PLASMA SEROTONIN AND PSYCHOPATHY

by

THERESA ANNE NEWLOVE

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(Sig)

Department of Psychology
The University of British Columbia
Vancouver, Canada

Date April, 1992
Abstract

It has been consistently demonstrated that reduced serotonergic activity plays a mediating role in the manifestation of aggression regardless of psychiatric diagnosis or personality disorder classification. Specifically, decreased serotonin functioning is associated with irritable and impulsive aggression. The nature and degree of violence exhibited by individuals with diminished serotonergic activity is remarkably similar to the behaviour exhibited by psychopaths. However, no study to date has directly examined either central or peripheral indices of serotonergic functioning in a defined group of psychopaths. The present study was an examination of plasma 5-hydroxyindolacetic acid (5-HIAA) and plasma serotonin (5-HT) levels in incarcerated males (n=54). Assessment of psychopathy was made using the psychometrically validated Hare Psychopathy Checklist-Revised (PCL-R). PCL-R Factor 2 (a measure of social deviance) and the interaction between Factor 1 (interpersonal/affective) traits and Factor 2 were significantly correlated with plasma 5-HT and 5-HIAA concentrations, respectively. When the level of violence in the index crime (i.e. crimes resulting in death of the victim) was controlled for, psychopaths tended to have higher plasma 5-HIAA concentrations than did their nonpsychopath counterparts. The results are consistent with findings in the literature and are discussed in terms of the etiology of the psychopathic personality.
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I. Introduction

The behaviours and personality traits that define psychopathy are much better understood than is the etiology of the disorder. For more than a century clinicians and researchers have debated the relative importance of nature and nurture in the development of psychopathy. Although the issue is a long way from being resolved, laboratory studies of autonomic and electrocortical activity suggest that any etiological theory of psychopathy must make provision for the inclusion of biological factors. Whether or not some of these factors are biochemical in nature has yet to be determined.

Biochemical research has increased our understanding of a variety of psychiatric syndromes and provides a framework for the selection of appropriate treatment strategies. A key finding in this research has been the important mediating role played by serotonin in several psychiatric disorders, as well as in a variety of related personality traits and behaviours, including extraversion, aggressiveness, alcoholism, impulsivity, and impulsive violence. Although these traits and behaviours are typically found in psychopaths, serotonergic activity has not yet been investigated systematically in well-defined groups of psychopaths. The purpose of the present study is to investigate the possible role of serotonergic activity in psychopathy.

A. The Construct of Psychopathy

Psychopathy is a personality disorder characterized by a particular pattern of interpersonal, affective, and behavioural
symptoms. Interpersonally, psychopaths are grandiose, egocentric, manipulative, dominant, forceful, and cold hearted. Affectively, they display shallow and labile emotions, are unable to form long-lasting bonds to people, principles, or goals, and are lacking in empathy, anxiety and genuine guilt or remorse. Behaviourally, they are impulsive and sensation seeking, and tend to violate social norms; the most obvious expressions of these predispositions involve criminality, substance abuse, and a failure to fulfill social obligations and responsibilities. These personality traits and behaviours are reliably and validly measured by the Psychopathy Checklist (PCL; Hare, 1980; 1985a; 1985b) and its recent revision (PCL-R; Hare, 1991).

The psychometric properties of the PCL and PCL-R have been well established. The PCL-R Total scores can range from 0 to 40 and represent the extent to which an individual matches the prototypical psychopath. In criminal populations the distribution of psychopathy ratings is approximately normal with a slight negative skew. Although the scale is considered dimensional, a categorical diagnosis can be made by defining as psychopaths those with a score of at least 30. Defined in this way, psychopaths are clearly differentiated from other criminals: they perpetrate a larger proportion of violent crimes (Hare & McPherson, 1984; Serin, 1990; Williamson, Hare & Wong, 1987); they demonstrate poor institutional adjustment and response to treatment (Wong, 1984; Ogloff, Wong & Greenwood, 1990; Harris, Rice & Cormier, 1990; Rice, Harris & Quinsey, 1990); and, their
behaviour following conditional release from prison is characterized by higher rates of recidivism (Hart, Kropp & Hare, 1988; Serin, Peters & Barbaree, 1990).

The PCL-R meets the statistical criteria for a homogeneous, unidimensional scale, but there is empirical evidence that two oblique factors underlie the scale (Hare, 1991; Harpur, Hare & Hakstian, 1988). The correlations between the factors are about the same in samples of prison inmates (.56 on average) as in samples of forensic patients (.53 on average). Factor 1 reflects a cluster of affective and interpersonal traits central to traditional clinical conceptions of psychopathy; these include egocentricity, manipulativeness and callousness. Moreover, Factor 1 is correlated with self-report measures of machiavellianism, narcissism, empathy, and anxiety. Factor 2 reflects traits and behaviours which are associated with an unstable and antisocial lifestyle, social deviance and violence (Harpur and Hare 1991). This factor is most strongly correlated with the diagnosis of antisocial personality disorder. In addition, recent evidence indicates that Factor 2 is much more strongly related to substance abuse than is Factor 1 (Hart & Hare, 1989; Smith & Newman, 1990).

The specificity of the PCL-R becomes apparent when one considers the asymmetrical relationship between the concept of psychopathy, as defined by the PLC-R, and a diagnosis of Antisocial Personality Disorder (APD), as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R;
American Psychiatric Association, 1987). A diagnosis of APD is based primarily on behavioural measures of antisocial and criminal behaviours. This personality disorder can be diagnosed reliably but the behavioural criteria do not capture the affective and interpersonal characteristics of psychopathy (Harpur et al, 1991). This results in as many as 80% of incarcerated male offenders in Canadian federal prisons meeting the APD diagnostic criteria (Correctional Service of Canada, 1990). In contrast to the large percentage of offenders receiving a diagnosis of APD, only about 15% to 25% of offenders meet the PCL-R criteria for psychopathy (Hare, 1991). This asymmetrical relationship accounts for the ability of the PCL-R to define a subgroup of incarcerated individuals who are distinguished from their nonpsychopathic criminal counterparts in terms of the degree and nature of their violence, recidivism and response to treatment (see above).

B. Physiological Correlates of Psychopathy

There are limited data on the physiological correlates of psychopathy, most of it based on psychophysiological activity, adrenal catecholamine secretion, and glucose metabolism. Little is known about neurotransmitter function in psychopaths.

(1) Autonomic and Central Nervous System

Hare (1980a) provided an early review on the psychophysiological correlates of psychopathy. Psychopaths appear to be electrodermally hyporesponsive to relatively strong stimuli and to the threat of pain or punishment. These findings
are open to several interpretations. However, since the stimuli used typically are considered painful and highly aversive, a reasonable interpretation is that psychopaths experience little apprehension or anticipatory fear. Complicating the picture is the finding that while anticipating delivery of a painful stimulus psychopaths show relatively large increases in heart rate. This pattern of electrodermal hyporesponsivity and cardiac hyperresponsivity to threat has been interpreted as reflecting the operation of an active, efficient coping process and the inhibition of fear arousal (see Hare, Frazelle & Cox 1978; Olgloff and Wong, 1990). Presumably, situations that have great emotional consequences for most people have little impact on psychopaths.

An interesting relationship between underarousal and criminality has recently been reported in a prospective study (Raine, Venables & Williams, 1990). Both central and autonomic nervous system arousal were indexed using electrodermal, cardiovascular and cerebral cortical activity measures. A discriminant function analysis correctly classified (utilizing all three measures) 75% of youths at age 15 who subsequently engaged in criminal behaviour nine years later. Specifically, these youths had lowered electrodermal, cardiovascular and cortical activity. The authors suggested that a diffuse brainstem mechanism may be dysfunctional in populations of criminals (Raine et al, 1990). This criminal group was not diagnosed for psychopathy per se; however, it would be reasonable
to assume that a proportion of these individuals were psychopaths or that they exhibited psychopathic tendencies.

(2) Adrenal Catecholamine Activity

Lidberg, Levander, Schalling, & Lidberg (1978) measured catecholamine (adrenalin and noradrenalin) secretion in males awaiting what is ordinarily a stressful event: a court appearance. They found that psychopaths (defined by low scores on self-report measures of socialization and empathy, and a high score on a self-report measure of impulsivity) showed less of an increase in catecholamine secretion prior to their court appearance than did nonpsychopaths (high socialization and empathy scores and a low impulsivity score). The authors suggested that the psychopathic subjects experienced less anticipatory discomfort and excitement than did the nonpsychopaths.

Woodman and colleagues (Woodman, Hinton & O'Neill, 1978; Woodman & Hinton, 1978) found that a violent subgroup of maximum security patients could be differentiated from nonviolent patients on the basis of their adrenal response to a stressor. Thus, in response to both psychological and physiological stressors the violent patients showed less of an increase in adrenalin, noradrenalin and cortisol secretion than did the nonviolent patients.

(3) Glucose Metabolism

In a series of studies Virkkunen and associates have consistently reported reduced glucose metabolism in habitually
violent offenders when compared to control groups. In response to the glucose tolerance test, these individuals had the lowest blood glucose nadir and displayed a prolonged return from the reactive hypoglycemia to basal levels (for an extensive review see Roy, Virkkunen, Guthrie & Linnoila, 1986).

Although the functional link between reduced glucose metabolism and human impulsive violence remains to be established, animal research may provide clues as to potential mediating mechanisms. For example, lesions of the suprachiasmatic nucleus, in addition to disrupting behavioural circadian rhythmicity, increase the susceptibility of rats to hypoglycemia (Roy et al, 1986). These authors have speculated that the reduced glucose metabolism and altered behaviour in the impulsive violent offender may be related to a dysfunction of the suprachiasmatic regulatory system. This notion is strengthened by the anatomical evidence that the suprachiasmatic nucleus is densely innervated by serotonergic neurons originating in the midbrain raphe nuclei (Steinbusch & Nieuwenhuys, 1983). Based on this evidence, Roy, Virkkunen and Linnoila (1990) have proposed that a functional serotonergic deficit may manifest itself in poor impulse control, circadian rhythm dysregulation, and impaired glucose metabolism, which may in turn contribute to impulsive behaviour, suicide attempts and type II alcohol abuse.

The studies cited above suggest that individuals who are considered to have psychopathic tendencies may be constitutionally different from their nonpsychopathic
counterparts. They also suggest that serotonin may play a functional role in psychopathy.

C. Serotonin: A Biogenic Amine

(1) Synthesis, Storage and Metabolism of Serotonin

Serotonin (5-HT), a biologically active amine, is distributed widely, both in plants and animals. It has complex physiological and pathological effects (Burkhalter and Frick, 1989). Central levels of serotonin reflect approximately 1-2% of the total serotonin concentration in the body. This monoamine cannot cross the blood-brain barrier; thus, 5-HT in the central nervous system is synthesized locally. Serotonin is synthesized by hydroxylation of L-tryptophan to 5-hydroxytryptophan which is then decarboxylated to serotonin. L-tryptophan, an essential amino acid, competes with neutral amino acids for facilitated carrier transport across the blood-brain barrier (Marsden, 1991). Since neuronal synthesis of 5-HT depends on circulating levels of L-tryptophan, central concentrations of serotonin can be altered by dietary intake of this amino acid.

Serotonin is metabolized by monoamine oxidase (type A; MAO-A) yielding an intermediate product, 5-hydroxyindolacetaldehyde, which is oxidized further to yield the major metabolite, 5-hydroxyindolacetic acid (5-HIAA) (Burkhalter & Frick, 1989).

Peripherally 5-HT is synthesized in most of the tissues in which it is stored with the exception of the platelets found in the blood. Platelets do not contain the necessary enzymes for synthesis of serotonin; therefore, circulating serotonin is
actively transported through the platelet membrane (Verbeuren, 1989). Peripheral concentrations of serotonin are typically reported in terms of whole blood, platelet, and plasma concentrations (Anderson, Feibel & Cohen, 1987). Plasma 5-HT concentrations are correlated with whole blood 5-HT and platelet 5-HT levels; however, plasma 5-HIAA concentrations are not significantly correlated with whole blood, platelet or plasma 5-HT (Ortiz, Artigas & Gelpi, 1988).

(2) Measurement of Serotonergic Activity

There are a number of methods available to study the status of serotonergic functioning in humans. Central serotonin activity can be measured through direct and indirect methods. Peripheral serotonin activity is measured directly by assessing whole blood, platelet or plasma concentrations. An exhaustive review of the various methods assessing serotonergic functioning in humans is not provided; however, a brief discussion of the methods used in the studies reported herein is given:

(i) Central Measures: 5-Hydroxyindolacetic acid

Lumbar cerebrospinal fluid (CSF) contains marginally detectable concentrations of 5-HT. However, the principal metabolite of 5-HT, 5-HIAA is readily detectable and commonly measured in CSF (Murphy, Mellow, Sunderland, Aulakh, Lawlor & Zohar, 1990; Murphy, 1990; Boyer & Feighner, 1991). CSF concentrations of 5-HIAA are usually considered to be a reflection of the metabolism of serotonin in the brain. It has been argued, however, that concentrations of 5-HIAA in fact
reflect MAO-A activity and not serotonergic activity per se (Wolf, Youdim & Kuhn, 1985).

(ii) Central measures: Hormonal probes

It has been suggested that the neuroendocrine consequences of manipulating the serotonergic system (through peripheral administration of centrally active serotonergic agents) may provide an indirect measure of central 5-HT activity (Cocarro, Siever, Klar, Maurer, Cochrane, Cooper, Mohs & Davis, 1989). A promising, though somewhat controversial, index of central 5-HT activity is the prolactin response to fenfluramine (van Praag, Lemus & Kahn 1987). Fenfluramine is a serotonin agonist which acts by stimulating the presynaptic release of serotonin and by inhibiting 5-HT reuptake, thus increasing the amount of 5-HT available to the central nervous system (Quattrone, Di Renzo, Schettini, Tedeschi & Scopacasa, 1978). In addition to its presynaptic effects, fenfluramine stimulates the 5-HT postsynaptic receptor via its active metabolite, norfenfluramine (Cocarro et al, 1989). Because of the simultaneous action pre- and postsynaptically, it has been suggested that measurement of the peripheral effects of fenfluramine can provide a net index of central 5-HT functioning (Murphy, 1990). Whereas prolactin release from the pituitary is inhibited by dopamine, there is evidence to suggest that 5-HT acts to release prolactin. Serotonergic neurons projecting from the raphe nuclei to the mediobasal hypothalamus provide an anatomical pathway for the release of prolactin (Murphy et al, 1990). Thus, since
fenfluramine both releases serotonin from presynaptic stores and also acts postsynaptically, greater functional serotonergic responsivity to fenfluramine stimulation, indicated by higher levels of prolactin or cortisol, may reflect an increased intracellular presynaptic availability of the transmitter or changes in postsynaptic sensitivity. Those individuals who have blunted prolactin responses are presumed to have diminished central serotonergic availability.

The use of hormonal probes as indices of central serotonergic functioning has been questioned. The primary concern is that pharmacological agents such as fenfluramine are relatively nonselective (van Praag et al, 1987). Despite this controversy these hormonal probes offer an alternative to the invasive techniques of a lumbar puncture. Further, the results of investigations using hormonal probes are consistent with data obtained by more direct measures of central serotonergic functioning.

(3) Relationship Between Central and Peripheral 5-HT

Just as alterations in CSF 5-HIAA concentrations may reflect a myriad of underlying processes, a large number of factors may underlie a change in peripheral serotonin levels. For example, blood serotonin is dependent on peripheral levels of tryptophan and platelet physiology dynamics (Raleigh, McGuire, Brammer & Yuwiler 1984). Furthermore, the relationship between blood and brain serotonin levels has yet to be fully specified. Under some conditions changes in blood serotonin levels parallel changes in
brain serotonin levels. Both brain and blood serotonergic activity are similarly affected by pharmacological interventions that augment precursor availability (e.g. tryptophan loading), that inhibit biosynthetic enzymes (e.g. p-chlorophenylalanine treatment), and that disrupt serotonin storage (e.g. fenfluramine hydrochloride treatment) (Murphy et al, 1990).

Plasma concentration of 5-HIAA provides a rough estimate of 5-HT catabolism. It has been suggested that the plasma measurement of 5-HT, 5-HIAA and platelet 5-HT provides a peripheral model for studying the presynaptic physiology of 5-HT in terms of synthesis, uptake, and degradation by MAO-A (Sarrias, Artigas, Martinez & Gelpi, 1989). These same authors suggest that they have preliminary evidence demonstrating that 5-HT and 5-HIAA in the CSF correlate with several of the measures in the blood. Assuming that they are correct, changes seen in peripheral 5-HT may also occur in the functionally active fraction of 5-HT in the CNS. The importance of free 5-HT and the factors that control free 5-HT levels in the general circulation are unclear (Anderson, Feibel & Cohen, 1987).

(4) Methodological Considerations

It has been well established that serotonergic activity has an annual rhythmicity. This has been found both in CSF 5-HIAA measures (Brewereton, Berrettini, Nurnberger & Linnoila, 1988), and plasma 5-HIAA levels (Ortiz et al, 1988; Sarrias et al, 1989). Plasma pools of 5-HIAA range from mean values of 4.8 to 9.3 ng/ml throughout the year, with fall/winter values showing an
average of 7.7 ng/ml and spring/summer values averaging 5.6 ng/ml. The trend for plasma 5-HT however varies in the opposite direction, with lowest values reported in the fall (Sarrias, et al, 1989). This implies that it is essential to report the time of year in which plasma 5-HT and 5-HIAA are measured, and to make within and between subject comparisons during a very circumscribed time period.

Peripheral measures of 5-HT and 5-HIAA are considered to be somewhat variable over time and thus two measurements taken over two different days are required for the data to be reliable (Davis, Yu, Durden, Pease, Green, Menzies, Gordon, Templema & Boulton, 1991).

The relationships between subject variables such as age, height, weight, race, diet, smoking and alcohol consumption are well documented for CSF measures of 5-HIAA (Davis, 1989). CSF measures of 5-HIAA are negatively correlated with height, positively correlated with age, generally lower in men than in women, independent of alcoholism and smoking, and under familial influence--determined largely by cultural heritability rather than genetics.

The relationship between peripheral concentrations of plasma 5-HT and 5-HIAA and subject variables has only recently been reported (Ortiz et al, 1988). Plasma and whole blood 5-HT are significantly higher in women than men whereas plasma 5-HIAA is found to be lower in women compared to men (note: this relationship is the inverse of differences in CSF 5-HIAA between
men and women). Small but significant positive correlations are found between 5-HIAA, age and weight, while plasma 5-HT is negatively correlated with weight and independent of age. The authors suggest that some of the relationships between plasma 5-HT and 5-HIAA may be a result of the mixed gender nature of their sample. However, a separate analysis of these demographic variables and their relationship to gender has not been performed. Meal intake does not appreciably change baseline plasma 5-HT levels whereas plasma 5-HIAA levels are substantially increased from pre-meal levels. Finally, Ortiz et al (1988) suggest that the circadian changes of 5-HT may be, in part, a consequence of general activity level, although the nature of the relationship has yet to be determined.

The demographic and lifestyle variables and their purported relationship to plasma 5-HT and 5-HIAA are based on a single study. When compared with reports from the numerous studies investigating the relationship between these variables and central measures of 5-HIAA, the plasma findings are less robust. What is evident, however, is that both demographic and lifestyle variables must not only be recorded but taken into consideration when investigating any behavioural correlates of plasma 5-HT and 5-HIAA concentrations.

D. Serotonin as a Biochemical Marker of Psychopathology

The central serotonin pathways represent a complex neuroanatomical system in terms of morphological differences in the innervation of cortical structures and the diversity of
serotonin receptors and their biochemical or functional linkages (Marsden, 1991). This diversity in part explains how a transmitter system derived from discrete groups of nerve cells in the midbrain raphe nuclei, yet providing a wide innervation of forebrain areas, is involved in the control of behaviours such as mood, motor function, cognition, feeding and sex (Meltzer, 1991).

Reduced serotonergic functioning, indexed through CSF levels of 5-HIAA in living subjects or by postmortem imipramine or 5-HT₂ binding in the brain, is associated with a variety of psychiatric disturbances and personality disorders. For example, low CSF 5-HIAA has been associated with individuals suffering from obsessive-compulsive disorder, schizoaffective disorder, anxiety, schizophrenia and unipolar depression (Depue & Spoont, 1986). Further, low metabolite concentrations have been associated with personality disorders, such as Borderline or Antisocial. Cutting across personality disorders and psychiatric syndromes are specific traits, such as aggression and impulsivity, which are consistently related to lowered serotonergic functioning (Coccaro, 1989).

It is difficult to understand how a deficiency or increase in the activity of only one neurotransmitter could result in a diversity of apparently unrelated behavioural conditions (Boyer and Feighner, 1991). Indeed this criticism could be aimed at any study assessing neurotransmitter levels in vivo. No matter how sophisticated and technologically advanced the measurement technique is, it seems simplistic to assume that a single
neurotransmitter would be correlated with numerous behavioural conditions. However, multiple 5-HT receptor subtypes are known to exist and could account in part for the diversity. At least seven different 5-HT receptor subtypes have now been identified (Peroutka, Schmidt, Sleight & Harrington, 1990). It seems likely that over time many more will be isolated. Furthermore, brain regions receiving serotonergic innervation differ from each other in terms of the concentration of particular receptor subtypes. Thus, it is conceivable that a net increase or decrease in central 5-HT activity could account for a variety of seemingly unrelated behavioural symptoms.

A number of investigators who study serotonergic activity and its relation to psychiatric/personality dimensions provide additional considerations for the discussion of the results of their biobehavioural studies: 1) The serotonergic system is anatomically and functionally linked to the other neurotransmitter systems so that alterations in 5-HT activity often produce changes in measures of dopaminergic and noradrenergic functioning (Boyer & Feighner, 1991; Soubrie, 1986; Coccaro & Murphy, 1990); 2) Many separate metabolic processes are involved in the formation, storage and release of 5-HIAA and 5-HT. Therefore, altered levels of 5-HT in the CSF may reflect a gross abnormality in 5-HT synthesis and/or storage, or even deficiencies in serotonergic neurons (Miczek & Donat, 1989; Coccaro & Murphy, 1990); 3) Functional consequences cannot readily be inferred from a single set of CSF 5-HIAA
values. It is necessary to understand the dynamic processes that may contribute to the values, such as receptor hypo- versus hypersensitivity (van Praag et al, 1987; Murphy et al, 1990; Wetzler, Kahn, Asnis, Korn & van Praag, 1991); and, 4) The validity of some of the serotonin research methods needs to be more clearly established. For example, the relationship between brain and lumbar CSF levels of 5-HIAA is unresolved (Murphy, 1990; Boyer & Feighner, 1991).

E. Behavioural Correlates of Serotonin

(1) Generalized Aggression

The animal literature suggests that multiple-transmitter systems (e.g. noradrenergic, dopaminergic, and serotonergic) modulate the complex behavioural patterns of aggression (Olivier, Mos, Tulp, Schipper & Bevan, 1989). However, there appears to be consistent evidence that serotonin plays a major role in the modulation of aggression. In fact, 5-HT attenuation of aggression has been observed irrespective of the species under consideration (Bevan, 1989). Early work suggested that increased 5-HT activity was associated with a decrease in aggressive behaviour whereas an overall decrease in serotonergic activity was associated with increased aggressiveness (Valzelli, 1981). For example, muricidal behaviour, shock-induced fighting and filicide are all increased by chemical or electrolytic lesioning of central serotonergic neurons and these behaviours are inhibited by various pharmacological serotonergic antagonists (for review see Olivier et al, 1989; and, Soubrie, 1986).
In parallel with the animal literature, this same inverse relationship between decreased serotonergic activity and increased aggressiveness has been demonstrated in humans. Brown and colleagues first reported a significant correlation between history of aggressive behaviour and CSF levels of 5-HIAA (Brown, Goodwin, Ballenger, Goyer & Major, 1979). In military men with a variety of personality disorders, aggressiveness was negatively correlated with lowered CSF concentrations of 5-HIAA. These results were replicated in a later study and, at that time, it was reported that the psychopathic deviate scale (Pd) of the Minnesota Multiphasic Personality Inventory (MMPI) was correlated with CSF 5-HIAA concentrations (Brown, Ebert, Goyer, Jimerson, Klein, Bunney & Goodwin, 1982). Normal volunteers produced similar results: the "urge to act out hostility" was negatively correlated with CSF 5-HIAA levels (Roy, Adinoff & Linnoila, 1988). Similarly, children and adolescents who were classified as having disruptive behaviour disorders associated with aggression displayed low concentrations of 5-HIAA in the CSF (Kruisi, Rapoport, Hamburger, Hibbs, Potter, Lenane & Brown, 1990).

Moss, Yao and Panzak (1990) compared prolactin responses to the 5-HT agonist, m-chlorophenylpiperazine (m-CPP) in individuals diagnosed with Antisocial Personality Disorder and in a control group of normal subjects. A significant inverse relationship between prolactin responses and indices of assaultive aggression was found. The reduced prolactin response to m-CPP by those in
the APD group suggests decreased serotonergic functioning. This pattern of response parallels the response to fenfluramine described previously.

Based on the large animal literature and the limited human data, the link between serotonergic activity and aggression has been well established. However, as discussed earlier it is difficult to assume that the serotonergic system with its wide distribution of various 5-HT receptors, cell bodies and projections in the CNS mediates aggression in an unidimensional manner (Olivier et al, 1989). That is, 5-HT may not precipitate generalized aggression per se but may play a more modulatory role in the expression of aggression (Coccaro, 1989). More detailed analysis of the behavioural components of animal and human aggression supports the notion that central 5-HT activity may be more specifically related to a lowered threshold for aggressive responses rather than to the actual manifestation of aggression.

Based on reports from the animal literature, which indicate that decreased serotonergic functioning is associated with facilitation of aggression and facilitation of other interactions with conspecifics (e.g. social exploration and sexual behaviour), Soubrie (1986) suggests that decreased 5-HT functioning results in the triggering of behaviours which are normally subject to inhibitory influences. Consistent with this suggestion, previous exposure of mice to rats can prevent muricidal responses elicited by chemical lesioning of 5-HT neurons (Mizcek & Donat, 1989). Further, animals with reduced 5-HT activity are characterized as
hyperexcitable, hyperirritable, and hypersensitive (Valzelli, 1981). While consistent with Soubrie's (1986) suggestion, Coccaro et al (1989) formulate a more specific inference; that is, that decreased serotonergic activity may more specifically reflect irritable, impulsive aggression.

(2) Impulsivity and Irritable Aggression

An examination of the human literature reported above reveals that neither specific indices of the nature of the aggression (i.e. impulsive or premeditated) nor global, lifetime measures of impulsivity were assessed (e.g. Brown et al, 1979; Brown et al, 1982; and Roy et al 1988). In the one study cited above, in which impulsivity was measured, it was not found to be correlated with fenfluramine induced prolactin responses (Moss et al, 1990). These authors measured impulsivity via self-report indices and a cognitive tempo task between which they report a weak correlation. It would be interesting to assess whether their measures of 'assaultive aggression' would be considered impulsive in nature.

There is an increasing number of studies which support Roy and Linnoila's (1989) speculation that a deficit in serotonergic activity is manifested in poor impulse control. This weak inhibitory control is expressed in attempts at suicide, violence towards others and alcohol abuse. The relevant human literature is summarized below:

Coccaro and colleagues (1989) reported an inverse relationship between the prolactin response to fenfluramine and
severity of assaultiveness, impulsivity and a history of suicide attempts. Specifically, they found that reduced prolactin responses (which purportedly indicate lower availability of central serotonin) were significantly associated with self-report measures of irritable, impulsive, and motoric aggression in a heterogeneous group of personality disordered patients. Further, patients with Borderline Personality Disorder (of which one of the key characteristics is impulsivity) produced even smaller prolactin responses than did those with other types of personality disorders. It is interesting to note that these authors found reduced 5-HT activity associated with: (a) patients with affective disorders and personality disordered individuals; (b) a history of suicide attempts in patients in either group; and, (c) impulsive aggression in only the personality disorder patients.

Fishbein, Lozovsky & Jaffe (1989) examined both prolactin and cortisol responses to the fenfluramine challenge in a group of substance abusers. In their group of substance abusers the positive correlation between peak prolactin and cortisol response to the 5-HT agonist fenfluramine was stronger with impulsivity than with physical aggressiveness. These results are inconsistent with the findings cited above, where an inverse relationship was found between prolactin responses, impulsivity and aggression (Moss et al, 1990; and Coccaro, et al, 1989). However, in the Fishbein et al (1989) study, the impulsive subjects had higher baseline prolactin levels than did the non-
impulsive subjects. This may have confounded any subsequent response to fenfluramine. Moreover, the authors speculate that the discrepancies may be partially due to the differences in subject populations: Coccaro, et al (1989) had a mixed group of personality disorder patients; Moss et al (1990) employed a group of Antisocial Personality Disordered (APD) individuals who also met the criteria for a past or current psychoactive substance abuse disorder; and, all of the subjects employed in the study conducted by Fishbein et al, (1989) were patients admitted to an addiction research center of whom 72% met the criteria for alcohol abuse or dependence, 20% met the criteria for APD, and 8% met the criteria for Borderline Personality disorder. With these discrepancies it is difficult to reconcile the inconsistent findings reported by Fishbein et al (1989); however, it is consistent with the hypothesis that biological markers are more likely to be related to impulsivity than generalized aggression.

Linnoila and colleagues provide one of the most convincing studies to link impulsive violence with lowered serotonergic activity (Linnoila, Virkkunen, Scheinin, Nuutila, Rimon & Goodwin, 1983). All subjects involved in the study had either murdered or attempted to murder their victims. Two groups were established, differentiated solely on the degree of impulsivity involved in their crimes. The crimes committed by the impulsive offenders were carried out without provocation or premeditation and their victims were generally not known to them. In contrast,
the nonimpulsive offenders had murdered or attempted to murder after some premeditation; the victims were known to them; and, a rationale for the act could be formulated based on psychiatric evaluation. The subjects who were classified as 'impulsive' received a diagnosis of APD or Intermittent Explosive Disorder, and all of these subjects received a concurrent diagnosis of Borderline Personality Disorder.

In general the results of the study suggest that the number of violent episodes was associated with CSF levels of 5-HIAA: offenders with more than one episode of violence had significantly lower concentrations of 5-HIAA than did those who committed more than one crime. Specifically, the impulsive offenders had significantly lower CSF 5-HIAA concentrations than did the nonimpulsive violent offenders.

The relationship between low CSF 5-HIAA levels and impulsivity has been extended to include an examination of recidivism. Specifically, Virkunnen's group found that low CSF 5-HIAA concentrations and low blood glucose nadir measurements correctly predicted 84% of the recidivistic offenders in their sample (Virkunnen, De Jong, Bartko, Goodwin & Linnoila, 1989).

There is a dearth of evidence on the relationship between peripheral serotonergic activity and generalized or impulsive aggression. However, of the few studies reported to date, the results with peripheral indices are consistent with the data obtained from central measures. For example, blood platelet uptake of serotonin was lower in individuals diagnosed as having
episodic aggression than it was in a normal control group (Brown, Kent, Bryant, Gevendon, Campbell, Felthous, Barratt and Rose, 1989). Even more interesting is that in subjects diagnosed with episodic aggression, 5-HT was negatively correlated with impulsivity but not with anger expression. Similarly, Stoff and colleagues reported that reduced 5-HT platelet binding was lower in children with conduct disorder than in an age-matched control group (Stoff, George & Nathan, 1986). Since blood platelet indices may serve as a peripheral model for serotonergic neuronal functioning (Sarrias et al 1989), these findings are consistent with the relationship between diminished central 5-HT functioning and aggressive/impulsive behaviour.

There have been only two investigations of the relationship between whole blood 5-HT concentrations and aggressive behaviour. The first study, reported by Greenberg and Coleman (1976), found an inverse relationship between 5-HT and both hyperactivity and aggression in mentally retarded patients. In contrast, a more recent investigation found a positive correlation between whole blood 5-HT and conduct disorder ratings (Plizsa, Rogeness, Renner, Sherman & Broussard, 1988). It is difficult to reconcile these findings; however, in a separate study investigating the relationship between serotonergic activity and autism, whole blood 5-HT levels were found to be negatively correlated with the prolactin response to fenfluramine and positively correlated with platelet 5-HT binding (McBride, Anderson, Hertzig, Sweeney, Kream, Cohen, & Mann, 1989). This suggests that decreased
central serotonergic activity (as indexed by blunted prolactin responses) is associated with decreases in platelet binding and uptake of peripheral 5-HT, and increases in whole blood serotonin levels. These putative relationships between peripheral and central indices of serotonergic functioning must be evaluated with caution as they were obtained in a small sample.

From the evidence cited above it is clear that serotonin modulates rather than initiates aggression. That is, serotonin does not appear to be responsible for the manifestation of aggression per se, but decreased serotonergic activity is associated with the expression of aggression. This expression of aggression appears to be linked to a more basic underlying trait of impulsivity whereby a lowered threshold of responsivity increases the propensity for aggressiveness. We still lack a clear understanding of how peripheral indices of serotonin reflect central indices, or how the effects of serotonin on aggression and impulsive aggressive behaviours are mediated.

(3) The Proposed Serotonin and Psychopathy Relationship

Most of the studies cited above have used as subjects individuals who have either come into contact with correctional services or psychiatric settings for criminal or violent behaviour, or, in the case of juveniles, who displayed disruptive behaviour. Despite a wide variety of personality diagnoses based on DSM-III-R criteria, a common theme emerges: decreased serotonergic activity is associated with impulsive aggressive/violent behaviour. Characteristics which ordinarily
help to inhibit antisocial and aggressive behaviour, such as empathy, close emotional bonds, and fear of punishment, are lacking or impaired in psychopaths (Hare, 1991). Given this absence of behavioural constraint it is not surprising that psychopaths are responsible for a disproportionate amount of serious repetitive crime and violence in society (Hare and MacPherson, 1984). Indeed, the degree and nature of violence that psychopaths exhibit are similar to the behaviours associated with diminished serotonergic functioning.

Williamson, Hare and Wong (1987) reviewed the nature of the violent acts perpetrated by psychopaths and nonpsychopaths. The results of the review can be summarized as follows: (1) The motive for offences involving a victim was generally material gain for the psychopaths and strong emotional arousal (e.g. jealousy, heated arguments, etc.) for the nonpsychopaths. (2) When murder was the target offence, the victim of the psychopath was very likely to be a stranger whereas the victim of the nonpsychopath was more likely known to him. (3) Psychopaths and nonpsychopaths did not differ in the degree of non-lethal harm inflicted on their victims; however, there is evidence that psychopaths commit a much greater number of violent crimes than do other criminals (Hare & McPherson, 1984; Wong 1984). These conclusions are in line with the suggestion that the violent and aggressive behaviour of psychopaths is frequently associated with a lack of emotions and relatively weak inhibitory constraints (Cleckley, 1976).
In summary, serotonergic 'traits' reported in the literature are remarkably similar to psychopathic traits as defined by the PCL-R.

F. Purpose

The purpose of this study is to provide much needed data on the biochemical correlates of psychopathy. Specifically, the study attempts to integrate theory and findings from two areas of research: psychopathy and altered serotonergic functioning. The literature has consistently revealed a relationship between serotonin and impulsive/violent and aggressive behaviour. Psychopathy, as measured by the PCL-R, provides a reliable and valid unifying construct for both behaviour and personality traits which, to a large extent, are also typically associated with altered serotonergic functioning.

In this study plasma 5-HT and its major metabolite 5-HIAA were examined in a group of male offenders, assessed for psychopathy according to Hare's Psychopathy Checklist-Revised (Hare, 1991). This is the first attempt to systematically investigate the relationship between serotonin and the clearly defined construct of psychopathy at either the central or peripheral level. Based on the available literature it is predicted that plasma 5-HT and 5-HIAA levels will correlate significantly with ratings of psychopathy, particularly with the PCL-R Factor 2 characterized by violent, aggressive and impulsive behaviours (Harpur & Hare, 1991).
II. Method

A. Subjects

Subjects were male volunteers from a medium security federal institution located in Abbotsford, B.C. All participants were serving a minimum two year sentence. They were recruited by "word-of-mouth" advertising. Permission to conduct the study was obtained from the Ethics Committee at the University of British Columbia, the Warden of the Institution, and the Inmates' Committee. Each subject provided informed consent for blood sampling, permission to inspect his institutional files and, participation in a videotaped interview. Each subject's anonymity was assured through the use of a data coding system. Subjects were assured the results would be confidential and that the exclusive purpose of the blood sampling was to analyze the presence of naturally occurring substances, thereby reducing their concern about potential drug testing or AIDS testing. For his participation, each subject was paid a total of $25.00, deposited directly into his institutional account.

Blood samples were obtained from 60 subjects between the dates of December 3rd and 14th. The data from six of these subjects were not included in the analyses for the following reasons: two subjects were transferred prior to completion of the psychopathy assessment; one subject admitted to eating prior to blood sampling; and the data for three subjects were eliminated due to difficulties with the biochemical assays. The final sample consisted of 54 subjects ranging in age from 18-53
years ($M = 27.3$, $SD = 6.2$) and the racial composition of the sample was 74% white, 22% Native American Indian, and 4% other.

B. Procedure

A laboratory was installed in one of the rooms available for psychological testing within the institution. Subjects were asked to fast from midnight of the night before sampling. Two blood samples were taken from each subject approximately one week apart (range 6-8 days), between the hours of 7:30 and 10:00 am. This time interval was kept constant for the two blood samples in order to minimize the effect of circadian rhythmicity in serotonin levels and metabolism.

Prior to the first blood draw (obtained in week one), the subject was asked to sign the appropriate consent form (see Appendix A). After providing consent, he was weighed and asked to complete the self-report forms (see Appendices B and C) which asked about lifestyle variables. These self-report measures were completed prior to the blood draw on both week one and week two. The subject was then seated in the testing room and his arm was sterilized with an alcohol swab and a tourniquet applied. Blood samples were collected by a registered medical technician. A total of between 16 to 20 ml of blood was collected from each subject into four 4.5 ml vacuum tubes containing sodium citrate as an anticoagulant. After the blood sampling the subjects was assessed for faintness or weakness before leaving the testing room.

The four vacu-tubes were labelled and placed into the
centrifuge within thirty minutes of the initial draw. These whole blood samples were centrifuged at 2000 x g for approximately 30 minutes or until the sample had adequately separated and the plasma was clear. The plasma fraction was pipetted, using a single-use disposable pipette, and transferred into two 12 -15 ml plastic centrifuge tubes. This plasma was centrifuged for approximately 20 minutes at 3000 x g to separate the platelet sample from the plasma. The new fraction of plasma was transferred into four 5 ml glass tubes. One of these tubes was designated for a biochemical assay of serotonin and its metabolite, 5-hydroxyindolacetic acid. To this tube, an antioxidant was added. All plasma and platelet samples were labelled and stored in dry ice and transported to an ultra-low temperature freezer (-70 C) outside of the institution. Within two weeks of the final blood sampling all samples were packed in dry ice and shipped in a light-proof box by air freight to the Neuropsychiatry Research Unit (NRU) at the University of Saskatchewan. Assays for plasma concentrations of 5-HT and 5-HIAA were conducted under the supervision of Dr. A. Boulton, director of NRU, Dr. B. Davis and Dr. P. Yu of NRU, within 3 months of receipt of the samples. All personnel were blind to the ratings of psychopathy.

The PCL-R interview was conducted either prior to or after the subject had provided the blood samples. Institutional file information was obtained within two weeks of the PCL-R interview. File information was updated on subjects who had completed the
PCL-R interview prior to the initiation of this study.

C. Measures

(1) Assessment of Psychopathy

Psychopathy ratings were based on a semi-structured interview and file information. Institutional files typically contained background and demographic information, criminal history, institutional progress reports, and parole or probation officer reports.

(i) Total Scores

The Psychopathy Checklist contains 20 items which are scored on the basis of the file and interview information (see Appendix D). Each item is scored on a scale of 0 - 2: 2 indicates that the item definitely applies; 1 indicates that it may or may not apply; and, 0 indicates that it definitely does not apply. Items are summed to yield a total score which can range from 0 - 40 and can be pro-rated (for omitted items) if necessary.

(ii) Factor Scores

Factor scores are obtained by summing the scores on items 1, 2, 4, 5, 6, 7, 8, and 16 of the PCL-R for Factor 1 and summing the scores on items 3, 9, 10, 12, 13, 14, 15, 18, and 19 for Factor 2.

Interrater reliability (intraclass correlation coefficient, or ICC-1) for the PCL-R was determined for twenty subjects by independent raters, using both the videotaped interviews and file information. An intraclass correlation of 0.83 was obtained for the PCL-R ratings. All clinical interviews and psychopathy
ratings were blind to the results of the biochemical assays.

The total mean checklist score obtained for this sample was 26.4 (SD = 7.0), a score that is slightly higher than that obtained with much larger samples of inmates (Hare, 1991). Although the primary analyses were correlational in nature, a supplementary analysis was performed on group data. For the latter analysis the total scores were used to form two groups: psychopaths (n=20) were defined by a score of at least 30 on the PCL-R; the remaining subjects (n=34) were defined as nonpsychopaths.

(iii) Impulsivity Scores

In light of reports in the literature of the putative relationship between serotonin and impulsivity, a separate impulsivity sub-scale of the PCL-R checklist was calculated. This subscale consists of four items which are characterized by impulsive behaviour. These are: Item (1) Proneness to boredom/need for stimulation; Item (10) Poor behavioural controls; Item (11) Promiscuous Sexual Behaviour; and, Item (14) Impulsivity.

These items are scored using the information detailed above, and represent lifetime impulsive behaviour. For the behaviours and personality characteristics considered in each item please see Appendix E.

(vi) Interaction Variable

Most recently, an interaction of the factor structure of the PCL-R (Factor 1 x Factor 2) was found to provide a unique
contribution, above and beyond the contribution of Factor 1, Factor 2, and Total PCL-R scores to the post-diction of violence variables (Harpur & Hare, 1991). In consideration of these results, the interaction variable (\(F1 \times F2\)) was calculated by multiplying Factor 1 by Factor 2 and included in the statistical analyses.

(2) **Index Crime Variables**

In an attempt to replicate reports that serotonergic indices are correlated with type of index crime the following variables were coded:

(i) **Type of Index Crime**

Information on the nature of the index crime (the crime committed resulting in the offender's current incarceration) was obtained from the PCL-R interview questions and from police reports and victim statements. Six classes of index crime were categorized (see Appendix F).

(ii) **Level of Aggression**

Each coded index crime was rated for the level of aggression involved during its commission. A seven point scale was used, with scores ranging from 1 (resulted in death) to 7 (no aggression (See Appendix G).

(iii) **Motive**

Motives were determined for index crimes that resulted in the death of a victim. The motives were categorized as follows: 1) material gain; 2) strong emotional arousal (jealousy, rage, heated arguments); 3) revenge or retribution; 4) sexual
gratification; 5) self-defense; 6) none; and 7) no information. Assessment of the motive behind the crime was determined from self-report information contained in the PCL-R interview and from police reports.

(iv) Impulsivity versus Premeditation

This variable was coded categorically: impulsive versus premeditation. The coding proved to be somewhat difficult since in a large number of cases one aspect of the crime, say robbery, was planned whereas the subsequent violence was impulsive. For the purposes of this study, if a premeditated act resulted in impulsive violence, the index crime was coded as impulsive. This is in line with rating the index crime in terms of the level of aggression involved.

(vi) Relationship to the Victim

This variable was coded for those index crimes that resulted in the death of a victim. The status of the victim was categorized as 1 = family; 2 = acquaintance/friend; and, 3 = stranger.

(3) Demographic Variables

Subjects' birthdates and weights were recorded. Race was also coded: Caucasian (n=40) and non-Caucasian (n=14).

(4) Lifestyles Variables

(i) Alcohol Use Ratings

A five point global rating for history of alcohol abuse was completed: the scores ranged from 1 (no use) to 5 (chronic problematic use). Each rating was based according to (a) DSM-III-
R criteria; (b) medical and file information indicating history of alcohol abuse; and, (c) self-report information regarding history of alcohol use. Interrater reliability was established for history of alcohol use. The ICC-1 was 0.85. Use of alcohol (yes /no ) during the twenty-four hours period prior to blood draw was determined from self-report measures (see Appendix B).

(ii) Substance Use Ratings

A five point global rating for history of substance abuse was completed for each subject 1 (no use) to 5 (chronic problematic use). Each substance abuse rating was made according to (a) DSM-III-R criteria; (b) medical and file information indicating history of substance abuse; and, (c) self-report information regarding history of substance use. Interrater reliability was established for history of substance use. The ICC-1 was 0.93.

Substance use during the twenty-four hours prior to the blood draw was estimated from self-report (see Appendix B). It was apparent that some subjects were using both prescription and nonprescription drugs. Subjects were asked to describe any medication they were currently taking. They were able to describe fairly well the type of nonprescription drugs they had used; however, their description of prescribed medication was sometimes vague (e.g. "bug juice"). The variety of drugs used, and the difficulty of estimating the amount of drug intake without the aid of blood assay or urinanalysis, precluded a detailed analysis of the effect of drugs on biochemical activity.
In order to analyze the relationship between substance use and biochemical variables, a score of 0 = absent or 1 = present was assigned to each of the following nine categories for each of the 24 hour periods prior to blood sampling. The categories were: 1) Narcotic analgesics (e.g. heroin, morphine, demerol); 2) Sedatives (e.g. hypnotics, tranquilizers); 3) Stimulants (e.g. amphetamine, cocaine); 4) Hallucinogens (e.g. LSD, mescaline); 5) Cannabis derivatives (e.g. marijuana, hashish); 6) Solvents (e.g. toluene); 7) Anti-psychotic and anti-depressant medication; 8) Non-prescription drugs (e.g. acetylsalicylic acid); and, 9) Alcohol.

In addition to examining the relationship between each category of substance use and 5-HT and 5-HIAA, a mixed substance abuse rating was made based on the types of drugs taken over the last month period. Subjects were given one point for each category of drug reported taken over the last month. The total number of points accumulated could range from 0 to 9, provides a gross index of the variety of substance use.

(iii) Other Lifestyle Variables

Information about lifestyle was obtained from a self-report questionnaire that was designed specifically for this study (see Appendix B and Appendix C). Key information included smoking, coffee consumption, and exercise habits. These variables were calculated for the 24-hour period prior to blood sampling, the previous 2 week period, and the previous month.

(5) Biochemical Assays
Plasma 5-HT and 5-HIAA samples were analyzed using high performance liquid chromatography coupled with electrochemical detection as described by Sloley and Yu (1986).

(6) Data Analysis

The key analyses included: (a) calculation of correlations between PCL-R scores and biochemical variables; and (b) a series of initial multiple regressions to analyze the relationship between the groups of independent variables (demographic measures and lifestyle measures) and the dependent variables 5-HT and 5-HIAA. These analyses were performed to assess the contribution, if any, these variable would have in predicting plasma 5-HT and 5-HIAA levels. Any variable found to significantly contribute to the regression on the biochemical variables would then have to be considered when examining the relationship between PCL-R variables and plasma serotonergic activity. Two separate regression analyses were conducted to decrease the independent/dependent variable ratio.

A separate analysis involved employing t-tests of the biochemical differences between psychopathic and nonpsychopathic murderers. Group differences in the degree of impulsivity in the crime, relationship to the victim, and motivation behind the crime were also reported. Finally, two additional regression analyses were conducted to examine the ability of biochemical and PCL-R variable to predict level of aggression in the index crime (with and without a victim).

All statistical analyses were performed using SPSS PC+.
III. Results

A. PCL-R Factors and Plasma Concentrations of 5-HT & 5 HIAA

A correlational analysis was initially undertaken to examine the relationship between PCL-R ratings (Total Score, Factor 1, Factor 2 and the interaction variable (F1xF2) and serotonergic activity (5-HT and 5-HIAA) expressed in ng/ml. Results from the correlational analysis are presented in Table 1. The values denoted in square brackets are partially disattenuated correlation coefficients (Hakstian, Schroeder and Rogers, 1989). The reliability coefficients (ICC-2) of both 5-HT and 5-HIAA were disattenuated to compensate for their low values. Thus, these disattenuated correlation coefficients represent the correlation between PCL-R measures and biochemical variables, if one were to assume that the biochemical variables were 100% reliable. All of the tests of significance were computed on the unattenuated correlations.

Factor 2 of the Psychopathy Checklist was significantly correlated with plasma 5-HT levels; and, 5-HIAA concentrations varied in the predicted direction but did not achieve statistical significance. The interaction variable (F1xF2) was correlated significantly with plasma 5-HIAA concentrations.

B. Regression Analyses: Demographic Variables on Plasma 5-HT & 5-HIAA Concentrations

A standard multiple regression analysis was performed using 5-HT (see Table 2) and 5-HIAA (see Table 3) as the dependent variables and age, weight, and race as the independent
<table>
<thead>
<tr>
<th>Variables</th>
<th>5-HT</th>
<th>5-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL-R</td>
<td>.20 [0.30]</td>
<td>.20 [0.26]</td>
</tr>
<tr>
<td></td>
<td>p=0.07</td>
<td>p=0.08</td>
</tr>
<tr>
<td>FACTOR 1</td>
<td>.14 [0.20]</td>
<td>.17 [0.22]</td>
</tr>
<tr>
<td></td>
<td>p=0.16</td>
<td>p=0.12</td>
</tr>
<tr>
<td>FACTOR 2</td>
<td>.24 [0.36]</td>
<td>.22 [0.29]</td>
</tr>
<tr>
<td></td>
<td>p=0.04</td>
<td>p=0.06</td>
</tr>
<tr>
<td>F1 x F2</td>
<td>.18 [0.27]</td>
<td>.25 [0.33]</td>
</tr>
<tr>
<td>INTERACTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p=0.10</td>
<td>p=0.04</td>
</tr>
</tbody>
</table>

1 5-HT & 5-HIAA concentrations expressed in ng/ml.


** Note: p values do not reflect disattenuated correlations
variables. Tables 2 and 3 display the correlations (2-tailed) between the variables; the unstandardized regression coefficients (b); the intercept; the standardized regression coefficient (b); and, R, R^2, and adjusted R^2. None of the independent variables significantly predicted either 5-HT or 5-HIAA in the regression analysis.

C. Regression Analyses: Lifestyle Variables on Plasma 5-HT & 5-HIAA Concentrations

Prior to multiple regression analysis, the relationship between specific substance use (i.e. categories 1-9 above) during the 24 hour time period prior to sampling and plasma concentrations of 5-HT and 5-HIAA was determined. If specific substance use was not predictive of plasma 5-HT and 5-HIAA, then only the more global substance use rating would be entered into the regression equation. Initially, correlational analyses between the nine categories of substances and each of the biochemical variables over the two sampling periods were performed. These analyses revealed that in week one the use of cannabis derivatives (category 5) was significantly correlated with plasma 5-HIAA levels (r = .35, p<.01). The only other significant correlation was between the use of non-prescription medication (category 8) and plasma levels of 5-HT in week two (r = .38, p<.01). To determine whether ingestion of these substances had an overall effect on the average 5-HIAA and 5-HT plasma concentrations, two one-way ANOVA's were performed. The average 5-HIAA and 5-HT values were compared between four
Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>5-HT</th>
<th>RACE</th>
<th>AGE</th>
<th>WEIGHT</th>
<th>B</th>
<th>b</th>
</tr>
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<tbody>
<tr>
<td>RACE</td>
<td>-.03</td>
<td></td>
<td></td>
<td></td>
<td>-.46</td>
<td>.00</td>
</tr>
<tr>
<td>AGE</td>
<td>-.05</td>
<td>-.04</td>
<td></td>
<td></td>
<td>-.39</td>
<td>-.05</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>-.19</td>
<td>.13</td>
<td>.001</td>
<td></td>
<td>-.38</td>
<td>-.19</td>
</tr>
</tbody>
</table>

Intercept = 129.5

Means
- 52.9
- 27.4
- 174.8

SD
- 46.3
- 6.2
- 23.3

R² = .04
Adjusted R² = -.02
R = .20

**None of the variables contributed significantly to the regression.**
Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>5-HIAA</th>
<th>RACE</th>
<th>AGE</th>
<th>WEIGHT</th>
<th>B</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>RACE</td>
<td>-.17</td>
<td></td>
<td></td>
<td>-.12</td>
<td>-1.2</td>
<td>-.16</td>
</tr>
<tr>
<td>AGE</td>
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<td>-.04</td>
<td></td>
<td>-.05</td>
<td>-.09</td>
<td></td>
</tr>
<tr>
<td>WEIGHT</td>
<td>-.12</td>
<td></td>
<td>.13</td>
<td>.001</td>
<td>-.01</td>
<td>-.10</td>
</tr>
</tbody>
</table>

Intercept = 13.4

Means

<table>
<thead>
<tr>
<th>5-HIAA</th>
<th>RACE</th>
<th>AGE</th>
<th>WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1</td>
<td>27.4</td>
<td>174.8</td>
<td></td>
</tr>
</tbody>
</table>

SD

| 13.3 | 6.2 | 23.3 |

$R^2 = .05$

Adjusted $R^2 = -.01$

$R = .22$

**None of the variables contributed significantly to the regression.**
groups of individuals designated as follows: Group 1 = ingestion of substance on week 1 but not on week 2; Group 2 = ingestion of substance on week 1 and week 2; Group 3 = ingestion of substance on week 2 but not on week 1; and Group 4 = no ingestion of substance on either week 1 or week 2. It was expected that if ingestion of either nonprescription medication or cannabis derivatives were to affect mean 5-HT and 5-HIAA levels, this would be reflected in group differences, particularly between Group 4 and the other three groups. The results of the ANOVA employing mean 5-HIAA concentrations as the dependent variable revealed no significant differences among the four groups (F(3,50)=2.05, p=.12). Similarly, the ANOVA using 5-HT as the dependent variable revealed no significant differences among the four groups (F(3,50)=1.5, p=.23). These results suggest that the ingestion of substances during the 24 hour period prior to blood sampling did not affect mean 5-HT and 5-HIAA levels. Therefore, individual substance use categories were not included in the regression instead the global substance use rating was used.

Standard multiple regression analyses were performed using 5-HT (see Table 4) and 5-HIAA (see Table 5), as the dependent variables. The independent variables were: average daily measures of cigarette and coffee consumption; average number and type of exercise activities participated in per week; and lifetime assessment of alcohol and substance use. None of the independent variables contributed significantly to the regression analysis.
Table 4

<table>
<thead>
<tr>
<th>Variables</th>
<th>5-HT</th>
<th>EXERCISE</th>
<th>ALC</th>
<th>SUB</th>
<th>COF</th>
<th>CIG</th>
<th>SUB TOT</th>
<th>B</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXERCISE (# aerobic workouts/wk)</td>
<td>.05</td>
<td>.93</td>
<td>.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALCOHOL USE (lifetime)</td>
<td>.07</td>
<td>.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.8</td>
<td>.18</td>
</tr>
<tr>
<td>SUBSTANCE USE (lifetime)</td>
<td>.15</td>
<td>.04</td>
<td>.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.0</td>
<td>.06</td>
</tr>
<tr>
<td>COFFEE (avg. cups/day)</td>
<td>-.08</td>
<td>-.13</td>
<td>-.08</td>
<td>.09</td>
<td></td>
<td></td>
<td></td>
<td>-.20</td>
<td>-.06</td>
</tr>
<tr>
<td>CIGARETTES (avg. no./day)</td>
<td>.07</td>
<td>-.38</td>
<td>-.34</td>
<td>-.04</td>
<td>-.06</td>
<td></td>
<td></td>
<td>.43</td>
<td>.14</td>
</tr>
<tr>
<td>TOTAL NUMBER OF SUBSTANCES USED (month)</td>
<td>-.10</td>
<td>-.21</td>
<td>.03</td>
<td>.15</td>
<td>.02</td>
<td>-.04</td>
<td></td>
<td>-.53</td>
<td>-.11</td>
</tr>
<tr>
<td>Intercept = 12.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean 52.9 1.4 4.0 3.8 10.0 18.0 1.1
SD 46.3 1.7 1.1 1.4 14.2 14.8 .93

**None of the variables contributed significantly to the regression.**
Table 5

STANDARD MULTIPLE REGRESSION OF LIFESTYLE VARIABLES ON 5-HIAA
(n=54)

<table>
<thead>
<tr>
<th>Variables</th>
<th>5-HIAA</th>
<th>EXERCISE</th>
<th>ALC</th>
<th>SUB</th>
<th>COF</th>
<th>CIG</th>
<th>SUB TOT</th>
<th>B</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXERCISE ( # aerobic workouts/wk)</td>
<td>-.08</td>
<td>-.12</td>
<td>-.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALCOHOL USE (lifetime)</td>
<td>-.17</td>
<td>.20</td>
<td>-.63</td>
<td>-.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBSTANCE USE (lifetime)</td>
<td>-.04</td>
<td>.04</td>
<td>.18</td>
<td>-.03</td>
<td>-.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COFFEE (avg. cups/day)</td>
<td>-.16</td>
<td>-.13</td>
<td>-.08</td>
<td>.09</td>
<td>-.04</td>
<td>-.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIGARETTES (avg. no./day)</td>
<td>-.01</td>
<td>-.38</td>
<td>-.34</td>
<td>-.04</td>
<td>-.06</td>
<td>-.02</td>
<td>-.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL NUMBER OF SUBSTANCES USED (month)</td>
<td>.20</td>
<td>-.21</td>
<td>.03</td>
<td>.15</td>
<td>.02</td>
<td>-.04</td>
<td>.70</td>
<td>.20</td>
<td></td>
</tr>
</tbody>
</table>

Intercept = 11.01

Mean | 8.1  | 1.4  | 4.0  | 3.8  | 10.0 | 18.0 | 1.1
SD   | 3.3  | 1.7  | 1.1  | 1.4  | 14.2 | 14.8 | .93

\[ R^2 = .11 \]
\[ \text{Adjusted } R^2 = -.004 \]
\[ R = .33 \]

**None of the variables contributed significantly to the regression.**
D. Plasma 5-HT & 5-HIAA Concentrations in Psychopathic and Nonpsychopathic Murderers

Table 6 shows plasma 5-HT and 5-HIAA concentrations in psychopathic and nonpsychopathic murderers. The psychopaths had higher plasma 5-HIAA levels than did the nonpsychopaths, but the difference was not statistically significant (p < .10). Moreover, the crimes of the psychopaths were more likely to be without an apparent motive than were those of the nonpsychopaths. These trends suggest that subsequent research with larger n's is warranted.

Psychopaths scored significantly higher than nonpsychopaths in the impulsivity subscale of the PCL-R (p < .05). This is not surprising since by definition, psychopaths should have higher impulsivity scores; moreover the impulsivity items are themselves a part of the PCL-R. However assessment of the impulsivity subscale was necessary since theoretically the nonpsychopathic murderers could have high impulsivity scores yet not be diagnosed as psychopathic.

E. Biochemical Variables and PCL-R variables on Level of Aggression in Index Crime

Two separate multiple regression analyses were performed. First a standard multiple regression was performed, with the level of aggression used in crimes involving a victim as the dependent variable, and the PCL-R variables (Factor 2 and F1xF2) and the two biochemical variables (plasma 5-HT & 5-HIAA concentrations) as the independent variables (see Table 7). The
Table 6

<table>
<thead>
<tr>
<th>Variables</th>
<th>NONPSYCHOPATHS (n =6)</th>
<th>PSYCHOPATHS (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-HT</strong> (ng/ml)</td>
<td>59.2 +- 67.6</td>
<td>69.8 +- 49.9</td>
</tr>
<tr>
<td><strong>5-HIAA</strong>(^1) (ng/ml)</td>
<td>7.8 +- 2.0</td>
<td>11.8 +- 5.3</td>
</tr>
<tr>
<td><strong>IMPULSIVITY</strong>(^2) (lifetime)</td>
<td>4.8 +- 2.1</td>
<td>7.6 +- 5.55</td>
</tr>
<tr>
<td><strong>IMPULSIVITY</strong> (index crime)</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>MOTIVE:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material Gain</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Emotional Arousal</td>
<td>75%</td>
<td>--</td>
</tr>
<tr>
<td>No Motive</td>
<td>--</td>
<td>80%</td>
</tr>
<tr>
<td><strong>PREMEDITATION</strong> (index crime)</td>
<td>34%</td>
<td>--</td>
</tr>
<tr>
<td><strong>MOTIVE:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material Gain</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Emotional Arousal</td>
<td>100%</td>
<td>--</td>
</tr>
<tr>
<td>No Motive</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>VICTIM STATUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>--</td>
<td>20%</td>
</tr>
<tr>
<td>Friend/Acquaintance</td>
<td>67%</td>
<td>20%</td>
</tr>
<tr>
<td>Stranger</td>
<td>33%</td>
<td>60%</td>
</tr>
</tbody>
</table>

\(^1\) p<.10
\(^2\) p<.05
multiple R for the regression approached statistical significance ($p < .10$). The regression coefficient for plasma 5-HIAA was significantly different from zero ($p < .05$) and the proportion of unique variance contributed by this independent variable ($sr^2$) was .16. That is, plasma 5-HIAA contributed this amount of variance to the multiple R above and beyond the contribution of all the independent factors combined. These results suggest that with increasing levels of aggression in crimes involving a victim, plasma 5-HIAA levels are elevated.

Table 8 displays the results of the regression analysis of biochemical variables and PCL-R variables regressed on the level of aggression used in all index crimes. Once again, the regression coefficient of plasma 5-HIAA approached statistical significance ($p < .10$). The unique proportion of variance ($sr^2$) contributed by 5-HIAA in predicting the level of aggressiveness in all crimes was .05. It is interesting to note that the correlation between 5-HIAA and level of aggressiveness in crimes involving victims is $r = -.37$, compared to $r = -.22$ in level of aggressiveness in all crimes.
Table 7

STANDARD MULTIPLE REGRESSION OF PCL-R VARIABLES AND BIOCHEMICAL VARIABLES ON AGGRESSION (index crimes with victims) (n=31)

<table>
<thead>
<tr>
<th>Variables</th>
<th>AGGR.</th>
<th>5-HT</th>
<th>5-HIAA</th>
<th>F2</th>
<th>F1xF2</th>
<th>B</th>
<th>b</th>
<th>sr²</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>-.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-.01</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>5-HIAA</td>
<td>-.37</td>
<td>.08</td>
<td></td>
<td></td>
<td></td>
<td>** .25</td>
<td>-.41</td>
<td>.16</td>
</tr>
<tr>
<td>FACTOR 2</td>
<td>.11</td>
<td>.12</td>
<td>.25</td>
<td></td>
<td></td>
<td>.11</td>
<td>.19</td>
<td></td>
</tr>
<tr>
<td>F1 x F2</td>
<td>.05</td>
<td>.23</td>
<td>.27</td>
<td>.78</td>
<td></td>
<td>.00</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

Intercept= 3.9

Means   | 3.2  | 51.4 | 8.1  | 13.8 | 151.5
SD      | 1.9  | 43.3 | 3.1  | 3.4  | 69.9

R² = .22
Adjusted R² = .10
R = *.47

** p < .05
* p < .10
Table 8

STANDARD MULTIPLE REGRESSION OF PCL-R VARIABLES AND BIOCHEMICAL VARIABLES ON AGGRESSION (all index crimes) (n=45)

<table>
<thead>
<tr>
<th>Variables</th>
<th>AGGR.</th>
<th>5-HT</th>
<th>5-HIAA</th>
<th>F2</th>
<th>F1xF2</th>
<th>B</th>
<th>b</th>
<th>$sr^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>-.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-.01</td>
<td>-.16</td>
<td></td>
</tr>
<tr>
<td>5-HIAA</td>
<td>-.22</td>
<td>-.07</td>
<td></td>
<td></td>
<td></td>
<td>*-.15</td>
<td>-.24</td>
<td>.05</td>
</tr>
<tr>
<td>FACTOR 2</td>
<td>-.03</td>
<td>.21</td>
<td>.20</td>
<td></td>
<td></td>
<td>.05</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>F1 x F2</td>
<td>-.05</td>
<td>.15</td>
<td>.23</td>
<td>.76</td>
<td></td>
<td>.00</td>
<td>-.03</td>
<td></td>
</tr>
<tr>
<td>INTERACTION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.2</td>
</tr>
<tr>
<td>Means</td>
<td>4.1</td>
<td>53.6</td>
<td>8.0</td>
<td>13.4</td>
<td>142.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.2</td>
<td>49.4</td>
<td>3.3</td>
<td>3.3</td>
<td>71.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$R^2 = .07$

Adjusted $R^2 = -.02$

$R = .27$

* $p < .10$
IV. Discussion

This is the first investigation of plasma 5-HT and 5-HIAA concentrations and their relationship to psychopathy as measured by the PCL-R. The findings indicate that: (1) Plasma 5-HT levels are positively correlated with Factor 2 of the PCL-R; (2) Plasma 5-HIAA levels are positively correlated with the interaction between Factor 1 and Factor 2 (F1xF2) of the PCL-R; (3) In a small sample of murderers, plasma 5-HIAA concentrations tended to be higher in psychopaths than nonpsychopaths; and, (4) The amount of aggression displayed in an index crime involving victims was significantly predicted by plasma 5-HIAA values.

The plasma 5-HIAA levels reported here are within the range of previously reported values (Sarrias et al, 1989; Ortiz et al, 1988; Virkkunen and Narvanen, 1987). Note, however, that the reliability of sampling over the two week period was only .58. This is reflected in the discrepancies between the correlations in week one and week two. For example, although in the predicted direction, 5-HIAA concentrations measures in week two were correlated to a much lesser degree with psychopathy than were measures in week one. Similar correlations were found for 5-HT, except that psychopathy was more strongly correlated with concentrations in week two than in week one.

The 5-HIAA concentrations reported here were consistent with findings in the literature; however, 5-HT concentrations were markedly higher than many of those previously reported. Anderson et al, (1987) have suggested three possibilities for
high concentrations of 5-HT: platelet contamination of the platelet-poor plasma, platelet contamination at the time of the draw and platelet contamination at the time of centrifugation. Through their own experimental manipulation of these possibilities, they concluded that reported high levels of 5-HT in plasma are most likely the result of platelet contamination at the draw. That is, there is a three-fold increase in the concentration of plasma 5-HT if the sample is drawn into a syringe without anticoagulant added when compared to 5-HT plasma concentrations if the syringe is prepared with anticoagulant. The absence of anticoagulant in the syringe leads to temporal instability of the sample resulting in release of 5-HT from the platelets (Anderson et al., 1987). In the present study, blood was drawn directly into tubes that contained the anticoagulant. Thus, it is unlikely that contamination at the time of the draw is an explanation of the present results. Alternatively, one might speculate that release of platelet serotonin occurred during centrifugation or when the plasma was drawn from the sample containing both plasma and the platelet pellet. The former explanation is unlikely, however, because platelet stability is relatively uncompromised during centrifugation (Anderson et al., 1987). Alternatively, sample degradation could have occurred during the three month period between collection and analysis. That is, if the plasma samples were contaminated by the presence of platelets and these platelets, even under ultra-low temperature conditions, may have been susceptible to
degradation and release of 5-HT (Davis, 1989). In summary, the 5-HT plasma concentrations reported in the present study are rather high and resemble those of whole blood measures.

The results of this study suggest that peripheral indices of serotonergic activity are primarily related to Factor 2 of the PCL-R. Plasma 5-HT was significantly correlated with Factor 2 and plasma 5-HIAA was also correlated with this factor, though to a lesser degree. The correlation between Factor 2 and plasma serotonergic activity is not surprising. Factor 2 of the PCL-R captures primarily deviant social behaviour characterized to a large extent by involvement in violent and aggressive acts and, closely resembles the criteria for APD (Harpur, Hare & Hakstian, 1989). The relationship between increased serotonergic activity and Factor 2 is in line with recent evidence that whole blood 5-HT is correlated positively with the propensity for aggressive behaviour (Plizsa et al, 1988). More interesting, however, is the finding that the interaction factor (F1xF2) is most strongly correlated with plasma 5-HIAA and provides a large proportion of unique variance to the overall regression. If this relationship is replicable, it suggests that increased plasma 5-HIAA levels are associated most strongly with subjects who score high on both factors. Thus, while Factor 2 accounts for most of the variance seen in plasma 5-HIAA levels, the personality dimensions of psychopathy as defined by Factor 1, further contribute to the biochemical relationship. This evidence is consistent with the relationship between F1xF2 and violent behaviour. For violence
variables such as conviction rate, weapon use, rated frequency of violence, and violent behaviours while incarcerated, only those individuals who scored high on both factors had high predicted levels of violence (Harper et al, 1991).

Further, if one can assume that peripheral indices of serotonin functioning are inversely related to central measures, then these findings are consistent with the literature relating decreased serotonergic functioning to impulsive violent behaviour (for review see Coccaro, 1989) including an increased rate of recidivism (Virkunnen et al, 1989).

The finding that plasma 5-HIAA tends to differentiate psychopathic from nonpsychopathic murderers is in line with the previous findings of Linnoila et al (1983). The method of classification of offenders varied slightly in the present study when compared with that used by Linnoila's group. They divided offenders on the basis of impulsivity of the crime and/or whether or not a motive was present for the offense. It is difficult to ascertain whether or not any of their impulsive offenders (without premeditation) had a motive for their crime. In the present study subjects were classified as psychopathic or nonpsychopathic with impulsivity (life-time and in index crime) and motive being compared separately. The classification appears to parallel that of Linnoila's group since all of the crimes committed by psychopathic offenders were considered impulsive and 80% of them had no apparent motive. These results support the hypothesis that altered serotonergic functioning is primarily
manifested in the control of violent behaviour. That is, among individuals who display equal levels of violence, only those who display unprovoked violence or violence without a motive have altered serotonergic functioning.

In an attempt to predict level of aggression displayed in the index crime, it is not surprising that the PCL-R variables were not entered into the regression equation; over half of the murderers (highest level of aggression) were nonpsychopaths. The correlation between aggressiveness involved in all index crimes and 5-HIAA was considerably weaker than the correlation between 5-HIAA and aggressiveness in those crimes involving victims, even though the sample size was larger. Perhaps in those crimes in which a specific victim is involved, plasma 5-HIAA levels are related to the degree of violence used in the crime whether or not the offender is a psychopath. However, beyond this relationship, it appears that a diagnosis of psychopathy is associated with yet a further increase in 5-HIAA levels. As suggested above, perhaps the impulsive and callous nature of psychopaths contributes to this further biochemical distinction. It is difficult to ascertain the strength of the actual relationship between plasma serotonergic activity and psychopathy. Although the relationship obtained in the present study is relatively tenuous, methodological confounds may have prevented a stronger relationship from emerging. At this point it cannot be unequivocally concluded that plasma serotonin indices are related to psychopathy.
The link between indices of central serotonergic functioning and peripheral indices is unclear. This uncertainty, however, does not preclude investigation at this level. Given the noninvasiveness of peripheral measures, it seems worthwhile to determine whether peripheral indices, like central indices, are associated in a consistent way with personality and behaviour traits. If a relationship can be reliably established, then the next question to be answered is: what are the underlying mechanisms which result in altered serotonergic functioning?

**Psychopathy in the context of Biobehavioural Theories**

van Praag & colleagues (1990) state that the relationship between 5-HT disturbances found in psychiatric disorders appears at best chaotic. That is, if viewed in the context of a nosological or categorical point of view, integration of the findings is almost impossible. They purport, and sensibly so, that 5-HT research should be viewed in terms of a functional and dimensional approach to psychopathology. Briefly discussed below are theories in which to place specific biochemical findings, namely those relating to serotonin, and the construct of psychopathy in the context of a dimensional approach.

Depue and Spoont (1986) have provided a theory which provides a framework for how hyposerotonergic activity in the brain is manifested as a serotonin 'trait'. These authors propose that since a diversity of response patterns or behaviours are mediated by 5-HT (e.g. locomotor activity, aggression, sexual activity and social interactions), the influence of 5-HT is not
specific to a circumscribed response system; instead, it is best conceived as a generalized behavioural constraint system. They have designated this constraint system as the behavioural inhibitory system (BIS) which inhibits engagement patterns in response to signals of nonreward, punishment, or uncertainty. They suggest that the BIS system exercises its influence on a more generalized behavioural facilitation system (BFS) characterized by locomotor activity and an incentive motivational state. These two systems are proposed to interact in a manner such that the BIS modulates specific engagement patterns. This interaction between the relative strength of the BFS/BIS determines the amplitude of engagement.

It is suggested that increased amplitude of engagement is associated with increased BFS and decreased BIS responsivity, and that behavioural indices of increased engagement should be most obvious in situations which contain strong controlling signals of both systems. Relevant to this discussion is the example in which a highly irritative aggressive or violent act occurs. In this case, there are relevant aversive cues which can be internal (such as cognitions of harming, killing someone or going to jail) or external (such as signs of fear from the victim). These cues would generally inhibit or reduce intensity of engagement; however, in the "low 5-HT" individual, the relatively reduced effectiveness of the BIS to respond to relevant signals, combined with a relatively higher BFS system, would result in engagement. The characteristics of psychopathy which have been described
throughout this paper appear to be in line with those exhibited by the "low 5-HT" individual.

Fowles (1980) has suggested that some clinical characteristics of psychopathy are the result of an inefficient or weak behavioural inhibition system (BIS). This BIS, first proposed by Gray (1977), is purported to respond to threatening situations by producing anxiety and the inhibition of behaviour. Specifically, a weak BIS system results in: an anxiolytic effect on the responses to normally threatening stimuli; an inability to inhibit behaviour in the presence of threats of punishment and nonreward; a lower tolerance to alcohol; and strong reward behaviour which appears impulsive. Fowles (1980) further suggests that the recidivistic behaviour of psychopaths is indicative of the inability to learn from past experiences and to inhibit behaviour.

The role of serotonin in this model is as a mediator in the inhibition of anxiety. The disruption of serotonergic activity impairs passive avoidance, and increases hyperactivity, distractibility, aggression and sexual activity. The benzodiazepines have much the same effects on passive avoidance learning as does reduced serotonergic activity. Although this may reflect mere coincidence, it has nevertheless been suggested then that the actions of the benzodiazepines on the GABAergic (gamma-aminobutyric acid) system are manifested through a GABA-mediated reduction in serotonergic activity (Lewis, 1991). Soubrie (1986) has challenged the notion of a specific
serotonergic modulation of anxiety *per se*, in contrast to a more generalized serotonergic behavioural suppression. Specifically, he states that because both benzodiazepines and reduced 5-HT activity disinhibit behaviour, it does not necessarily follow that they do this via the same mechanism. That is, he argues that serotonin depletion is not anxiolytic in nature. Moreover, apparent antianxiety effects may in fact be an artifact of behavioural suppression. This issue has not been resolved.

Cloninger's (1987) biosocial approach to classification of personality variants provides a global yet elegant perspective which integrates behavioural indices of the dopaminergic, serotonergic and noradrenergic systems. Three dimensions of personality are discriminated in terms of basic stimulus-response characteristics of novelty seeking, harm avoidance, and reward dependence, which are reflected in the variation of the three central brain systems. He proposes that the tridimensional combinations of extreme variants on these basic stimulus-response characteristics correspond to traditional descriptions of personality disorders. The three dimensions described below are taken directly from Cloninger's proposed classification:

(1) Behavioural activation (novelty seeking) is principally modulated by dopamine. The relevant stimuli and subsequent behavioural responses are a) novelty - exploratory pursuit; b) potential reward - appetitive approach; and c) potential relief of monotony and punishment - active avoidance and escape.

(2) Behavioural inhibition (harm avoidance) is principally
modulated by the serotonergic system. The relevant stimuli are conditioned signals for punishment, novelty or frustrative non reward. The behavioural response is defined as passive avoidance and extinction.

(3) Finally, the noradrenergic system modulates behavioural maintenance (reward dependence) whereby the relevant stimuli are conditioned signals for reward or relief from punishment and the behavioural response is resistance to extinction.

These three systems are independently set for each individual; however, the systems functionally interact, giving rise to integrated patterns of responses to punishment, reward and novelty. Based on Cloninger's model, a deficient serotonergic system combined with facilitation of the dopaminergic system provides a profile of an individual who is high in novelty seeking and low in harm avoidance and whose clinical characteristics are remarkably similar to those of a psychopath:

"Danger seeking behaviour or impulsive acts involving high risk of personal injury, highly aggressive and competitive behaviour, including offensive initiation of violence, bullying or forceful domination of others; highly impatient and easily annoyed; reckless and quick decisions are often made without regard for consequences" (pg 582).

The relationship between the noradrenergic system (reward dependence) and high novelty seeking is also reminiscent of descriptions of psychopathy. For example, high novelty seeking and low reward dependence is characterized as:

"opportunistic or acting for own advantage without regard to traditional principles or consequences; pathologic lying or enjoyment in charming or misleading others for its own sake"
without regard for truth or personal advantage; and seldom able to delay gratification, work hard and sacrifice for postponed benefits". (pg 583).

However, the opposite bipolar relationship seen in high novelty seeking behaviour combined with high reward dependence is also characteristic of psychopaths:

"excessive attention seeking and reckless, wasteful, extravagant self indulgence" (pg. 583).

In summary there appears to be a consistency in terms of the relationship between the combined serotonergic and dopaminergic behavioural manifestations and the parallel these behaviours have with psychopathy. Psychopathy is not neatly slotted in this dimensional approach; however, Cloninger has provided a framework in which both the serotonergic and catecholaminergic systems work in concert to contribute to a unique pattern of behavioural indices. Further, his conceptualization suggests that investigation of the serotonergic functioning in psychopaths is a rational first step towards understanding the biochemical etiology of psychopathy.

**Future Directions**

What is proposed as a next step towards the investigation of the putative biochemical correlates of psychopathy is (1) a replication of the present study; and (2) extension of the serotonin investigation to include a hormonal probe of central functioning (e.g. fenfluramine). If both of these studies were performed, it would allow a comparison, albeit indirect, of
peripheral and central indices of serotonergic activity and psychopathy. This addition of the fenfluramine challenge to our protocol will be done in collaboration with Dr. L. Sievers of the Bronx Veterans Hospital (V.A.). Through a collaborative effort between the research group at the V.A. and our laboratory the two research teams will be able to simultaneously examine the relationship between psychopathy and central serotonergic functioning. Results of this investigation will allow direct comparison between serotonergic activity described in terms of DSM III-R classification of personality disorders (see Coccaro et al 1989) and psychopathy. Additionally, the group at the V.A. Hospital will be using Single Positron Emission Computed Tomography. The possibility exists that measures of receptor density, specifically serotonergic receptors, will be assessed. A combination of peripheral and central indices of serotonin and anatomical measures will provide a more comprehensive picture of the status of serotonergic functioning in psychopaths. Through the thoughtful integration of both animal and human biochemical literature, the ultimate goal is to develop hypotheses regarding risk assessment and early intervention in psychopathy.

This study represents an early step in the investigation of the biochemical correlates of psychopathy. The results suggest that altered serotonergic functioning may be a promising lead in the investigation of the biological etiology of this disorder.
References


APPENDIX A

CONSENT FOR BIOCHEMICAL MEASURES OF BEHAVIOUR

I hereby consent to participate in the Biochemical Measures of Behaviour Study being conducted by the UBC research group. I understand that participation in this study will involve the extraction of a sample of blood by a registered medical technician, hired by the UBC research group. The purpose of this research is to investigate levels of naturally occurring substances in the body and to compare this information with data obtained from personality assessments and file information. The UBC research group is not measuring drug levels or testing for viruses. Results from the samples obtained will not be available to the staff or administration of the Matsqui Institute.

I understand that the equipment to be used will include a single-use sterile syringe, needles and storage vessels. I understand that all reasonable precautions will be taken to minimize my physical discomfort. This procedure should take about half an hour per session to complete, and I will be paid $20 for participation in two sessions.

I understand that any information that is obtained will be used for research purposes only. It has been explained to me that biochemical data obtained may be used for research in association with other behavioural or historical details that I have volunteered to the UBC research group in previous studies. I understand that my anonymity will be assured through the use of a data coding system, whereby data retrieved by my participation will be coded through the use of numbers. I understand that personal specifics (such as name, exact date of birth etc.) will not be used by the researcher.

As a research participant, I acknowledge the right to refuse to participate, and the right to terminate or withdraw at any time without penalty. I acknowledge receipt of a copy of the consent form. If I want more information about this study, I can contact the UBC research group in the hospital wing of Matsqui Correctional Institute, or Dr. R.D. Hare in the Department of Psychology, University of British Columbia, at 228-3611.

Name ___________________________ Signature ___________________________

Date ___________________________

Witness ________________________
APPENDIX B

BIOCHEMICAL MEASURES OF BEHAVIOUR

Date:__________ I.D.:__________

These are a few questions about your activities of the past 24 hours.

***ALL ANSWERS WILL BE KEPT STRICTLY CONFIDENTIAL***

1. How many cigarettes have you smoked
OVER THE PAST 24 HOURS? ________________

2. How many cups of coffee have you had
OVER THE PAST 24 HOURS? ________________

3. Have you consumed any alcohol
OVER THE PAST 24 HOURS? ________________
   If so, how MUCH?_____________________

4. Have you taken any prescription drugs
OVER THE PAST 24 HOURS? ________________
   If so, WHAT?________________________

5. Have you taken any non-prescription drugs
OVER THE PAST 24 HOURS? ________________
   If so, WHAT?________________________

6. Have you had any physical fights
OVER THE PAST 24 HOURS? ________________
   If so, WHEN?________________________

7. Have you had any arguments
OVER THE PAST 24 HOURS? ________________
   If so, WHEN?________________________

8. Have you done any exercise
OVER THE PAST 24 HOURS? ________________
   If so, WHEN?________________________
APPENDIX C

BIOCHEMICAL MEASURES OF BEHAVIOUR

Date:__________ I.D.:__________

These are a few questions about your activities of the past 2 weeks and 1 months period.

*All answers will be kept strictly confidential*

1. How many cigarettes have you smoked per day
   OVER THE PAST 2 WEEKS?
   OVER THE PAST 1 MONTH?

2. How many cups of coffee do you drink per day
   OVER THE PAST 2 WEEKS?
   OVER THE PAST 1 MONTH?

3. How much alcohol have you consumed
   OVER THE PAST 2 WEEKS?
   OVER THE PAST 1 MONTH?

4. Have you taken any prescription drugs
   OVER THE PAST 2 WEEKS?
   If so what?
   OVER THE PAST 1 MONTH?
   If so what?

5. Have you taken any non-prescription drugs
   OVER THE PAST 2 WEEKS?
   If so what?
   OVER THE PAST 1 MONTH?
   If so what?

6. Do you follow a regular exercise routine? _____
   If so, what?
   OVER THE PAST 2 WEEKS?
   OVER THE PAST 1 MONTH?
APPENDIX D

ITEMS IN THE PSYCHOPATHY CHECKLIST  
(Hare, 1991)

<table>
<thead>
<tr>
<th></th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glibness/superficial charm</td>
</tr>
<tr>
<td>2</td>
<td>Grandiose sense of self-worth</td>
</tr>
<tr>
<td>3</td>
<td>Need for stimulation/proneness to boredom</td>
</tr>
<tr>
<td>4</td>
<td>Pathological lying</td>
</tr>
<tr>
<td>5</td>
<td>Conning/manipulative</td>
</tr>
<tr>
<td>6</td>
<td>Lack of remorse or guilt</td>
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<tr>
<td>7</td>
<td>Shallow affect</td>
</tr>
<tr>
<td>8</td>
<td>Callous/lack of empathy</td>
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<tr>
<td>9</td>
<td>Parasitic lifestyle</td>
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<tr>
<td>10</td>
<td>Poor behavioral problems</td>
</tr>
<tr>
<td>11</td>
<td>Promiscuous sexual behavior</td>
</tr>
<tr>
<td>12</td>
<td>Early behavioral problems</td>
</tr>
<tr>
<td>13</td>
<td>Lack of realistic, long-term goals</td>
</tr>
<tr>
<td>14</td>
<td>Impulsivity</td>
</tr>
<tr>
<td>15</td>
<td>Irresponsibility</td>
</tr>
<tr>
<td>16</td>
<td>Failure to accept responsibility for own actions</td>
</tr>
<tr>
<td>17</td>
<td>Many short-term marital relationships</td>
</tr>
<tr>
<td>18</td>
<td>Juvenile delinquency</td>
</tr>
<tr>
<td>19</td>
<td>Revocation of conditional release</td>
</tr>
<tr>
<td>20</td>
<td>Criminal versatility</td>
</tr>
</tbody>
</table>
APPENDIX E

PCL-R ITEM DESCRIPTION OF THE 'IMPULSIVITY' VARIABLE
(Hare, 1991)

ITEM (3) Need for stimulation/proneness to boredom
Describes an individual who demonstrates a chronic and
excessive need for novel and exciting stimulation, and
an unusual proneness to boredom. He frequently
complains that school, work, and long term
relationships are boring and tedious. He may comment
that he has itchy feet, needs to be on the go, and
can't imagine working at the same job for any length of
time. He will often refuse to attempt, or will
readily quit any task that he finds routine,
monotonous, or uninteresting.

ITEM (10) Poor Behavioral Controls
He may be described as short-tempered or hot-headed.
He tends to respond to frustration, failure,
discipline, and criticism with violent behaviour or
with threats and verbal abuse. He takes offense easily
and becomes angry and aggressive over trivialis;
these behaviours will often seem inappropriate, given
the context in which they occur. They are often short
lived, and the individual may quickly act as if nothing
out of the ordinary has happened. His behavioral
controls, ordinarily not very strong, appear to
be further weakened by alcohol.

ITEM (11) Promiscuous Sexual Behaviour
Describes an individual whose sexual relations with
others are impersonal, casual, or trivial. This may be
reflected in frequent casual liaisons, indiscriminate
selection of sexual partners, maintenance of several
sexual relationships at the same time, frequent
infidelities, prostitution, or a willingness to
participate in a wide variety of sexual activities.

ITEM (14) Impulsivity
Describes an individual whose behaviour is generally
impulsive, unpremeditated, and lacking in reflection or
forethought. He usually does things on the "spur of
the moment" because he "feels like it" or because an
opportunity presents itself. He is unlikely to spend
much time weighing the pros and cons of a course of
action, or in considering the possible consequences of
his actions to himself or to others. He will often
break off relationships, quit jobs, change plans
suddenly, or move from place to place, on little more
than a whim and without bothering to inform others.
APPENDIX F

DESCRIPTION OF 'TYPE OF CRIME' VARIABLE
(Scale 1 - 6)

(1) Murder (1st, 2nd, manslaughter)

(2) Serious violent assaults (attempted murder assault causing bodily harm, wounding)

(3) Robbery with violence

(4) Armed robbery

(5) Kidnapping

(6) Robbery, property offenses (theft, break and enter, possession), fraud, false pretences, trafficking in narcotics
APPENDIX G

DESCRIPTION OF 'AGGRESSION IN INDEX CRIME' VARIABLE
(Scale 1 -7)

(1) Resulted in death
(2) Resulted in coma/serious permanent damage
(3) Resulted in hospitalization
(4) Resulted in physical injury (bleeding, bruises, broken bones)
(5) Threatened with a weapon but weapon not used
(6) Simple assault (accosts; threatens without weapon; slaps; punches or pushes without injury)
(7) No aggression