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Serotonergic Function And Impulsive Aggression In Alcoholics And Their Male And Female Offspring

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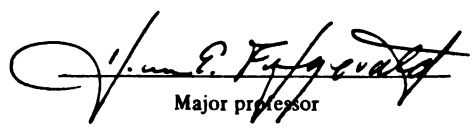

Major professor

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SEROTONERGIC FUNCTION AND IMPULSIVE AGGRESSION IN ALCOHOLICS AND THEIR MALE AND FEMALE OFFSPRING

By

Geoffrey Raymond Twitchell

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ABSTRACT

SEROTONERGIC FUNCTION AND IMPULSIVE AGGRESSION IN ALCOHOLICS AND THEIR MALE AND FEMALE OFFSPRING

By

Geoffrey Raymond Twitchell

A large literature describes an inverse relationship between a variety of measures of serotonergic function and both alcoholism and impulsive aggression in adults recruited from clinical settings. However, studies among children with these behavioral characteristics are rare, have only minimally sampled female subjects, and the findings have been inconsistent. This study achieved two goals. First, it examined the relationship between serotonergic function, as measured by whole blood 5-HT and impulsive aggression in community recruited antisocial alcoholic, non-antisocial alcoholic, and non-alcoholic control men. Second, this study examined the relationship between serotonergic function and impulsive aggression in 33 male and 12 female offspring (Mean age = 10.47 $\pm$ 1.54 years) from these families. Results indicated that current child serotonergic function was significantly related to current child impulsive aggression as measured by Total Behavior Problem CBCL scores (r = -.36, p = .007, N = 45). High impulsive aggressive children exhibited greater serotonergic dysfunction (M = 171.13 ng/ml, SD = 62.13, N = 8) compared to low impulsive aggressive children (M = 229.81 ng/ml, SD = 58.67, N = 37; F (1,43) = 6.45, p = .02). Expected differences among adult groups identified by impulsive aggressiveness were not found. Limitations of the study were presented. Clinical and research implications were discussed.

To Clark, my family, and friends, for their support during the completion of this project.

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INTRODUCTION

The precise ways that parental alcoholism affect the development of children are still largely unknown, but they are most likely multifactorial with biological, as well as psychosocial components (Sher, 1991; Sher, Walitzer, Wood, & Brent, 1991; Zucker & Gomberg, 1986). However, most psychosocial studies neglect the biological bases of transmission and association whereas, interestingly, many of the genetic studies focus primarily on biological factors at the exclusion of a psychosocial contribution. The current study attempts to address this void by exploring the important biological role serotonergic dysfunction may play in the development of children of alcoholics who may be at increased risk for the development of impulsivity, aggressiveness, and alcoholism.

One model suggests that impulsivity in childhood can be precursive to the development of aggressiveness, and aggressiveness can be precursive to earlier and more severe alcoholism in later adolescence and adulthood (Zucker & Fitzgerald, 1991a; 1991b). There is an increasing literature suggesting that serotonergic dysfunction is associated with alcoholism, aggressiveness, and impulsivity in adults manifesting in lower whole blood serotonin (5-HT), lower cerebrospinal fluid monoamine metabolites of serotonin (5-HIAA), and increased serotonergic uptake (Moss, 1987). The current study was designed to examine the biologic contribution that serotonergic dysfunction may make to the development and emergence of impulsivity, aggressiveness, and ultimately alcoholism in adults and their offspring.

The current research builds on the notion that there is more than one kind of alcoholism, which in turn means that diagnostic specificity is necessary to fully understand

the symptomatic and etiologic variations of the disease over the life course (Zucker, Ellis, Fitzgerald, Bingham, & Sanford, 1996). This study relied on one such classification scheme which suggests that there are at the least two alcoholisms which can be differentiated by the level of antisociality present (Zucker, 1987; Zucker et al., 1996; Zucker, Fitzgerald, & Moses, 1995). It is hypothesized that alcoholics with higher levels of antisociality spanning childhood and continuing into adulthood (AALs) have a life course that is etiologically different and more severe than non-antisocial alcoholics (NAALs).

When comparing AALs with NAALs, Zucker et al. (1996) found AALs to have increased overall lifetime alcohol problem scores, including age first drunk, lifetime variety of alcohol problems, and life percent involving alcohol problems. Additionally, NAALs reported achieving higher socioeconomic status in adulthood, although childhood status did not differ between the two groups. AALs had higher rates of separation and divorce, increased levels of depression, and greater drug involvement in comparison to NAALs. On the drinking variables of current frequency and quantity-variability of drinking, there was no difference between AALs and NAALs.

Few studies have gathered data on serotonergic function in children, and none to date have examined offspring of AALs and NAALs to help determine what role serotonergic function may play in later development. Furthermore, studies of adults have been inconclusive as to whether serotonergic dysfunction in alcoholics is heritable or caused by previous alcohol consumption (Moss, 1987). Hopefully, data obtained from children before the onset of alcohol use can help clear up that question.

Background Of the Proposed Model

The model used in this study came from developmental data exploring early risk pathways for future development of alcoholism (Zucker & Fitzgerald, 1991a; 1991b). When exploring the etiology of alcoholism, the co-occurrence of other difficulties and disorders may give clues to causation. To date, the strongest association with alcoholism is the co-action of antisocial personality disorder. The co-action of antisocial personality disorder has been cited at 14% in samples of alcoholics (Regier et al., 1990). While prevalence data are confounded by the issues of primary versus secondary occurrence and base rate expression, using odds-ratios helps correct for the latter attenuation. When using this technique, antisocial personality disorder shows the strongest possibility of being causally connected to alcoholism at an odds ratio of 21:1 (Zucker & Fitzgerald, 1991). This means antisocial personality disorder is 21 times more likely to be found in alcoholics than in the general population. Considering the strength of this connection, it seems reasonable to hypothesize that such a connection may begin as early as childhood. Additionally, a review by Zucker and Gomberg (1986) cited several studies which also indicated that antisocial behavior is a risk pathway to the manifestation of alcoholism.

Longitudinal studies using a high risk design compare individuals at known risk for developing alcoholism (e.g. offspring of alcoholics) with lower-risk individuals to track differential alcoholic outcome and premorbid indicators that proved predictive of such outcome. Several of these studies have found that antisocial behavior is often associated with the development of alcohol problems, with increased antisocial and aggressive activity among later alcoholics, and with increased achievement related difficulties such as

poor school performance, poor productivity, high truancy, and high drop out rates (Zucker & Gomberg, 1986). These data support the hypothesis that antisocial behavior is connected to the development of alcoholism and also suggest that parental antisocial behavior may play a role in child development (Zucker & Fitzgerald, 1991).

While these data come from longitudinal studies spanning adolescence through adulthood, it is still necessary to determine the pathway from childhood risk to adolescent manifestation. Using data from the Michigan State University/University of Michigan Family Study (Zucker, Noll, & Fitzgerald, 1986), childhood risk factors from as early as age 3-5 were explored (Zucker & Fitzgerald, 1991). Using the Child Behavior Checklist (CBCL: Achenbach & Edelbrock, 1983), those children considered at risk showed consistently elevated symptomatology in all behavioral areas except depression. The differences between high risk and control children was 3:1 for overall problem behavior, global externalizing symptoms including impulsivity, hyperactivity, and aggressiveness, as well as a content specific measure of aggressiveness (Zucker & Fitzgerald, 1991).

This evidence of increased levels of difficulties in early childhood parallels the evidence of later childhood and adolescent difficulty and may indicate an extension of a continuous lifetime process. These data may also support the hypothesis of increased impulsivity, as defined by CBCL scores, leading to greater aggressiveness in adolescence, and finally, to the development of greater life difficulty with alcohol. The current study used biological data to test the hypothesis that serotonergic dysfunction is involved in the development of impulsivity, aggressiveness, and ultimately, alcoholism.

Serotonergic Functioning

The central serotonergic system reaches to the cortex and the limbic structures. The limbic system is an area of the brain implicated in the coordination of feelings and perception through its many connections to the frontal lobe. Consequently, the serotonergic system is involved in the regulation of several physiologic and affective functions. These include sleep, appetite, cognition, mood, sexual, and motoric activity (Vogt, 1982). Therefore, it has been suggested that any disturbance or dysfunction in this system may contribute to the development of various psychiatric behavior disorders involving abnormalities in these functions, such as affect (depression), anxiety (obsessive compulsive disorder, alcoholism), eating, and personality disorders (Coccaro & Murphy, 1990).

Neurotransmission: The basic function of the central nervous system is the transfer of information from one area of the brain to another. This system of intercellular communication is composed of billions of neurons which interact with one another through characteristic processes. Since these interconnections can work in synchrony, this system is capable of producing graded responses which result in a vast array of cognitive, affective, and behavioral responses (Gitlin, 1990).

The synaptic unit is the functional building block of the central nervous system and consists of two neurons (presynaptic and postsynaptic) and a physical gap between them called the synapse, see Figure 1 (Gitlin, 1990). For these neurons to communicate with each other, a combination of bioelectrical and chemical processes must take place. Neurotransmitter is released when an electrical impulse called the action potential arrives

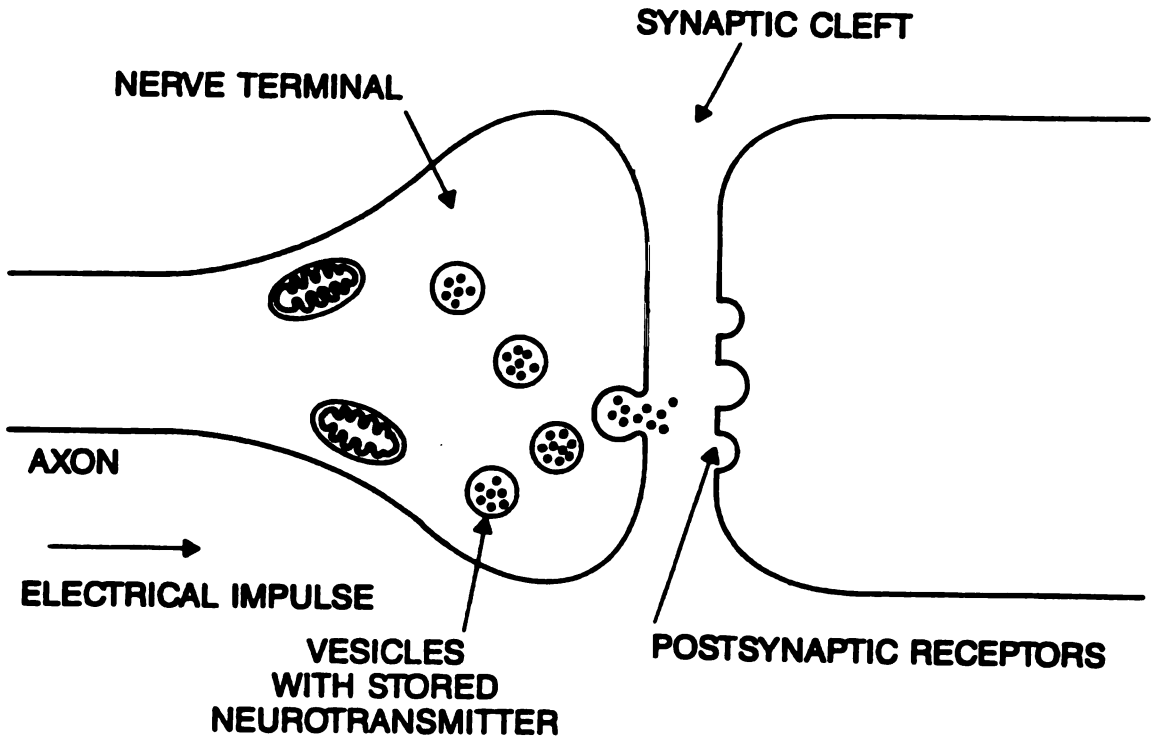

Figure 1 The Synapse

at the axon terminal. This depolarizes the presynaptic terminal membrane, opening voltage gated calcium channels. The resulting elevation in the internal calcium ion concentration signals the release of neurotransmitter from the synaptic vesicles into the synaptic cleft in a process called exocytosis (Bear, Connors, & Paradiso, 1996). The neurotransmitter spreads across the gap and binds to specialized receptor sites on the membrane of the postsynaptic neuron. The postsynaptic receptor then interprets the information within the neurotransmitter and begins a physiologic response that can be either inhibitory or excitatory (Martin, Owen, & Morihisa, 1987).

The neurotransmitter serotonin is found in large quantities within blood platelets and the central nervous system and is synthesized within the presynaptic neuron from the common amino acid L-tryptophan (Levitan & Kaczmarek, 1997). Synthesis of serotonin occurs in two steps. First, tryptophan is converted into 5-HTP (5-Hydroxytryptophan) by the enzyme tryptophan hydroxylase. Next, 5-HTP is converted to 5-HT (serotonin) by the enzyme 5-HTP decarboxylase (Bear, Connors, & Paradiso, 1996).

Serotonin is then packaged into secretory granules by special proteins embedded in the vesicle membrane called transporters and stored in the terminal bouton of the presynaptic neuronal axon. Once the released serotonin has interacted with the postsynaptic receptors, it must be cleared from the synaptic cleft to allow future transmission. Serotonin can be removed from the synaptic cleft by a specific transporter through reuptake into the presynaptic terminal where it can either be recycled and repackaged into synaptic vesicles or degraded by monoamine oxidase, resulting in the metabolite 5-Hydroxyindoleacetic acid (5-HIAA).

Central 5-HT neurons are localized in tracts within the brainstem, but affect most brain areas (Levitan & Kaczmarek, 1997). The neurotransmitter serotonin appears to be involved in several modulatory physiologic processes (Tollefson, 1989). There is a widespread consensus that serotonin has an inhibitory effect on behavior. Specifically, decrements in serotonergic function (decreased neurotransmission shown by lowered 5-HT turnover) have been linked to behavioral disinhibition (impulsivity), low frustration tolerance, (Moss, 1987; Jones, 1968; Goodwin, Schulsinger, Hermansen, et al., 1975; Robins, 1966) attention deficits, (Rydelius, 1983; Tarter, Hegedus, Goldstein et al., 1984) increased motor activity, (Jones, 1968; McCord, McCord, & Gudeman, 1968) emotionality, (Rosenberg, 1969; Tarter, 1982) and aggressiveness (Guze, Goodwin, & Crane, 1969).

Clinical Advances: One of the most important clinical advances to date is the use of specific serotonergic uptake inhibitors to treat depressive symptomatology. Several compounds such as fluoxetine (Prozac), citalopram, and zimeldine have been shown to have antidepressant effects through their ability to inhibit the serotonin uptake carrier (Fuller, 1992). While the antidepressant effects are clear, it is unknown how this specific alteration in the dynamic, homeostatic, and complex serotonergic system produces these positive effects.

Data on enhancing serotonergic function from rat studies show that serotonergic uptake inhibitors increase serotonergic function by decreasing serotonin synthesis, but at the same time, increasing extracellular serotonin. It is believed that the increased extracellular serotonin leads to increased neurotransmission which causes positive

functional changes and decreased serotonin synthesis and neuron firing (Fuller, 1992). Uptake inhibitors increase serotonin concentration in the synaptic cleft which results in increased activation of all post-synaptic serotonin receptors.

Most psychiatric medications work by affecting some aspect of the neurotransmitter/receptor system. The mechanisms of action can be explained by seven different effects of this system as diagramed in Figure 2 (Gitlin, 1990). 1.) First, a medication can directly bind to the receptor site. A receptor agonist is one that mimics the neurotransmitter by stimulating the receptor. Also, a medication can bind to the receptor causing no response and effectively block the neurotransmitter from binding to the receptor (antagonists). 2.) Medications can also cause the release of more neurotransmitter, functionally increasing the effect of the system. 3.) Medications can also block the reuptake of neurotransmitters back into the presynaptic neuron which allows the neurotransmitter to have more time in the synapse, increasing the possibility of stimulating the receptor in the postsynaptic neuron and thereby increasing neurotransmission. This is best illustrated by the action of selective serotonergic reuptake inhibitors (SSRIs) such as the widely used antidepressant, Prozac. 4.) Medications can also cause an increase or decrease in the number of receptor sites (up or down regulation). 5.) Medications may also alter the sensitivity of receptors, changing the magnitude of response that results from receptor stimulation. 6.) Medications can alter the metabolism of a neurotransmitter which changes the amount of neurotransmitter that is available for release. The monoamine oxidase inhibitors work as antidepressants primarily by decreasing the metabolism of a variety of neurotransmitters including serotonin, which are metabolized by

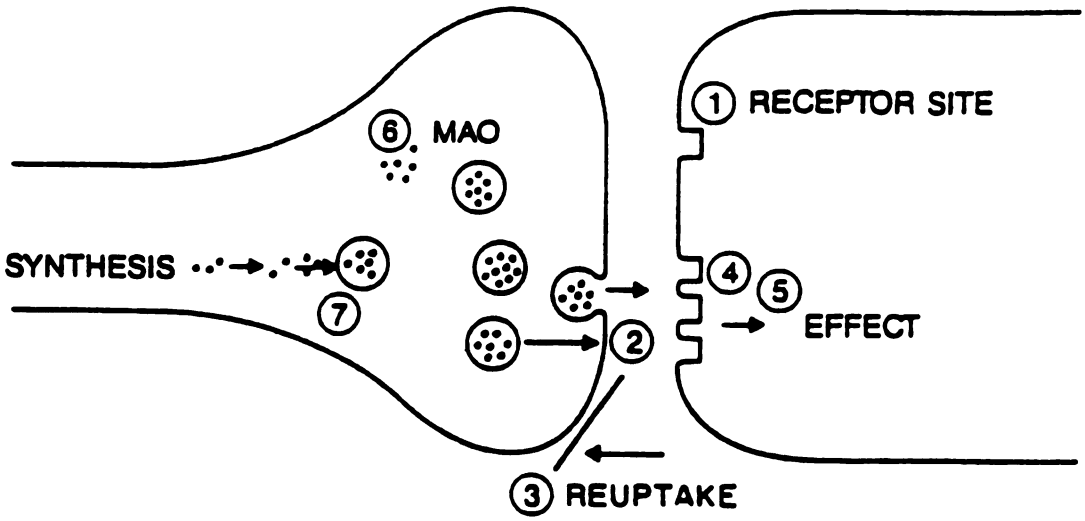

Figure 2 The Mechanisms of Action for Psychiatric Medications

the enzyme MAO. 7.) The amount of available neurotransmitter can be altered by increasing the amount of the precursor ingredients that are used in synthesizing neurotransmitters. For example, a dietary increase in L-tryptophan, the amino acid synthesized into serotonin, can result in an increase in serotonin (Gitlin, 1990).

The brain reacts to internal influences and external influences such as medications by trying to maintain homeostasis. For example, a medication such as Prozac that blocks the reuptake of serotonin, thereby functionally increasing the amount of available neurotransmitter, produces a decrease in the amount of serotonin released in an attempt to provide homeostasis (Gitlin, 1990). In essence, medications compete with a naturally adapting system whose goal is to prevent changes. Other than agonists which mimic the neurotransmitter by stimulating the receptor, medications appear to provide their clinical effects by exerting a continual influence over neurotransmitter systems for extended periods of time, thereby altering the regulatory mechanisms.

Indices of Serotonergic Activity: Serotonergic activity can be studied by measuring the concentration of the neurotransmitter, its metabolites, or metabolic enzymes, in plasma, cerebrospinal fluid, and urine. All studies using measures of 5-HT concentration are evaluating the presynaptic processes (e.g., metabolic turnover of the neurotransmitter; Martin, Owen, & Morihisa, 1987). All are peripheral measures of brain serotonin, and as such provide only an indirect measure of brain levels of the neurotransmitter. Cerebrospinal fluid 5-HIAA concentrations have been used, but it is unclear if CSF 5-HIAA adequately reflects brain serotonin function (Murphy, 1990). CSF samples are particularly problematic because they reflect an average of brain **and** spinal

cord CNS concentrations and, therefore, cannot provide information regarding localization of an observed abnormality (Martin, Owen, & Morihisa, 1987). Additionally, many subjects refuse to consent to the invasive and sometimes painful spinal tap required.

Since most of the body's serotonin is synthesized within the gastrointestinal tract, it has been suggested that measuring serotonin or its metabolites in urine or blood plasma are inadequate (Fuller, 1992). Blood platelets, however, contain common constituents with serotonin neurons such as serotonin storage granules and serotonin transporters (Pletscher, 1987) which make it a more valid measure of central serotonergic function. Measures from blood platelets such as serotonin content, serotonin transport, and radioligand-binding to transporter have been used successfully to study autism, aggression in males, and alcoholism, respectively (Fuller, 1992). Because of these benefits blood platelets have been called "models of brain serotonin neurons" (DaPrada, Cesura, Launay, & Richards, 1988). Additionally, since blood platelets have been found to contain serotonin receptors, blood platelet studies allow an examination of the less well understood connection between post-synaptic 5-HT functioning and suicidal and/or impulsive aggressive behavior (Coccaro, Kavoussi, Sheline, Berman, & Csernansky, 1997). Blood platelets are also easily obtainable and accessible which increases the attractiveness of their use.

Blood platelets do differ from brain serotonin in significant ways. Since blood platelets do not synthesize serotonin but derive it completely by uptake, continuous inhibition of the uptake carrier results in marked depletion of serotonin content in platelets. However, brain serotonin content is not decreased by uptake inhibition, and

extracellular serotonin concentration in the brain is actually increased (Fuller, 1992). Given the similarities between blood platelets and serotonin neurons and the ease of obtaining such samples, blood platelets were deemed the most promising measure of serotonergic function for this study.

REVIEW OF THE LITERATURE

Alcohol and Serotonergic Function

The association between alcoholism and serotonergic function has been shown in both animal and human studies. Research suggests that alcohol consumption and preference in humans may be related to decreased serotonergic neurotransmission as measured by the presynaptic measures of increased serotonin uptake and higher mean maximal-velocity-of-serotonin-transport (Vmax, density of platelet uptake sites; Boismare et al., 1987; Bokii, Kiseleva, Lapin, Prakhe, Rybakova, 1984; Daoust, et al., 1991; McBride, Murphy, Lumeng, & Li, 1989; Naranjo, et al., 1984; Naranjo, et al., 1987; Naranjo, Sellers, & Larwin, 1986; Neiman, Beving, Malmgren, 1987; Rausch, Monteiro, & Schuckit, 1991; Tollefson, 1989). Given this data, it should be possible to identify such a dysfunction and educate those individuals in this group to their increased risk for the development of alcoholism should they expose themselves to alcohol.

Animal Studies: Data from animal studies have shown an association between alcohol preference in rats and low brain serotonin turnover (Li et al., 1989). Increased serotonin uptake has also been found in alcohol preferring rats (Daoust et al., 1985). Additionally, serotonin reuptake inhibitors have been found to reduce ethanol consumption in rats (Daoust et al., 1984; Murphy et al., 1985; Waller, Murphy, McBride, Lumeng, & Li, 1985).

5-HT level has also been linked to alcohol preference and consumption in animal studies, but the results are somewhat contradictory. One group found lower 5-HT levels in brains of inbred alcohol preferring rats versus non alcohol preferring rats (Murphy,

McBride, Lumeng, & Li, 1982) Another study showed an ability to decrease ethanol consumption in rats by administration of a 5-HT inhibitor (Rockman, Amit, Carr, Brown, & Ogren, 1979). However, Kiianamaa (1976) found no difference in voluntary alcohol consumption in rats after lowering brain serotonin by three different methods.

Therefore, evidence for the link between serotonin and alcohol in the animal literature is strongest in regard to alcohol preference, serotonergic uptake, and serotonin turnover. The link between serotonin and alcohol is less strong in regard to 5-HT concentration's connection to voluntary consumption of alcohol. One reviewer has suggested that rat strain differences, methodologic considerations, and differential food intake could be responsible for some of the discrepancies in the animal literature (Moss, 1987).

Human Studies: Serotonin reuptake inhibitors have been found to reduce ethanol consumption in male drinkers (Naranjo et al., 1984; Naranjo et al., 1987). In aggregate, the data support the hypothesis that decreased serotonergic neurotransmission might facilitate alcohol intake, whereas increases in 5-HT function may inhibit alcohol intake (McBride, Murphy, Lumeng, & Li, 1989; Naranjo et al., 1986; Tollefson, 1989).

In a group of men with and without family histories of alcoholism, the family history positive subgroup had a higher mean density of platelet serotonin uptake sites (Vmax; Rausch, Monteiro, & Schuckit, 1991). Another study showed increased Vmax of serotonin uptake in alcoholics versus controls (Daoust et al., 1991). The same group also noted an increase in platelet 3H-serotonin uptake in former alcoholics with eleven years

abstinence versus non-alcoholics (Boismare et al., 1987). D'aoust et al., (1991) suggest that serotonin uptake is altered during chronic alcohol consumption.

Two other studies have also shown abnormalities in serotonin uptake in the platelets of detoxifying alcoholics (Bokii, Kiseleva, Lapin, Prakhe, & Rybakova, 1984; Neiman, Beving, & Malmgren, 1987). It should be noted that one study found contrasting results with a sample of withdrawaled alcoholic patients showing a decrease in platelet serotonin uptake (Kent et al., 1985).

One hypothesis that has evolved from these data suggests that alcoholics may have a pre-existing low brain serotonin level that can be transiently raised by alcohol consumption, but in the long run, actually leads to further depletion. This has lead to the suggestion that the alcoholic may drink repeatedly to pharmacologically modify a serotonin deficiency in the brain (Ballenger, Goodwin, Major, & Brown, 1979). D'aoust et al., (1991) cite their previous study of former alcoholics with 11 years abstinence where serotonin uptake was always increased (Boismare et al., 1987) as supporting evidence of this hypothesis.

Platelet 5-HT concentration is another measure that can be used as a measure of central serotonergic activity. One study found reduced platelet 5-HT content in alcoholics (Banki, 1987) and another found lower mean platelet 5-HT levels in a sample of male and female alcoholic patients during withdrawal and after 2 weeks of abstinence versus non-alcoholic controls (Bailly et al., 1990).

Cerebrospinal fluid (CSF) monoamine metabolites of serotonin such as 5-hydroxyindoleacetic acid (5-HIAA) provide another measure of central serotonergic

function. Research on 5-HIAA in alcoholics is rare, but one study has shown abstinent alcoholic men to have lower CSF-5-HIAA levels than controls (Ballenger et al., 1979). Ballenger studied alcoholic men entering an inpatient program for treatment and measured CSF 5-HIAA in the immediate post-intoxication period and after 4 weeks of abstinence. While CSF 5-HIAA measures in alcoholics could not be differentiated from controls in the post-intoxication period, there was a difference shown after four weeks of abstinence, with the alcoholic group having lower concentrations of CSF 5-HIAA.

Aggression and Serotonergic Function

Animal Studies: Data linking serotonin with aggressive behavior in animals have existed since a 1959 study that showed 5-HT reduced isolation-induced aggression in mice (Yen, Stangler, & Millman, 1959). Currently, there exists a large literature of animal studies supporting the hypothesis that central 5-HT is involved in the regulation of aggressive behavior (Eichelman, 1979; Soubrie, 1986; Valzelli, 1981). Data cited by Soubrie show an inverse correlation with central 5-HT activity and shock-induced fighting (Kantak, Hegstrand, & Eichelman, 1981; Sewell, Gallus, Gault, & Cleary, 1982), muricidal or mouse killing behavior (Katz, 1980; Waldbillig, 1979), and filicidal or pup killing behavior (Copenhaver, Schalock, & Carver, 1978). It appears that each of these behaviors can be increased or decreased by neurochemical manipulations of central 5-HT activity.

Studies of isolation-induced fighting in male mice and mouse-killing behavior in rats found an association between violence and a low 5-HIAA to serotonin ratio (Valzelli, 1969, 1971). A low ratio indicates a low serotonin turnover rate, and reducing CNS

serotonin by diet or pharmacological means leads to increased shock induced fighting or mouse-killing behaviors (Kantak et al., 1981; Katz, 1980). Further evidence of this was shown when mouse-killing behavior that is produced by p-chlorophenylalanine which decreases the synthesis of serotonin could also be reduced by the serotonin reuptake inhibitor fluoxetine (Berzenyi, Galateo, & Valzelli, 1983).

Interestingly, some evidence suggests that central 5-HT activity is associated more with reactive aggressive behavior versus the frank expression of aggression (Coccaro, 1989). When rats were previously exposed to mice the muricidal response produced by decreased 5-HT was prevented (Marks, O'Brien, & Paxinos, 1977). These findings suggest that when sufficient arousal is not present, central 5-HT may not be associated with aggression. In a study of non-human primates, no aggression was found unless conditions of increased arousal were present (Chamberlain, Pihl, & Young, 1987) as occurs upon the insertion of a nasogastric tube.

Similarly, Soubrie (1986) argues that serotonin acts as an endogenous inhibitor for various behaviors. Reduced serotonin may not lead to aggressive behaviors but may be a catalyst for the expression of aggressive impulses. This model suggests that serotonin depletion results in a primary increase in impulsiveness, and the increased aggressiveness is just one of the more observable manifestations of behavioral change.

Human Studies: Many human studies have consistently shown reduced levels of CSF 5-HIAA in patients with a history of aggressive behavior as manifested by outward violence (Brown, Goodwin, Ballenger, Goyer, & Major, 1979; Brown et al., 1982; Linnoila et al., 1983; Roy, Adinoff, & Linnoila, 1988). Additionally, aggressiveness

directed inward which may be conceptualized as suicide attempts are also associated with reduced CSF 5-HIAA (Asberg, Traskman, & Thoren 1976; Banki & Arato, 1983; Traskman, Asberg, Bertilsson, & Sjostrand, 1981; van Praag, 1982, 1983). For a comprehensive review of this literature, please see Asberg et al., 1987.

Impulsivity, Aggressiveness, and Serotonergic Function

Many of the human studies on serotonergic dysfunction focus on impulsive aggression (Coccaro, 1989; Asberg et al., 1987; Roy & Linnoila, 1988). In a study of 36 male murderers and attempted murderers under forensic evaluation, lower levels of CSF 5-HIAA were found among those whose crimes were impulsive versus premeditated (Linnoila, Virkkunen, Scheinen, Nuutila, Rimon, & Goodwin, 1983). Interestingly, further analyses found that those offenders who had committed more than one violent crime had significantly lower CSF 5-HIAA levels than the offenders who had committed only one violent crime. Additionally, the impulsive offenders who had attempted suicide had significantly lower CSF 5-HIAA levels than the non-impulsive offenders who had not attempted suicide. These findings support the hypothesis that low CSF 5-HIAA may be associated with impulsive violent behavior either towards others or oneself.

A later study was conducted of incarcerated male arsonists (mean age =29.8 $\pm$ 9.6 years) to determine whether low CSF 5-HIAA levels were associated with aggressiveness or impulsivity (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). Arsonists whose crimes were motivated by uncontrollable impulsive urges to set fires were selected because they show little interpersonal aggressiveness. Using a subset of the male violent offenders from the previous study as well as a control group of 10 community recruited healthy subjects

(3 female, 7 male) who were free of any history of mental illness, CSF 5-HIAA levels were found to be lower in the arsonist group than either the violent offenders or controls. The authors suggest that this gives further evidence that low CSF 5-HIAA is associated with violent behavior through an effect on poor impulse control.

In one review, Coccaro (1989) cites various studies of clinical samples comprised largely of male subjects in their 20's giving evidence that CSF 5HIAA levels are negatively correlated with both clinician and self-reported aggression (Brown et al., 1979; Brown et al., 1982; Lidberg, Tuck, Asberg, et al., 1985; Linnoila et al., 1983), irritability and hostility (Brown & Goodwin, 1984; Roy et al., 1988; Rydin et al., 1982; van Praag, 1986) as well as criminal behavior (Lidberg et al., 1985; Linnoila et al., 1983; van Praag, 1983; Virkkunen et al., 1987). A negative correlation was also found in retrospective self reports of childhood and adolescent behavioral difficulties (Brown et al., 1985) which may also indicate that reduced 5-HT activity is associated with early behavioral difficulties.

Coccaro (1989) also cites evidence from other peripheral measures of 5-HT functioning (whole blood 5-HT, plasma tryptophan/neutral amino acid ratio, and platelet 3H-IMI binding) which also indicate an inverse correlation with aggressive behaviors. Three out of 4 of these studies showed a negative correlation with clinician rated measures of current aggressive behavior or historic accounts of serious aggressive acts that led to jail time. One study found an inverse relationship between whole blood 5-HT and hyperactivity and aggression in a sample of 30 mentally retarded patients (age 4-39) with hyperactivity and aggressive behavior (Greenberg & Coleman, 1976). A second study found a low ratio of tryptophan to amino acids which signifies lowered synthesis of

sertonin in male alcoholics who had histories of aggression when compared to male alcoholics without such histories (Branchey, Branchey, Shaw, & Lieber, 1984). A third study of pre-pubertal children found that a group diagnosed with DSM-III conduct disorder (14 male/3 female) had lower levels of H-IMI binding (Bmax) compared to an age and sex matched group of control children (Stoff, Pollack, Vitiello, Behar, & Bridger, 1987). However, one study showed a positive correlation between whole blood 5-HT and ratings of conduct disorder in male adolescents (Pliszka et al., 1988).

These data suggest that indices of 5-HT function correlate more strongly with irritable, impulsive, aggression versus premeditated aggression or violence. This is bolstered by the Linnoila studies (1983, 1985) of impulsive violent offenders versus non-impulsive violent offenders, with the non-impulsive violent offenders exhibiting normal CSF 5-HIAA concentrations. Coccaro also points out that several studies have noted that low CSF 5-HIAA patients exhibit increased irritability and hostility (Brown & Goodwin, 1984; Roy et al., 1988; Rydin et al., 1982; van Praag, 1986). Coccaro argues that reduced 5-HT function may lead to vulnerability to increased response to noxious stimuli. Brown and Linnoila agree with Coccaro that there is increasing evidence for the hypothesis that impulsivity, disinhibition, or dyscontrol is the behavioral variable linked to low levels of CSF 5-HIAA rather than antisocial or violent acts themselves.

Impulsive, Aggressive Alcoholics

Studies of impulsivity, aggressiveness, and alcoholism have found abnormal serotonergic function in early onset male alcoholics with paternal history of alcoholism and impulsive aggressiveness when drunk (Buydens-Branchey, Branchey, Noumair, Lieber,

1989; Virkkunen & Linnoila, 1990). This subgroup of alcoholics has been classified by Cloninger as the Type II alcoholic (Cloninger, Bohman, & Sigvardsson, 1981; Cloninger, Sigvardsson, von Knorring, & Bohman, 1988). However, several research groups note that these characteristics are associated with individuals who are suffering from antisocial personality disorder (Irwin, Schuckit, & Smith, 1990), borderline personality disorder, and intermittent explosive disorder (Linnoila et al., 1983; Linnoila et al., 1989; Virkkunen, DeJong, Goodwin, & Linnoila, 1989; Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). All of these disorders have been associated with reduced brain serotonergic function. Additionally, one group has noted that there is strong evidence that antisocial personality disorder and alcoholism are distinct entities (Schuckit, Klein, Twitchell, & Smith, 1994), and others stress that alcoholism accompanied with antisocial personality disorder should be differentiated from alcoholism outside the context of antisocial personality disorder (von Knorring, von Knorring, Smigan, Lindberg, & Edholm, 1987).

Evidence given by Virkkunen and Linnoila (1990) linking abnormal serotonergic metabolism with impulsivity in the group of early onset alcoholics comes from Monoamine Oxidase (MAO) and CSF 5-HIAA studies. Low platelet MAO has been linked with alcoholism since the 1980's (Oreland, 1983; Oreland, Gottfries, Kiianmaa, Wiberg, & Winblad 1983). When using Cloninger's proposed classification schema of Type I (history of maternal alcoholism, later onset of problems, less life difficulty, low aggressiveness) and Type II alcoholics (paternal history of alcoholism, early onset of life problems, greater severity of life interference, and increased aggressiveness), it was found that Type II's were primarily characterized by low platelet MAO activity (Oreland, von Knorring, von

Knorring, & Bohman, 1985; von Knorring, Bohman, von Knorring, & Oreland, 1985) which has also been found in criminals with antisocial personality disorder (Lidberg, Modin, Oreland, Tuck, & Gillner, 1985). Interestingly, only 1.5% of the population belong to this group characterized by low platelet MAO (Cloninger, von Knorring, & Oreland, 1985). Moreover, there is an over-representation of Type II's within this subgroup that demonstrates low platelet MAO, which comprises between 15-25% of male alcoholics (Linnoila & Virkkunen, 1989). There is also evidence that personality characteristics such as impulsiveness and sensation seeking which are typical of Type II's and antisocial personality disorder are also linked to low platelet MAO activity (Von Knorring, Oreland, & Winblad, 1984).

Virkkunen and Linnoila (1990) also note from previously cited studies that habitually violent, impulsive offenders who behave violently when drunk and have a low concentration of CSF 5-HIAA also fit the criteria for Cloninger's Type II alcoholics (Linnoila et al., 1983; Virkkunen et al., 1987). These authors also point out that in a study of violent offenders and their families, low CSF 5HIAA was associated with paternal alcoholism (Linnoila et al., 1989).

Another study looked at early onset of alcohol related problems in male alcoholics (Buydens-Branchey, Branchey, Noumair, & Lieber, 1989). Those who were age 20 or below when problem drinking began comprised early onset alcoholics, while males whose problems emerged after age 20 comprised the late onset alcoholics. These authors noted that the group with early alcohol problems had higher rates of incarceration for violent offenses, more suicide attempts, and more depression. To see if they could differentiate

between the two groups by serotonergic function, tryptophan availability was measured. The ratio of tryptophan over other amino acids competing for entrance into the brain determines the amount of tryptophan available for synthesis into serotonin. It was found that patients with early onset alcoholism had lower ratios of tryptophan compared with other amino acids. Therefore, these authors hypothesize that altered serotonergic neurotransmission plays a role in alcohol-seeking behavior by early onset drinkers.

Studies With Children And Adolescents

While studies with adults show that serotonergic function is negatively associated with aggressiveness and impulsivity, results with children and adolescents are less consistent. In one review of CSF serotonin metabolites, Brown and Linnoila, (1990) point out that high levels of CSF 5-HIAA have been found in infancy and adolescence (Riddle et al., 1986; Kruesi, Swedo, Hamburger, Potter, & Rapoport, 1988). These authors conclude that it is unclear how early age-associated changes in CSF 5HIAA relate to aggressive/impulsive and self-destructive behaviors.

Brown et al., (1986) showed that low CSF 5-HIAA in young adult males was associated with childhood conduct problems, and Kruesi et al., (1990, 1992) found lower CSF 5HIAA in children with disruptive behavior disorders (27 male/2 female) versus age, sex, and race matched controls both at assessment (mean age = 11.3 $\pm$ 3.6 years) and 2 year follow-up (mean age = 13.8 $\pm$ 3.9 years). Another study used platelet imipramine binding as yet another measure of peripheral serotonergic function in a study of 23, 10-16 year old males recruited from an inpatient psychiatric unit, and who all fulfilled criteria for conduct disorder, and 16 who also fulfilled criteria for attention deficit hyperactivity

disorder (Birmaher et al., 1990). Results showed that the number of imipramine binding sites correlated inversely with total problems scores on the Child Behavior Checklist (CBCL: Achenbach, & Edelbrock, 1983), as well as externalizing, hostility, and aggressiveness scores on the CBCL. Data from these three studies coincide with the mass of adult literature suggesting a negative correlation between serotonergic function and aggressiveness. However, it should be noted that one additional study found conflicting results with an increase in whole blood 5-HT among incarcerated adolescent males with conduct disorder with or without anxiety or depression (mean age = 15.5 $\pm$ 1.43 years) compared to a male adolescent sample recruited from a community mental health clinic with anxiety or depressive symptoms alone (mean age = 12.4 $\pm$ 2.0 years; Pliszka et al., 1988). Importantly, this study did not have a control sample of healthy controls to determine how whole blood 5-HT in conduct disordered males compares to a healthy, non-clinical sample. However, the same study also noted that 5-HT correlated positively with clinician ratings of conduct symptoms, as well as a trend for higher 5-HT concentration in violent versus non-violent offenders in this conduct disorder sample.

Still other studies have shown consistent results with the adult data. 3H-Imipramine binding, the distribution of which closely parallels the distribution of serotonin neurons, was reduced in children with mixed conduct disorder and ADHD (Stoff, Pollack, Vitiello, Behar, & Bridger, 1987), but was not found in a sample of children with only ADHD diagnosis without conduct disorder (Weizman, Bernhout, Weitz, Tyano, & Rehavi, 1988). Central 5-HT function was studied in 25, 7-11 year old boys with aggressive and non-aggressive ADHD by Prolactin response to fenfleuramine challenge

(Halperin et al., 1994). The findings showed the aggressive group had greater response to the challenge which is consistent with altered central 5-HT function. It must be noted that controls were not used and results cannot unequivocally identify which group had the deviant response to fenfleuramine challenge. It must also be noted that the peripheral measures such as platelet 5-HT, plasma MHPG (3-methoxy-4hydroxy-phenylglycol, a norepinephrine metabolite), or plasma HVA (homovanillic acid, a dopamine metabolite) did not show any between group differences.

STATEMENT OF THE PROBLEM

The literature reviewed indicates that serotonergic dysfunction may be a factor in the development of impulsivity, aggressiveness, and alcoholism in samples recruited from clinical settings. Therefore, the current study used classification schemas based on variables thought to be related to impulsivity and aggressiveness (Antisocial Behavior Scores for fathers and CBCL Total Behavior Problem scores for children) to explore the relationship between impulsive aggression and serotonergic function. While the adult data clearly show that alcoholism and impulsive aggression are marked by decreased serotonergic neurotransmission as measured by low CSF 5HIAA, low whole blood platelet 5-HT, and increased 5-HT uptake, the data from children and adolescents are less clear. While one study found a positive correlation between serotonergic neurotransmission and aggressive and impulsive children and adolescents, the majority of the studies agree with the adult data which show a negative correlation.

First, the present study hoped to add to the sparse literature of children's studies by examing serotonergic function and impulsive aggression in both male and female children. Second, this study was designed to further contribute to the existing literature by examining this relationship in a sample of individuals who differ from previous samples in that they are community recruited and were not comprised of clinical treatment or incarcerated groups. Given the wealth of consistent data from adult samples and the similar findings in the large majority of child and adolescent studies, the current study predicted a negative relationship between both adult and childhood impulsive aggression and serotonergic function.

HYPOTHESES

1.) Greater serotonergic dysfunction will be demonstrated in AALs when compared with NAALs. Specifically, this dysfunction will manifest in AALs having lower serotonergic neurotransmission as indicated by lower levels of whole blood 5-HT. Relatedly, it is expected that there will be a negative correlation between father's serotonergic function and impulsive aggression, as measured by the Antisocial Behavior Checklist (Zucker & Noll, 1980)

2.) Greater serotonergic dysfunction will be demonstrated in children who are rated as high impulsive aggressive when compared to children rated as low impulsive aggressive. Relatedly, it is expected that with all children combined, there will be a negative correlation between serotonergic function (as measured by whole blood 5-HT) and scores on the Child Behavior Checklist (Achenbach & Edelbrock, 1983).

3.) Children's serotonergic function will be positively correlated with parent's serotonergic function.

METHOD

SUBJECTS

Subjects for the present study were drawn from an already existing longitudinal data set of the Michigan State University/University of Michigan Family Study which is tracking the etiology of alcoholism in a sample of 215 alcoholic families and 96 non-alcoholic control families. Alcoholic fathers for the original study were recruited from local district court records of all male drunk driving offenders who had a blood alcohol concentration of 0.15% or higher at the time of arrest, or 0.12% or higher if that arrest was the second or more documented offense. Court personnel approached these men and obtained consent to release their phone numbers to research staff for potential involvement in a study of child development and family health.

Participation criteria for the larger study included having a biological son between age 3.0 and 6.0 living in an intact family with the biological mother. Evidence of fetal alcohol syndrome resulted in exclusion from study participation (Fitzgerald et al., 1993). Subjects were informed that participation was entirely voluntary, confidential, and unrelated to court outcome. Seventy-nine percent of the men agreed to release their names to study personnel and 91% of these men and their wives agreed to participate. The original sample was comprised of non-Hispanic Caucasians due to the limited ethnic/racial make-up of the catchment area. Additionally, it should be noted that the larger sample is comprised of convicted drunk drivers which may indicate that an antisocial component is also present in the sample. All of these men were later screened and met diagnosis of probable or definite alcoholism using Feighner diagnostic criteria

(Feighner et al., 1972). This diagnosis incorporated information from the Short Michigan Alcohol Screening Test (Selzer, 1975) and the Diagnostic Interview Schedule (Robins et al., 1981). Diagnostic status of the mothers in these families was free to vary, although a subset (41%) made a lifetime DSMIII-R alcohol abuse/dependence diagnosis.

To insure demographic comparability, non-alcoholic control families were recruited through door to door canvassing which started one block away from each alcoholic family and stayed within the same census area. Other criteria for control families included the presence of a male biological child who was within 6 months of the same age as the experimental target child. Feighner criteria were used for both fathers and mothers to rule out probable or definite alcohol or other drug abuse/dependence.

The sampling design for the present study is shown in Table 1. Given that some families were not able to produce usable blood samples for a complete family (father, mother, and son), the final sample included 13 AALs, 13 NAALs, and 12 NCs. Children's ages ranged from 7-15 (sons and daughters combined, N = 45, M = 10.48, SD = 1.65). Within each father's group we selected 6 fathers who had sons with high Total Behavior Problem scores on the CBCL and 6 fathers who had sons with low Total Behavior Problem scores on the CBCL. AAL families were those that had fathers with Antisocial Behavior Scores of 24 or greater on the Antisocial Behavior Checklist (Zucker & Noll, 1980) while NAAL families were characterized by fathers with ASB scores below 24. High impulsive aggressive children were classified by CBCL T-scores of 60 or greater, and low impulsive aggressive children were characterized by scores of 59 or less. Subjects

for the current study included the following: biological father, biological mother, male target child, and a female child if available and age appropriate.

Table 1

Sampling Design

		Father's Classification		
		AAL	NAAL	NC
Son's Classification	Hi TBP	6	6	6
	Lo TBP	6	6	6

PROCEDURE

Participant Consent

Prior to sample collection, the study coordinator contacted each participating family and gave an introduction to the proposed study. Then a follow-up phone call was made by the author, outlining detailed procedures of this separate in-home session and the voluntary nature of their participation. Participants were then asked to give written consent to this procedure with the understanding that they could withdraw at any time without risk of penalty.

Materials and Preparation

Each subject had 24ml of whole blood collected by venipuncture in polystyrene ethylenediaminetetraacetic acid (EDTA) Vacutainer brand collection tubes by the author who is a trained phlebotomist. Twenty-one gauge Vacutainer brand needles were used to insure platelet integrity. All Vacutainer tubes were labeled beforehand with an indelible marker with the subject's 6-digit identification number, date, and time of blood draw. All identifying information, collection time, and number of tubes were logged in a lab book immediately following venipuncture.

Health History Questionnaire: While the MSU/U of M Family Study already has a self reported life history of physical health for each study participant, a general medical screen in the form of a health history questionnaire was administered to each participant prior to venipuncture to ascertain any current medications, illnesses, or difficulties that might have confounded sample results, see Appendix A. Relatedly, this health screen also inquired about recent alcohol abuse of the respondent and their spouse

as well as recent cigarette use. All family members were informed that they would be paid $10 for their participation. Each family member was informed that if they were injured as a result of participation in this study, Michigan State University would provide emergency medical care if necessary. Sample collection proceeded following a full review and approval by Internal Review Boards at Michigan State University and at the collaborating institution, the University of Michigan.

Venipuncture: Each subject was seated in a comfortable supine position for the single blood draw. The antecubital area of the most appropriate arm for draw was prepared for venipuncture with alcohol pad and tourniquet. Venipuncture proceeded with a single needle stick. A total of 24 mls of whole blood was collected into (6), 4ml EDTA Vacutainer tubes. As soon as a steady flow of blood was apparent, the tourniquet was undone to prevent any subject discomfort. Following venipuncture completion and needle withdrawal, the puncture site was observed, and the subject was instructed to place sterile gauze with pressure to the site to prevent any further bleeding. The site was then covered with a band-aid to prevent any irritation of the area. All tubes were then gently inverted approximately 5-6 times to thoroughly mix blood with EDTA anti-coagulant.

Sample Storage and Transportation: Blood for whole blood serotonin assay was immediately frozen in dry ice pellets, then stored in a -70° C freezer upon arrival at Michigan State University. Later, these samples were batch shipped in dry ice to the University of Chicago for laboratory analysis.

Whole Blood 5-HT Assay: Whole blood 5-HT was analyzed by high pressure liquid chromatography with fluoremetric detection (Anderson, Young, Cohen, & Schlicht,

1981). 5-Hydroxytryptophan was used as an internal standard. Intra-assay and interassay coefficients of variation were 2.3% and 4.0%, respectively. Assays were performed blind to all demographic and diagnostic information in the Developmental Neuroscience Laboratory of the Brain Research Institute at the University of Chicago.

Methodological Considerations

Some evidence suggests that whole blood 5-HT decreases moderately between ages 10 and 12, but after this time period, there is no correlation of whole blood 5-HT and age (Ritvo et al., 1971). Since the children for this study were within this age range, statistical analyses of this dataset took this variable into account. Other evidence suggests that whole blood 5-HT is not affected by ordinary changes in diet (Ritvo et al., 1970), therefore fasting was not required in the present study. Prior work has shown that there is no significant diurnal variation in blood 5-HT content in adults (Kremer, Goekoop, & Van Kempen, (1990). However, seasonal effects on platelet 5-HT content have been found in children and adolescents with OCD and matched normal controls (Brewerton, Flament, Rapoport, & Murphy, 1993). Therefore, analyses controlled for season of blood draw through the use of a dichotomous covariate. This covariate was created by dividing the calendar year by equinox. Thus, blood samples drawn in Winter (September 21-March 20) were coded as low photo period and samples drawn in Summer (March 21-September 20) were coded as high photo period.

MEASURES

Demographic Variables

The families in this study were characterized by the demographic measures of socioeconomic status, current educational degree, years of education, family income, and age. All measures were reported by respondents on a demographic instrument administered as part of the protocol of the parent study except the variable of age which was calculated using date of birth and date of blood draw.

Parental Socioeconomic Status: Information regarding parental socioeconomic status (SES) was measured by the Revised Duncan Socioeconomic Index (TSE12, Stevens & Featherman, 1981). The TSE12 is a measure of occupational attainment which has been suggested as a more contemporary indicator of SES than measures based solely on income.

Parental Education: Two measures of education were used to describe the sample. The first measure, years of education, denotes the number of years of academic or vocational education achieved. Scores ranged from 10-20 years of education. The second measure denotes the highest degree achieved. Scores ranged from 0 to 4 (0=high school diploma or less, 1=vocational or technical degree, 2=Bachelors degree, 3=Masters degree, 4=Doctorate, Medical degree, or Veterinarian degree).

Family Income: Family income was measured as each family's gross annual income in dollars as reported by father. Subjects responded to a 10-point scale in which a score of 1 represented income of $4,000 or less; 2=$4,001-$7,000; 3=$7,001-$10,000; 4=$10,001-$13,000; 5=$13,001-$16,000; 6=$16,001-$20,000; 7=$20,001-$30,000;

8=$30,001-$50,000; 9=$50,001-$75,000; 10=$75,001-$100,000; 11=Over $100,000. The midpoint dollar level of each interval was used in computing mean income level for the sample. For example, an interval score of 3 was coded as $8500.

Current Alcohol and Cigarette Use

Quantity and frequency measures of alcohol and cigarette use for all subjects were gathered at the time of blood draw through subject responses to related items on the Health History Questionnaire (see Appendix A). Parents were asked to provide a self report of their own alcohol use as well as a collateral report of their spouse's alcohol use in an attempt to reduce possible reporting bias. These data were coded such that the highest report of alcohol use by either the subject or the subject's spouse was used for analyses. Children were asked to report on their own alcohol and cigarette use in an abbreviated version of this instrument which was administered privately.

Paternal Impulsive Aggression Indicator

The Antisocial Behavior Checklist (Zucker & Noll, 1980) was used to assess father's level of impulsive aggression. The ASB is a 46-item self report inventory that measures the frequency of participation in various aggressive and antisocial activities both in childhood and adulthood. The current version is a revision of an earlier instrument used in the Rutgers Community Study (Zucker & Barron, 1973) and was modified to make items salient for both childhood and adulthood activities.

Reliability and validity studies of college students and inmates have found the ASB to have adequate test-retest reliability (.91 over 4 weeks) and internal consistency (coefficient alpha =.93) (Zucker & Noll, 1980). The ASB has also been shown to

differentiate between groups with heavy antisocial histories (inmates), individuals with minor district court offenses, and university students (Zucker, Noll, Ham, Fitzgerald, & Sullivan, 1992; Fitzgerald, Davies, Zucker, & Klinger, 1993), and between those with antisocial personality disorder and those without it (Zucker, Ellis, Fitzgerald, Bingham, & Sanford, 1996).

Alcoholic Subtype

Family classification as AAL or NAAL was assigned using the father's Time 1 score on the Antisocial Behavior Checklist. The overall ASB index was computed by first summing the father's childhood and adulthood domain scores. This procedure was used to insure that high scoring fathers had evidenced a lifetime pattern of aggressive and antisocial behavior beginning in childhood and continuing into adulthood as evidenced by alcoholism and sociopathy. Thus, high-scoring fathers (AALs) are those who have evidenced a lifetime pattern of sustained antisociality rather than a sporadic or more intermittent history of antisocial difficulties.

Scores of 24 or greater on the ASB served as the cutoff for classification as AALs while those less than 24 were classified as NAALs. This cutoff was chosen by computing sensitivity and specificity of scores using DSM-IIIR codings of antisociality as a standard. The sensitivity of the ASB score of 24 was calculated to be .85 while specificity was calculated to be .83. By comparison, cutoff scores of 21 and 27 yielded sensitivity and specificity scores of .94 and .75 and .79 and .87 respectively. Therefore, the ASB score of 24 proved to be the best combination of sensitivity and specificity and was also a comparable classification compared to the DSM-IIIR category for antisocial personality.

Childhood Impulsive Aggression Indicator

The 4-16 year old version of the Child Behavior Checklist (Achenbach & Edelbrock, 1983) was used to classify sons as high or low on a behavioral phenotype indicator of impulsive aggression. The CBCL provides an objective measure of the child's social and emotional functioning. It is comprised of 113 items regarding prevalence and frequency of child problem behavior. When summed, these items yield a total behavior problem score (TBP) as well as two broadband scores (internalizing and externalizing behaviors) and eight narrow band scores. For child classification in the present study, fathers' (TBP) ratings of their sons when they were 3-6 years of age were used, so that this indicator is one of the early appearance of impulsive aggression. Although mother's ratings on their children's behavior have been more heavily utilized in the literature (Barber, Olsen, & Shagle 1993; Fitzgerald, Zucker, Maguin, & Reider, 1994; Prior, Smart, Sanson, Pedlow, & Oberklaid, 1992), data from the larger parent study indicate that mothers and fathers rate their son's behavior similarly (Bingham, Fitzgerald, Zucker, under review). Since the primary focus was on fathers and sons, it was decided that fathers' ratings of their children were most appropriate for this classification.

The Total Behavior Problem Score was selected for this categorization because it is the indicator with the greatest range, and because it correlates very highly with both the CBCL Aggression subscale ($r=.88$, $p \leq .01$) and the CBCL Externalizing Broad Band scale ($r=.91$, $p \leq .01$) in analyses of the larger longitudinal sample; correlations of similar magnitude are also reported in the norming of the instrument (Achenbach & Edelbrock,

1983). In addition, in the larger longitudinal study the TBP score correlated moderately with ratings of impulsivity and hyperactivity on the Conners Impulsivity/Hyperactivity Scale ($r=.31$, $p, \leq .01$, Conners, 1990).

Using sample distribution characteristics and CBCL clinical scoring criteria as a base, we established a TBP T-score of 60 or greater (borderline clinical cutoff) as the cutoff for the high impulsive aggression categorization; boys with TBP T-scores of 59 or less were classified as being low on this behavioral dimension. Reliability coefficients for the CBCL range from .84 to .93 (Achenbach and Edelbrock, 1983).

RESULTS

Exclusionary Criteria

Before beginning analyses, subjects taking any potentially serotonergic altering medications were identified from self report data in the Health History Questionnaire. The 5-HT value for each of these 12 individuals was then excluded from analyses. The composition of these exclusions by medication status were broken down into the following groups: Boys (3-Ritalin, 1-Tofranil, 1-Ritalin and Buspar), Fathers (1-Calan), Mothers (1-Xanax and Dyazide, 1-Xanax and Cardizem, 1-Prozac, 1-Valium, 1-Effexor and Pamelor, 1-Prozac and Effexor).

Given that this study examined only fully biologically related family members, one girl's 5-HT value was excluded from analyses based on her father's report of questionable paternity. Overall, a total of 13 individual 5-HT values (10% of total samples drawn) were excluded from analyses. This resulted in a total of 117 analyzable whole blood 5-HT values (Fathers-38, Mothers-32, Boys-34, Girls-13). Table 2 shows their group membership characteristics.

Demographic Characteristics

Table 3 presents the Time 1 parental sociodemographic and educational characteristics of this study's families which were classified by father's Time 1 indices of impulsive aggression and alcoholism. Parental SES as measured by the Revised Duncan Socioeconomic Index (TSE12, Stevens & Featherman, 1981) revealed that mean occupational attainment scores for AAL fathers were 28.55 which reflect technical repair occupations (e.g., structural metal craftsmen). Mean occupational attainment scores for

Table 2

Group Membership Characteristics of Family Members With Analyzable Whole Blood 5-HT Samples; N=117, (Fathers=38, Mothers=32, Sons=34, Daughters=13)

FATHER'S CLASSIFICATION

SON'S CLASS		AAL		NAAL		NC		Total	
	HI TBP	Father	7	Father	5	Father	6	FA	18
		Mother	5	Mother	5	Mother	6	MO	16
		Son	6	Son	6	Son	5	S	17
		Daughter	3	Daughter	2	Daughter	4	D	9
	LO TBP	Father	6	Father	8	Father	6	FA	20
		Mother	5	Mother	7	Mother	4	MO	16
		Son	5	Son	7	Son	5	S	17
		Daughter	1	Daughter	1	Daughter	2	D	4
		FA	13	FA	13	FA	12		
		MO	10	MO	12	MO	10		
		S	11	S	13	S	10		
		D	4	D	3	D	6		

Table 3

Time 1 Parental Sociodemographic Characteristics of Families Classified by Father's Time 1 Indices of Antisociality and Alcoholism

	AAL N=13		NAAL N=13		NC N=12		
	M	SD	M	SD	M	SD	F
Father							
Age	32.14	3.66	31.27[c]	3.88	34.88[c]	4.17	3.64*
Education (Years)	12.77[c]	2.17	13.23[d]	1.79	15.25[cd]	2.70	4.30*
Degree[a]	.15	.55	.46	.78	1.00	1.60	1.50
Socioeconomic Status[b]	28.55	14.13	30.09	18.46	42.28	22.41	2.03
Family Income	24,923	11,755	36,230	23,398	43,833	19,793	3.17
	AAL N=10		NAAL N=12		NC N=10		
	M	SD	M	SD	M	SD	F
Mother							
Age	28.90	3.39	31.72	4.76	31.71	3.52	1.71
Education (Years)	13.00	1.33	13.25	2.83	13.90	2.13	.43
Degree[a]	.30	.67	.58	.90	.60	.97	.21
Socioeconomic Status[b]	26.49	7.92	28.91	16.96	24.59	5.08	.38

[a]See text for coding formula

[b]Duncan TSE12 (Stevens & Featherman, 1981)

[c,d]Means labeled with the same superscript differ from one another at the $p<.05$ level of significance.

*$p<.05$

NAAL fathers were 30.09 which reflect low level clerical occupations and craftsmen (e.g., postal clerks and office machine repairmen). Mean occupational attainment scores for NC fathers were 42.28 [e.g., health technician occupations, (radiological technician)].

Results from individual one-way ANOVAs found that NAAL fathers were significantly younger than NC fathers. Additionally, results found that AAL fathers and NAAL fathers had achieved significantly less years of education than NC fathers. These differences in paternal education parallel those found in the larger sample (Ellis, Bingham, Zucker, & Fitzgerald, 1996). Univariate analyses failed to find any significant differences between demographic variables for mothers in these families.

Table 4 presents the Time 1 sociodemographic characteristics of the children in the sample who were originally classified by father's Time 1 ratings of impulsive aggression. Univariate analyses of these variables did not show any significant differences between these two groups.

Table 5 presents the current sociodemographic characteristics of the parents classified by father's Time 1 indices of antisociality and alcoholism. Univariate analyses found AAL and NAAL fathers to have significantly less years of education than NC fathers. No significant differences were found for mothers.

Table 4

Time 1 Sociodemographics of Sons Classified by Father's Time 1 Rating of Impulsive Aggressiveness

	High Impulsive Aggressive N=17		Low Impulsive Aggressive N=17		
	M	SD	M	SD	F
Son's Age	4.04	.95	4.08	.86	.01
Father's Years of Education	14.29	3.06	13.47	1.77	.92
Mother's Years of Education	13.18	2.53	13.82	1.94	.70
Father's Degree[a]	.88	1.41	.29	.69	2.40
Mother's Degree[a]	.47	.87	.65	.86	.35
Father's Socioeconomic Status[b]	32.20	19.83	34.88	19.77	.16
Mother's Socioeconomic Status[b]	24.01	4.93	32.04	15.82	3.99
Family Income	32,618	17,755	39,029	22,673	.84

[a]See text for coding formula
[b]Duncan TSE12 (Stevens & Featherman, 1981)

Table 5

Current Parental Sociodemographic Characteristics of Families Classified by Father's Time 1 Indices of Impulsive Aggressiveness and Alcoholism

	AAL N=13		NAAL N=13		NC N=12		
	M	SD	M	SD	M	SD	F
Father							
Age	37.90	4.12	37.96	4.09	41.18	4.04	2.59
Education	12.23[c]	2.45	13.62[d]	1.66	15.58[c,d]	2.43	4.04*
Degree[a]	.46	1.13	.54	.88	1.08	1.56	.96
Socioeconomic Status[b]	29.61	18.76	33.75	22.86	48.58	19.33	2.94
Family Income	45,885	27,502	44,962	23,164	53,125	19,746	.44
	AAL N=10		NAAL N=12		NC N=10		
	M	SD	M	SD	M	SD	F
Mother							
Age	33.51	3.37	38.58	4.59	38.04	3.84	1.74
Education	13.20	1.87	13.67	2.67	13.90	2.13	.24
Degree[a]	.30	.67	.67	.89	.60	.97	.56
Socioeconomic Status[b]	27.03	8.42	32.18	19.05	33.11	14.54	.48

[a]See text for coding formula

[b]Duncan TSE12 (Stevens & Featherman, 1981)

[d,c]Means labeled with the same superscript differ from one another at the $p<.05$ level of significance.

*$p<.05$

Hypothesis 1

Adult Impulsive Aggression

To test hypothesis 1, which predicted lower 5-HT in AALs when compared to NAALs, two analytic strategies were utilized. Given the literature's focus on categorical comparisons of clinical samples and the resulting database from which comparisons between various clinical groups can then be made, it was decided to first use ANOVAs to test mean differences in whole blood 5-HT. Results from this approach could then contribute data to the existing literature regarding mean level whole blood 5-HT data from not only two well documented subtypes of alcoholics (AALs and NAALs), but also the much less studied population of normal community controls (NCs). Ultimately, this approach provides a metric from which comparisons can be made between a wide variety of clinical and normal control samples. Secondly, correlational analyses using the range of ASB scores were deemed necessary in examining the relationship between whole blood 5-HT and impulsive aggression due to increased statistical power. Additionally, it was assumed that the level of pathology differs between the individuals within each dichotomous grouping and that correlational analyses allow meaningful clinical information to be obtained.

First, a one way ANOVA with the independent variable of father's alcohol classification at Time 1 (AAL, NAAL, or NC) and father's 5-HT as the dependent variable was performed. Results failed to show a significant main effect and did not support a difference in 5-HT level between AALs and NAALs, see Table 6.

Table 6

Summary F Table For One Way ANOVA With The Independent Variable of Father's Alcoholism Status at Time 1 (AAL, NAAL, NC) And The Dependent Variable of Father's Current Whole Blood 5-HT(ng/ml)

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig. of F
Between Groups	441.12	2	220.56	.13	.87
Within Groups	57526.25	35	1643.61		
Total	57967.37	37			

Means, Standard Deviations, and N's for One Way ANOVA With The Independent Variable of Father's Alcoholism Status at Time 1 (AAL, NAAL, NC) and The Dependent Variable of Father's Current Whole Blood 5-HT (ng/ml)

	AAL N=13	NAAL N=13	NC N=12	Total N=38
Father's 5-HT (ng/ml)	M=157.69 SD=34.11	M=157.46 SD=48.06	M=150.25 SD=37.96	M=155.26 SD=39.58

Alcoholics versus Controls: To test whether alcoholism at Time 1 was significantly related to decreased current 5-HT, a one way ANOVA with the independent variable of father's alcoholism classification at Time 1 (alcoholic or non-alcoholic) and father's 5-HT as the dependent variable was performed. Thus, AAL and NAAL fathers were combined into a Time 1 alcoholic group while non-alcoholic controls were used as the comparison. Results failed to show a significant main effect and did not support the hypothesis of differences in current 5-HT between Time 1 alcoholic fathers and Time 1 non-alcoholic fathers, see Appendix B, Table B1.

Covariates: Given the lack of significant differences in father's 5-HT by father's classification as AAL, NAAL, or NC in the initial analysis, the potential effect of covariates was examined. First, a correlation between father's 5-HT and variables other than AAL, NAAL, or NC classification hypothesized to be related to father's serotonin was conducted. These variables included, measures of father's current alcohol use as reported on the health history questionnaire administered at blood draw (1. quantity X frequency=average drinking days per week in last 4 weeks multiplied by usual number of drinks consumed per drinking occasion; 2. in last 4 weeks, average number of days alcohol consumed per week; 3. average number of drinks consumed per occasion in the last 4 weeks), measures of dad's current cigarette use as reported on the health history questionnaire (1. quantity X frequency= average days smoking in last 4 weeks multiplied by average number of cigarettes smoked per occasion; 2. average number of days smoked cigarettes in past 4 weeks, 3. average number of cigarettes per occasion in last 4 weeks), father's age, and seasonal variation (amount of daylight calculated by splitting the calendar

year by the equinox). Average number of days smoking was the only variable significantly correlated with father's 5-HT, see Appendix B, Table B2. A simple factorial ANOVA, with father's classification as the independent variable, father's 5-HT as the dependent variable, and father's average number of days smoking as a covariate failed to show a significant main effect for father's classification, see Appendix B, Table B3.

Next, the relationship between father's impulsive aggression and serotonergic function was examined by two one-tailed Pearson product moments correlations. First, a correlation was conducted between father's 5-HT and father's Time 1 total score on the Antisocial Behavior Checklist. Results did not show a significant correlation (N=38, r = -.07, p = .34). Second, a one-tailed PPMC was conducted between father's 5-HT and current total score on the ASB. Results failed to show a significant correlation between fathers' 5-HT and current impulsive aggression as measured by the ASB (N=38, r = .19, p = .13). These results failed to support Hypothesis 1.

Hypothesis 2

Childhood Impulsive Aggression

Hypothesis 2, which predicted greater serotonergic dysfunction in high impulsive aggressive children when compared to low impulsive aggressive children was also tested by categorical comparisons and correlations for reasons identical to those outlined in Hypothesis 1.

While father's ratings were used to categorize their sons into high and low impulsive aggressive groups during the design stage of this study, later findings from the longitudinal study indicated that maternal ratings of children were more accurate indicators of impulsive aggression (Loukas et al., 1997). Therefore, in all subsequent analyses, maternal ratings of child behavior were used to categorize the children.

Time 1 Ratings of Son's Impulsive Aggression: First, a 2 (mother's classification of son at Time 1=high or low impulsive aggression) X 3 (father's alcoholism status at Time 1=AAL, NAAL, NC) ANOVA with son's whole blood 5-HT as the dependent variable was conducted. While neither of the main effects were significant, results indicated a significant interaction. See Table 7 for ANOVA table, means, and standard deviations.

Next, the potential effects of covariates were examined. Results from analyses with sons corroborated findings in the literature supporting a significant negative correlation between serotonergic function and age for children in the 10-12 age range [$N = 34$, $r = -.36$, $p = .02$; (PPMC)] as well as a positive relationship between 5-HT and amount

Table 7

Summary F Table for 2 (Mother's Classification of Son at Time 1=High or Low Impulsive Aggressive) X 3 (Father's Alcoholism Status at Time 1=AAL, NAAL, NC) ANOVA With Son's Current 5-HT (ng/ml) as The Dependent Variable

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Main Effects	16828.163	3	5609.388	1.478	.242
MBOYGRP1	4234.220	1	4234.220	1.115	.300
RISK	16290.463	2	8145.232	2.146	.136
2-Way Interactions	46073.764	2	23036.882	6.068	.006
MBOYGRP1 RISK	46073.764	2	23036.882	6.068	.006
Explained	46811.241	5	9362.248	2.466	.057
Residual	106292.524	28	3796.162		
Total	153103.765	33	4639.508		

Means, Standard Deviations, and N's for 2 (Mother's Classification of Son at Time 1=High or Low Impulsive Aggressive) X 3 (Father's Alcoholism Status at Time 1=AAL, NAAL, NC) ANOVA With Son's Current 5-HT (ng/ml) as The Dependent Variable

	AAL	NAAL	NC	
Low Impulsive Aggression	M=237.33 SD=60.48 N=6	M=237.86 SD=63.37 N=7	M=198.75 SD=62.92 N=8	M=224.65 SD=62.26 N=21
High Impulsive Aggression	M=194.00 SD=15.23 N=5	M=203.17 SD=83.65 N=6	M=351.00 SD=16.97 N=2	M=249.39 SD=38.62 N=13
	M=216.67 SD=37.86 N=11	M=220.52 SD=73.51 N=13	M=274.88 SD=39.95 N=10	

of available sunlight (N = 34, r = .29, p = .049, Spearman Correlation).

Therefore, the same 2 X 3 ANOVA with son's 5-HT as the dependent variable was performed adding both age and season as covariates. Results with these covariates added did not change the relationship (see Appendix C, Table C1 for ANOVA table and adjusted means). Neither the covariates nor the main effects were significant. As previously found, results indicated a significant interaction. Contrary to expectations, for non-alcoholic control fathers, sons who were rated as low impulsive aggressive had significantly lower mean 5-HT than those sons rated as high impulsive aggressive. This result may be spurious and may be related to the small number of subjects in the high impulsive group (N = 2).

Current Ratings of Son's Impulsive Aggression: Analyses were then performed with mother's ratings of son's current behavior. First, a one-way simple factorial ANOVA with mother's classification of son's current impulsive aggression as the independent variable (high impulsive aggression=clinical range as measured by CBCL Total Behavior Problem T-scores of 63 or greater, low impulsive aggression=borderline clinical and normal range as measured by Total Behavior Problem T-scores of 62 or less) and son's 5-HT as the dependent variable was conducted. The main effect was not significant, see Table 8. Second, the same ANOVA using son's 5-HT as the dependent variable was run, adding both son's age and season of blood draw as the covariates. While the covariate of son's age was significant, the second covariate, season, and the main effect were not. See Appendix C, Table C2 for ANOVA table and adjusted means.

Table 8

Summary F Table For One Way ANOVA With The Independent Variable of Mother's Classification of Son's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Son's Current Whole Blood 5-HT (ng/ml)

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig. of F
Between Groups	15435.66	1	15435.66	3.52	.07
Within Groups	135965.85	31	43865.00		
Total	151401.52	32			

Means, Standard Deviations, and N's for One Way ANOVA With The Independent Variable of Mother's Classification of Son's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Son's Current Whole Blood 5-HT (ng/ml)

	HI IMPULSIVE AGGRESSIVE N=6	LOW IMPULSIVE AGGRESSIVE N=27	Total N=33
Son's 5-HT (ng/ml)	M=178.00 SD=71.70	M=234.07 SD=65.12	M=206.04 SD=68.41

Current Ratings of Daughter's Impulsive Aggression: Given these suggestive findings, similar analyses were conducted on the sample of daughters. First, a one-way ANOVA with mother's rating of current behavior as the independent variable and daughter's 5-HT as the dependent variable was conducted. The main effect was significant, with high impulsive aggressive daughters having lower whole blood 5-HT than low impulsive aggressive daughters, see Table 9. Second, an ANOVA with daughter's 5-HT as the dependent variable was performed adding daughter's age and season of blood draw as the covariates. While neither the covariate of daughter's age or season was significant, the main effect remained highly significant, see Appendix C, Table C3. Given that the high impulsive aggressive group consisted of only two subjects, a non-parametric test was run on the two groups. Results from a Mann Whitney U-Wilcoxon test confirmed the previous analyses (W = 3.0, two-tailed P = .03).

Is There a Gender Effect in Children for Whole Blood 5-HT?: Before performing analyses on the larger combined sample of sons and daughters (N=45), we explored the possibility of a significant main effect by gender for the dependent variable of child's 5-HT. While the literature does not support a significant difference in 5-HT related to gender, we ran a series of analyses on our own sample to verify this observation. As expected, an analysis of variance using gender as the independent variable and child's 5-HT as the dependent variable failed to show a significant main effect, see Appendix C, Table C4. Second, an ANOVA using gender as the independent variable and child's 5-HT as the dependent variable was run adding both age and season as covariates. Neither the covariates, nor the main effect were significant, see Appendix C, Table C5 for

Table 9

Summary F Table For One Way ANOVA With The Independent Variable of Mother's Classification of Daughter's Current Behavior (High or Low Impulsive Aggressive), and Dependent Variable of Daughter's Current Whole Blood 5-HT (ng/ml)

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig. of F
Between Groups	7661.40	1	7661.40	6.37	.03
Within Groups	12036.60	10	1203.66		
Total	19698.00	11			

Means, Standard Deviations, and N's for One Way ANOVA With The Independent Variable of Mother's Classification of Daughter's Current Behavior (High or Low Impulsive Aggressive), and Dependent Variable of Daughter's Current Whole Blood 5-HT (ng/ml)

	HI IMPULSIVE AGGRESSIVE N=2	LOW IMPULSIVE AGGRESSIVE N=10	Total N=12
Daughter's 5-HT (ng/ml)	M=150.50 SD=13.44	M=218.30 SD=36.29	M=184.40 SD=24.87

ANOVA table and adjusted means. Given these results, combining 5-HT scores across gender was deemed appropriate; it also would increase power in analyses.

Current Ratings of Son's and Daughter's Impulsive Aggression Combined: Next, an ANOVA with mother's rating of child's current behavior as the independent variable and child's current 5-HT as the dependent variable was conducted. Results indicated a significant main effect, with children rated as high impulsive aggressive having lower 5-HT levels than children classified as low impulsive aggressive, see Table 10. Second, a similar ANOVA with child's 5-HT as the dependent variable was performed with both child's age and season as the covariates. While neither of the covariates was significant, the main effect of child classification remained highly significant, see Appendix C, Table C6 for ANOVA table and adjusted means. Table 11 provides a description of the sociodemographics of these children classified by mother's rating of current behavior.

Importantly, this is the first study to show an inverse relationship between childhood impulsive aggression and whole blood 5-HT. These results indicate that the inverse relationship between serotonergic function and impulsive aggression found in adult samples can also be found in a high risk sample of children who exhibit similar behavioral characteristics. The lack of previous findings is partially attributable to the dearth of studies which examine the relationship between the childhood behavioral characteristics of impulsive aggression and serotonergic function in children. However, the lack of such findings and the inconsistencies in the literature regarding this phenomena may also result from methodological differences and inadequacies in the existing studies (Pine et al., 1996). It has been suggested that studies of children are hampered by the use of small

Table 10

Summary F Table For One Way ANOVA With The Independent Variable of Mother's Classification of Child's Current Behavior (High or Low Impulsive Aggressive) and The Dependent Variable of Child's Current Whole Blood 5-HT (ng/ml)

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig. of F
Between Groups	22654.03	1	22654.03	6.45	.02
Within Groups	12036.60	43	1203.66		
Total	19698.00	44			

Means, Standard Deviations, and N's For One Way ANOVA With The Independent Variable of Mother's Classification of Child's Current Behavior (High or Low Impulsive Aggressive) and The Dependent Variable of Child's Whole Blood 5-HT (ng/ml)

	HI IMPULSIVE AGGRESSIVE N=8 (6 Boys, 2 Girls)	LOW IMPULSIVE AGGRESSIVE N=37 (27 Boys, 10 Girls)	Total N=45
Child's 5-HT (ng/ml)	M=171.13 SD=62.13	M=229.81 SD=58.67	M=200.47 SD=60.40

Table 11

Sociodemographics of High and Low Impulsive Aggressive Children (N=45; Boys=33, Girls=12) as Classified by Maternal Ratings of Current Child Behavior

	High Impulsive Aggressive N=8; 6 boys, 2 girls		Low Impulsive Aggressive N=37; 27 boys, 10 girls		
	M	SD	M	SD	F
Child's Age	11.26	1.53	10.31	1.65	.61
Dad's Years of Education	13.00	1.73	15.03	2.72	3.57
Mom's Years of Education	12.88	2.47	14.19	2.33	2.22
Dad's Degree[a]	.29	.76	1.08	1.50	1.86
Mom's Degree[a]	.38	.74	.76	.93	.86
Dad's Socioeconomic Status[b]	25.33	6.07	43.69	24.98	3.67
Mom's Socioeconomic Status[b]	35.01	19.95	32.30	14.20	.01
Family Income	41,071	20,044	53,722	25,594	1.52

[a]See text for coding formula

[b]Duncan TSE12 (Stevens & Featherman, 1981)

Note: one boy did not have a rating from mom, hence number of boys =33 not 34. Analyses with fathers variables include a family where the father had committed suicide. The son was rated low impulsive aggression and the girl was rated high impulsive aggression. Hence the analyses of paternal demographic variables for both high and low groups have an N of 7 and 36 respectively.

samples; typically 30 subjects or less. Additionally, few of the existing studies have taken seasonal rhythms on serotonergic measures into account.

Correlations Between Child 5-HT and Impulsive Aggression: Next, the relationship between child serotonergic function and impulsive aggression was tested by a series of Pearson product moment correlations. The first set of analyses examined the relationship between current child 5-HT and child behavior problem ratings at Time 1. Since 7 of the 13 girls in the sample were enrolled in the parent study at time periods following Time 1, T1 ratings and classifications were available for only 6 girls (total sample N=40). Additionally, it should be noted that one mother's rating of her son at Time 1 was missing, hence only 39 subjects are available for analyses using mother's Time 1 ratings. A one-tailed PPMC was run between CBCL total behavior problem raw scores, total behavior problem T-scores, classification as high or low impulsive aggressive, and current 5-HT. No significant correlations between childs' 5-HT and Time 1 ratings of child were observed, see Table 12.

Although under only special circumstances would a covariate analysis render a non-significant zero order relationship significant, nonetheless, for sake of completeness, an examination of possible effects of covariates was conducted through a correlational analysis, controlling for childs' age and season. As expected, none of these correlations were significant, see Appendix C, Table C7.

The next set of analyses examined the association between current child 5-HT and current child behavior problem ratings. First, a one-tailed PPMC was conducted between

Table 12

Correlations Between Child's Current 5-HT (ng/ml) and Time 1 Total Behavior Problem Ratings (N=40; Sons=34, Daughters=6)

	1	2	3	4
1.Childs' 5-HT (ng/ml)	1.00	-.12	-.06	-.01
2.TBP Raw Score		1.00	.96**	.75**
3.TBP T-Score			1.00	.82**
4.Impulsive Aggression Classification				1.00

*p<.05, **p<.005

One-tailed Pearson Product Moment Correlations

N=39 for those analyses using mother's TBP raw score, mom's TBP T-score, and mom's classification, due to one missing rating of a son by his mother.

current CBCL total behavior problem raw scores, total behavior problem T-scores, classification of child as high or low impulsive aggressive, and current 5-HT. As predicted, results indicated significant negative correlations between child's' 5-HT and all three ratings of child behavior by mother, see Table 13. To examine the possible effects of covariates, the same correlations were re-run, controlling for both child's age and season of blood draw. As expected, all ratings of children remained significantly negatively correlated with childs' 5-HT. See Appendix C Table C8 for complete listing of correlations.

Table 13

Correlations Between Child's 5-HT (ng/ml) and Current Ratings of Child Total Behavior Problems (N=45; Sons=33, Daughters=12)

	1	2	3	4
1.Childs' 5-HT (ng/ml)	1.00	-.33*	-.34*	-.36*
2.Mom's TBP Raw Score		1.00	.96**	.69**
3.Mom's TBP T-Score			1.00	.61**
4.Mom's Class. Of Child				1.00

*p<.05, **p<.005

One-tailed Pearson Product Moment Correlations

Hypothesis 3

Intrafamilial Correlations in Serotonergic Function

To examine the relationship between parental 5-HT and child 5-HT, a correlation matrix was performed between father's 5-HT, mother's 5-HT, son's 5-HT, and daughter's 5-HT, see Table 14. Results indicated that son's 5-HT was not significantly correlated with father's 5-HT nor mother's 5-HT. To examine the potential effects of covariates a correlation between son's 5-HT, father's 5-HT, and mother's 5-HT was performed, adding son's age and season of son's blood draw as covariates. Results indicated that son's 5-HT was not significantly correlated with fathers' 5-HT (N=32, $r = .07$, $p = .35$) or mothers' 5-HT (N=29, $r = .23$, $p = .12$).

Results from the first correlational analysis above found that daughters' 5-HT was significantly correlated with father's 5-HT, but was not significantly correlated with mother's 5-HT, see Table 14. To examine the potential effects of covariates a correlation was performed between daughter's 5-HT, father's 5-HT, and mother's 5-HT, adding daughter's age and season of daughters' blood draw as covariates. Daughters' 5-HT remained significantly correlated with fathers' 5-HT (N=12, $r = .61$, $p = .03$), but was not significantly correlated with mothers' 5-HT (N=11, $r = .05$, $p = .45$).

While no formal predictions were made in regard to the relationship between 5-HT in brothers and sisters, exploratory analyses were performed. Results from the original correlation between all family members indicated that brother's 5-HT was significantly correlated with sister's 5-HT, see Table 14. To examine the potential effects of covariates a correlation was performed between brother's 5-HT and sister's 5-HT, adding brother's

Table 14

Intrafamilial Correlations in Serotonergic Function

	1	2	3	4
1. Son's 5-HT (ng/ml)	1.00	.59* (12)	.20 (29)	.10 (32)
2. Daughter's 5-HT (ng/ml)		1.00	.08 (11)	.61* (12)
3. Mother's 5-HT (ng/ml)			1.00	.20 (31)
4. Father's 5-HT (ng/ml)				1.00

*$p<.05$, **$p<.005$

One-tailed Pearson Product Moment Correlations

( )=number of subjects

age, sister's age, and season of blood draw as covariates. Brother's 5-HT was not significantly correlated with sister's 5-HT (N=12, $r = .51$, $p = .08$). The non-significant findings in this covariate analysis are most likely a product of low power resulting from the use of three covariates and small sample size. Overall, the data suggest that there is a positive relationship between 5-HT in brothers and sisters.

DISCUSSION

A large literature spanning the last 20 years describes an inverse relationship between impulsive aggression and a variety of measures of serotonergic function in adult alcoholics and clinical samples of non-alcoholics (Asberg et al, 1987; Buydens-Branchey et al., 1989; Coccaro, 1989; Coccaro, Kavoussi, & Lesser, 1992; Linnoila, 1990; Virkkunen & Linnoila et al., 1983; Virkkunen et al., 1987; Roy & Linnoila, 1988). However, studies among children and adolescents with these behavioral characteristics have only recently been undertaken and are rare. Additionally, these few studies have been restricted almost exclusively to male clinical samples and the results have been inconsistent (Birmaher et al., 1990; Halperin et al., 1994; Kruesi et al, 1990; Kruesi et al., 1992; Pliszka et al., 1988; Stoff et al., 1987; Weizman et al., 1988). The relationship is of particular interest as a phenotypic marker of biological vulnerability to impulsive aggression, which itself has been hypothesized to be a risk factor for the development of antisocial alcoholism.

The current study adds valuable information to the research literature through two unique aspects of the study's design. First, this study was designed to contribute further data regarding the role of childhood serotonergic function in the development of impulsive aggressiveness through a mixed gender sample of children . Secondly, this study was designed to contribute information regarding serotonergic functioning in not only two samples of alcoholics (AALs and NAALs), but also in healthy community controls, a group that has been largely neglected.

Childhood Impulsive Aggression

The hypothesized relationship between serotonergic dysfunction and childhood impulsive aggression was largely supported by the present findings. Although results are not entirely uniform, in instances where the most powerful tests (large N) were run and where the phenotypic classification of impulsive aggression was most proximal to the assay of serotonergic function (i.e., ratings of **current** child functioning), results unambiguously show the hypothesized negative relationship. Thus, results showed that children currently rated as high impulsive aggressive had a significantly lower level of whole blood 5-HT than children currently rated as low impulsive aggressive, but no parallel finding was found when using Time 1 classifications of children. However, results from the analysis using Time 1 ratings of children are hard to interpret given the low number of children in the control group who were classified as high impulsive aggressive.

Relatedly, while a negative and substantial correlation was found between children's current 5-HT and current rating of impulsive aggression as measured by CBCL Total Behavior Problem Raw Scores, Total Behavior Problem T-Scores, and child classification, no parallel relationship was found for Time 1 ratings of children.

Importantly, the present findings give further support to the majority of available studies on children and adolescents which suggest that decreased serotonergic function is positively related to impulsive aggression, (Brown et al., 1986; Kruesi et al., 1990; Kruesi, et al., 1992; Birmaher et al., 1990; Stoff et al., 1987). However, the lack of an observed relationship between current serotonergic function and developmentally earlier (i.e., Time 1) impulsive aggression make it difficult to be unequivocally confident about

the initial model. Further research is necessary to adequately test the hypothesized role serotonergic dysfunction may play in the developmental trajectory of childhood impulsivity and conduct problems, adolescent aggressiveness and alcohol use, and later alcoholism.

Intrafamilial Correlations of Serotonergic Function

The present findings also provided only partial support for the predicted positive relationship between serotonergic function in parents and their offspring. The only parent-child dyad to exhibit a statistically significant, positive relationship in serotonergic function was fathers and their daughters. Importantly, there was no relationship between father's 5-HT and son's 5-HT. Given that the design of the study chose fathers and sons who shared behavioral dimensions related to serotonergic function, this finding is in direct contrast to the expected relationship.

Additionally, a statistically significant, positive relationship in serotonergic function was found between brothers and sisters. While the relationships between fathers and their daughters and brother and sisters were robust, the lack of familiality for whole blood 5-HT between mothers and their children and between fathers and their sons is in contrast to data from studies of autism and attention-deficit hyperactivity disorder (Abramson et al. 1989; Cook et al., 1990; Cook, Stein, Ellison, Unis, & Leventhal, 1995; Kuperman, Beeghly, Burns, & Tsai, 1985; Leventhal, Cook, Morford, Ravitz, & Freedman, 1990). Perhaps a more sophisticated analytical approach may be necessary to accurately measure intrafamilial correlations of whole blood 5-HT.

Adult Impulsive Aggression

The current study chose to examine serotonergic function in families headed by antisocial alcoholic and non-antisocial alcoholic men; populations that have demonstrated decreased serotonergic function. This population is of particular interest since parental alcoholism has been shown to be a risk factor for the development of behavior problems and later alcoholism in their offspring (Cotton, 1979; West & Prinz, 1987). Consequently, this design allowed us to examine associations between childhood impulsive aggression and serotonergic function in children at risk for later problems. Additionally, given that much of the research suggests that behavioral disinhibition or impulsive aggression is the behavioral correlate associated with decreased serotonergic function, we chose to examine populations marked by higher and lower impulsive aggression (AALs and NAALs respectively).

While it was hypothesized that impulsive aggressive alcoholics (AALs) would exhibit decreased serotonergic function in comparison to non-antisocial alcoholics (NAALs), results did not support this hypothesis. Relatedly, results failed to show significant differences in serotonergic function between alcoholics (AAL + NAALs) and non-alcoholic controls (NCs).

The lack of expected findings for decreased serotonergic function in alcoholics may be related to the fact that this study classified fathers as alcoholic or non-alcoholic through measures of behavior exhibited nearly 6.5 years prior to the current study (N = 38, M = 6.59, SD = 1.13). While this sampling design was utilized in an attempt to maximize the identification of a longstanding pattern of alcoholism, alcoholism diagnosis has been

shown to be an epiphenomenal process that ebbs and flows over time (Zucker et al., 1997). Consequently, it would be likely that alcoholism diagnosis and impulsive aggression have changed for some of the men in the current sample over the intervening years since classification at Time 1. Hence, more current indices of alcoholism may be necessary to accurately assess the relationship between alcoholism and serotonergic function.

Results from correlational analyses also failed to support the predicted negative relationship between fathers' serotonergic function and impulsive aggression as measured by the total score on the Antisocial Behavior Checklist (Zucker & Noll, 1980) both at Time 1 and the current time period. These results are in contrast to the large literature documenting a negative relationship between impulsive aggression and serotonergic function (Coccaro, 1989; Asberg et al., 1987; Roy & Linnoila, 1988; Linnoila et al., 1983; Linnoila et al., 1985). It is possible that the construct of impulsive aggression hypothesized to be most closely associated with behavioral disinhibition or the propensity to impulsively and violently react to irritable or noxious stimuli is more accurately captured by measures other than the Antisocial Behavior Checklist.

Methodological Limitations

Given that the likelihood of a Type 1 error was increased as a result of the large number of statistical tests performed, the reader is alerted to interpret the statistically significant results with caution. While all significant results reported herein are judged worthy of attention and interpretation, they should be subject to replication. In relation to the subject pool, it should be noted that since this sample is restricted to non-Hispanic

Caucasian families, the results may not be generalizable to other ethnic groups and races. Additionally, given that the study design attempted to maximize the presence of alcoholism in all but the control fathers, results may not generalize to non-alcoholic families.

Given the literature documenting an inverse relationship between impulsive aggression and serotonergic function in adults, and the lack of such results in the present work, this study may have been restricted by the use of Antisocial Behavior Checklist scores as a measure of impulsive aggression. While this instrument measures a variety of aggressive behaviors (gang fighting, hitting a teacher, beating up another person, teasing or killing an animal) as a whole, it may not adequately target the dimension of irritable, impulsive aggression hypothesized to result from behavioral disinhibition. Other measures including the Buss-Durkee Hostility Inventory Assault Scale (Buss & Durkee, 1957), Aggression score from the Life History Aggression interview (Brown et al., 1979), total score from the self report Barratt Impulsiveness Scale (BIS-11; Barratt, 1985), and DSM-IV antisocial personality diagnoses may be useful in accurately measuring impulsive aggression.

Similarly, future investigations may want to replicate the present findings from the analyses with children by using impulsivity and aggression measures such as the Brown-Goodwin Assessment for Life History of Aggression (Brown et al., 1979; Brown et al., 1982), the aggressiveness scale from the CBCL (Achenbach & Edelbrock, 1983), the Iowa Conners Aggression Factor from the Conners Rating Scales (Conners, 1990), and DSM-IV Conduct Disorder diagnoses.

While this study attempted to capitalize on the earliest behavioral manifestation of impulsive aggression in children, results indicate that this construct may be epiphenomenal, not static, and change considerably over time. Relatedly, the current study may have been confounded by the use of Time 1 measures of alcohol problems in adults which in many cases may not have accurately reflected current alcohol diagnosis. Importantly, this study may have been limited by the small sample of participants which may have produced a lack of power for some analyses.

Another limitation of this study is the use of only one measure of serotonergic function, whole blood platelet 5-HT to characterize central serotonergic function. While future studies may want to replicate the current findings with whole blood platelet 5-HT, it will also be important to gather other indices of central serotonergic function, including postsynaptic measures.

Implications

One interpretation that can be made of these data is that the observed negative relationship between current childhood impulsive aggression and serotonergic function may indicate the presence of a phenotypic marker of biological vulnerability to impulsive aggression. While the expected relationship between current serotonergic function and Time 1 impulsive aggression was not found, this may be related to problems in the design of the study. The potential for the observed relationship to represent a marker for later development of antisocial alcoholism or other behavioral difficulties will need to be assessed by continued study of this population through time.

Given that the present data did not find an overall relationship between father's and son's 5-HT, an alternative interpretation that needs to be explored is that the expected relationship is not present. Clearly, additional research needs to be conducted to determine this. Within the context of the present study, this would entail increasing the number of children available for the Time 1 high impulsive aggressive group with non-alcoholic control fathers as well as increasing the overall sample size.

These findings suggest that it may be possible to identify children at risk for the future development of problem behaviors. There is consensus that attending to behavioral characteristics in children is important, especially in relation to impulsive aggressiveness. Relatedly, parental ratings are one method of obtaining such information. Importantly, the current study has shown that maternal ratings of current child behavior are related to a biological substratum within the child. This emphasizes the clinical importance of attending to maternal ratings of children's behavior and provides construct validity for maternal ratings. In addition, early identification of at risk individuals makes it possible to clinically intervene early in the life course, possibly disrupting the developmental trajectory before such problems become more stable and problematic.

Future Directions

The results of the current study indicate that current serotonergic function is negatively related to current impulsive aggression in male and female children and differentiates between high and low impulsive aggressive children in a sample at risk for the future development of alcohol problems. These results are consistent with adult data and suggest that childhood serotonergic dysfunction is related to impulsive aggressive

behavior which is hypothesized to be a result of behavioral disinhibition. Future studies are needed to replicate the present findings and to continue to explore the relationship between childhood serotonergic dysfunction as it relates to the later development of aggressiveness, antisociality, and alcoholism in AAL, NAAL, and NC families. Future studies may also examine the relationships between social and environmental factors, such as harsh parenting environments and childhood serotonergic function. Additionally, the relationship between serotonergic function and other psychiatric problems such as depression should be explored to determine whether these relationships parallel those found in adults.

APPENDICES

APPENDIX A

PARENT HEALTH HISTORY
FORM BBS (8/95)

Q1. Within the past 3 years, have you had a regular physician or a clinic you usually attend?

1 . . . . . YES
2 . . . . . NO [GO TO Q2]

Q2. Do you remember the date of your **last** physical examination within the past 3 years?

1 . . . . . YES
2 . . . . . NO [GO TO Q3]

____/____/____
(Month, day, year of last physical)

Q3. What is your **current** height? _____ ft. _____ ins.

Q4. What is your **current** weight? _____lbs.

Q5. Have you been on a medication program for hyperactivity for a period of time, such as ritalin or other medication in the past year?

1 . . . . . YES
2 . . . . . NO [GO TO Q6]

AGE STARTED: _____ AGE ENDED: _____

Q6. Have you been on a medication program for any other long term or chronic condition in the past year (such as asthma, cystic fibrosis, etc.)?

1 . . . . . YES
2 . . . . . NO [GO TO Q7]

MEDICATION	AGE STARTED	TO AGE ENDED	REASON (CONDITION)
1._____	_____	_____	_____
2._____	_____	_____	_____
3._____	_____	_____	_____

The next set of questions deal with other medications you have taken in the **past month**. If you have taken the medication, write in the brand of medication taken, **TOTAL** number of days you have taken the medication in the past month (estimate, if necessary), and the reason(s) for taking them.

Q7. Have you taken any pain or fever relievers *(aspirin, Tylenol, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q8]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q8. Have you taken any cough medicine *(Robitussin, Pediacare, Triaminic, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q9]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q9. Have you taken any decongestants/nasal spray *(Sudafed, Dimetapp, Actifed, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q10]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q10. Have you taken any Antihistamines *(Chlortrimaton, Actifed, Benadryl, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q11]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q11. Have you taken any multisympton cold remedies *(Nyquil, Coridiidin, Cotylenol, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q12]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q12. Have you taken any antibiotics *(Penicillin, Amoxicillin, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q13]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q13. Have you taken any asthma medication in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q14]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q14. Have you taken any allergy medication in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q15]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q15. Have you taken any vitamins/dietary supplements in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q16]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q16. Have you taken any neuroleptic medications *(Thorazine, Mellaril, Stelazine, Prolixin, Haldol, Clozaril, Risperidol, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q17]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q17. Have you taken any tricyclic antidepressants *(Prozac, Zoloft, Desyrel, Effexor, etc)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q18]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q18. Have you taken any monoamine oxidase inhibitors *(Nardil, Parnate, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q19]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q19. Have you taken lithium in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q20]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q20. Have you taken any anticonvulsant medication *(Depacote, Tegretol, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q21]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q21. Have you taken any anti-anxiety medication *(Buspar, Valium, Librium, Dalmane, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q22]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q22. Have you taken any stimulant medication *(Ritalin, Cylert, Dexedrine, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q23]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q23. Have you taken any anti-hypertensive medication *(Inderal, Catapres, Tenex, etc.)* in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO Q24]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q24. Have you taken any other medications in the past month?

1 . . . . . YES
2 . . . . . NO [GO TO 25]

MEDICATION	*DAYS*	*REASON (ILLNESS/CONDITION)*

Q25. Have you been hospitalized <u>in the past 3 years</u>?

1 . . . . . YES
2 . . . . . NO [GO TO 26]

AGE IN..	REASON: OPERATION OR ILLNESS	# OF DAYS
a._____	_____	____
b._____	_____	____
c._____	_____	____
d._____	_____	____
e._____	_____	____

Q26. Have you been in an accident resulting in injury serious enough to require immediate medical treatment *(e.g., broken bones, concussion, stitches, burns, poisonings/accidental ingestion, etc.)* in the past 3 years?

1 . . . . . YES
2 . . . . . NO [GO TO Q27]

AGE IN..	REASON: INJURY OR ACCIDENT	# OF DAYS
a._____	_____	____
b._____	_____	____
c._____	_____	____
d._____	_____	____
e._____	_____	____

Cigarette Use

Q27. Have you ever smoked cigarettes?

___ Never ___ Once or twice ___ Occasionally, but not regularly

___ Regularly in the past ___ Regularly now

Q28. Over the past 4 weeks, **on average** how many days did you smoke cigarettes?

___ days

Q29. Over the past 4 weeks, on days you did smoke, how many cigarettes did you usually smoke?
___ cigarettes

Q30. When was the last time you smoked any cigarettes?
_____ date of last cigarette **or** number of days since last cigarette

YOUR RECENT ALCOHOL USE

31. Over the past 4 weeks, **on the average,** how many days a week did you have a drink?
___ days a week

32. Over the past 4 weeks, on a day when you did drink, **how many drinks** did you usually have in 24 hours? (One drink is a 12 oz. can of beer, a 4 oz. glass of wine, or a single shot of 80 proof)
___ drinks per 24 hours

33. Over the past 4 weeks what is the **most number of days** per week you had a drink?
___ days

34. Over the past 4 weeks, what is the **most number of drinks** you've had in 24 hours?
___ drinks

35. Over the past 4 weeks, how long was the longest period you were abstinent (went without drinking)?
___ days
When was that? _____(date) to _____ (date)

36. Were your drinking patterns over the last 4 weeks fairly typical for you?

__No, it was less than usual __Yes, it was fairly typical

__No, it was more than usual

YOUR SPOUSE'S RECENT ALCOHOL USE

37. Over the past 4 weeks, **on the average,** how many days a week did **your spouse** have a drink?
___ days a week

38. Over the past 4 weeks, on a day when you spouse drank, **how many drinks** did **he/she** usually have in 24 hours? (One drink is a 12 oz. can of beer, a 4 oz. glass of wine, or a single shot of 80 proof)
___ drinks per 24 hours

39. Over the past 4 weeks what is the **most number of days** per week **your spouse** had a drink?
___ drinks

40. Over the past 4 weeks, what is the **most number of drinks your spouse** had in 24 hours?
___ drinks

41. Over the past 4 weeks, how long was the longest period **your spouse** was abstinent (went without drinking)?
___ days When was that? _____(date) to _____ (date)

42. Were your spouse's drinking patterns over the last 4 weeks fairly typical for him/her?

__No, it was less than usual __Yes, it was fairly typical
__No, it was more than usual

APPENDIX B

Table B1

Summary F Table For One Way ANOVA With The Independent Variable of Father's Alcoholism Classification at Time 1 (Alcoholic or Non-Alcoholic) With The Dependent Variable of Father's Current Whole Blood 5-HT (ng/ml)

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig. of F
Between Groups	440.77	1	440.77	.28	.60
Within Groups	57526.60	36	1597.96		
Total	57967.37	37			

Means, Standard Deviations, and N's For One Way ANOVA With The Independent Variable of Father's Alcoholism Classification at Time 1 (Alcoholic or Non-Alcoholic) With The Dependent Variable of Father's Current Whole Blood 5-HT (ng/ml)

	ALCOHOLIC (AAL+NAAL) N=26	NON-ALCOHOLIC N=12	TOTAL N=38
Father's 5-HT (ng/ml)	M=157.58 SD=40.83	M=150.25 SD=37.96	M=155.26 SD=39.58

Table B2

Correlations Between Father's Current 5-HT and Potential Covariates, (N = 38)

	1	2	3	4	5	6	7	8	9
1.5-HT	1.00	.11	.09	.04	.26	.41**	.26	-.12	-.07
2.Alcohol Q X F		1.00	.78**	.89**	.13	.23	.10	-.07	-.16
3.Avg. Days Drank			1.00	.68**	.03	.06	.00	-.15	.00
4.Avg. Drinks/Occasion				1.00	.24	.32*	.22	-.18	-.20
5.Smoking Q X F					1.00	.89**	.99**	-.21	-.10
6.Avg. Days Smoked						1.00	.88**	-.27*	-.21
7.Avg. Cig./Occasion							1.00	-.20	-.08
8.Age at Blood Draw								1.00	-.18
9.Season of Blood Draw									1.00

Table B3

Summary F Table For Simple Factorial ANOVA With The Independent Variable of Father's Alcoholism Status at Time 1 (AAL, NAAL, NC), The Dependent Variable of Father's Current Whole Blood 5-HT (ng/ml), and Covariate of Father's Average Number of Days Smoking

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Covariates	9988.072	1	9988.072	7.147	.011
DSMOKE2	9988.072	1	9988.072	7.147	.011
Main Effects	465.469	2	232.734	.167	.847
RISK	465.469	2	232.734	.167	.847
Explained	10453.541	3	3484.514	2.493	.077
Residual	47513.827	34	1397.466		
Total	57967.368	37	1566.686		

Adjusted Means and N's For Simple Factorial ANOVA With The Independent Variable of Father's Alcoholism Status at Time 1 (AAL, NAAL, NC), The Dependent Variable of Father's Current Whole Blood 5-HT (ng/ml), and Covariate of Father's Average Number of Days Smoking

	AAL N=13	NAAL N=13	NC N=12	TOTAL N=38
Father's 5-HT (ng/ml)	M=151.61	M=153.29	M=160.54	M=155.26

APPENDIX C

Table C1

Summary F Table For 2 (Mother's Classification of Son at Time 1=High or Low Impulsive Aggressive) X 3 (Father's Alcoholism Status at Time 1=AAL, NAAL, NC) ANOVA With The Dependent Variable of Son's Current 5-HT (ng/ml), and The Covariates of Age and Season

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Covariates	25247.488	2	12623.744	3.627	.041
BSERAGE	13560.928	1	13560.928	3.896	.059
BSEASON2	5388.533	1	5388.533	1.548	.225
Main Effects	996.149	3	332.050	.095	.962
MBOYGRP1	2.206	1	2.206	.001	.980
RISK	941.697	2	470.849	.135	.874
2-Way Interactions	36355.325	2	18177.662	5.222	.012
MBOYGRP1 RISK	36355.325	2	18177.662	5.222	.012
Explained	62598.962	7	8942.709	2.569	.037
Residual	90504.803	26	3480.954		
Total	153103.765	33	4639.508		

Adjusted Means and N's for 2 (Mother's Classification of Son at Time 1=High or Low Impulsive Aggressive) X 3 (Father's Alcoholism Status at Time 1=AAL, NAAL, NC) ANOVA With The Dependent Variable of Son's Current 5-HT (ng/ml), and The Covariates of Age and Season

	AAL	NAAL	NC	
Low Impulsive Aggressive	M=237.93 N=6	M=248.87 N=7	M=192.64 N=8	M=226.48 N=21
High Impulsive Aggressive	M=207.56 N=5	M=207.41 N=6	M=327.70 N=2	M=247.55 N=13
	M=222.75 N=11	M=228.14 N=13	M=260.17 N=10	

Table C2

Summary F Table For Simple Factorial ANOVA With The Independent Variable of Mother's Classification of Son's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Son's Current Whole Blood 5-HT (ng/ml), Covariates of Age and Season

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Covariates	25983.863	2	12991.931	3.343	.049
BSERAGE	15238.407	1	15238.407	3.921	.057
BSEASON2	4065.209	1	4065.209	1.046	.315
Main Effects	12706.553	1	12706.553	3.269	.081
MBGRPCUR	12706.553	1	12706.553	3.269	.081
Explained	38690.416	3	12896.805	3.318	.034
Residual	112711.100	29	3886.590		
Total	151401.515	32	4731.297		

Adjusted Means and N's for Simple Factorial ANOVA With The Independent Variable of Mother's Classification of Son's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Son's Current Whole Blood 5-HT (ng/ml), Covariates of Age and Season

	HI IMPULSIVE AGGRESSIVE N=6	LOW IMPULSIVE AGGRESSIVE N=27	TOTAL N=33
Son's 5-HT (ng/ml)	M=179.58	M=232.50	M=206.04

Table C3

Summary F Table For Simple Factorial ANOVA With The Independent Variable of Mother's Classification of Daughter's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Daughter's Current Whole Blood 5-HT (ng/ml), and Covariates of Age and Season

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Covariates	659.914	2	329.957	.360	.708
GSERAGE	443.914	1	443.914	.484	.506
GSEASON2	448.778	1	448.778	.490	.504
Main Effects	11704.098	1	11704.098	12.767	.007
MGGRPCUR	11704.098	1	11704.098	12.767	.007
Explained	12364.012	3	4121.337	4.496	.040
Residual	7333.988	8	916.749		
Total	19698.000	11	1790.727		

Adjusted Means and N's for Simple Factorial ANOVA With The Independent Variable of Mother's Classification of Daughter's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Daughter's Current Whole Blood 5-HT (ng/ml), and Covariates of Age and Season

	HI IMPULSIVE AGGRESSIVE N=2	LOW IMPULSIVE AGGRESSIVE N=10	TOTAL N=12
Daughter's 5-HT (ng/ml)	M=138.19	M=230.61	M=184.40

Table C4

Summary F Table For One Way ANOVA With The Independent Variable of Gender and the Dependent Variable of Child's Current Whole Blood 5-HT (ng/ml)

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig. of F
Between Groups	2802.39	1	2802.39	.73	.40
Within Groups	173208.84	45	3849.09		
Total	176011.23	46			

Means, Standard Deviations, and N's for One Way ANOVA With The Independent Variable of Gender and the Dependent Variable of Child's Current Whole Blood 5-HT (ng/ml)

	BOYS N=34	GIRLS N=13	TOTAL N=47
5-HT (ng/ml)	M=222.65 SD=68.11	M=205.38 SD=40.93	M=214.02 SD=54.52

Table C5

Summary F Table For Simple Factorial ANOVA With The Independent Variable of Gender, Dependent Variable of Child's Current Whole Blood 5-HT (ng/ml), and Covariates of Age and Season

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Covariates	10547.573	2	5273.787	1.398	.258
SERAGE	1852.247	1	1852.247	.491	.487
SEASON	5979.173	1	5979.173	1.585	.215
Main Effects	3225.463	1	3225.463	.855	.360
GENDER	3225.463	1	3225.463	.855	.360
Explained	13773.036	3	4591.012	1.217	.315
Residual	162238.198	43	3772.981		
Total	176011.234	46	3826.331		

Adjusted Means and N's for Simple Factorial ANOVA With The Independent Variable of Gender, Dependent Variable of Child's Current Whole Blood 5-HT (ng/ml), and Covariates of Age and Season

	BOYS N=34	GIRLS N=13	TOTAL N=47
5-HT (ng/ml)	M=223.28	M=204.75	M=214.02

Table C6

Summary F Table For One Way ANOVA With The Independent Variable of Mother's Classification of Child's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Child's Current Whole Blood 5-HT (ng/ml), and Covariates of Age and Season

Source of Variation	Sum of Squares	DF	Mean Square	F	Sig of F
Covariates	11747.428	2	5873.714	1.765	.184
SERAGE	2127.029	1	2127.029	.639	.429
SEASON	6493.749	1	6493.749	1.951	.170
Main Effects	25401.231	1	25401.231	7.632	.009
MGRPCUR	25401.231	1	25401.231	7.632	.009
Explained	37148.659	3	12382.886	3.721	.019
Residual	136457.919	41	3328.242		
Total	173606.578	44	3945.604		

Adjusted Means and N's for One Way ANOVA With The Independent Variable of Mother's Classification of Child's Current Behavior (High or Low Impulsive Aggressive), Dependent Variable of Child's Current Whole Blood 5-HT (ng/ml), and Covariates of Age and Season

	HI IMPULSIVE AGGRESSIVE N=8 (6 Boys, 2 Girls)	LOW IMPULSIVE AGGRESSIVE N=37 (27 Boys, 10 Girls)	TOTAL N=45
Child's 5-HT (ng/ml)	M=167.80	M=233.15	M=200.48

Table C7

Correlations Between Child's Current 5-HT (ng/ml) and Time 1 Total Behavior Problem Ratings, Controlling For Childs' Age and Season of Blood Draw (N = 40; Sons = 34, Daughter = 6)

	1	2	3	4
1.Childs' 5-HT	1.00	-.10	-.05	.00
2.TBP Raw Score		1.00	.96**	.74**
3.TBP T-Score			1.00	.75**
4.Classification				1.00

*p<.05, **p<.005

One-tailed Pearson Product Moment Correlations

N=39 for those analyses using mother's TBP raw score, mom's TBP T-score, and mom's classification, due to one missing rating of a son by his mother.

Table C8

Correlations Between Child's Current 5-HT (ng/ml) and Current Behavior Problem Ratings, Controlling For Childs' Age and Season of Blood Draw (N = 45; Sons = 33, Daughters = 12)

	1	2	3	4
1.Childs' 5-HT	1.00	-.34*	-.36**	-.39**
2.Mom's TBP Raw Score		1.00	.96**	.70**
3.Mom's TBP T-Score			1.00	.61**
4.Mom's Class. Of Child				1.00

*p<.05, **p<.005

One-tailed Pearson Product Moment Correlations

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