, 3.2 g; L-histidine, 3.2 g; L-isoleucine, 8.0 g; L-leucine, 13.5 g; L-lysine monohydrochloride, 11.0 g; L-methionine, 3.0 g; L-phenylalanine, 5.7 g; L-proline, 12.2 g; L-serine 6.9 g; L-threonine, 6.5 g; L-tyrosine, 6.9 g; L-valine, 8.9 g; and for the control (balanced) mixture, L-tryptophan, 1.92 g. The AA mixture for females consists of L-alanine, 4.58 g; L-arginine 4.08 g, cysteine, 2.25 g; glycine, 2.67 g; L-histidine, 2.67 g; L-isoleucine, 6.67 g; L-leucine, 11.25 g; L-lysine monohydrochloride, 9.17 g; L-methionine, 2.50 g; L-phenylalanine, 4.75 g; L-proline, 10.17 g; L-serine 5.75 g; L-threonine, 5.42 g; L-tyrosine, 5.75 g; L-valine, 7.42 g; and for the control (balanced) mixture, L-tryptophan, 1.92 g.

The drinks were prepared a few minutes before oral administration by mixing the powdered amino acids with either (1) 150 ml water, 45 ml chocolate syrup, and 0.6 g of sodium cyclamate or (2) 180 ml of orange juice and sodium cyclamate, according to the preference of the participants. Because of the unpleasant taste of methionine, cysteine, and arginine, these amino acids were encapsulated in gelatin-based capsules and administered separately. Due to dietary restrictions, two participants chose not to consume the gelatin capsules and the three amino acids were incorporated into the drink.

Determination of Plasma Tryptophan Concentrations

Plasma Trp was measured in all blood samples as an index of the extent of ATD.

The free (non albumin bound) plasma Trp concentration was assumed to be equivalent to the concentration of Trp found in an ultrafiltrate of plasma prepared at 25C by centrifugal ultrafiltration (MPS-1, Amicon Inc, Beverly, Mass.) through YMT membranes (Millipore Waters, Bedford, Mass). Trp in the ultrafiltrate and in deproteinized plasma were measured by high performance liquid chromatography on a Waters μBondapak C18 (Millipore Waters) reverse phase column with fluorometric detection (Anderson, Young, & Cohen, 1979).

Mathematical Task

The mathematical subtraction task (math-task) consisted of the Computerized Subtraction Task Version 1.21 computer program (Turner, Sherwood & Lutz, 1989), an IBM PC computer, and a computer mouse. The 9-minute math task, divided into three 3-minute trials, consisted of a series of mathematical subtraction equations presented with either correct or incorrect solutions. During each 3-minute trial, 60 equations were presented for a task total of 180 equations. Each equation was presented for a duration of three seconds, first appearing as white characters against a black background and switching to yellow characters if the participant did not respond within the first two seconds. The participant responded by pressing the right computer mouse button if he/she thought the answer was correct or by pressing the left button if he/she thougt the answer on the screen was incorrect. The participant was instructed to respond as rapidly as possible. If the participant's answer was correct, the computer emitted a high pitched tone indicating that the participant had responded accurately. If the participant's answer was

incorrect. the computer emitted a low pitched tone indicating that the participant had responded inaccurately. Participants were informed that if they failed to respond within the three seconds. their non-response would be considered as an incorrect response. however. no tone would be emitted. The math task is designed in such a way that each participant attained a 50 to 60 percent correct response rate. that is. equations became easier or more difficult depending on each participant's performance.

Harassment Procedure

Following the second set of baseline measurements. Researcher A explained the math-task instructions to the participant (see Appendix K). Researcher B. a male for male participants and a female for female participants. knocked on the door of the room adjoining the testing room. interrupting Researcher A's instructions. to tell Researcher A that she had a phone call from their supervisor. After completing the current sentence. Researcher A excused themselves and exited to the adjacent room. In a loud voice. Researcher A pretended to engage in a telephone conversation in which they were being asked to leave the testing session. Researcher A then asked Researcher B to continue the testing for them. Researcher B voiced their opposition. stating angrily that he or she would not be responsible for any problems. Researcher A returned to the testing room. completed the instructions and explained to the participant that Researcher B would be taking over and then left the room. Researcher B. feigning anger. entered the testing room to start the math-task (see Appendix L for a more detailed script).

During the math-task. Researcher B delivered six anger-provoking statements to

the participant, at predetermined times. Sample statements include: "Did you understand the instructions?!" and "Can't you do better than this?!" (see Appendix M). Participant comments were ignored, unless the participant wanted to discontinue the experiment. The testing session was stopped following a 10-minute rest period. All participants were then debriefed about the deception (see Appendix N), the purpose of the harassment and the true rationale for the experiment. Participants who reported feeling suspicious about the harassment manipulation were excluded from the final data set, if their physiological measurements were atypical.

Data Analysis

All statistical data analyses were conducted using SPSS for Windows, Release 10.1.4, 16 March 2001 (SPSS Inc.), running on an IBM personal computer with the Windows 98 4.10 1998 operating system and an AMD-K6 3D processor. Demographic characteristics of the participants were compared using a one-way analysis of variance (ANOVA), to verify equivalence of the experimental and control groups. Blood Trp levels were analyzed and compared using repeated measures ANOVA, to verify the effect of the ATD or control procedure on the experimental and control groups respectively. Mood and cardiovascular measurements were analyzed on an individual measure basis, as is the accepted practice in this area of research. Each measure was analyzed using a repeated measures ANOVA (mixed within subjects factorial design), 2(B + T-) x 2(LoHo x HiHo) x 3(Pre-Ingestion + Baseline + Harassment), in order to examine the effect of time (i.e., the effect of the 5.5 hour wait and the effect of harassment regardless of hostility and Trp.

effects of Trp and hostility and the interaction of the two, and the possible time by Trp x hostility interaction). Simple effects analysis, with correction for family wise error, were carried out in investigating the source of the statistically significant higher order findings.

Ethics

All participants who participated in the study gave written informed consent to their participation in the study (see Appendix O), as well as written consent for release of their medical information by the physician to the research team (see Appendix P). The recruitment, selection, and study procedures were approved by the Research Ethics Board of the Department of Psychiatry, McGill University, Montreal, Quebec, Canada and the Ethics Review Board of Concordia University, Montreal, Quebec, Canada. Participants were paid $100 for their participation in the study.

Results

Demographic Characteristics and Pre-ingestion Measures of the Study Sample

Demographic characteristics of the study sample are shown in Table 1. Approximately 700 individuals were pre-screened, of whom approximately 350 were rejected as their Cook-Medley scores fell within the central region of scores (14 - 22). An additional 100 individuals were rejected at this stage based on the results of the Prime MD interview and the General Health Questionnaire, with approximately half for mental health reasons, such as depression and anxiety, and one quarter for physical health reasons, such as ulcers, asthma, etc. A smaller number were rejected based on substance use patterns, oral or injected contraceptives, language difficulties, a history of the study of psychology, etc.

In all, approximately 250 individuals were invited to participate in the comprehensive interview, of whom more than 100 withdrew of their own volition by either not returning calls or for personal reasons. In total, 133 potential participants were evaluated in person to assess mental health status. Sixteen participants were excluded on the basis of a probable DSM-IV Axis I or Axis II disorder (American Psychiatric Association, 1994), four revealed a substance use pattern, three disclosed contraceptive use, two revealed a previous history of the study of psychology, and one was excluded based on physical health concerns. Approximately 100 individuals were invited to undergo the medical examination. Eighty-five potential participants were seen by the physician and two were advised that they should not continue with the study. Subsequent to these steps, approximately 15 individuals chose not to continue with the study, with

Table 1

Mean Sex, Age, Weight, Height, Education, Ho, BDI, STAI and Standard Errors as a Function of Balanced or Depleted Condition and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
	M	SE	M	SE	M	SE	M	SE
Sex: M	4		11		9		7	
F	7		5		4		3	
Age (yrs)	25.3	1.6	25.1	1.4	24.2	1.4	24.6	1.5
Weight (kg)	67.4	3.3	69.1	3.9	70.5	2.7	71.8	3.6
Height (m)	1.7	0.0	1.7	0.0	1.7	0.0	1.7	0.0
Education (yr)	15.8	0.6	15.7	0.7	15.4	0.4	15.7	0.6
Cook-Medley	9.6	0.6	22.8	1.8	10.6	0.9	25.4	2.2
BDI	0.7	0.3	3.1	0.7	2.8	0.7	3.1	0.8
STAI	28.6	1.4	34.2	1.4	32.1	2.4	34.2	2.6

most simply not responding to the invitation to schedule the test day. An additional six participants began the actual test day but did not complete the protocol. Reasons included two positive drugs screens, one individual fainting during the initial blood draw and one fainting during the preliminary blood pressure measurement. Two were asked to withdraw when they revealed a history of substance use not previously disclosed. In contrast to similar studies (Moore et al, 2000), there were relatively few individuals who reported feelings of nausea subsequent to the ingestion of the amino acid mixtures, and these who experienced symptoms reported that they were of short duration. Four individuals suffered emesis approximately one hour after ingestion, a lower number than is typically reported. None of these participants chose to withdraw from the study. Subsequent plasma analysis revealed no reason to exclude the data of these individuals, as their Trp levels were consistent with their group assignment.

Sixty participants completed the entire protocol. A total of 10 participants were excluded from the final analysis due to ambiguous depletion status (n = 1), questionable language competency (n = 2), problems with the data acquired (n = 4), and failure to be deceived with corroborating evidence from their data (n = 3).

Verification of Pre-Ingestion Homogeneity

A series of 2(B + T-) x 2(LoHo + HiHo) ANOVAs were conducted on the demographic data, as well as on pre-ingestion mood and cardiovascular measures. Demographic measures did not differ between groups, with the exception that the HiHo participants had statistically significantly higher BDI scores, F (1, 40) = 4.192, p = .047.

This difference is not clinically significant and should not effect the validity of the study findings. Participants differed by definition with respect to Ho scores, however, there were no between Trp group differences on this measure. Pre-ingestion mood measures on the POMS and VAMS did not differ between groups. Pre-ingestion mood means and standard errors for the POMS are presented in Table 2, and for the VAMS in Table 3.

Pre-ingestion cardiovascular measures between the groups differed for four variables. High Hostiles (HiHo's), statistically, differed significantly from Low Hostiles (LoHo's) F (1, 46) = 9.604, p = .003 with regards to systolic blood pressure (SBP). This result may indicate differences that are inherent in the nature of these individuals, however, as HiHo's are equally divided between the two Trp conditions, there was no statistically significant difference between the two Trp conditions in this respect. An interaction of Trp x hostility, was found for CO, F (1, 45) = 12.100, p = .034, as well as for TPR F (1, 45) = 4.889, p = .032. These latter results should be viewed with caution, given the concern about the validity of absolute values of volume-based impedance measures (Sherwood et al., 1990). Pre-ingestion cardiovascular means and standard errors are presented in Table 4.

Changes in Plasma Tryptophan Concentrations

The Trp deficient amino acid mixture resulted in a marked decline in total (see Table 5) and free (see Table 6) plasma Trp concentrations, with an almost 90% decline in total Trp for both HiHo and LoHo participants, with similar results for free Trp. The balanced mixture resulted in an almost 60% increase in total Trp and an almost 100%

Table 2

Means and Standard Errors of Pre-ingestion POMS Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
POMS	M	SE	M	SE	M	SE	M	SE
CA	32.4	1.1	30.8	1.2	31.2	1.0	31.9	1.5
ED	27.1	1.5	28.2	1.1	26.6	1.1	27.3	0.9
ET	24.0	2.5	23.3	1.7	21.1	3.7	22.0	2.5
AH	29.4	1.1	29.8	1.1	28.8	1.2	32.3	0.7
CU	26.0	1.3	26.3	1.2	24.6	2.4	25.7	1.5
CC	28.8	1.5	28.0	1.5	28.4	1.8	30.3	1.3

Table 3

Means and Standard Errors of Pre-ingestion VAMS Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
VAMS	M	SE	M	SE	M	SE	M	SE
Nervous	1.7	0.3	1.8	0.3	1.9	0.3	1.5	0.1
Agreeable	10.6	0.7	10.7	0.6	10.9	0.6	11.4	0.5
Happy	9.8	0.6	10.0	0.5	9.6	0.7	9.2	1.2
Tense	2.6	0.6	2.7	0.7	2.9	0.6	3.4	1.2
Anxious	2.2	0.5	2.6	0.7	2.4	0.4	2.2	0.4
Relaxed	11.0	1.1	10.8	0.7	11.0	0.4	11.1	0.8
Discouraged	2.4	0.5	1.8	0.3	2.5	0.4	1.9	0.3
Annoyed	2.2	0.5	2.4	0.6	2.7	0.4	1.7	0.2
Sad	1.8	0.3	1.9	0.5	2.8	0.4	1.6	0.2
Irritated	2.0	0.5	1.9	0.5	2.2	0.2	2.1	0.5
Angry	1.6	0.3	1.3	0.1	2.1	0.3	1.3	0.1
Depressed	2.2	0.5	1.5	0.2	1.9	0.2	1.6	0.3
Guilty	1.7	0.3	1.7	0.4	2.3	0.5	1.4	0.2

Table 4

Means and Standard Errors of Pre-ingestion Cardiovascular Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
CV	M	SE	M	SE	M	SE	M	SE
HR	63.0	3.2	65.1	2.6	65.5	3.3	54.7	2.1
SBP	97.6	2.2	106.3	1.8	103.7	2.9	110.7	3.4
DBP	67.7	2.1	64.3	2.7	66.1	3.1	68.0	2.6
SV	110.4	10.3	113.5	9.6	114.9	11.1	105.4	14.8
CO	6.7	0.5	7.2	0.4	7.3	0.5	5.7	0.7
PEP	131.4	4.5	127.5	4.7	130.4	4.1	141.0	5.6
LVET	301.1	7.9	293.1	6.3	282.2	7.8	302.0	6.9
HI	18.4	2.2	15.3	1.6	14.3	1.1	11.8	1.0
TPR	762.1	81.6	749.6	46.0	721.4	67.4	1165.9	265.9

Table 5

Mean Total Plasma Tryptophan Concentrations and Standard Errors as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Total Plasma Tryptophan Concentration (nmol/L)							
	Balanced (B)				Depleted (T-)			
	LoHo (n=10)		HiHo (n=13)		LoHo (n=16)		HiHo (n=10)	
Time	M	SE	M	SE	M	SE	M	SE
Pre-Ingestion	58.0	2.2	55.4	2.3	54.4	2.0	58.3	1.7
Ingestion + 5hr	101.3	12.9	81.6	7.0	5.4	0.2	7.7	1.3
Percent Change	74.7		47.3		-90.1		-86.8	

Table 6

Mean Free Plasma Tryptophan Concentrations and Standard Errors as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Free Plasma Tryptophan Concentration (nmol/L)							
	Balanced (B)				Depleted (T-)			
	LoHo (n=10)		HiHo (n=13)		LoHo (n=16)		HiHo (n=10)	
Time	M	SE	M	SE	M	SE	M	SE
Pre-Ingestion	7.6	0.4	7.6	0.4	7.2	0.3	8.2	0.6
Ingestion + 5hr	17.6	3.0	13.1	1.2	1.2	0.2	1.3	0.2
Percent Change	131.6		72.4		-83.3		-86.8	

increase in free Trp for both HiHo and LoHo participants. Repeated measures ANOVA for total and free Trp concentrations revealed statistically significant (T- vs B) condition, F (1, 45) = 149.906, p < .000, and time effects (baseline vs post-manipulation), F (1, 45) = 4.885, p = .032, with a statistically significant condition by time interaction, F (1, 45) = 154.217, p < .000.

Changes in Mood

Changes in Mood as Measured by the POMS

Main effects of time were found for five of the six POMS subscales. There were no statistically significant findings for Energetic - Tired (ET). Statistically significant findings were as follows: Composed - Anxious (CA), F (2, 86) = 40.898, p < .000; Elated - Depressed (ED), F (2, 86) = 22.664, p < .000; Agreeable - Hostile (AH), F (2, 86) = 35.425, p < .000; Confident - Unsure (CU), F (2, 86) = 4.522, p = .014 and Clearheaded - Confused (CC), F (2, 86) = 18.757, p < .000; Total, F (2, 86) = 31.992, p < .000 (Partial Eta^2 = .427)

. Main comparisons did not reveal any statistically significant changes in mood as a function, strictly, of the 5.5 hour post-ingestion waiting period, with the exception of a marginal finding along the agreeable–hostile dimension, F (1, 43) = 3.942, p = .053. There were, however, statistically significant effects of harassment on CA, F (1, 43) = 51.303, p < .000 (Partial Eta^2 = .544); ED, F (1, 43) = 21.171, p < .000 (Partial Eta^2 = .330); AH, F (1, 43) = 34.310, p < .000 (Partial Eta^2 = .444); CU, F (1, 43) = 4.390, p = .042 (Partial Eta^2 = .093); CC, F (1, 43) = 23.510, p < .000 (Partial Eta^2 = .353) and Total, F (1, 43) =

36.407, $p < .000$ (Partial $Eta^2 = .458$). The results indicate that the harassment of the participants was successful, as all of the statistically significant changes were in the expected direction. A lowering of positive mood measures and an increase in negative mood measures, including hostility-related affect measures, was experienced by all participants regardless of their Trp or hostility status.

The means and standard errors for the POMS subscales 5.5 hours post amino acid ingestion are presented in Table 7. Table 8 contains the means and standard errors for the POMS subscales after the harassment.

Statistically significant interactions were found for time x Trp conditions, following the 5.5 hour post amino acid ingestion phase of the study for CA, $F(1, 43) = 4.257$, $p = .045$ (Partial $Eta^2 = .090$), and AH, $F(1, 43) = 4.636$, $p = .037$ (Partial $Eta^2 = .097$). On the CA subscale, the two groups did not differ during the harassment phase, with mean changes and standard errors of -7.7 (1.6) and -8.3 (1.6) for the balanced and depleted groups respectively (indicating that there was no differential effect for Trp on CA during the harassment). However, for the 5.5 hour wait phase, the mean change scores and standard errors were 0.4 (1.1) and -2.8 (1.1) for the balanced and depleted groups respectively, demonstrating an effect for the Trp manipulation, regardless of the hostility status of the participants. As the partial eta^2 of .090 indicates, this effect of Trp lowering the participants mood, as measured on the Composed - Anxious scale, reveals a modest increase in anxiety for the depleted participants with no change for the control group. Similar findings were revealed for the Agreeable - Hostile subscale. Following the the 5.5 hour post-ingestion waiting phase, the mean change scores and standard errors were 0.1

Table 7

Means and Standard Errors of 5.5 Hours Post-Ingestion POMS Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
POMS	M	SE	M	SE	M	SE	M	SE
CA	32.7	1.6	30.8	1.1	28.6	2.8	29.1	2.2
ED	27.5	1.9	25.8	1.6	24.1	2.4	27.4	2.4
ET	23.7	3.0	20.7	1.9	19.6	3.0	26.7	2.7
AH	29.9	1.4	29.6	1.0	24.8	2.9	27.9	3.2
CU	24.8	1.7	25.6	1.4	24.4	2.4	28.3	1.9
CC	28.8	1.8	26.5	1.5	26.7	2.8	30.4	1.6

Table 8

Means and Standard Errors of Post-Harassment POMS Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
POMS	M	SE	M	SE	M	SE	M	SE
CA	24.8	3.3	24.0	2.4	19.1	4.0	23.4	2.6
ED	24.2	2.7	22.4	2.1	18.4	3.1	21.1	1.8
ET	23.9	2.8	22.2	2.3	18.0	2.5	27.6	2.9
AH	23.9	3.3	21.7	3.1	16.1	4.4	19.0	2.7
CU	23.3	2.6	23.9	2.0	19.6	3.0	25.3	3.1
CC	25.3	2.6	22.6	2.1	19.9	3.8	26.1	2.6

(1.1) and -3.3 (1.1) for the control and depletion groups respectively. As above, there is a modest effect of the Trp manipulation increasing hostility levels in the depleted group, with little change in the control group, with no influence of original hostility status. During the harassment phase there was no effect of Trp manipulation, nor of original hostility status.

Changes in Mood as Measured by the VAMS

Main effects of time were found for 10 of the 13 VAMS subscales. There were no statistically significant findings for the Sad, Depressed, or Guilty subscales. Statistically significant findings were as follows: Nervous, F (2, 88) = 10.506, $p < .000$; Agreeable, F (2, 88) = 21.185, $p < .000$; Happy, F (2, 88) = 9.827, $p < .000$; Tense, F (2, 88) = 21.381, $p < .000$; Anxious, F (2, 88) = 14.844, $p < .000$; Relaxed, F (2, 88) = 23.756, $p < .000$; Discouraged, F (2, 88) = 8.696, $p < .000$; Annoyed, F (2, 88) = 21.337, $p < .000$; Irritated, F (2, 88) = 29.542, $p < .000$ and Angry, F (2, 88) = 19.543, $p < .000$.

Main comparisons revealed statistically significant effects of the 5.5 hour post-ingestion waiting period and harassment. Effects of the waiting period were found for: Nervous, F (1, 44) = 4.103, $p = .049$ (Partial $Eta^2 = .085$); Agreeable, F (1, 44) = 4.833, $p = .033$ (Partial $Eta^2 = .099$); Annoyed, F (1, 44) = 5.429, $p = .024$ (Partial $Eta^2 = .110$) and Irritated, F (1, 44) = 4.337, $p = .043$ (Partial $Eta^2 = .090$). Participants reported feeling more negative on the above listed three negative affect subscales and less positive on the positive subscale. These findings are in contrast to the lack of statistically significant changes in mood as assessed by the POMS.

Effects of harassment were found for: Nervous. F (1, 44) = 7.860, p = .007 (Partial Eta^2 = .152); Agreeable, F (1, 44) = 14.715, p < .000 (Partial Eta^2 = .251); Happy, F (1, 44) = 11.205, p = .002 (Partial Eta^2 = .203); Tense, F (1, 44) = 27.760, p < .000 (Partial Eta^2 = .387); Anxious, F (1, 43) = 13.990, p = .001 (Partial Eta^2 = .245); Relaxed, F (1, 43) = 26.542, p < .000 (Partial Eta^2 = .382); Discouraged, F (1, 43) = 8.809, p = .005 (Partial Eta^2 = .170); Annoyed, F (1, 44) = 16.703, p < .000 (Partial Eta^2 = .275); Irritated, F (1, 44) = 26.862, p < .000 (Partial Eta^2 = .379) and Angry, F (1, 44) = 21.210, p < .000 (Partial Eta^2 = .325). All of the statistically significant changes were in the expected direction: positive affect decreased and negative affect increased. These findings are consistent with the findings observed on the POMS and indicate an effective harassment protocol.

An interaction between Trp condition and hostility status was found during the harassment phase F (1, 44) = 4.446, p = .041 (Partial Eta^2 = .092) for only one measure: Happy. The B LoHo's and the T- HiHo's did not differ statistically from each other nor from their previous levels; however, the B HiHo's and the T- LoHo's reported a decrease in happiness as a result of the harassment, but did not differ from each other F (1, 43) = 5.328, p = .009 (Partial Eta^2 = .199) and F (1, 43) = 4.493, p = .017 (Partial Eta^2 = .173) respectively.

The means and standard errors for the VAMS subscales 5.5 hours post amino acid ingestion are presented in Table 9. Table 10 contains the means and standard errors for the VAMS subscales after the harassment.

Table 9

Means and Standard Errors of 5.5 Hours Post-Ingestion VAMS Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
VAMS	M	SE	M	SE	M	SE	M	SE
Nervous	3.1	0.9	1.7	0.2	3.3	1.2	1.2	0.1
Agreeable	10.1	1.0	10.0	0.6	8.8	1.3	10.4	1.6
Happy	9.2	1.0	9.8	0.6	9.1	1.2	9.7	1.6
Tense	3.2	0.9	2.4	0.6	3.2	1.3	1.4	0.1
Anxious	3.2	1.2	3.0	1.0	3.3	1.3	2.6	1.1
Relaxed	10.9	1.1	11.2	0.5	9.6	1.1	11.1	1.0
Discouraged	2.6	0.8	1.8	0.5	2.6	0.7	1.3	0.2
Annoyed	3.2	1.1	2.1	0.4	4.7	1.5	3.4	1.4
Sad	2.4	0.6	1.5	0.3	3.6	0.9	1.3	0.1
Irritated	2.3	0.6	2.4	0.5	4.2	1.4	1.9	0.6
Angry	2.4	0.6	1.2	0.1	3.6	1.0	1.6	0.4
Depressed	2.4	0.6	1.6	0.3	3.5	1.0	1.3	0.1
Guilty	2.0	0.5	1.4	0.2	3.2	0.9	1.2	0.1

Table 10

Means and Standard Errors of Post-Harassment VAMS Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
VAMS	M	SE	M	SE	M	SE	M	SE
Nervous	3.3	1.0	3.8	1.1	4.7	1.4	2.5	0.8
Agreeable	9.4	1.1	6.5	1.2	6.1	1.4	7.8	1.7
Happy	9.6	1.1	6.9	0.9	6.9	1.3	7.8	1.4
Tense	5.2	1.3	6.3	1.3	6.6	1.7	4.9	1.4
Anxious	4.4	1.2	5.0	1.4	6.6	1.7	4.4	1.6
Relaxed	9.2	1.2	6.7	1.2	6.1	1.4	7.2	1.5
Discouraged	3.2	1.1	3.1	1.1	5.8	1.7	2.4	0.8
Annoyed	5.4	1.3	5.8	1.4	6.4	1.6	6.4	2.0
Sad	2.6	1.0	3.5	1.0	4.1	1.1	1.4	0.2
Irritated	5.0	1.3	6.4	1.4	6.3	1.6	7.1	1.9
Angry	2.8	1.1	4.0	1.2	1.5	0.6	5.1	1.3
Depressed	2.2	0.8	2.5	0.7	3.9	1.0	1.2	0.1
Guilty	1.6	0.2	2.5	0.8	3.5	1.2	1.4	0.1

Cardiovascular Responses

Main effects of time were found for all nine cardiovascular measures. Statistically significant findings were as follows: HR, F (2, 86) = 84.792, p < .000; SBP, F (2, 86) = 102.956, p < .000; DBP, F (2, 86) = 31.388, p < .000; SV, F (2, 86) = 13.700, p < .000; CO, F (2, 86) = 66.061, p < .000; PEP, F (2, 86) = 140.939, p < .000; LVET, F (2, 86) = 5.779, p = .004; HI, F (2, 86) = 56.055, p < .000 and TPR, F (2, 86) = 29.200, p < .000.

Main comparisons revealed statistically significant effects of the 5.5 hour post-ingestion waiting period and harassment. Effects of the waiting period were found for: DBP, F (1, 43) = 28.235, p < .000 (Partial Eta^2 = .396); SV, F (1, 43) = 34.677, p < .000 (Partial Eta^2 = .446); CO, F (1, 43) = 40.091, p < .000 (Partial Eta^2 = .482); PEP, F (1, 43) = 66.029, p < .000 (Partial Eta^2 = .606); HI, F (1, 43) = 67.044, p < .000 (Partial Eta^2 = .609) and TPR, F (1, 41) = 38.092, p < .000 (Partial Eta^2 = .482). DBP, SV, CO, and HI increased while TPR and PEP decreased at the end of the 5.5 hour wait.

Effects of harassment were found for: HR, F (1, 43) = 117.343, p < .000 (Partial Eta^2 = .732); SBP, F (1, 43) = 122.881, p < .000 (Partial Eta^2 = .741); DBP, F (1, 43) = 58.910, p < .000 (Partial Eta^2 = .578); CO, F (1, 43) = 50.884, p < .000 (Partial Eta^2 = .542); PEP, F (1, 43) = 99.168, p < .000 (Partial Eta^2 = .698); LVET, F (1, 43) = 9.165, p = .004 (Partial Eta^2 = .176) and HI, F (1, 43) = 20.635, p < .000 (Partial Eta^2 = .324). All of these changes were in the expected direction, with increases in HR, SBP, DBP, CO, and HI, and decreases for PEP and LVET.

Following the 5.5 hour post-ingestion waiting period, there were statistically significant differences as a function of original hostility status for SV, F (1, 43) = 5.656, p

= .022 (Partial Eta^2 = .116), with volume increasing less among the HiHo's. Similarly for CO, F (1, 43) = 8.068, p = .007 (Partial Eta^2 = .158), output increased less among the HiHo's and HI, F (1, 43) = 5.161, p = .028 (Partial Eta^2 = .107), again with a similar pattern. During the harassment phase there was a statistically significant change for LVET, F (1, 43) = 4.995, p = .031 (Partial Eta^2 = .104), as a function of hostility status, with LoHo's showing a shorter ejection time and HiHo's remaining virtually unchanged.

Between subjects effects of hostility status were found for SBP, F (1, 43) = 6.341, p = .016 (Partial Eta^2 = .129); HI, F (1, 43) = 5.053, p = .030 (Partial Eta^2 = .105) and TPR, F (1, 41) = 4.369, p = .043 (Partial Eta^2 = .096). Pre-ingestion SBP measures indicated a difference between the LoHo's and the HiHo's and this difference remained constant across all time periods, with no change in relative difference between the groups throughout the remaining two time points. For HI, pre-ingestion differences failed to reach significance F (1, 45) = 3.548, p = .066, however when the scores from the three time periods were averaged the difference became statistically significant, though the spread between them remained almost constant. A between subjects effect of Trp condition was found for TPR, F (1, 41) = 4.644, p = .037 (Partial Eta^2 = .102). This is most likely due to initial group differences as well, as the spread between the groups remained relatively constant throughout the remaining two time periods. An interaction of Trp x hostility status was found for TPR, F (1, 41) = 4.809, p = .034 (Partial Eta^2 = .105). Independent sample T-tests revealed that there were no statistically significant differences between the B LoHo, B HiHo, and T- LoHo groups; however, the T- HiHo group marginally differed from the B LoHo group, t (1, 19) = -1.916, p = .071 as well as differing from the B HiHo

and T- LoHo groups, t (1, 20) = -2.096, p = .049 and t (1, 24) = -2.309, p = .030 respectively. This finding and the two main effects indicate that this likely results from the initial group differences, as there were no relative changes over the course of the 5.5 hour post-ingestion waiting period or the harassment. The HiHo group had the highest initial mean TPR value as well as the largest variance. This, in combination with the small number of participants in this group, indicates that this measure should be looked at with caution.

The means and standard errors for the CV measures 5.5 hours post amino acid ingestion are presented in Table 11. Table 12 contains the means and standard errors for the CV measures after the harassment.

Table 11

Means and Standard Errors of 5.5 Hours Post-ingestion Cardiovascular Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
CV	M	SE	M	SE	M	SE	M	SE
HR	66.8	3.0	64.3	2.8	65.0	3.5	55.7	2.3
SBP	100.0	3.3	105.3	2.3	106.6	1.9	110.9	3.7
DBP	63.2	2.5	61.3	2.5	62.4	3.4	64.2	2.4
SV	125.1	10.8	118.8	8.7	135.5	13.9	118.1	16.0
CO	8.2	0.6	7.5	0.4	8.5	0.5	6.5	0.9
PEP	117.7	4.4	114.6	4.4	116.4	4.0	129.6	7.5
LVET	299.0	6.9	299.0	7.0	284.3	7.1	284.8	6.1
HI	15.8	1.9	13.4	1.5	12.1	0.9	11.0	0.8
TPR	784.0	64.9	851.8	47.8	756.8	58.2.0	1211.5	314.7

Table 12

Means and Standard Errors of Post-Harassment Cardiovascular Scores as a Function of the Ingestion of a Balanced or Tryptophan Deficient Mixture and Hostility Status

	Balanced (B)				Depleted (T-)			
	LoHo		HiHo		LoHo		HiHo	
CV	M	SE	M	SE	M	SE	M	SE
HR	84.2	5.1	80.2	3.1	83.4	4.2	67.6	4.2
SBP	111.9	3.3	121.6	2.4	125.0	5.0	123.0	4.9
DBP	71.1	2.3	67.7	2.5	68.8	3.2	71.7	2.7
SV	117.6	13.9	121.5	7.8	129.5	12.8	114.1	15.8
CO	9.8	0.9	9.6	0.6	10.7	1.0	7.6	1.1
PEP	99.8	5.8	94.6	5.2	95.3	4.7	109.8	8.1
LVET	282.4	9.2	284.2	6.3	270.2	7.2	302.3	5.9
HI	12.6	1.4	11.8	1.4	9.6	0.8	9.1	0.7
TPR	977.7	89.3	915.5	68.5	903.4	79.0	1398.3	331.6

Discussion

The data reported here are part of an ongoing larger study looking at the effects of hostility, sex, and serotonin on mood and cardiovascular reactivity to interpersonal conflict. The author recognizes the many limitations due to small sample size and between group differences, especially related to sex and racial differences and these are discussed in greater detail below. Caution is advised in interpreting any of these preliminary data and analyses.

Methodological limitations related to sampling and the experimental manipulation present in this study have implications for all that will follow. Participants were recruited from two university campuses and were initially screened based on the Cook-Medley Hostility Inventory. The means of the LoHo and HiHo groups that were subsequently tested were lower than those used by Miller, Dolgoy, Friese, and Sita (1998), who found statistically significant CV responses to the same math task – harassment stressor utilized in this study. In a recent study by Suarez et al. (1998), a tercile split was used in order to accentuate the mean differences between groups, with the means of the HiHo group substantially higher than in this study and their LoHo group's mean similar to those obtained here.

Participants in this study were excluded if they had a history of substance abuse or an Axis I disorder. Previous studies have often failed to exclude individuals based on past substance abuse, either implicitly as in the Miller et al. (1998) study or explicitly as in the Dougherty, Bjork, Marsh, and Moeller (1999) study. In order not to exclude aggressive/hostile individuals, studies such as theirs do not use substance usage history as

a criterion. While many recent studies assess recent substance use on the testing day through blood or urine samples, several, such as the study by Finn et al. (1998) that looked at the influence of trait hostility on mood as a function of Trp manipulation, relied on self report or researcher observations, such as no smell of alcohol. The Suarez et al. (1998) study did not report any participant evaluative criteria that included substance usage pattern issues, not reporting the utilization of either urine analysis or self-report on the day of the laboratory testing.

Although no statistical analysis was conducted, it became apparent to the researchers involved in this study that the higher hostile individuals, both men and women, who applied to this study, were more likely to indicate having histories of elevated substance use. It was extremely difficult to locate, recruit, and include in this study higher hostile individuals who were not disqualified based on these exclusion criteria . It is thus possible that the studies with higher hostility means may have included individuals who would have been excluded from this study. For women, the hypothesized serotonergic effects of oral and injected contraceptives resulted in this being an exclusionary criterion. Most females, particularly those who appeared to be high hostiles, were excluded on this basis. Although there were no mean differences in Ho levels for the males and females included in this study, with similar means for male and female HiHo's and LoHo's in their respective groups, the number of HiHo females was substantially smaller (less than half) than their male counterparts. As will be discussed later, this under-representational factor may have a bearing on the findings of this study.

The Cook-Medley Hostility Inventory as an Appropriate Measure of Hostility

As described previously, various measures have been utilized in assessing hostility and have been hypothesized to tap into different elements of what increasingly appears to be a multidimensional construct. Anger-related aspects, such as Spielberger's anger-in, anger-out, and anger expression constructs, have been shown to elicit different patterns of autonomic response to varied stressors. Additionally, expressive and neurotic (suppressed) hostility have been shown to differentially effect cardiovascular responses to harassment (Miller, Dolgoy, Friese, & Sita, 1996). Studies using similar stressors have found or failed to find differences based on the hostility measure used (Mills, Schneider, & Dimsdale, 1989).

The Ho scale has been characterized as a measure of hostility, however, Costa, Zonderman, McCrae, and Williams (1986) argue that this is misleading since anger items are not represented in the Ho. According to the authors, "cynical mistrust" might better describe the dimension that the Ho taps, as two main factors, cynicism and paranoid alienation, emerged from their analysis. Sallis, Johnson, Trevorrow, Kaplan, and Hovell (1987) failed to find an association between hostility and blood pressure during their mental arithmetic and cold pressor studies, concluding that the Ho and cynical hostility are unrelated to blood pressure reactivity. As discussed earlier, this may have more to do with the lack of elicitation of hostility-related affect during stressors that are less related to the interpersonal domain (in which hostility and anger are more likely to be factors). In the Suarez et al. (1993) study on cardiovascular and emotional responses in women, an increase in cardiovascular reactivity was reported, including blood pressure increases as a

function of higher Ho scores and harassment, with no differences in a non-harassment unsolvable anagram task. An interesting finding of this study was that, unlike men, whose reactivity was differentially effected by levels of anger, the women in this study showed no differential effects of anger. These factors may have implications for the findings in the present study.

Racial Representation in the Study Sample: A Caveat Based on Mood and Cardiovascular Reactivity Findings

The design of this study included representation of racial groups based on a stratified representation. The sample from which these results are derived included four Blacks, five Hispanics, four individuals of Middle-Eastern descent, and five of East-Asian descent. Racial differences have been reported with regard to cardiovascular function (see Anderson, McNeilly, & Myers, 1993, for a full review), with vascular reactivity more prominent among Black adults than White adults and less prominent heart rate reactivity in younger Black adults than White adults of similar age. Among Black men and women positive correlations were found between resting DBP and trait or cognitive anger; however, for males, this was not seen during a laboratory stressor, whereas Black women not only demonstrated an increased resting DBP but also a stress-related increase and SBP increases as well. Anderson and colleagues conclude that, in general, Blacks show greater laboratory based cardiovascular reactivity, especially related to increased peripheral vasoconstriction, whereas Whites exhibit greater cardiac activity.

Differences between Asian and Caucasian individuals, with regard to mood,

behavior, and anger expression, have been reported. Friesen's study (as cited in Drummond & Quah, 2001) reported that Japanese individuals attempted to mask negative emotions by smiling, whereas their North American counterparts did not typically do so. In the current study, three participants of Asian descent were the only ones to describe the harassing confederate as pleasant and helpful and only when pressed for details did they admit that the confederate was "difficult". In a study by Drummond and Quah, Asians reported a smaller increase in anger-related feelings, when describing situations that would typically elicit such feelings, than their Caucasian counterparts; this difference failed to reach a statistically significant level.

Cardiovascular responses were also reported in the Drummond and Quah (2001) study. They did not find any statistically significant differences between the groups for HR, SBP, and DBP. Williams et al. (2001) reported, as previously described, decreased cardiovascular reactivity in individuals with lower levels of CSF 5-HIAA. This unexpected finding was similar to that reported from this laboratory when data from the first phase of this study were completed (Neumark et al., 2002). Williams and his colleagues attribute this finding to an effect of the 5-HTTLPR genotype influencing the cardiovascular responses to stress, independent of CSF 5-HIAA level.

5-HTTLPR is a polymorphism of the promoter region of the serotonin transporter gene. They report that the long (*l*) allele is associated with twice the basal and stimulation activity of the short (*s*) allele. This increased transcriptional efficiency is associated with *l-l* White males scoring lower on personality dimensions such as anxiety, angry hostility, depression, and impulsiveness than individuals with a heterogenous genotype or a

homogenous *s-s* genotype. This effect is not consistent. with White women and Black Americans of either sex showing the opposite pattern. With regard to cardiovascular reactivity. they conclude that individuals with an *l-l* or *l-s* genotype have higher levels of CSF 5-HIAA than those with the *s-s* genotype and that both these factors. of genotype and CSF 5-HIAA levels. are independently associated with greater cardiovascular responses to stress. Race did not appear related to CSF 5-HIAA levels. whereas sex was. with men having lower CSF 5-HIAA levels than women. Race was associated with 5-HTTLPR genotypes. with significant variation in the frequency of the *l* allele. Blacks exhibit this allele in more than 70% of their population. Whites exhibit between 50% to 60%. and less than 30% of Asians have the *l* allele. Subsequent to the publication of the initial results from this study. the authors have reported that further research is necessary. as new data resulted in different findings and may necessitate reinterpretation (R. B. Williams. personal communication. March 14-15. 2002).

These between-racial factors may have implications for the findings in the current study. due to the unequal representation of particular racial groups in the four study conditions. Whereas Asians were almost equally represented in each condition (+1 in the T- HiHo). there were no Blacks in the B HiHo and T- LoHo conditions. Additionally. Caucasians were under-represented in both HiHo conditions.

Sex Differences

Stress Differences Related to Hostility and Cardiovascular Reactivity

Sex differences in both mood and cardiovascular reactivity have been reported.

with some studies reporting effects of hostility for men but not for women (Lawler, Harralson, Armstead,& Schmied, 1993; Rasmussen, Willingham, & Glover, 1996; Smith & Brown, 1992). Davis, Matthews, and McGrath (2000), found increased reactivity to an interpersonal stress in high versus low hostile individuals, however they found no differences between men and women. In the study by Powch and Houston (1996), mentioned earlier, the authors reported that women high on cynical hostility, as assessed by the Buss-Durkee Hostility Inventory (Buss & Durkee, 1957), had increased SBP in response to an interpersonal discussion of affectively laden topics, with no other statistically significant differences on other cardiovascular measures. Girdler, Turner, Sherwood, and Light (1990) found no differences between the sexes on blood pressure measures in response to a variety of stressors; however, they found differences in the underlying hemodynamic mechanisms that combine to influence blood pressure, with men showing higher blood pressure due to greater TPR and women demonstrating equivalent blood pressure increases due to greater increases in HR and CO. Approximately half of the women in this study were oral contraceptive users who showed greater increases in HR, SBP, and DBP, relative to their non-using counterparts, which may have obscured the between sexes differences. As none of the women in the present study were oral contraceptive users, the mean results on these measures should be more similar to the males, as was the case in the study just discussed. These and other studies highlight the variability of cardiovascular reactivity in men and women to various stressors and the difficulty related to the interpretation of statistically significant findings.

Effects of Menstrual Cycle Phase on Mood and Cardiovascular Reactivity

A further potential complication in interpreting mood and cardiovascular reactivity measures in females relates to the phase of the menstrual cycle during which the testing is carried out. A study that examined the effect of various stressors on women with and without a family history of hypertension, found menstrual cycle phase effects in family history positives for baseline HR, DBP, CO, and PEP; reactivity measures of HR and DBP were higher for those in the luteal phase, who also reported higher levels of anger (Sita, 1992). In a review of twelve published studies that examined women's cardiovascular responses to stress throughout the menstrual cycle, Stoney (1992) concluded that menstrual cycle phase influences some cardiovascular measures, but in an inconsistent and modest manner, with several studies failing to find any cardiovascular reactivity effects. Few, if any, of these studies have examined cycle phase influence on cardiovascular measures other than HR, SBP, and DBP. Stoney concludes by saying that, if phase of cycle controls are not utilized, large enough samples should be included to randomize any effects.

Sex Effects on 5-HT Function

Leibenluft, Fiero, and Rubinow (1994) examined the literature pertaining to menstrual cycle phase influence on various variables utilized in mood and mood disorder research. Estrogen studies in animals have shown clear modulatory effects on 5-HT synthesis, turnover, uptake, content, and binding sites. In humans, lower plasma levels of 5-HT have been found during ovulation, compared to the follicular or luteal phases. This

difference may be of little consequence with regards to females in the T- groups, however these differences may remain for those in the B groups.

Nishizawa et al. (1997) reported differences between males and females with regard to 5-HT synthesis and storage. Males were reported to have a more than 50% higher mean synthesis rate than females, while their brain stores where found to be similar. Additionally, following an ATD, males exhibited a reduction in 5-HT synthesis to 10% of baseline levels and to 2.5% in females. The authors hypothesize that, under stressful conditions, the lower synthesis rate may lead to more rapid depletion of stored 5-HT in females and may be responsible for the general finding of a greater decrease in mood for women under stressful conditions (e.g. Ellenbogen, Young, Dean, Palmour, & Benkelfat, 1996).

In summary, sampling and representation issues, with regard to both race and sex, may impose limitations on the interpretation of the results found in this study.

Acute Tryptophan Depletion: Results and Methodological Issues

The results of the plasma Trp concentration assays revealed an effective depletion protocol with reductions in both total and free Trp as large or larger than in similar studies. The findings of Nishizawa et al. (1997) raise an important issue related to ATD studies. Using PET imaging Nishizawa et al. demonstrated that the decline in brain 5-HT synthesis was greater than the decline in free plasma Trp levels. The ATD effect on 5-HT synthesis was uniform across all brain areas, however, 5-HT synthesis continued subsequent to the depletion and was measurable. Given that levels of 5-HT storage vary

across brain structures. the effects of depletion on 5-HT levels may vary across different brain structures. For example, Nishizawa et al. point out that, in cortical regions where the rate of 5-HT synthesis is large compared to its relatively low storage levels, an ATD will likely cause a more rapid decline in 5-HT than in other brain areas. Stressors that have a greater cognitive element (e.g. mental arithmetic) may be influenced differently by the ATD than stressors that may be more "limbic" in nature (e.g. interpersonal conflict).

Harassment: Results and Methodological Issues

Results of both the mood and cardiovascular measures support an effective harassment protocol. As discussed previously, stressors that elicit an anger component are more likely to result in cardiovascular hyperreactivity; the results of the present study are consistent with this. Five of the six subscales of the POMS showed lowered scores after the harassment, indicting that participants in all conditions felt more anxious, depressed, hostile, unsure, and confused. The only subscale that showed no change was along the energetic – tired dimension, remaining at pre-harassment levels. On the VAMS, negative affect increased and positive affect decreased.

Cardiovascular measures confirm the effectiveness of the harassment as well as supporting the general finding that interpersonal conflict elicits cardiovascular reactivity. Only two of the nine measures failed to reach statistically significant differences resulting from the stressor. SV decreased, a change in the expected direction, and TPR increased, in its respective expected direction, however, the changes did not reach statistically significant levels. The remaining measures all moved as expected and showed partial eta^2

effect sizes ranging from .176 to .741 or fairly to very large effects with an average effect size of .542.

Effects of the Tryptophan Manipulation on Mood

Exploration of the POMS Findings

Passage of time during the 5.5 hour wait did not result in any statistically significant changes on the subscales of the POMS. Results of the ATD on mood and, in particular hostility-related mood, revealed an increase in hostility-related affect scores on the POMS. (i.e. increased anxiety or tension as it is referred to in other studies. There was no decrease in mood levels on the subscales more closely associated with depression. This latter finding is consistent with much of the literature that found no depressed affect in healthy adults solely as a function of ATD. The former finding, of increased hostility scores, is less consistent with the literature. Finn et al. (1998) reported changes in hostility-related affect only among high hostile individuals; in the present study, although there was an increase, there was no difference between the LoHo's and the HiHo's. Ravindran et al. (1999) found a marginal effect of ATD for the same two POMS subscales and in the same direction, however, their study also found general depressed affect. This contrasts against the present study and the Finn et al. study, which both found no increase in the level of depression. Ravindran et al. were unable to explain the inconsistency between the two findings since there were no differences in the susceptibility to depression (e.g. positive family history of mood disorders or previous mood disorders in the participants themselves) between the two study samples, an explanation that has been

proffered by Benkelfat et al. (1994) for the differing results of other studies.

A plausible hypothesis for the non-finding related to hostility is, as discussed earlier, that the means of both groups in the previous study were higher than the means of the groups in the present study. Although the means spread between the two groups was the same in both studies, it is possible that only very high hostile individuals show a differential effect.

There is a difference between this study and those just mentioned that may partially explain the discrepant findings on the POMS. In both the Ellenbogen et al. (1996) and the Finn et al. (1998) studies, the experiment ended after the second set of measures and the participants knew that their involvement was over. In the present study, the participants were aware that the mental math task, an anxiety producing task for most participants, would follow the second set of POMS measures. As a result, the second set of measures was not a set of pure ATD measures but included an anticipatory component of what the participants expected to be a negative experience.

Exploration of the VAMS Findings

In contrast to the POMS, passage of time during the 5.5 hour wait yielded statistically significant effects on several of the VAMS items, with small increases in nervousness, annoyance, and irritation and a decrease in agreeableness, a measure that, on the POMS, is the polar opposite of hostility. As mentioned before, these findings may be related to the negatively anticipated upcoming stress period or may be a function of the test measures themselves, with the POMS arriving at the dimensions through multiple

items that may, for better or worse, reflect the uni-dimensionality of the VAMS measures.

On the VAMS no statistically significant difference findings resulted from the ATD. Although the differences in the hostile and anxiety measures on the POMS were small, relative to other findings in this study, they were nevertheless present and showed a moderate effect size of .090 and .097, respectively. The Ellenbogen et al. (1996) study utilized both the POMS and the VAMS. On the POMS they found no differences on the anxiety or hostility subscales, but did find mood lowering on the four other subscales, a difference, discussed earlier, that contrasted against the results of the present study. They reported similar results based on the VAMS scores as well, which differed from the findings reported here. There is a major difference between the two VAMS scales. The VAMS used in their study reflected the same items as on the POMS, with a two adjective bi-polarity. The items at either end of the same line were, for example, Clearheaded–Muzzy, which is similar to the Clearheaded–Confused of the POMS, and Energetic–Lethargic, which is similar to the Energetic–Tired of the POMS, etc. This differs from the single adjectives utilized on the VAMS in the present study. What, if any, influence the different formats, content, or implied meanings have on the self-reported values is unclear.

As reported earlier, a single Trp by hostility interaction of modest effect size reached statistical significance. The two extreme groups, B LoHo and T- HiHo, showed no difference as a result of the harassment, whereas the two intermediate groups, B HiHo and T- LoHo, showed a decrease in happiness associated with the harassment. As this is the sole finding of its type and is not a pronounced effect, any attempt to explain its

relevance is deferred.

Exploration of the Cardiovascular Reactivity Findings

Following the 5.5 hour waiting time, DBP, TPR, and PEP decreased, while SV, CO, and HI increased. While the changes in DBP, TPR, and SV suggest a more relaxed state in the participants at the end of the waiting period, the changes in the three other measures suggest the opposite.

Research has shown that individual variables can move in unexpected directions. For example, while TPR is generally thought to increase during stressor periods and influence the increase in SBP and DBP, a study by Allen and Crowell (1989) reported increases in SBP and DBP, as a function of various stressors, accompanied by decreases in TPR during a mental arithmetic task and increases in TPR during a cold pressor activity. HR increased as function of all stressors, however SV increased during a reaction time task, decreased during the cold pressor, and was relatively unchanged as a function of the mental arithmetic task. HR and SV combine to influence CO and generally, if either measure (HR or SV) is held constant, then an increase in the other will lead to greater CO. In the cold pressor task, although HR increased, CO was relatively unchanged, due to the decrease in SV. Similar variations can occur for PEP, which is a measure of myocardial contractility. Generally, as HR increases, PEP decreases, however, during the cold pressor activity, which was associated with an increased HR, the PEP was greater as well. LVET, PEP, and HI are all indices of myocardial contractility, yet they can move in similar or opposing directions. Mezzacappa, Kelsey, and Katkin (1999) demonstrated a decreased

PEP and increased HI in response to an administration of epinephrine, while LVET was not effected.

The mechanisms underlying these different measures are varied and perhaps different neuroendocrine or hormonal pathways are differentially effected during the different stressors, eliciting differing patterns of autonomic response. Epinephrine, for example, is a vasoconstrictor, heart stimulator, and is the principal blood-pressure raising hormone secreted by the adrenal medulla. Further, its release is modulated by serotonergic pathways. Decreased brain 5-HT function in Ecstasy users is associated with elevated peripheral adrenergic activity along with unchanged peripheral serotonergic activity (Stuerenburg at al., 2002). ATD may well activate some of these same responses. Suls and Wan (1993) describe some of these coactivations of multiple sympathetic and parasympathetic systems, as well as the possible "decoupling" of the two, based on reactions to different types of stressors, and the concomitant cardiovascular variability.

The findings related to mood, specifically depressed and hostile mood, may be associated with different pathways, which result in interacting responses. An anticipatory effect, if it does exist, occurring prior to the mental arithmetic task may also be responsible for some of the varied results. This anticipatory explanation is problematic, however, since, as Schneiderman (as cited in Suls & Wan, 1993) describes, the anticipation of coping with stressors is associated with decreased CO and HR and accompanied by higher TPR.. The pattern found by Schneiderman is inconsistent with the findings of the present study. As discussed previously, the mixed findings related to mood changes during this period, especially anger/hostile mood, in combination with the varied findings related to

mood and cardiovascular reactivity, regarding men and women, for example, may be associated with these results.

The differential effect of hostility status during the waiting period on SV, CO, and HI is partially consistent with findings in other studies. Davis, Matthews, and McGrath (2000) reported dampened CO responses in HiHo's during the preparatory period prior to the stressor phase. HR did not differ between the hostility groups and, though they did not use SV as a measure, given the typical HR, CO, and SV model, SV would have increased less in the HiHo's, consistent with our findings. HI, although described above as more variable in its pattern, would likely attenuate along with the other two measures (i.e., less contractile force) and this was the result found in the present study.

The finding that LVET was reduced in LoHo's during the harassment phase, while the HiHo's showed no difference along this measure, remains a singular finding which is out of context of a pattern of cardiovascular changes. Although this finding would have been more likely in the HiHo's, its singular manifestation in the LoHo's makes it difficult to explore.

Acute Tryptophan Depletion and Cardiovascular Reactivity

The absence of any noteworthy cardiovascular findings related to the ATD, while a marked absence, is not surprising given the limitations described above and the more recent finding related to 5-HT and cardiovascular reactivity by Williams et al. (2001), previously described. Suls and Wan (1993), in their review on the relationship between trait hostility and cardiovascular reactivity, discuss some findings that may help explain

these results. In Cook-Medley based studies that have used very harassing manipulation, similar to the protocol used in this study, both high and low hostile individuals have exhibited similar levels of hyperreactivity (Allred & Smith, 1991). Research that has shown marked differences in reported anger levels between the two groups, has been more likely to show a differential effect of hostility (e.g. Suarez & Williams, 1989) or, as in the study by Hardy and Smith (1988), an increase in unfriendliness in the high hostiles, relative to the low hostiles, in response to provocation. It would appear, according to Suls and Wan, that a differential cardiovascular hyperreactivity does not emerge unless the high hostiles experience the provocation with more negative affect. If the provocation is very great, they argue, "then equivalent levels of reactivity may occur in both low- and high-hostility subjects" (Suls and Wan, p.622). This line of reasoning is similar to that of Bjork, Dougherty, Moeller, Cherek, and Swann (1999), who found that moderate levels of provocation resulted in increased aggressive responses as a function of an ATD, whereas a high level of provocation did not produce these differences.

Given the findings on mood and cardiovascular reactivity of this study and the large effect that harassment appeared to have on all participants, this "ceiling effect" explanation is plausible. Serotonin may be viewed as a mediator of mood and cardiovascular responses and, as such, the lack of significant findings is difficult to explain, especially in light of the ATD plasma results indicating a successful differentiation between the groups. However, as noted above, many biological systems are involved in the regulation of mood, cardiovascular function and the response to stress. If one views serotonin as a modulator of these other systems, as opposed to a direct mediator, the

findings of this and other studies may be more understandable. The capacity of serotonin to modulate the responses of the other systems, such as neuroendocrine systems, may be overwhelmed during extremely stressful and provocative situations, allowing more direct unmodulated effects of the underlying mechanisms, resulting in varied responses. The differential storage of serotonin in different brain structures may, as discussed earlier, interact with the particular type and duration of the stressor, as well as preexisting dispositional traits, resulting in variable sub-mechanism activity, along with the accompanying variations in response patterns, with further differences between sex and races being another possibility.

Mood lowering effects of ATD are hypothesized to result from reduced transmission through post-synaptic 5-HT_{1A} receptors in the hippocampus (McAllister-Willams, Ferrier, and Young, 1998), though it is unclear if all moods, and not solely depression type moods, are regulated in the same manner or even if non-manipulated natural moods and mood disorders are effected by this system. Serotonin storage in the hippocampus may differ substantially from levels in other brain areas. The hippocampus inhibits most aspects of the hypothalamic-pituitary-adrenal (HPA) axis and the increased stress response of the HPA axis following hippocampal damage is well documented; McAllister-Williams, Ferrier & Young (1998) point out that there is little, if any, research on the effect of selectively activating 5-HT_{1A} hippocampal receptors on the functioning of the HPA axis. As in all areas of brain function, the picture is even more complex, with Lopez, Liberazon, Vazquez, Young, and Watson (1999) pointing out the complex triangular relation among the HPA axis, glutamate, and 5-HT in the neural circuits

implicated in stress responses. Additionally, as Moore et al. (2000) and others have stated, that although, given the current evidence, 5-HT is the most parsimonious Trp metabolite capable of producing the observed spectrum of ATD effects, there has been limited investigation of other Trp containing compounds such as neurotransmitter receptors, ion channels, and enzymes that are involved in neurotransmitter synthesis and breakdown. Further research is needed into the role of serotonin and the stress-related mood and cardiovascular responses.

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Appendix A.

Cook Medley Hostility Inventory

Subject# _____

Date _____

This questionnaire consists of numbered statements. Read each statement and decide whether it is true as applied to you or false as applied to you. If the statement is TRUE or MOSTLY TRUE, circle the (T). If it is FALSE or NOT USUALLY TRUE, circle the (F). Remember to give your own opinion of yourself. Do not leave any blank spaces if you can avoid it; please answer every statement.

(T) (F) 1. When I take a new job, I like to be tipped off on who should be gotten next to.
(T) (F) 2. When someone does me a wrong, I feel I should pay him back if I can, just for the principle of the thing.
(T) (F) 3. I prefer to pass by school friends, or people I know but have not seen for a long time, unless they speak to me first.
(T) (F) 4. I have often had to take orders from someone who did not know as much as I did.
(T) (F) 5. I think a great many people exaggerate their misfortunes in order to gain the sympathy and help of others.
(T) (F) 6. It takes a lot of argument to convince most people of the truth.
(T) (F) 7. I think most people would lie to get ahead.
(T) (F) 8. Someone has it in for me.
(T) (F) 9. My relatives are nearly all in sympathy with me.
(T) (F) 10. Most people are honest chiefly through fear of being caught.
(T) (F) 11. Most people will use somewhat unfair means to gain profit or an advantage, rather than to lose it.
(T) (F) 12. I commonly wonder what hidden reason another person may have for doing something nice for me.
(T) (F) 13. It makes me impatient to have people ask my advice or otherwise interrupt me when I am working on something important.
(T) (F) 14. I feel that I have often been punished without cause.
(T) (F) 15. I am against giving money to beggars.
(T) (F) 16. Some of my family have habits that bother me and annoy me very much.
(T) (F) 17. My way of doing things is apt to be misunderstood by others.
(T) (F) 18. I can be friendly with people who do things which I consider wrong.
(T) (F) 19. I don't blame anyone for trying to grab everything they can get in this world.
(T) (F) 20. No one cares much what happens to you.
(T) (F) 21. It is safer to trust nobody.
(T) (F) 22. I do not blame a person for taking advantage of someone who lays himself open to it.
(T) (F) 23. I have often felt that strangers were looking at me critically.

(T) (F) 24. Most people make friends because friends are likely to be useful to them.
(T) (F) 25. I am sure I am being talked about.
(T) (F) 26. I am not likely to speak to people until they speak to me.
(T) (F) 27. Most people inwardly dislike putting themselves out to help other people.
(T) (F) 28. I tend to be on my guard with people who are somewhat more friendly than I had expected.
(T) (F) 29. People often disappoint me.
(T) (F) 30. I have often met people who were supposed to be experts who were no better than I.
(T) (F) 31. It makes me feel like a failure when I hear of the success of someone I know well.
(T) (F) 32. I am not easily angered.
(T) (F) 33. People generally demand more respect for their own rights than they are willing to allow for others.
(T) (F) 34. I am quite often not in on the gossip and talk of the group to which I belong.
(T) (F) 35. I have often found people jealous of my good ideas, just because they had not thought of them first.
(T) (F) 36. I have sometimes stayed away from another person because I feared doing or saying something that I might regret afterwards.
(T) (F) 37. I would certainly enjoy beating a crook at his own game.
(T) (F) 38. I have, at times, had to be rough with people who were rude or annoying.
(T) (F) 39. There are certain people whom I dislike so much that I am inwardly pleased when they are catching it for something they have done.
(T) (F) 40. I am often inclined to go out of my way to win a point with someone who has opposed me.
(T) (F) 41. The man who had most to do with me when I was a child (such as my father, stepfather, etc.) was very strict with me .
(T) (F) 42. I like to keep people guessing what I'm going to do next.
(T) (F) 43. When a man is with a woman he is usually thinking about things related to her sex.
(T) (F) 44. I do not try to cover up my poor opinion or pity of a person so that he won't know how I feel.
(T) (F) 45. I strongly defend my own opinions, as a rule.
(T) (F) 46. I frequently ask people for advice.
(T) (F) 47. I have frequently worked under people who seem to have things arranged so that they get credit for good works, but are able to pass off mistakes onto those under them.
(T) (F) 48. People can pretty easily change me, even though I thought that my mind was already made up on a subject.
(T) (F) 49. Sometimes I am sure that other people can tell what I am thinking.
(T) (F) 50. A large number of people are guilty of bad sexual conduct.

Thank you for your cooperation. Your answers will be kept confidential!

Appendix B.

GENERAL HEALTH SURVEY

Please answer the following questions to the best of your ability. All of the information will be kept confidential.

Date: _____

1. Name: _____

2. Address: _____

3. Telephone Number (s): _____ (home) _____ (work)

4. Date of Birth: _____

5. Sex: Male _____ Female _____

6. If university student or university graduate: Year of Study _____

Program of Study - Major _____ Minor _____

7. Please list any prescription medications (including birth control) you take regularly or occasionally: _____

8. Please describe any major illnesses, health problems or hospitalizations you have had during your adult life: _____

_____

9. Has a doctor ever told you that your blood pressure was high?

Yes _____ No _____

If yes, please give the date it was found to be high: _____

If yes, what is your blood pressure? _____

10. Have you ever been prescribed medication to lower your blood pressure?

Yes _____ No _____

If yes, specify drug name: _____

Are you currently taking such medication? Yes _____ No _____

11. When was the last time you were examined by a physician or other health care provider? Within the last month _____ Within the last 6 months _____
Within the last year _____ More than one year ago _____

12. Have you ever been told that you have had: (check yes or no)

	Yes	No
Chest pains or angina	_____	_____
High blood pressure	_____	_____
Coronary artery disease	_____	_____
Rheumatic heart disease	_____	_____
Hardening of arteries (arteriosclerosis)	_____	_____
Heart attack	_____	_____
Blood disorders (hemophilia)	_____	_____
Any other heart or circulatory problem	_____	_____
Kidney disease (other than stones)	_____	_____
Diabetes (high blood sugar)	_____	_____
Respiratory disorder	_____	_____
Gastrointestinal disorder	_____	_____
Ulcer	_____	_____
Nervous or Mental disorder	_____	_____
Asthma	_____	_____
Allergies	_____	_____
History of high/marginally high cholesterol	_____	_____
Reproductive system disease or disorder	_____	_____
Cancer	_____	_____
Arthritis or joint condition	_____	_____

Appendix C.

Exclusion Criteria

1) **History of Cardiovascular Disease or other systemic disease:**
Coronary heart disease, hypertension, asthma, thyroid, angina, etc.
Hypertension - High Blood Pressure:
Above 130/80 mmHg (determined by 3 measurements).

2) **Chronic or current use of medications which affect Cardiovascular Hemodynamics:**
Allergy medications, Steroid based bronchodilators etc.

3) **Coronary Heart Disease/Hypertension**

4) **Pregnancy & Birth Control:**
Oral and injectable forms of birth control. (estrogen/progestogen or progestogen alone, and Depo-Provera)

5) **Alcohol and other substance abuse including non-clinical elevated levels:**
More than 5-6 drinks on a regular basis.
A history of substance usage pattern that is atypical.
Over 3 MDMA uses, if whole pills, (5 uses if some were ½s,) at least 6 months ago.

6) **History of psychiatric illness:**
Depression – history of depressive episodes (more than mild "blue" periods).
OCD – current or in remittance.
Anxiety – current anxiety at more than mild levels or past history.

7) **Body Morphology**:
15 % overweight for height

8) **Chronic heavy smokers:**
Over 1 pack / day, or if they are irritated if they cannot smoke for 24 hours.

9) **Heavy coffee drinkers:**
If they will become irritated or agitated by not drinking caffeine for approximately 48 hours.

Appendix D.

PHYSICAL EXAMINATION REPORT

Family Name: _____ **Given**: _____ **Sex**: F/M

DOB: _____ **Height**: _____ **Weight**: _____

Blood Pressure: _____ **Pulse**: _____ **Respiration**: _____

HEENT: _____
_____

PERL:_____ **EOM**:_____
_____

Thyroid: _____ **Lymph**: _____

Respiration: _____
_____
_____

Cardiovascular: _____
_____
_____
_____

GI: _____
_____

GU: _____ **U/A**: _____
_____

Central Nervous System: _____
_____

Skin: _____
_____

Musculo Skeletal: _____
_____
_____

Pregnancy: Yes: __ No: __ **L.M.P**: _____

ECG: _____

HPI: _____

_____

Allergies: _____

_____

Previous Medical History: _____

_____

_____

Family History:

Mother: _____

_____

Father: _____

_____

Sibling(s): _____

_____

Functional Inquiry:

HEENT: _____

Thyroid: _____ **Lymph**: _____

Resp: _____

CVS: _____

GI: _____

GU: _____ **CNS**: _____

SKIN: _____ **MUSKO**: _____

I see no medical contraindication to his/her participation in your tryptophan depletion – serotonin and stress - study.

Signature: _____ **Date**: _____

Appendix E.

LOW PROTEIN DIET

	Weight (g)	Protein (g)	Fat (g)	Carbohydrate (g)	kcal
BREAKFAST					
Banana 2	228	2.4	2	54	210
Orange juice 1/2 cup	120	0.8	0	13	52
White toast 2 slices	42	4.0	2	24	128
Margarine	10	0	8	0	68
Jelly 16ml	42	0	0	30	116
Decaffeinate coffee or tea		0	0	0	
1/2 & 1/2 cream 15ml	20	0.5	2	1	27
Sugar 2 x 800mg	8	0	0	8	32
LUNCH					
Shredded lettuce	80	0.7	0	2	10
Raw carrots	55	0.6	0	5	23
Raw celery (1 stalk)	40	0.3	0	2	6
Tomato (1)	123	1.3	0	6	27
Cucumber (1/2 cup)	52	0.3	0	2	7
Oil (1 tbsp)	15	0	14	0	129
Vinegar (1 package)	20	0	0	0	1
Raisins 42g	45	1.5	0	36	136
Apple (1)	140	0	0	21	82
Peach (1)	90	0.6	0	10	38
Twix	48	1.0	6	16	118
Decaffeinated coffee or tea		0	0	0	
1/2 & 1/2 cream 15ml	20	0.5	2	1	27
Sugar 2 x 800mg	8	0	0	8	32
DINNER					
Stir fried vegetables:					
Onions (4 tbsp)	40	0	0	3	12
Carrots	55	0.5	0	4	17
Celery (1 stalk)	40	0.3	0	1	6
Broccoli (1/2 cup)	44	1.4	0	2	11
Cauliflower (1/2 cup)	50	1.2	0	2	11
Mushrooms (1/2 cup)	35	0.9	0	1	39
Green pepper (1/2 cup)	50	0	0	3	13
Oil (3 tbsp)	45	0	44	0	386
Applesauce (1/2 cup)	128	0.2	0	25	97
1/2 & 1/2 cream 15ml	20	0.5	2	1	27
Sugar 2 x 800mg	8	0	0	8	32
Peach (1)	90	0.6	0	10	38
SNACK					
Raisins 42g	45	1.5	0	36	136
Twix	48	1.0	6	16	118
TOTAL		**22.6**	**88**	**351**	**2212**

Appendix F.

PREPARATORY DAY INSTRUCTIONS

Laboratory Telephone: 398-7156
Emergency Telephone (Erwin): 781-4626

On the day preceding our dietary experiment, we would like you to follow a low protein diet that begins at breakfast and ends at 12 AM.

This diet includes:

1. Breakfast
2. Lunch
3. Dinner
4. Snacks

If any of the items listed below are missing or if you have any questions, please call our lab at 398-7156. If there is no answer, please call 781-4626.

Please Note: Underlined items are provided in your meals package.

1. Breakfast

Your breakfast consists of 2 bananas, orange juice, and 2 slices of bread. You may toast the two slices of bread and eat them with margarine and/or jam. You may not eat any peanut butter or drink any milk (except the small amount provided to you, for your coffee). You may have one cup of decaffeinated coffee or tea with milk and sugar.

2. Lunch

Your lunch consists of salad, celery, carrots, fruit, raisins, and a chocolate bar. You are provided with salad dressing.

3. Dinner

Your dinner consists of stir-fried vegetables, which are to be kept frozen until meal time. The frozen dinner container can be heated in the oven, with the lid removed, for about 35 to 45 minutes at 325°F. It can also be heated in a microwave oven by removing it from the aluminum container, placing it in a microwave safe container, and heating it as required. You may have one cup of decaffeinated coffee or tea with milk and sugar.

4. Snacks

The remaining items (fruit, raisins, applesauce, and chocolate bar) are meant to be eaten at any time during the day, but we suggest that you save them for the evening.

Important!!

You do not have to eat everything listed on this sheet of paper, **but you cannot replace one food item for another or eat anything outside the diet** (the same applies to beverages and, most importantly, no alcohol!)

You may drink as much water as you'd like throughout the day.

You do not have to eat the food in the order presented here; you can eat the food in any order you wish.

Please stop eating at 12:00 AM the night before the experiment day at McGill.

Do not eat any breakfast.

If you are a smoker, do not smoke on the morning you are to come to McGill.

Appendix G.

Spielberger Trait Anxiety Inventory (STAI)

Participant # _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then circle in the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which describes how you generally feel.

1 = Almost Never 2 = Sometimes 3 = Often 4 = Almost Always

21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am calm, cool, and collected	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Appendix H.

BECK DEPRESSION INVENTORY

DATE OF VISIT: _____ SUBJECT NUMBER: _____

On this questionnaire are groups of statements. Please read each group of statements carefully. Pick out the one statement in each group which best describes the way you have been feeling the PAST WEEK, INCLUDING TODAY! Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one.

Be sure to read all the statements in each group before making your choice.

1	0	I do not feel sad
	1	I feel sad
	2	I am sad all the time and I can't snap out of it
	3	I am so sad or unhappy that I can't stand it
2	0	I am not particularly discouraged about the future
	1	I feel discouraged about the future
	2	I feel that I have nothing to look forward to
	3	I feel that the future is hopeless and that things cannot improve
3	0	I do not feel like a failure
	1	I feel I have failed more than the average person
	2	As I look back on my life, all I can see is a lot of failures
	3	I feel I am a complete failure as a person
4	0	I get as much satisfaction out of things as I used to
	1	I don't enjoy things the way I used to
	2	I don't get real satisfaction out of anything anymore
	3	I am dissatisfied or bored with everything
5	0	I don't feel particularly guilty
	1	I feel guilty a good part of the time
	2	I feel guilty most of the time
	3	I feel guilty all of the time
6	0	I don't feel I am being punished
	1	I feel I may be punished
	2	I expect to be punished
	3	I feel I am being punished
12	0	I have not lost interest in other people.
	1	I am less interested in other people than I used to be
	2	I have lost most of my interest in other people
	3	I have lost all of my interest in other people
13	0	I make decisions about as well as I ever could
	1	I put off making decisions more than I used to
	2	I have greater difficulty in making decisions than before
	3	I can't make decisions at all anymore
14	0	I don't feel I look any worse than I used to
	1	I am worried that I am looking old or unattractive
	2	I feel that there are permanent changes in my appearance that make me look unattractive
	3	I believe that I look ugly
15	0	I can work about as well as before
	1	It takes an extra effort to get started
	2	I have to push myself very hard to do anything
	3	I can't do any work at all
16	0	I can sleep as well as usual
	1	I don't sleep as well as I used to
	2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
	3	I wake up several hours earlier than I used to and cannot get back to sleep
17	0	I don't get more tired than usual
	1	I get tired more easily than I used to
	2	I get tired from doing almost anything
	3	I am too tired to do anything

7	0	I don't feel disappointed in myself
	1	I am disappointed in myself
	2	I am disgusted with myself
	3	I hate myself
8	0	I don't feel I am any worse than anybody else
	1	I am critical of myself for my weaknesses or mistakes
	2	I blame myself all the time for my faults
	3	I blame myself for everything bad that happens
9	0	I don't have any thoughts of killing myself
	1	I have thoughts of killing myself, but I would not carry them out
	2	I would like to kill myself
	3	I would kill myself if I had the chance
10	0	I don't cry anymore than usual
	1	I cry now more than I used to
	2	I cry all the time now
	3	I used to be able to cry, but now I can't cry even though I want to
11	0	I am no more irritated now than I ever am
	1	I get annoyed or irritated more easily than I used to
	2	I feel irritated all the time now
	3	I don't get irritated at all by the things that used to irritate me
18	0	My appetite is no worse than usual
	1	My appetite is not as good as it used to be
	2	My appetite is much worse now
	3	I have no appetite at all
19	0	I haven't lost much weight, if any, lately
	1	I have lost more than 5 pounds.
	2	I have lost more than 10 pounds.
	3	I have lost more than 15 pounds
		I am purposely trying to lose weight by eating less Yes _____ No _____
20	0	I am no more worried about my health than usual
	1	I am worried about physical problems such as aches and pains; or upset stomach; or constipation
	2	I am very worried about physical problems and it is hard to think about anything else
	3	I am so worried about my physical problems that I cannot think about anything else
21	0	I have not noticed any recent change in my interest in sex
	1	I am less interested in sex than I used to be
	2	I am much less interested in sex than I used to be
	3	I have lost interest in sex completely

Appendix I.

NAME: _____ DATE: _____

Below are words that describe feelings and moods people have. Please read **EVERY** word carefully. Then fill in **ONE** space under the answer which best describes how you feel. Suppose the word is happy, mark the one answer which is closest to how you have been feeling right now. The numbers refer to the phrases indicated below.

0 — much unlike this 1 — slightly unlike this 2 — a little like this 3 — much like this

1. Composed	0	1	2	3	25. Peaceful	0	1	2	3	49. Calm	0 1 2 3
2. Angry	0	1	2	3	26. Furious	0	1	2	3	50. Mad	0 1 2 3
3. Cheerful	0	1	2	3	27 Lighthearted	0	1	2	3	51. Jolly	0 1 2 3
4. Weak	0	1	2	3	28. Unsure	0	1	2	3	52. Uncertain	0 1 2 3
5. Tense	0	1	2	3	29. Jittery	0	1	2	3	53. Anxious	0 1 2 3
6. Confused	0	1	2	3	30. Bewildered	0	1	2	3	54. Muddled	0 1 2 3
7. Lively	0	1	2	3	31. Energetic	0	1	2	3	55. Ready-to-go	0 1 2 3
8. Sad	0	1	2	3	32. Lonely	0	1	2	3	56. Discouraged	0 1 2 3
9. Friendly	0	1	2	3	33. Sympathetic	0	1	2	3	57. Good-natured	0 1 2 3
10. Tired	0	1	2	3	34. Exhausted	0	1	2	3	58. Weary	0 1 2 3
11. Strong	0	1	2	3	35. Powerful	0	1	2	3	59. Confident	0 1 2 3
12. Clearheaded	0	1	2	3	36. Attentive	0	1	2	3	60. Businesslike	0 1 2 3
13. Untroubled	0	1	2	3	37. Serene	0	1	2	3	61. Relaxed	0 1 2 3
14. Grouchy	0	1	2	3	38. Bad tempered	0	1	2	3	62. Annoyed	0 1 2 3
15. Playful	0	1	2	3	39. Joyful	0	1	2	3	63. Elated	0 1 2 3
16. Timid	0	1	2	3	40. Self-doubting	0	1	2	3	64. Inadequate	0 1 2 3
17. Nervous	0	1	2	3	41. Shaky	0	1	2	3	65. Uneasy	0 1 2 3
18. Mixed-up	0	1	2	3	42. Perplexed	0	1	2	3	66. Dazed	0 1 2 3
19. Vigorous	0	1	2	3	43. Active	0	1	2	3	67. Full of pep	0 1 2 3
20. Dejected	0	1	2	3	44. Downhearted	0	1	2	3	68. Gloomy	0 1 2 3
21. Kindly	0	1	2	3	45. Agreeable	0	1	2	3	69. Affectionate	0 1 2 3
22. Fatigued	0	1	2	3	46. Sluggish	0	1	2	3	70. Drowsy	0 1 2 3
23. Bold	0	1	2	3	47. Forceful	0	1	2	3	71. Self-assured	0 1 2 3
24. Efficient	0	1	2	3	48. Able to concentrate	0	1	2	3	72. Mentally alert	0 1 2 3

Appendix J.

Subject Code: _____

Visual Analog Mood Scale (VAMS)

Indicate on each of the scales below, by making a **vertical stroke** through the line at the appropriate point, **how you are feeling right now**.

Not at all Nervous	_____	Very Nervous
Not at all Agreeable	_____	Very Agreeable
Not at all Happy	_____	Very Happy
Not at all Tense	_____	Very Tense
Not at all Anxious	_____	Very Anxious
Not at all Relaxed	_____	Very Relaxed
Not at all Discouraged	_____	Very Discouraged
Not at all Annoyed	_____	Very Annoyed
Not at all Sad	_____	Very Sad
Not at all Irritated	_____	Very Irritated
Not at all Angry	_____	Very Angry
Not at all Depressed	_____	Very Depressed
Not at all Guilty	_____	Very Guilty

Appendix K.

MATHEMATIC SUBTRACTION TASK INSTRUCTIONS

A series of mathematical subtraction equations are going to be presented on the monitor. You must respond by pressing the right button (the one with the C on it), if you think that the answer on the screen is correct, or by pressing the left button (the one with the I on it), if you think the answer on the screen is incorrect.

If your response is accurate, in that you say the answer on the screen is correct and it is or you say the answer on the screen is incorrect and it is, then you will hear a high-pitched tone indicating that you have responded correctly.

If you are inaccurate in your response, that is, you say the answer on the screen is correct and it is incorrect or you say it is incorrect and it is correct, you will hear a low-pitched tone indicating that you have not responded accurately.

The task is nine minutes long and during that time the machines in the other room will continue to take readings. They will also take further readings after you have completed the math task.

Also, when you are done the math task I will be asking you to complete these questionnaires and to do two saliva collections. Please don't move too much while completing the questionnaires as the machines will still be taking readings.

Anyways, you have three seconds to respond to every equation. When the color of the mathematical equation on the monitor turns yellow, you have one second left to respond. If you are unsure at this point, guess, because a non-response is considered an incorrect response.

*** harasser's cue, request harasser to enter at this point.**

Appendix L.

Confederate Introduction Protocol

While the Research Assistant (R.A.) is explaining the math-task instructions to the subject, the Confederate knocks on the door and enters the testing room to tell R.A. that their supervisor is on the phone.

Conf: "Dr. Miller is on the phone."
R.A: "Just a minute please."

R.A. completes the instructions, excuses herself and exits to the adjacent room, leaving the door ajar. In a loud voice R.A. pretends to talk on the phone.

Conf: "Hello Dr. Miller. Right now? Well, I'm running a subject right now. Oh, okay, I'll ask if "Confederate" can take over for me. Okay, thanks, goodbye"

Confederate pretends to be angry with R. A.

Conf: "Now what?!" (angrily)

R.A: "Shhhh! (pause) that was Dr Miller."
Conf.: "And?"

R.A: "He wants to see me right away."
Conf: "Now? - but you have a subject in there!"

R.A: "I know - but it sounds really important - would you mind taking over for me?!"
Conf: "Look - I won't be responsible if your results screw up!"

R.A: "Don't worry - nothing will go wrong - everything is set up in there - just follow the instructions."
Conf: "I don't normally deal the subjects - that's your job you know!"

R.A: "You know I wouldn't ask you if I didn't have to -everything will be fine! (pause) okay? Thanks, I'll be back as soon as I can."

R.A. returns to the testing room and tells the subject that she must leave and that another researcher will be taking her place. R.A. then leaves the testing room and Confederate enters it, pretending to be angry.

Appendix M.

Anger Induction Statements

The 9-minute subtraction task stressor consists of three 3 minute trials. During each trial, two anger-provoking statements are delivered, one at 30-45 seconds into each trial when participant gets two answers wrong in a row, and the other 2/3 of the way through each 3-minute trial, again when the participant gets two in a row wrong.

Trial 1

1. Did you understand the instructions?
2. The right button is correct, the left button is incorrect.

Trial 2

3. Could you try harder this time?
4. Can't you do better than this?

Confederate: Give participant saliva container at end of second trial.

Trial 3

5. It isn't that hard you know.
6. I can do better than that.

Confederate: At the end of task, turn off the computer screen and hand participant last set of questionnaires. Leave the room (or pretend to), closing door with sounds.

Appendix N.

Post-Stressor Debriefing Instructions

RA: Oh. I guess "Confederate" left... Well. you're done... Here. could you please do this last saliva collection. I'm just going to go check the machines.

Go into other room and make noises like those that would be made had you been checking the machines.

RA: Sorry I had to leave so quickly. How did it go? Did "Confederate" help you? Did you have any trouble with the instructions?

1. If P mentions trouble with "Confederate" ask : 'What do you mean?'. What happened?'. mentio:n '"Confederate" didn't seem pleased to replace me.'. 'Some people don't like "Confederate"'. '"Confederate" is sometimes hard to get along with.'

2. If P states they knew Confederate was part of the study find out: at what point they realized they were being deceived and how they figured it out.

(Video tape is running. however. note anomalies in the participant log).

DEBRIEF

RA: "Confederate" is part of the study. This is the only deception in the study: everything else I told you about the study is true. Everyone goes through the same thing. Everyone gets read the same comments about their performance on the math task. The math task is not an IQ test. it is designed to become harder every time you get a correct answer such that you cannot get more than 50% correct.

The reason we had to use deception for this study is that a math task is not a realistic stressor. The math task is hard. and it is programmed so that you get no more than 50% right so that "Confederate" can deliver the statements. but it is not a stress you would encounter regularly. More often than not. stress is inter-personal. The situation created by the deception is meant to be a more realistic stressor. The "Confederate" isn't really a nasty person. Invite the participant to meet the "Confederate".

Do you have any questions? (If you are unable to answer the question. then let the participant know someone will call them with the answer.)

Appendix O.

GENERAL CONSENT FORM

RESEARCH PROJECT CONDUCTED AT

Department of Psychiatry, McGill University

Chawki Benkelfat M.D.
Syd Miller Ph.D. Department of Psychology, Concordia University
Dr. Simon N. Young, Department of Psychology, McGill University
Dr. Robert Pihl, Department of Psychology, McGill University
Dr. Blaine Ditto, Department of Psychology, McGill University

The Effects of Gender, Emotion, Stress and Serotonin on Mood and Blood Pressure

We would like to invite you to participate in a study investigating the effects of gender, emotion, stress and serotonin on mood and blood pressure. In this study, you will undergo a brief interview to determine your current and/or past psychiatric history, a more detailed physical, mental and family history interview (approximately 2 hours) as well as a general medical exam in which physical and mental health will be assessed. You will be provided with a 24 hour low protein diet. You will spend approximately 8 hours at our laboratory, where you will first supply a urine sample for an illegal drug screen, a urine pregnancy screen for females, and a registered nurse will then take a blood sample. There are minimal risks associated with blood draws, which include the possibility of bruising, minor bleeding, and transient pain, however these effects are rare. Physiological measurements such as heart rate and blood pressure will be taken for a ten minute baseline period. You will ingest a 100g amino-acid drink containing the same proportion of amino-acids as found in human breast milk, together with either no tryptophan or 2.3g of tryptophan. Tryptophan is one of the essential amino acids found in the body, and is not unnatural or harmful. The amino acids will be mixed with water, chocolate syrup, and sweetener. Due to the constituents and consistency of the mixture you may experience slight nausea and/or vomiting following its ingestion. However, this occurs very rarely and passes very quickly (1.5 hrs.). It is also possible that you may experience some changes in mood (e.g., lowering of mood, sadness) as a result of ingesting this mixture. However, these changes are only temporary and will return to normal by the end of the experiment.

After ingesting the mixture, there is a 5 hour waiting period. During this time you will complete a questionnaire package, watch a movie, and be permitted to read the magazines provided. At the end of

the 5 hours a registered nurse will take a second blood sample. Physiological measures will again be taken and physiological changes will be examined while you play a computerized math task. Your performance on the math task will also be measured. During the experiment, changes such as an increase in heart rate and blood pressure will occur. These changes will be only temporary, returning to normal after the experiment and causing no harmful effects. These changes will be recorded through safe, painless, and non-invasive means, which will only require the placement of transducers on the skin. Salivary samples will be collected in order to measure the levels of various stress hormones. During these procedures you will be monitored via a video camera and recorded during the math task. These videotapes will be stored in a locked desk accessible only by study personnel, coded, analyzed for use in the current study and then erased within 3 months.

All subjects will undergo a urine sample based illegal drug screen. Subjects will be excluded from the study if the urine screen is positive. If a subject is excluded for this reason, the results of the urine test any data collected will be destroyed. Females will be screened for pregnancy and excluded if there is a positive result.

Participating in this study has no direct benefit for the subject.

You should not participate in this study if you are or think you might be pregnant.

To summarize, your participation will require you to:

1) Undergo a brief interview regarding your psychiatric history, as well as a more detailed (approximately 2 hours) personal interview regarding your physical, mental and family history.
2) Undergo a medical examination.
3) Eat a 24 - hour low protein diet.
4) Attend a laboratory session that will last approximately 8 hours.
5) Undergo a urine screen for illegal drugs.
6) Undergo a urine pregnancy screen (females only).
7) Ingest an amino acid drink.
8) Provide 2 blood samples.
9) Engage in a mathematical subtraction task during the laboratory session. The session will be videotaped.
10) Permit the measurement of several physiological responses including heart rate and blood pressure and salivary stress hormones.
11) Complete a series of questionnaires.

You will be paid $100.00 for your participation. This remittance will be paid to you right after you have completed the experiment. All information we obtain about you is strictly confidential and will not be seen by anyone who is not a member of the research team. Ultimately, all data will be coded using subject numbers rather than names. All data will be kept confidential unless otherwise required by law. Your participation in this study is completely voluntary and you will be free to withdraw from the study at any time. You have the right to ask questions at any time. You will receive payment proportionate to your time spent should you decide to withdraw before completion of the study.

Once you have carefully studied and understood this form, you may sign it in indication of your free consent to participate in the study.

Contacts:

Serotonin Testing Laboratory	398-7156
Regarding your rights as a subject:	
MUHC Ombudsman - Lamy, Danielle	934-8306
Concordia University Ombudsman	848-4964

In the case of an adverse event following your participation:

Chawki Benkelfat M.D.	398-6732
Sydney Miller Ph.D.	848-2183

NAME (PLEASE PRINT) _____

SIGNATURE _____

DATE _____

INVESTIGATOR'S SIGNATURE _____

Appendix P.

CONSENT FOR RELEASE OF MEDICAL INFORMATION FORM

Release of Subject's Medical Information from Evaluating Physician to Researchers

RESEARCH PROJECT CONDUCTED AT

Department of Psychiatry, McGill University
Chawki Benkelfat M.D.
Syd Miller Ph.D. Department of Psychology, Concordia University
Dr. Simon N. Young, Department of Psychology, McGill University
Dr. Robert Pihl, Department of Psychology, McGill University
Dr. Blaine Ditto, Department of Psychology, McGill University

The Effects of Gender, Emotion, Stress and Serotonin on Mood and Blood Pressure

I hereby authorize Lawrence Morris M.D. to release to the researchers, and/or their representatives, the results from the medical (physical) examination that I underwent as a preparatory step to my inclusion in this research project.

NAME (PLEASE PRINT) _____

SIGNATURE _____

DATE _____

PHYSICIAN'S SIGNATURE _____