SEROTONIN AND AGGRESSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PROSPECTIVE FOLLOW-UP STUDY

by

JESSICA HIMELSTEIN

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2002

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

9/13/02
Date

Chair of Examining Committee

9/18/02
Date

Executive Officer

Doreen Berman, Ph.D.

Jeffrey Newcorn, M.D.

Tina Moreau, Ph.D.

Antonia New, M.D.

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

Serotonin and Aggression in Children with Attention-Deficit/Hyperactivity Disorder: A Prospective Follow-up Study

By

Jessica Himelstein

Adviser: Dr. Jeffrey M. Halperin

Considerable data indicate an association between low serotonergic (5-HT) function and aggression in animals and human adults. The relationship between 5-HT and aggression is less apparent in children. Cross sectional data in children provide some information on the effects of neurochemical, behavioral, and environmental factors on the development of aggression and lead to several compelling hypotheses. Yet, hypotheses about the relationship between childhood neurochemical, behavioral and environmental status and adolescent behavior can only be adequately tested through a prospective study.

This dissertation reevaluated a sample of children with disruptive behavior disorders who underwent extensive clinical evaluations and an assessment of central 5-HT function at baseline. The participants were re-tested during a post-pubertal period of high risk for antisocial behavior to determine their behavioral status in the areas of physical aggression, antisocial behavior and substance use. It was hypothesized that aggressive children with low 5-HT function at baseline would progress to more severe aggression, whereas those aggressive children with high 5-HT would desist in their aggression. Furthermore, it was hypothesized that a significant portion of the variance

in outcome not explained by early 5-HT would be accounted for by psychosocial factors, specifically, the number of children and adults in the home, familial socioeconomic status, and the degree of parental psychopathology at baseline. Finally, it was hypothesized that symptoms in the domain of overactivity would be more predictive of behavioral outcome, than would inattentive symptomatology.

Results indicated that early aggression accounted for the greatest portion of variance in adolescent behavioral outcome. Data also showed that early 5-HT function helped predict progression or reduction of aggressive behavior across time. Psychosocial factors did not make a significant contribution to adolescent behavioral outcome, beyond that accounted for by early behavior and neurochemistry. After controlling for early aggression, inattentive symptomatology, as opposed to overactivity, made a greater contribution to adolescent behavioral outcome. These findings are consistent with literature demonstrating the stability of aggression over time and the inverse relationship between 5-HT function and aggressive behavior and provide evidence for the combination of childhood aggression and attenuated 5-HT functioning as risk factors for poor outcome in adolescence.

ACKNOWLEDGEMENTS

There are so many that deserve my thanks in the completion of this dissertation, but there a few to whom I am especially grateful.

Firstly, Jeffrey Halperin, Ph.D., your guidance, patience, intelligence and scientific integrity have encouraged me throughout this process. You have taught me many valuable lessons as a researcher and a person and I will remain forever grateful for all you have done.

To Drs. Doreen Berman and Jeffrey Newcorn, I am indebted to you for your generosity of time, effort, and advice. Your expertise and attention to detail have added so much to the quality of my work.

To Drs. Tina Moreau and Antonia New, I am grateful for your insightful comments and helpful suggestions that have made this a document of which I am proud.

To the Disruptive Behavior Disorders Research Team, without your contributions this work would not have been possible. And a special thank-you to the participants for giving so graciously of their time and effort.

To my family (old and new) and friends, for their limitless love, encouragement and support in helping me to achieve this goal.

Lastly, I would like to thank Wes Kalmar, for his love and faith in me. Without his quiet strength and CLAFTR this project would not have reached completion.

Dedicated with love to

Rebbetzin Rivka Horowitz and Dr. Martin Kalmar, of blessed memory

May your children make you as proud as you have made us

TABLE OF CONTENTS

LIST OF TABLES

Figure Captions

INTRODUCTION

"Violence among youths is an important public health problem. Between 1985 and 1991, homicide rates among youths 15-19 years of age increased 154% and remain, today, at historically high levels." (Dahlberg, 1998)

Externalizing disorders of childhood, including Attention-deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), impact the child as well as his/her family, peers, academic environment, and society as a whole. These disorders are believed to result in the greatest burden of suffering of all the childhood mental disorders (Beitchman, Inglis, and Schachter, 1992). Regarding the course of these disorders, longitudinal studies have shown that a substantial portion of children with ADHD and other disruptive behavior disorders (DBDs) progress to a poor outcome. However, a portion of children with DBDs experiences a positive outcome, including remission of early symptomatology. The specific mechanisms that mediate the developmental trajectory from externalizing disorders in childhood to outcome in adolescence are unclear. Research has identified a number of risk factors including early aggression, academic failure, parental antisocial behavior, and environmental stressors that may predispose children with ADHD and other DBDs to a poor outcome (Cadoret et al., 1981; Kolvin et al., 1988; Loeber et al., 1993; Olweus, 1979). Data also indicate that neurobiological factors are related to aggression, a behavior that commonly co-occurs with ADHD, and therefore may serve as additional risk factors for poor outcome in aggressive children with ADHD. Specifically, diminished central nervous system function of the neurotransmitter serotonin (5-HT) has consistently been shown to be related to aggressive behavior in animals (Higley et al., 1992; Kraemer & Clarke, 1996;

Soubrie, 1986) and human adults (Brown et al., 1982; Coccaro et al., 1989; Lidberg et al., 1985; Linnoila et al., 1983; O'Keane et al., 1992).

In contrast to the inverse association between 5-HT function and aggression in animals and human adults, findings in children have been quite variable. Among the eight published studies that investigated the relationship between central 5-HT and aggressive behavior in children, two reported the inverse relationship typically reported in adult and animal studies (Clarke et al., 1999; Kruesi et al., 1990), three found no association between 5-HT function and aggressive behavior (Halperin et al., 1997a; Schulz et al., 2001; Stoff et al., 1992), and three additional studies reported enhanced 5-HT function in aggressive children (Castellanos et al., 1995; Halperin et al., 1994; Pine et al., 1997). It is evident that the significance of diminished or enhanced 5-HT function in aggressive children is not yet understood.

A possible explanation for the diverse findings in children is the existence of distinct subgroups of aggressive children. One way to categorize aggressive children is based on neurbiological status, such as children who are characterized by either relatively enhanced or diminished 5-HT function. In this dissertation, it was hypothesized that those aggressive children who exhibit low 5-HT function progress in their maladaptive behavior, while those aggressive children with relatively high 5-HT function are more likely to show a reduction in their aggression. This hypothesis is supported by emerging evidence that indicates that, among aggressive children, low 5-HT function is associated with a number of risk factors for the persistence of disruptive behavior. When aggressive children with diminished 5-HT function are compared to

aggressive children with relatively enhanced 5-HT function, they are more likely to: suffer from CD and be rated as more aggressive (Halperin et al., 1997b), have parents who are aggressive (Halperin et al., 1997b), exhibit aggressive behavior in multiple settings (McKay et al., 1996), and have first and second degree relatives who exhibit antisocial behavior (McKay et al., 1995). Furthermore, the sample in Kruesi et al.'s (1990) study, which found an inverse relationship between 5-HT function and aggression in children, was far more aggressive than the samples in subsequent studies that found a positive association between central 5-HT and aggression in childhood (Castellanos et al., 1995; Halperin et al., 1994; Pine et al., 1997). As approximately half of aggressive children desist in their maladaptive behavior, and 5-HT function has been shown to be associated with some of the risk factors for the persistence of aggression, it is possible that differences in early 5-HT function may have differential predictive value with regard to long-term outcome.

While some findings raise the possibility that 5-HT function in childhood may act as a determinant of the developmental trajectory towards antisocial behavior, it is not clear whether this represents a primary dysfunction or is secondary to environmental factors. A number of environmental factors influence both neurochemical and behavioral development. In addition to the extensive literature demonstrating an association between environmental factors and the development of antisocial behavior (Loeber et al., 1993; Olweus, 1979), evidence from animal studies has begun to accumulate showing that environmental manipulations cause changes in central 5-HT function (Higley, Soumi & Linnoila, 1991; Kraemer et al., 1989; Summers &

Greenberg, 1995; Yeh, Fricke, & Edwards, 1996). The relationship between neurochemical functioning, environmental factors and behavioral development has not been systematically studied in children, however. Such research may uncover protective factors for individuals at high biological and environmental risk for poor outcome.

To test hypotheses regarding the synergistic effects of early aggression, neurochemistry and psychosocial factors on the development of antisocial behavior, a prospective study is required. To date, only one published study has examined clinical characteristics of aggressive children who had earlier neurochemical evaluation and this study provided only two-year follow-up data (Kruesi et al., 1992). Pick et al. (1999) reported on the biological indices obtained at 2.5-year follow-up of aggressive children who had undergone earlier neurochemical evaluations. However, Pick et al.' s study did not examine the clinical characteristics of the participants at the time of the second evaluation (1999). Furthermore, few studies have focused specifically on adolescent aggression or delinquency (Farrington & Loeber, 2000). In the present study we had access to a sample of children with ADHD who were heterogeneous with regard to expression of aggressive behavior and for whom clinical and neurochemical assessments had been completed at baseline. The study was aimed at obtaining follow-up data at a point in time when the majority of the participants would have reached the post-pubertal period of high risk for antisocial behavior.

This prospective study allows a more direct determination of the extent to which: 1) early central 5-HT activity is predictive of aggressive behavior in

adolescence; and 2) psychosocial factors impact upon the association between early neurochemical function and adolescent behavioral outcome. It was hypothesized that early central 5-HT function would account for a portion of the variance in aggression at outcome unexplained by the level of early aggressive behavior. Specifically, it was hypothesized that relatively diminished central 5-HT function amongst aggressive children would be predictive of progression to more severe aggression, whereas enhanced central 5-HT function in aggressive children would contribute towards a reduction in maladaptive behavior. It was further hypothesized that a significant portion of the variance in outcome not explained by early 5-HT function or aggressive behavior would be accounted for by psychosocial factors, specifically, familial psychopathology, number of parents in the home, number of children in the home, and socioeconomic status. Children with reduced 5-HT function who do not show poor outcome, were expected to have had exposure to more psychosocial protective factors; while children with enhanced 5-HT function, who progress to a poor outcome, were expected to have experienced greater psychosocial adversity.

BACKGROUND

PRESENTATION AND COURSE OF ADHD

ADHD is one of the most frequently diagnosed childhood psychiatric disorders. Its core symptoms are developmentally inappropriate levels of inattention, impulsivity and hyperactivity that result in impairment across multiple settings (American Psychiatric Association, 1994). Children with ADHD are highly heterogeneous with regard to the nature and severity of the defining symptoms, the presence/absence of

comorbid psychiatric conditions, and long-term outcome.

Data abound with regard to the rates of comorbidity for this population. Several epidemiological studies have indicated that ODD and/or CD are present in 40-70% of children with ADHD (Anderson et al., 1987; Bird et al., 1988; Esser et al., 1990; Kashani et al., 1987; Szatmari et al., 1991). This points to the high rate of aggressive behavior amongst children with ADHD. In addition, comorbidity between ADHD and other diagnostic categories, such as mood disorders, learning disabilities, Tourette's Disorder, drug and alcohol abuse syndromes, and mental retardation, is quite common (Biederman, Newcorn, & Sprich, 1991; Livingston, Dykman & Ackerman, 1990; Spencer, Biederman & Wilens, 1999).

Children with ADHD are at high risk for poor long-term outcome relative to children without ADHD. Academic failure, school dropout, anti-social behavior, CD, continued ADHD symptomatology, substance abuse, and/or criminality characterize this poor outcome during adolescence and adulthood. The extent to which these adolescent and adult difficulties are due to early ADHD, as opposed to the numerous comorbid conditions typically seen in children with ADHD, remains unknown. Wallander (1988) conducted an eight-year follow-up study of children with attentional problems and found that 26% exhibited delinquent behavior in adolescence. However, the relationship between attentional problems in childhood and delinquency in adolescence was not significant after controlling for paternal alcoholism and childhood intelligence level. Thus, it is possible that the negative outcome for children with ADHD is mediated by factors independent of attentional difficulties.

A body of literature suggests that conduct problems, and specifically aggressive behavior, may account for the negative outcome seen in children with ADHD. After studying children with "minimal brain dysfunction," Loney et al. (1981) reported that early aggression predicted later antisocial behavior, whereas early inattention and overactivity were more closely associated with adolescent academic difficulties. Findings from another study showed that 30% of children with ADHD+CD continued to display a CD at follow-up, while no children with ADHD only progressed to a CD (August et al., 1999). Furthermore, it was reported that of a sample of ADHD boys who had been followed for 13 years, only those subjects with comorbid conduct problems during early childhood had adult felony convictions (Satterfield & Schell, 1997). Finally, epidemiological studies also support the hypothesis that the poor outcome commonly seen in children with ADHD is best accounted for by early aggressive behavior. Analyses have consistently shown that early aggression places children at greater risk for poor outcome, while inattention and/or hyperactivity have not been as consistently linked to poor outcome (Fergusson et al., 1996; MacDonald & Achenbach, 1996).

RISK FACTORS FOR DEVELOPMENT OF AND PERSISTENCE OF AGGRESSION

Research has identified numerous factors that predict the persistence of aggressive behavior from early childhood into adolescence and/or adulthood. The majority of these factors can be divided into three categories: those that involve the individual and the nature of behavior expressed by the child, those that relate to the

child's family, and those that relate to the child's environment. Investigators disagree as to whether it is the child's early behavior, familial variables or the environment that carries more import with regard to the developmental trajectory of aggressive and antisocial behavior. Several investigators are of the opinion that factors related to the individual's behavior carry the greatest weight in predicting outcome (as reviewed by Loeber, 1982). Roff (1992) conducted a longitudinal study focusing on one variable from each category: early aggression, social class, and peer status, and found that early aggression, the individual variable, was the most significant predictor of delinquency. However, social class also served as a significant predictor of outcome. Kelso and Stewart (1986) identified ten variables that contributed significantly to the variance in outcome of a sample of aggressive boys with CD. Several of these factors belonged in the child category and the remainder were familial factors. Child variables alone correctly differentiated 75% of the boys as either improved or unimproved, while familial factors were less accurate and only classified 64% of the sample correctly.

Other researchers suggest additive models, where risk factors from each category combine to mediate the child's development. A review of the literature conducted by Campbell, Shaw & Gilliom (2000) found that preschool boys who were most likely to evidence continuing problems at school entry were those with multiple risk factors, including high levels of early overactivity and aggression, negative parenting, and family stress. Similarly, Gagnon et al. (1995) reported that a combination of child and familial risk factors in kindergarten children predicted maladjustment at the end of elementary school. Another study that supported the additive model was that of

Singer et al. (1999), which reported that the combination of demographic variables, parental supervision, television-viewing habits, and exposure to violence explained 45% of the variance in self-reported violent behaviors in children. While this study included factors from each of the categories, the authors found that violence exposure (environmental factor) and lack of parental monitoring (familial factor) were the most influential contributors to violence in children. Finally, results of the Cambridge Study of Delinquent Development indicated that early aggressive behavior, parental criminality, low income, large family size, poor child rearing practices and low intelligence level in the child are the best predictors of juvenile delinquency (Farrington, 1988).

A third view of the development of aggressive behavior is that the three categories of risk factors contribute in an interactive fashion towards the development of adverse outcome. Cadoret et al. (1995) identified an interaction effect, such that, in the presence of both environmental adversity and familial psychopathology, adolescents displayed the most disruptive behavior. Conversely, a study assessing the contributions of parental alcoholism and physical abuse in childhood to antisocial behavior in young adult men did not find an interaction effect (Pollock et al., 1990). An additional longitudinal study pointed to interaction between predictive categories and reported that the level of aggressive behavior of the individual and also of his classmates interacted to contribute to the risk of being aggressive in later childhood, such that the most aggressive children in the most disruptive classrooms were in the greatest risk category (Kellam et al., 1998).

INDIVIDUAL'S BEHAVIOR AS RISK FACTOR

One theory of the development of delinquent behavior points to three separate pathways an individual may progress through (Loeber & Hay, 1997). The overt pathway begins with minor aggression that progresses to physical fighting and ends in adolescent violence. The covert trajectory starts with behaviors such as frequent lying and minor shoplifting, goes on to property damage and finishes with serious non-violent delinquent behaviors, such as burglary. The authority conflict course begins with stubborn behavior that develops into disobedience and defiance and terminates in authority avoidant behaviors, e.g., truancy and/or running away. Loeber and Farrington (2000) theorize that the probability of violent behavior in adolescence increases with the number of risk factors present for the child. However, they also point out that besides the long-term influences that engender long-term stable individual differences in behavior, situational factors are present that create short-term differences in courses of action chosen.

Overactivity and inattention in childhood, behaviors commonly comorbid with aggression, have been shown to be risk factors for violence and antisocial behavior in adolescence, independent of the degree of conduct problems in childhood (Taylor et al., 1996). On the other hand, a longitudinal study conducted by Biederman et al. (1996) reported that it was not ADHD, but rather the behavioral difficulties that frequently co-occur with ADHD, which contribute to risk for poor outcome. A third longitudinal study reported that hyperactivity in kindergarten children, and not inattention, was predictive of maladjustment at the end of elementary school. Teacher ratings of

behavior in kindergarten were used to predict the presence of behavior problems determined by numerous raters at three time points during the end of elementary school (Gagnon et al., 1995). Finally, Loeber et al. (1995) reported that a diagnosis of ADHD was predictive of early onset CD, but did not contribute towards prediction of later onset CD. Loeber's group agreed with the findings of Gagnon et al. in that overactive and impulsive symptomatology, not attentional difficulties, were particularly predictive of CD. It is noteworthy that the Taylor study (1996) used behavioral indices of overactivity and inattention as independent variables, while the Biederman (1996) group used ADHD diagnosis.

The factor most frequently associated with adolescent aggression is childhood aggression. Olweus (1979) pointed out that individual differences in the degree of aggressive behavior are almost as stable as those in intelligence, with a stability coefficient of .68 amongst males. A longitudinal study conducted in Finland demonstrated that ratings of aggression obtained on eight year-old children were predictive of violent acts at age 20 (Pulkkinen, 1987). Studies that followed children into adolescence found that childhood aggression was predictive of adolescent delinquent behavior (Brook et al., 1996; Brook, Whiteman & Finch, 1992; Kupersmidt & Coie, 1990). Loeber (1982) reported that the main predictors of outcome for aggressive children were the frequency, severity, pervasiveness, age of onset and variety of antisocial behaviors present in the child. Early age of onset of behavioral difficulties has also been mentioned elsewhere as a factor that increases the likelihood of adolescent violence (Dahlberg, 1998). A study conducted by Pierce et al. (1999) followed two

cohorts of preschool children with early behavior problems and a control group into early adolescence and found that children whose behavioral difficulties were persistent and stable in middle childhood were most likely to exhibit externalizing disorders in early adolescence. Finally, Vitaro et al. (1998) reported that it is specifically proactive, as opposed to reactive, aggression in children that is associated with delinquent and disruptive behaviors in mid-adolescence.

In a review of the literature on juvenile violence, Farrington and Loeber (2000) cited two additional long-term risk factors related to the individual: high impulsivity and low overall intellectual ability. Additionally, Loeber et al. (2000) demonstrated that physical fighting and an early diagnosis of ODD were strong predictors of a diagnosis of CD in adolescence. However, Biederman et al. (1996) indicated that two forms of ODD exist: that which is prodromal to CD and another that does not progress into CD. Loeber et al. (2000) reported that a relatively high intelligence level in childhood served as a protective factor and was related to the desistance of maladaptive behavior. Kerr et al. (1997) point to other aspects of a child's behavior that may serve as protective/risk factors. They demonstrated that behavioral inhibition, defined as a tendency to react fearfully to strange situations or a threat of punishment, serves as a protective factor against negative outcome. Conversely, a child who exhibits aggressive behavior and social withdrawal, a non-anxious preference for being alone, carries an increased risk for maladaptive behavior at outcome. A final risk factor related to the behavior of the individual is social problem-solving skill deficits (Dahlberg, 1998).

FAMILIAL VARIABLES AS RISK FACTORS

Reviews of the literature on juvenile violence have cited several long-term risk factors related to the family status of the child: parental criminality, poor supervision, harsh discipline, physical abuse of the child, low attachment, parental conflict, violent parents, large family size, poverty, and a single-parent household (Dahlberg, 1998; Farrington & Loeber, 2000). Arseneault et al. (2000) reported that the level of family adversity (determined by parental occupation and education level, age at birth of first child, and marital status) for children in kindergarten contributed significantly to outcome at age 17. When investigating the effects of a single-parent family, after accounting for the contribution of family income, urban area, and early aggressive behavior, Vaden-Kiernan et al. (1995) found that boys in families with two parental figures were less likely than males raised in single parent homes to exhibit aggressive behavior two years later. Similarly, Pearson et al. (1994) reported that children in single-parent families were more aggressive than children from two-parent families. However, the presence of two-parents did not act as a protective factor amongst low-income families.

Parent - Child Interaction: Although controversy abounds concerning the relationship between child maltreatment and development of aggressive behavior, a review of the literature indicates that child maltreatment is related to the development of aggression, delinquency and criminality (Frederickson, 1999). One prospective study showed that even when other variables that may contribute to the development of aggressive behavior are accounted for, physical abuse in childhood is a risk factor for

later aggressive behavior (Dodge, Bates & Pettit, 1990). Pollock et al. (1990) reported that adult males who were physically abused as children were more likely to exhibit aggressive and antisocial behavior than a comparison group. A study comparing boys with ADHD to those without the disorder found that after controlling for maternal symptomatology and the behavior exhibited by the boys during interactions with their mothers, negative maternal behavior predicted noncompliance and maladaptive behavior (Anderson, Hinshaw & Simmel, 1994). Lack of parental monitoring was associated with the degree of violent behavior exhibited by children in grades 3-8 (Singer et al., 1999). Olson et al. (2000) followed a sample of toddlers through mid-adolescence and found that sub-optimal patterns of caretaker-child interaction were predictive of externalizing behaviors in adolescence.

Parental psychopathology: Twin studies, adoption studies, and family aggregation research have demonstrated that there is a heritable component of aggressive behavior (Alsobrook & Pauls, 2000). Twin studies have shown a greater concordance for aggression in monozygotic twins than in dizygotic twins, with estimates of heritability of aggression ranging from .27 to .78 (for review see Cadoret, Leve & Devor, 1997). In an earlier review of the literature, Cadoret et al. (1995) found that 9/13 twin studies of aggression were consistent with a genetic transmission of aggressive behavior.

Although data supports the importance of genetically transmitted factors in the development of aggression, evidence also points to contribution of environmental factors. A meta-analysis of 24 twin and adoption studies conducted by Miles and Carey

(1997) indicated that both genetic and familial environmental factors accounted for variance in the level of aggression. The authors reported that across studies, as participants aged, the contribution of family environment decreased and the role of genetic factors increased. A difference in methodology was also reported, such that analyses using ratings of aggression supported genetic influences, while observation of aggressive behavior within a laboratory setting did not indicate any contribution of genetic factors. This measuring difference was also reported in the review conducted by Cadoret, Leve, and Devor (1997). A second meta-analysis of 51 twin and adoption studies reported that additive genetic factors accounted for 32% of the variance in aggression, nonadditive genetic factors accounted for 9% of the variance, shared environmental factors contributed 16% of the variance and nonshared environmental factors made the largest contribution with 43% of the variance (Rhee & Waldman, 2002).

Investigators have attempted to identify forms of psychopathology in parents that may be related to the expression of a heritable form of aggression in children or to the shared environmental influences. Cadoret et al. (1996) have suggested a pathway of genetic transmission from a biological parent with antisocial personality disorder (ASPD) to adolescent aggression and CD. Based on data from an adoption study, Cadoret et al. (1995) reported that ASPD in a biological parent and environmental adversity within the adoptive home (in the form of either marital problems, alcohol/drug use, other psychopathology in parents, legal problems for parents) were both predictive of aggression in adolescence. Furthermore, these two independent factors interacted,

such that the combination of a biologic background of ASPD and an adverse home environment resulted in the worst outcome.

Pollock et al. (1990) reported that paternal alcoholism did not increase the risk for antisocial behavior in adult males. Conversely, Carbonneau et al. (1998) found that sons of male alcoholics displayed a propensity towards physical aggression and oppositional behavior at ages 6 and 12, relative to males whose fathers were not alcoholics. Furthermore, boys with a family history of substance abuse have been shown to be more aggressive than boys without a family history of substance abuse (Giancola et al., 1996; Martin et al., 1994). Loeber et al. (2000) reported that a mother scoring low on measures of antisocial personality disorder served as a protective factor and was related to the desistance of maladaptive behavior.

Family Income: The poverty level of first grade children has been found to be positively associated with higher risk of being more aggressive and vulnerable to other risk factors for aggressive behavior (Kellam et al., 1998). Dodge, Pettit and Bates (1994) reported that socioeconomic status in a large sample of preschool children was predictive of externalizing behaviors and aggression in third grade. Socioeconomic status (SES) was significantly correlated with other factors related to the child's family and environment, such as harsh discipline, familial stressors and exposure to aggressive adult models. These factors, in turn, significantly predicted the child's level of externalizing and aggressive behavior at outcome and accounted for over 50% of the variance in outcome thought to be controlled by socioeconomic status. Thus, it may not be merely the socioeconomic status of a child's family that mediates his/her

development, but rather a whole host of variables that are commonly linked with a family's economic status. However, a longitudinal study conducted by Pagani et al. (1999) showed that family poverty in kindergarten increased the risk of extreme delinquency in adolescence, independent of maternal education, early childhood behavior, academic failure, parental supervision, and family configuration status.

ENVIRONMENT AS RISK FACTOR

Examples of risk factors for the development and persistence of aggressive behavior in the third category are peer delinquency, gang membership, urban residence, living in a high-crime neighborhood and access to firearms (Farrington & Loeber, 2000). Reviews of the literature state that exposure to violence (Dahlberg, 1998; Singer et al., 1999), negative peer influences, and living in neighborhoods characterized by high rates of poverty, transience, family disruption, and social isolation are environmental factors that contribute to aggressive behavior in adolescence (Dahlberg, 1998). Among a sample of inner-city youth, exposure to violence in the community was related to increases in aggressive behavior over a one-year period. This finding maintained statistical significance even after controlling for early behavior (Gorman-Smith & Tolan 1998). Environmental factors, specifically exposure to violence and possession of a weapon, have been shown to differentiate between aggressive and non-aggressive youth (Fitzpatrick, 1997). Kupersmidt et al. (1995) reported that living in a middle-SES neighborhood functioned as a protective factor for reducing aggressive behavior among children who were from high-risk families, where family risk level was determined by ethnicity, income and household composition. The level of aggressive

behavior amongst classmates in elementary school has also been shown to increase the risk for aggressive behavior in middle school (Kellam et al., 1998). Furthermore, children living in poor communities were at higher risk for aggressive behavior, regardless of their early behavior.

NEUROBIOLOGY

ASSOCIATION BETWEEN AGGRESSION AND 5-HT FUNCTION IN ANIMALS

Neurochemical factors, specifically 5-HT dysfunction, have been implicated in the manifestation of aggressive behavior. Animal studies have repeatedly shown that lesions of the 5-HT rich midbrain raphe nuclei, as well as chemical lesions to central 5-HT systems, result in aggressive behavior in rodents, cats and monkeys (Soubrie, 1986). Within the literature on non-primates, the relationship between central 5-HT function and aggression has been studied using various techniques including electrical brain stimulation, administration of 5-HT agonists and/or antagonists, and genetic engineering. While a comprehensive review of this literature is beyond the scope of the current dissertation, several recent studies from different non-primate and primate animal species are of particular interest. These studies will be reviewed to illustrate current relevant findings and issues in the field.

In non-primates, activation of 5-HT receptors in the midbrain periaqueductal gray has been reported to modulate an aggressive response in the cat (Shaikh, Lanerolle & Siegel, 1997; Siegel et al., 1999). Similarly, administration of 5-HT agonists has been shown to inhibit the attacks elicited by activation of the hypothalamic aggression

area (that includes the intermediate hypothalamic area and the ventrolateral pole of the ventromedial hypothalamic nucleus) in rats (Roeling et al., 1994; Siegel et al., 1999). Finally, studies with selective 5-HT receptor antagonists and genetically engineered mice strongly implicate 5-HT functioning in aggressive behavior. 5-HT depletion and deficient 5-HT receptor function have been reported to induce aggressive behavior in normal mice (Olivier & Mos, 1992; Olivier & Mos, 1995) and neuronal nitric oxide synthase knockout mice (Chiavegatto et al., 2001).

Numerous investigations of the neurochemical substrates of aggressive and impulsive behavior have also been conducted in non-human primates. Higley et al. (1992) and Kraemer and Clarke (1996) demonstrated that levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) were inversely correlated with measures of aggressive behavior. Furthermore, Higley et al. (1992, 1996a, 1996b) demonstrated that low 5-HT function in monkeys is not associated with prosocial skills and non-aggressive competitive behaviors necessary for the achievement of social dominance. Rather, higher levels of CSF 5-HIAA were associated with behaviors used to maintain higher social dominance rankings (Higley et al., 1996b; Westergaard et al., 1999). These differences in 5-HT function have been generalized across primate species with differing behavioral profiles (Westergaard et al., 1999). Using single photon emission computed tomography (SPECT), this group further demonstrated that increased availability of 5-HT transporter in the brainstem region is associated with higher rates of aggressive behavior, and negatively correlated with CSF 5-HIAA levels (Heinz et al., 1998). Importantly, these primate studies suggest that

central 5-HT function and behavioral status are relatively stable over time and representative of a characterological trait, rather than a temporary behavioral state (Higley & Linnoila, 1997).

AGGRESSION AND 5-HT FUNCTION IN HUMAN ADULTS

Considerable evidence in the literature on human adults supports an association between diminished 5-HT function and aggressive behavior, as seen in animals. Assessment of central 5-HT function in human adults has been conducted using several methods, including measurement of CSF 5-HIAA and responses to manipulations of the 5-HT system. Most recently, investigators have begun to use imaging techniques and genetic analyses to further probe the relationship between 5-HT function and behavior.

CSF 5-HIAA: Studies that measured CSF 5-HIAA levels in varied populations have repeatedly shown an inverse relationship between this index of central 5-HT function and aggressive behavior. A history of aggressive behavior was inversely correlated with 5-HIAA levels in individuals with borderline personality disorder (Brown et al., 1982). The inverse relationship was also shown in a sample of patients with varied psychiatric disorders that had no history of suicidal behavior and exhibited relatively mild forms of aggressive behavior (Stanley et al., 2000). Reduced 5-HIAA was reported in impulsive murderers, recidivists (Linnoila et al., 1983), homicide offenders and suicide attempters (Lidberg et al., 1985). Among felons convicted of violent offenses or setting fires, low 5-HIAA and early environmental adversity were predictive of recidivism (Virkkunen et al., 1996).

However, several studies have failed to show an inverse association between

CSF 5-HIAA levels and aggression (Coccaro et al. 1992; Coccaro et al., 1997a; Coccaro et al. 1997b; Coccaro et al. 1998; Gardner et al. 1990) or have reported a positive association (Moller et al., 1996). These divergent findings may be due to the differences in the nature of impulsive/aggressive behavior across study groups. Interestingly, the majority of the studies that reported negative associations between CSF 5-HIAA levels and aggressive behavior were those in which the participants were most deviant. Although the level of aggression in the sample of Stanley et al.'s study (2000) was relatively mild, the subjects were patients with serious Axis I disorders. The presence of these disorders may have potentiated the relationship between altered 5-HT function and aggression.

Dietary Manipulation of 5-HT: The above data are supported by studies focusing on manipulation of the 5-HT system via administration of 5-HT agonists or antagonists. One method of investigation has targeted the effects of tryptophan (the amino acid precursor of 5-HT) enhancement or depletion. Eriksson and Lidberg (1997) did not find any difference in plasma tryptophan levels between violent and non-violent offenders. However, several studies demonstrated that tryptophan depletion increased levels of aggressive behavior in normal adult males (Moeller et al., 1996; Pihl et al., 1995) and suggested that this behavioral change was related to decreased levels of central 5-HT. Furthermore, aggressive men are more prone than non-aggressive men to behave aggressively following tryptophan depletion (Bjork et al., 2000; Dougherty et al., 1999).

Pharmacological Probe Studies: Another approach to assessment of central 5-

HT function is the measurement of neuroendocrine response to 5-HT system activation after administration of a 5-HT agonist. This method has yielded a rich body of literature supporting the inverse association between central 5-HT function and aggression in human adults, regardless of the specific pharmacological agent used. Using buspirone, a 5-HT_{1a} agonist, a blunted hormonal response to pharmacological probe was demonstrated in violent vs. non-violent parolees (Cherek et al., 1999). Furthermore, hormonal response to buspirone was shown to be inversely related to levels of irritability amongst personality disordered patients (Coccaro et al., 1990). Ipsapirone, another 5-HT_{1a} agonist, was used in a pharmacological probe study where subjects who responded aggressively on an objective measure showed blunted temperature response relative to the non-aggressive group (Moeller et al., 1998).

Inconsistent results were found when meta-chlorophenylpiperazine (m-CPP, a partial 5-HT agonist) was used in pharmacological probe studies. Endocrine response to m-CPP administration was inversely (Coccaro et al., 1997a; Handelsman et al., 1996) or directly (Handelsman et al., 1998) associated with a measure of trait hostility in samples of personality disorder patients, alcoholics, and abstinent cocaine addicts, respectively. Furthermore, patients suffering from mood disorders with and without aggressive behavior did not differ in their hormonal response to a single dosage of m-CPP (Wetzler et al., 1991). Finally, men with antisocial personality disorder exhibited diminished hormonal response to administration of a single dose of m-CPP relative to normal controls, and these hormonal responses were inversely correlated with measures of assaultive aggression (Moss, Yao & Panzak, 1990).

Acute Response to Fenfluramine Administration: Most relevant to this dissertation are studies that measured neuroendocrine response to the 5-HT enhancer/reuptake inhibitor fenfluramine (FEN). FEN is a centrally acting pharmacological agent that releases stores of presynaptic 5-HT, inhibits reuptake of synaptic 5-HT, and stimulates postsynaptic 5-HT receptors indirectly through the enhancement of synaptic 5-HT and its active metabolite norfenfluramine (Rowland & Carlton, 1986). While it exists in a racemic mixture (*d,l* FEN), *d*-FEN has been shown to be the most selective isomer for the 5-HT system (Cowen, 1993). Administration of FEN results in a dose-dependent rise in prolactin (PRL), mediated by activation of ascending afferent 5-HT pathways from the midbrain raphe nuclei to the hypothalamus and ending in the anterior pituitary gland. Thus, measuring PRL following administration of FEN yields an indirect measure of central 5-HT function in the hypothalamic-pituitary axis.

Consistent with studies showing an inverse relationship between CSF 5-HIAA and aggressive behavior, PRL response to a single dose of FEN was inversely correlated with measures of impulsivity and aggression in patients with personality disorders (Coccaro et al., 1989; Coccaro et al., 1995; Coccaro et al., 1996; Coccaro et al., 1997a; Coccaro et al., 1997b; Coccaro et al., 1998) and post-traumatic stress disorder (Davis et al., 1999). Patients with personality disorders who exhibited high levels of violence, aggression and impulsivity were shown to have blunted PRL release following administration of FEN (O'Keane et al., 1992). Furthermore, patients who exhibited self-injurious behavior (New et al., 1997) and depressed patients who exhibited anger

attacks (Fava et al., 2000) showed blunted PRL response to FEN. Finally, even amongst normal healthy adults, those who showed the highest self-reported levels of aggression and impulsivity exhibited a blunted PRL response to FEN (Evans et al., 2000; Manuck et al., 1998).

Two studies of the PRL response to FEN have reported dissimilar results. Fishbein et al. (1989) found a positive relationship between PRL response to FEN and aggressive/impulsive behavior in a sample of substance abusers. However, these subjects were only drug-free for a period of five days prior to the study and therefore may have exhibited altered neurochemical functions. Cleare and Bond (1997) did not find any relationship between PRL response to FEN and aggression ratings in a sample of normals. Limitations of this latter study include the small spread of aggression values, as well as the inclusion of both genders in the sample. McBride et al. (1990) have shown gender differences in PRL response to FEN in a sample of normal adults. Specifically, women were shown to have greater PRL response to FEN than men. McBride et al. theorized that this difference was probably related to the effects of non-5-HT modulatory influences at the level of the lactotroph.

Behavior and 5-HT: Relative to pharmacological probe studies, a more recent development in the study of the relationship between aggression and central 5-HT function in humans has been the assessment of behavioral change following manipulation of the 5-HT system. Treatment with selective serotonergic reuptake inhibitors (SSRIs), such as sertraline and fluoxetine, was efficacious in reducing behavioral ratings of aggression and irritability (Coccaro & Kavoussi, 1997; Coccaro,

Kavoussi & Hauger, 1997; Kavoussi, Liu & Coccaro, 1994). Furthermore, acute doses of FEN induced a dose-dependent decrease in impulsive and aggressive responding on a laboratory measure (Cherek & Lane, 1999).

Genetic Research: Given the aforementioned evidence of the heritable component of aggression, as well as the association between attenuated 5-HT function and aggression, researchers have begun to investigate whether the genetic determinants of 5-HT function may be linked to a susceptibility to aggressive behavior. Polymorphisms in genes coding for products involved in 5-HT synthesis, reuptake, metabolism, and receptors have been identified in nonhuman primates and humans. Early work on a Finnish cohort of violent alcoholic offenders found an association between a polymorphism in the tryptophan hydroxylase (the first enzyme involved in the synthesis of 5-HT) gene and suicide related behaviors (Nielsen et al., 1994). A second research group that investigated this genotype found it to be associated with the level of impulsive aggression exhibited by males with a personality disorder (New et al., 1998). A third group studied the gene that codes for tryptophan hydroxylase in a non-patient sample and reported an association between aggressive behavior and a different genotype than that reported in the two previous studies (Manuck et al., 1999). While evidence seems to be accumulating for a relationship between aggressive behavior and a polymorphism of the tryptophan hydroxylase gene, these findings must be interpreted cautiously due to the differences in samples, methodologies and outcomes across studies, as well as the unknown functional significance of variation in the gene.

Other research efforts have focused on additional genes associated with 5-HT

function and have yielded less promising results. Investigation of 5-HT_{1B} receptor binding indices and genotype did not reveal any differences between subjects with and without a history of suicide, depression, alcoholism, or aggression (Huang et al., 1999). The same investigators later discovered a variant of the 5-HT_7 receptor gene that was more common among alcoholic offenders than in normal controls, but was not associated with alcoholism or impulsivity (Pesonen et al., 1998).

Imaging Techniques: The increasing application of brain imaging techniques to psychiatric research has produced additional evidence of central 5-HT dysfunction in adults with aggressive behavior. Positron emission tomography (PET) scans conducted after administration of FEN in impulsive-aggressive personality disordered patients revealed blunted metabolic responsivity in orbital frontal, ventral medial frontal and cingulate cortical areas relative to normal controls (Siever et al., 1999). Using similar methodology, Soloff et al. (2000) found that patients with borderline personality disorder exhibited a diminished response in areas associated with regulation of aggressive and impulsive behavior, specifically, medial and orbital right prefrontal cortex, left middle and superior temporal gyri, left parietal lobe and left caudate nucleus. Thus, evidence is beginning to accumulate pointing towards reduced 5-HT function in brain regions, such as frontal and cingulate cortex, that may play a role in modulating aggression.

5-HT FUNCTION IN AGGRESSIVE CHILDREN AND ADOLESCENTS

While substantial data from the literature on animals and human adults supports an association between diminished 5-HT functioning and aggressive behavior, data in

children are not as conclusive. Given the increased restrictions on conducting invasive research in children, relative to research with animals or human adults, developmental studies of the relationship between 5-HT function and behavior have tended to use peripheral indices. The majority of these studies employ the use of blood platelets. The relationship between this peripheral model and central 5-HT function is unclear. However, evidence suggests that platelets do not synthesize 5-HT, rather they absorb it from cells in the gut (Stahl, 1985). However, platelet 5-HT may be a useful research tool since neurons and platelets share similar receptor, release and transport mechanisms.

Peripheral 5-HT: Studies assessing whole blood 5-HT in subjects with DBDs have pointed towards a positive association between peripheral 5-HT and aggressive behavior. In 1988, Pliszka et al. reported that male adolescents with CD had higher whole blood levels of 5-HT than those with an anxiety or depressive disorder alone. Furthermore, 5-HT levels were directly correlated with clinician ratings of conduct symptoms. Cook et al. (1995) did not find any difference in whole blood 5-HT levels between children with ADHD and comorbid CD or ODD and children with ADHD only. However, 23% of ADHD children with a comorbid DBD had whole blood 5-HT levels higher than 270 ng/ml, while none of the ADHD-only children exhibited such high levels. In a subsequent study by this group, whole blood 5-HT was positively related to ratings of violent behavior and social skills impairment in juvenile offenders (Unis et al., 1997). The relevance of these findings is questionable, however, as whole blood 5-HT levels may not reflect CNS activity.

Other studies using peripheral models of 5-HT function have examined binding sites on platelets. Taken as a group, these studies support the inverse relationship between 5-HT and aggressive behavior typically reported in the literature on animals and human adults. Imipramine binding sites are located next to, and modulate, the 5-HT reuptake sites on presynaptic neuron terminals. Similarly, imipramine binding sites are associated with the 5-HT uptake site on platelets. Stoff et al. (1987) found a smaller number of imipramine binding sites on the platelets of prepubertal children with CD and ADHD, relative to normal controls. Furthermore, Stoff et al. reported a negative correlation between the number of imipramine binding sites and ratings of aggressive behavior. Birmaher et al. (1990) replicated these findings in a sample of impulsive aggressive children who had no history of suicidal attempts or mood disorders.

While imipramine binding sites are used as an indicator of presynaptic central 5-HT activity, ketanserin binding to $5HT_2$ receptors on platelets has been used as an index of postsynaptic central 5-HT activity. Support for this model has been found in the parallel changes with age in $5HT_2$ receptors located in the brain and in platelets. Blumensohn et al. (1995) reported reduced $5HT_2$ receptor binding on the platelets of male juvenile delinquents relative to normal controls.

Central 5-HT: Research on central 5-HT function in children has implemented similar methodology to that of the human adult studies. Three groups conducted research through measurement of CSF 5-HIAA concentrations. Kruesi et al. (1990) found that aggression was negatively correlated with CSF 5-HIAA in a sample of children with DBDs. These findings were substantiated by a two-year follow-up study

where early CSF 5-HIAA was negatively correlated with aggressive behavior exhibited two years later (Kruesi et al., 1992). Similarly, Clarke et al. (1999) demonstrated that CSF 5-HIAA levels at birth were moderately predictive of levels of externalizing behavior at 30 months. Conversely, Castellanos et al. (1994) found a positive relationship between indices of aggressive behavior and CSF 5-HIAA in a sample of hyperactive children. A comparison of samples across studies indicates that Castellanos's sample was younger and less aggressive than Kruesi's sample. Furthermore, whereas all of the subjects in the Castellanos study had ADHD, the ADHD diagnosis was not uniformly present in the Kruesi sample. Given that the sample in Clarke et al.'s work was composed of infants, it is difficult to compare their biological functioning and behavior to the samples in the Kruesi and Castellanos studies. Thus, developmental stage and/or behavior may be related to central 5-HT functioning and explain the divergent findings across studies.

Similarly, studies assessing 5-HT function in children using the FEN pharmacological probe procedure have yielded inconsistent results. Stoff et al. (1992) found no relationship between the PRL response to FEN and aggressive behavior in a sample of prepubertal boys with DBDs. Furthermore, no difference was indicated in PRL response between boys with DBDs and normal controls. However, the methodology used in Stoff's study may have affected his results, including feeding the subjects during the procedure and drawing baseline blood samples immediately following the insertion of the catheter. The stress of the needle stick has been shown to cause an increase in plasma levels of PRL (Grayson et al., 1997).

Halperin et al. (1994) reported an enhanced PRL response to FEN in aggressive relative to non-aggressive boys with ADHD. However, a second study conducted by Halperin et al. (1997a) failed to replicate these findings. Rather, post-hoc, cross sectional analyses suggested age effects and pointed to variability of 5-HT function amongst aggressive pre-pubertal boys, with both high and low groups represented as a function of age. Furthermore, in this sample, PRL response to FEN in aggressive boys was shown to vary as a function of parental history of aggressive behavior (Halperin et al., 1997b). Specifically, aggressive boys with parental history of aggressive behavior showed lower PRL response to FEN than that of aggressive boys whose parents did not exhibit aggressive behavior. In a third study conducted by Halperin's group (Schulz et al., 2001) there were no differences in PRL response to FEN between aggressive boys with or without ADHD and boys with ADHD only. Additionally, PRL response was not associated with levels of aggressive behavior or age. In a fifth study, Pine et al. (1997) reported findings similar to those exhibited in Halperin et al.'s first study, i.e., enhanced PRL response to FEN in a sample of male siblings of adjudicated adolescents.

The inconsistent findings regarding 5-HT function in aggressive children may be related to a myriad of factors, including, but not limited to, methodological and sampling differences across studies. Examples of sample features that may confound the investigation of central 5-HT function are age, diagnostic status, and severity of aggression. This dissertation focused on the possibility that there are distinct subgroups of aggressive children who differ with regard to 5-HT function. Whereas some aggressive children progress to greater violence in adolescence, others desist in their

maladaptive behavior. A multiplicity of risk and protective factors, which may include 5-HT function, are likely to influence whether a child progresses to violent behavior.

Low 5-HT function is associated with a number of risk factors for the persistence of aggressive behavior. Familial sociopathy, a known risk factor for aggressive behavior, appears to be associated with 5-HT dysfunction. A blunted PRL response to FEN was associated with high rates of aggression in the first-degree relatives of adults with personality disorders (Coccaro et al., 1994) and low CSF 5-HIAA was associated with a positive paternal history of violence in convicted violent offenders (Linnoila, DeJong & Virkkunen, 1989). Furthermore, Halperin et al. (1997b) reported that aggressive children differed in their response to FEN as a function of familial history of aggression. Specifically, aggressive children with an aggressive parent had a diminished PRL response to FEN and were more aggressive than aggressive children without parental history of aggression. The confluence of family history of aggression and increased aggressive behavior places these probands at increased risk for maladaptive behavior in adolescence. As this group of subjects also had attenuated 5-HT function, support is provided for the hypothesis that low 5-HT in children is a marker for increased risk for persistence of aggression.

Aggressive children are quite variable with regard to 5-HT function, with both high and low groups represented relative to non-aggressive children. Yet, low 5-HT is associated with several risk factors for the persistence of maladaptive behavior. As approximately half of aggressive children desist in their aggression, it is possible that high and low 5-HT subgroups of aggressive children differ with regard to long-term

outcome. This dissertation tested this hypothesis through a longitudinal design.

SUMMARY AND HYPOTHESES

Taken together, considerable data indicate an association between attenuated central 5-HT function and aggression in animals and human adults. While 5-HT function also appears to be involved in the manifestation of aggression in children, the nature of the relationship is less apparent and may be complicated by an array of familial and environmental factors. Cross-sectional data in children have provided some information on the relationships among neurochemical, behavioral, familial, and environmental factors, and these have led to several compelling hypotheses regarding the manifestation of aggressive behavior across development. A number of these hypotheses were tested in this dissertation using a prospective study.

This dissertation examined whether variability in 5-HT function is related to the heterogeneity of ADHD children who may or may not exhibit aggressive behavior at outcome in adolescence. In order to determine whether subgroups of aggressive ADHD children who vary in their levels of 5-HT function differ with regard to outcome in adolescence a prospective study design was required. Specifically, (Hypothesis 1) it was hypothesized that aggressive children who exhibited diminished 5-HT function at baseline would persist to poor outcome, while those children who had augmented 5-HT function at baseline would desist in their aggressive behavior. It was hypothesized that a substantial portion of the variance in outcome of these children would be accounted for by the presence/absence of early aggression and that an additional fraction of the variance would be accounted for by neurochemical functioning. This study examined

developmental changes in behavioral function using a longitudinal design. Due to substantial age-related changes in the nature and severity of aggression, a cross-sectional study would be inadequate for distinguishing cohort from developmental effects.

Hypothesis 2: It was hypothesized that a percentage of the variance that is not accounted for by early behavior and neurochemistry would be explained by psychosocial factors. In this dissertation, a family adversity index was used as a measure known to have predictive validity for the persistence of aggressive behavior into adolescence. The family adversity index used four factors identified as being associated with the development of antisocial behavior. These factors are: number of parents in the home, number of children in the home, SES and parental psychopathology. In a meta-analysis, Lipsey and Derzon (1998) identified anti-social parents, low SES and poor parent child rearing techniques as strong predictors of serious delinquency. Other familial risk factors had weaker contributions. Those children with a combination of the risk factors, i.e., early aggression, low 5-HT function in childhood and psychsocial adversity were expected to have the worst outcome in adolescence.

A secondary analysis was conducted related to the early diagnostic status of the participants. Some studies have demonstrated that a diagnosis of ADHD in early childhood is predictive of antisocial behavior in adolescence and adulthood, independent of early aggressive behavior. (Hypothesis 3) This study investigated whether the impulsive and hyperactive symptomatology contained more predictive

power than the inattention symptoms, as aggression is associated with impulsivity and hyperactivity, rather than inattention.

METHOD

Overview of Protocol

This dissertation used a longitudinal design and re-evaluated a population of 57 children with DBDs who underwent extensive clinical evaluations and participated in neurobiological assessments of 5-HT function. The initial evaluations were conducted between the years 1990-1994 when the subjects ranged in age from 7-11 years old. This dissertation sought follow-up data six years on average after participation in the first portion of the protocol. The time period of six years following the baseline evaluations was selected because it allowed the majority of the participants to reach the post-pubertal period of high risk for antisocial behavior. At the follow-up evaluations, parent, teacher, and self-report ratings of behavior were collected using various published scales. Psychiatric status of the subjects was assessed using structured interviews that were administered to the parent and child. This prospective study allowed a determination of the extent to which: 1) early central nervous system activity of 5-HT serves as a risk factor for subsequent aggressive/violent behavior in adolescence; and 2) psychosocial factors impact upon the association between early neurochemical function and adolescent behavioral outcome.

The subjects were re-evaluated in reverse age order, beginning with the oldest, such that the assessments were conducted when the participant was between the ages of 14 and 18 years. The Institutional Review Boards of Queens College of the City University of New York and of the Mount Sinai School of Medicine approved this protocol. Prior to participation in the study, written informed consent was obtained from both the adolescents and their parents. Verbal assent was obtained from

participants under the age of 18. Parent and teacher ratings were collected using the Child Behavior Checklist (CBCL) (Achenbach, 1991a) and the Teacher Report Form (TRF) (Achenbach, 1991b), respectively. Additionally, teachers completed the Dodge Teacher Checklist of Social Behavior (Dodge, Coie, Terry, & Underwood, unpublished manuscript) and the Teacher Impulsivity Scale (White et al., 1994). Each child completed the Youth Self-Report Scale (YSR) (Achenbach, 1991c), the Modified Eysenck Impulsiveness Scale (Eysenck, Easting & Pearson, 1984), and the Self-Reported Delinquency Scale (SRD) (Elliot et al., 1985). Psychiatric status, according to DSM-IV criteria, was systematically assessed using the Diagnostic Interview Schedule for Children (DISC) (Shaffer et al., 1997), which was administered separately to the parent(s) and child. The Wechsler Intelligence Scale for Children, Third Edition (WISC-III) (Psychological Corporation, 1991) and the Wechsler Individual Achievement Test (WIAT) (Psychological Corporation, 1992) were administered to each child to assess cognitive and academic status. The adolescent also underwent a urine analysis to screen for illicit substance use. Finally, the parent was administered a brief semi-structured interview that collected information on the psychiatric and social services received by the child and family since their initial evaluation. Table 1 lists the clinical assessment measures that were used to re-evaluate the children and their families.

Subjects at Baseline

The clinically referred population consisted of 57 children (54 males and 3 females) who met diagnostic criteria for a DBD at the time of recruitment. The subjects were referred to the initial study through a variety of sources including community

mental health centers, school professionals, local support groups, and pediatricians. At the time of their initial participation in the research, the subjects ranged in age from 7 to 11 years and were all of prepubertal endocrine status. Exclusionary criteria used in the original recruitment phase were as follows: chronic medical illness, use of systemic medication, diagnosed neurological disorder, Full Scale IQ below 70, a diagnosis of schizophrenia, major affective disorder, pervasive developmental disorder, or a chronic tic disorder; not English speaking, or not attending school.

Originally, only males were accepted into the research protocol, as its major focus was ADHD, a disorder that is most prevalent among males. Inclusion of females in the study would have significantly reduced the power of the statistical analyses to be conducted at the conclusion of the study by splitting the sample with another confounding variable. Subsequently, it was decided to include some females in the study in order to obtain pilot data for a comparison of the neurobiological profiles of males and females with ADHD. The population contains minority representation, as the hospital where the study was conducted is located in a major metropolitan area.

After passing through an initial screening process, which included a brief telephone intake interview and completion of rating scales by parents and teachers, the children and their families participated in the first portion of a two-day process. This first day was devoted to a thorough clinical evaluation. Informed consent was obtained from the parent or legal guardian of the child and verbal assent was obtained from the child. Intellectual functioning was assessed using the Wechsler Intelligence Scale for Children – Revised (Psychological Corporation, 1974) and a Full Scale IQ below 70, in the deficient range, was the cut-off used for exclusion from the study. Academic

achievement was measured using the Wide Range Achievement Test – Revised (Jastak &Wilkinson, 1984). Diagnostic status was determined via administration of the parent version of the DISC (Shaffer et al., 1989) and a mental status examination of the child. Completed rating scales included: the IOWA Conners Teacher's Questionnaire (IOWA) (Loney & Milich, 1982), the CBCL (Achenbach, 1991a), the Children's Aggression Scale – Parent and Teacher Versions (CAS-P,T) (Halperin et al., 2002; McKay et al., 1993). Parental history of psychiatric symptomatology was assessed via a semi-structured interview that was administered to the child's parent(s) (Halperin et al., 1997b).

Of the 57 children in the original sample, 34 adolescents and their families participated in the follow-up study. At the time of their baseline evaluations, the mean (standard deviation (SD)) age of the 34 subjects that participated in the follow-up study was 9.1 (1.24) years. The adolescent sample (34 subjects seen at follow-up) had a mean (SD) Full Scale IQ of 99.27 (12.31), with scores ranging from 76 to 117, at baseline (see Table 2). According to diagnostic information collected during the early study, of the 34 subjects, 32 (94.1%) met DSM-III-R criteria for ADHD, 25 (73.5%) met criteria for ODD, 11 (32.4%) met criteria for CD, 9 (26.5%) met diagnostic criteria for an anxiety disorder, and three (8.8%) met criteria for a mood disorder (see Table 3). Of the 34 subjects, the two participants who did not meet criteria for a diagnosis of ADHD displayed sufficient symptomatology to warrant a diagnosis but were reported to develop the behaviors after age 7. Among the sample, 11 (32.4%) are Caucasian, 11 (32.4%) are African-American, and 12 (35.3%) are of Hispanic descent. Tables 2 and 3 delineate the characteristics of the sample (34 subjects) at the time of initial evaluation

and the comparisons between the sample seen at follow-up and the 23 subjects who did not participate in the follow-up evaluation.

Comparisons of the sample characteristics at baseline of the two groups who did and did not participate in the follow up evaluation indicated that they differed on WRAT – R Reading ($t = -3.05$, $p < .01$) and Spelling ($t = -3.33$, $p < .01$). The group that did not participate in the follow-up evaluations scored significantly lower on these measures of academic achievement than the group that did participate in the follow-up evaluations. Furthermore, there was a trend for these two groups to differ on Verbal IQ ($t = -1.87$, $p < .10$) and delta PRL ($t = -1.94$, $p < .10$), such that the group that participated in the follow-up evaluations tended to have higher Verbal IQs and delta PRL levels. The two groups did not differ in age, Performance IQ, Full Scale IQ, Mathematics achievement scores, ethnicity, diagnostic status, or teacher and parent ratings of aggression, delinquency, inattention, and overactivity. Overall, those participants who were not seen for follow-up evaluations were more impaired in verbal academic and intellectual functioning relative to those participants seen at baseline and follow-up. Given the number of comparisons that were conducted between the two groups, it is to be expected that they would differ on some of the variables.

At the first evaluation point, the sample was divided into aggressive and non-aggressive subgroups based on the presence or absence of a persistent pattern of physically aggressive behavior. Physical aggression was defined by the presence of at least one of the following DSM-III-R CD symptoms: use of a weapon, stealing with confrontation of the victim, physical cruelty to animals or people, forcing another into sexual activity, or initiating physical fights. The presence/absence of these symptoms

was independently determined by three clinicians, who were each blind to biological, family history, and psychometric data. There was perfect concordance among all three raters for all but five cases. These cases, which were rated as equivocal by at least one reviewer, were discussed and placed by consensus. Among the 34 children who participated in the follow-up study, 18 were classified as aggressive and 16 as non-aggressive. This rate did not differ from the percentage of aggressive and non-aggressive subjects who were not seen for follow-up evaluations.

The aggressive (N = 18) and non-aggressive (N = 16) participants did not differ in age, delta PRL levels, indices of intelligence or academic achievement, or teacher and parent ratings of delinquency, inattention and overactivity at baseline. Furthermore, they did not differ in rates of ADHD, anxiety disorders or mood disorders. The two groups did differ in rates of ODD and CD, such that the aggressive group had a higher percentage of individuals diagnosed with these disorders than the non-aggressive group. Similarly, the groups differed significantly in parent and teacher ratings of aggression, such that the aggressive group received higher ratings on measures of aggression according to all respondents. Given the criteria used for forming these subgroups, these differences are in the expected direction. (See Table 4 for additional comparison of the baseline characteristics of the aggressive and non-aggressive participants who were seen for follow-up.)

Further characterization of the sample at baseline was accomplished through compilation of a psychosocial familial adversity index for each subject. This index was calculated using the information obtained at the first evaluation point regarding the number of children in the home, the number of parents in the home, socioeconomic

status and parental psychopathology. These four factors were chosen because they have been shown to function as risk factors for the development or persistence of aggressive behavior. A point for adversity was given for the presence of any of the following factors: 1) the number of children in the home exceeded 2; 2) the number of adults in the home was less than 2; 3) there was a history of either antisocial or aggressive behavior in either of the biological parents; 4) the Hollingshead factor (Hollingshead, 1975) for socioeconomic status for the family was at the lowest level of social stratum as outlined by Hollingshead. Thus, adversity scores for each subject ranged from 0 to 4. The mean (SD) adversity score for the 34 subjects seen at follow-up was 1.32 (1.07) and this average did not differ from the 23 subjects not seen at follow-up. Furthermore, the average adversity score did not differ between the 18 aggressive and 16 non-aggressive participants seen for follow-up. It should be noted that adversity scores were unavailable for 4 of the 23 subjects not seen at follow-up due to missing data at the baseline evaluations.

Measures

Clinical Measures at Initial Assessment

All children were assessed at baseline using the following diagnostic measures:

1) Diagnostic Interview Schedule for Children (DISC) (Shaffer et al., 1989)
2) Wechsler Intelligence Scale for Children - R (WISC-R) (Psychological Corporation 1974)
3) Wide Range Achievement Test – Revised (WRAT-R) (Jastak &Wilkinson, 1984)
4) IOWA Conners Teacher's Questionnaire (IOWA) (Loney & Milich, 1982)
5) Child Behavior Checklist (CBCL) (Achenbach, 1991a)
6) Children's Aggression Scale - Teacher Version (CAS-T) (McKay et al., 1993)
7) Children's Aggression Scale - Parent Version (CAS-P) (Halperin et al., 2002; McKay et al., 1993)
8) Family History Interview (Halperin et al., 1997b)

1. Diagnostic Interview Schedule for Children (DISC). Psychiatric assessment of the probands was based on interviews using the DISC - version 2.1 (Shaffer et al., 1989), which was administered to the child's parent(s) (usually mother). The DISC is a highly structured psychiatric interview that systematically probes symptomatology in the domains of Axis I disorders including anxiety, mood, disruptive behavior, elimination, eating, psychosis and substance use. The interview generated diagnostic information using scoring algorithms based on DSM-III-R criteria. The DISC was used to review inclusion and exclusion criteria and to characterize the sample with regard to diagnoses and patterns of comorbidity.

2. Wechsler Intelligence Scale for Children - Revised (WISC-R). All children were assessed using the WISC-R (Psychological Corporation, 1974). This well-normed and widely used test yields separate Verbal, Performance and Full Scale IQ scores along with 11 independent subtest scores. Children were accepted into the study only if they obtained a Full Scale IQ of 70 or higher.

3. Wide Range Achievement Test – Revised (WRAT-R). (Jastak & Wilkinson, 1984). The WRAT – R is an individually administered achievement test battery that was normed on a large sample of individuals from all sections of the United States. The WRAT – R contains three subtests that assess basic decoding, written spelling, and arithmetic skills. Scores in each of these three subtest areas are standardized via comparison to scores of children of the same age and/or grade level. These scores were used to measure overall academic achievement and to identify specific developmental disabilities.

4. IOWA Conners Teacher Questionnaire (IOWA). The IOWA (Loney & Milich, 1982) is made up of 10 items from the Conners Teacher Questionnaire (CTQ) (Goyette, Conners & Ulrich, 1978). The IOWA items were selected for their ability to discriminate between inattentive/overactive (I/O) and aggressive (A) children and allow for distinction between these two symptom profiles. At the initial assessment, the IOWA was used as a screening instrument and to assess the level of behavioral difficulties in school.

5. Children's Behavior Checklist (CBCL). The CBCL (Achenbach, 1991a) is a 113-item checklist that is completed by parents. It has been found to be highly reliable and generates standardized T-scores for a broad range of behavioral dimensions including hyperactivity, aggression, and delinquency. The CBCL was used as a screening instrument to assess the parent's perception of behavioral and emotional difficulties. Parents rated whether a given behavior was not true, sometimes or somewhat true, or very true/often true of their child.

6, 7. Children's Aggression Scale – Parent and Teacher Versions (CAS-P,T). The CAS-P,T (Halperin et al., 2002; McKay et al., 1993) evaluate the presence of verbal aggression, aggression toward objects or animals, physical aggression towards people and use of weapons in children. Unlike other "aggression" scales, these scales were designed to assess the frequency and severity of aggressive acts. The CAS-P is unique in that it discriminates between aggression in and outside of the home, and against children versus against adults. This distinction is important for distinguishing an aggressive trait in children, since fighting at home with siblings is quite common in children who would otherwise be considered non-aggressive.

8. Family History Interview. This semi-structured interview (Halperin et al., 1997b) consists of questions about problems in several symptom domains that each parent may have experienced as a child or adult. Probes were used to determine whether any behaviors that were endorsed caused impairment in functioning. Endorsement of impairment was viewed as indicative of a positive history. Problem areas assessed included aggressive behaviors (i.e., persistent fighting, causing injury to others, use of weapons and destruction of property) and anti-social behaviors (i.e., stealing, fire-setting, trouble with the law). Reliability of parental history of aggression and antisocial behaviors was good (α = .82) and adequate (α = .67), respectively, as measured by coefficient alpha.

Neurobiological Measure at Initial Assessment

Prolactin Response to Fenfluramine. Central 5-HT function was assessed in all children participating in this study by measuring the PRL response to a single oral dose of FEN. All subjects underwent this procedure prior to the withdrawal of FEN from the market by the FDA. FEN is a centrally acting pharmacological agent that releases stores of pre-synaptic 5-HT, blocks re-uptake of synaptic 5-HT, and indirectly stimulates post-synaptic 5-HT receptors (Rowland & Carlton, 1986). The resultant enhancement of central 5-HT activity is reflected in a dose-related PRL response, which is blocked by 5-HT receptor antagonists.

Prior to administration of FEN, children were medication-free for a minimum of 4 weeks and were maintained on a low MAO diet for at least 3 days. The protocol began after an overnight fast, at 8 a.m., with the insertion of an indwelling intravenous catheter (kept open with normal saline) into a forearm vein. Subjects then remained

awake, supine and fasting until 3 p.m. A television, VCR and large selection of videotapes were available to the child to help keep him/her entertained. Samples of blood for baseline plasma PRL were obtained at 9:45 and at 9:55 am (-15 and -5 min.). FEN 1 mg/kg was administered orally at 10 am (0 min). Post-FEN samples of plasma PRL were obtained hourly until 3 p.m. See Figure 1 for further explanation of the procedure. All samples were placed immediately on ice until centrifugation within 2 hours. After separation, samples remained frozen until assayed by RIA (Davis et al., 1983). The lower limit of detection for the PRL assay is <1.0 ng/ml. Intra- and inter-assay variability are less than 6.7% and 8.4%, respectively. Delta PRL (peak PRL minus the averaged baseline PRL) after FEN was the primary measure of maximal PRL responsiveness to the 5-HT system activation.

Post-FEN samples for plasma FEN and nor-fenfluramine (Nor-FEN, its active metabolite) were obtained hourly from +60 min until +300 min to ensure adequate absorption. Samples for plasma FEN/Nor-FEN levels were collected in a borosilicate acid-washed glass tube with balanced ammonium-potassium oxylate crystals as the anticoagulant and were placed immediately on ice until centrifugation within two hours. After separation, plasma samples were frozen at -20°C until assay by gas-chromatography with electrical detection (Krebs et al., 1984). The lower limit of sensitivity was 2 ng/ml for FEN and 3 ng/ml for Nor-FEN. Intra- and inter-assay variability are less than 7% for both FEN and Nor-FEN. These assays were conducted in the laboratory of Mr. Tom Cooper at the Nathan Kline Institute for Psychiatric Research.

The single one-mg/kg dose of FEN in children posed no risk to the children. Side effects were rarely exhibited and could not be directly attributed to any one aspect of the protocol. Among the 57 children who participated in this study, three had mild adverse effects consisting of headache, nausea and vomiting (in one) subsequent to the completion of the procedure. All children felt fine by the next day and returned to school.

FOLLOW-UP EVALUATION

Sample Retrieval: Follow-up was conducted in reverse order by age. Subjects were reassessed during a post-pubertal period of high risk for antisocial behavior. Starting with the oldest, all children were tested between the ages of 14-18 years. A key issue in this dissertation was the extent to which the children who initially participated in the study could be located and re-evaluated. While ideally all 57 families would be located and agree to re-evaluation, it was unlikely to occur because the families were not initially recruited for a follow-up study and the sample had not been systematically maintained. However, to date, two years is the longest clinical follow-up of aggressive children for whom neurochemical data were collected (Kruesi et al., 1992). Thus, a modest follow-up rate from this study would add considerably to our knowledge regarding the relationship between 5-HT function and the development of aggressive behavior in children. Subjects were tracked through sending of letters to the home address recorded at the time of initial assessment, phoning the last-known home telephone number, using computer tracking methods, and conducting searches of telephone directories. In order to provide encouragement, families were provided with a

free evaluation of the child and they were compensated $200 for their time and expenses related to their participation.

Measures at Follow-up

All subjects were assessed using the following measures, as listed in Table 1, to determine their cognitive, behavioral, and psychiatric status at follow-up:

Parent and Teacher Behavior Rating Scales

1. Child Behavior Checklist (CBCL). See description in section on Diagnostic Measures at Initial Assessment.

2. Teacher Rating Form (TRF). The TRF (Achenbach, 1991b) is a multidimensional rating scale that has excellent psychometric properties and yields narrow-band and broad-band factors that parallel those of the parent CBCL. The scales of greatest interest to this study were aggression, delinquency and attention. It is normed separately for boys and girls between the ages of 4 - 18 years. The TRF provides a dimensional assessment of the teachers' perception of behavioral and emotional difficulties in the children.

3. Dodge Teacher Checklist of Social Behavior. (Dodge, Coie, Terry, & Underwood, unpublished manuscript) This instrument was designed to collect information from teachers' regarding students' behavior, academic ability and physical characteristics. The items are rated on a seven-point scale ranging from never true of the student to almost always true of the student. The checklist is composed of six primary subscales: aggressive-dominant, disruptive, socially insecure, academic, prosocial and attractiveness. The items that target aggression have also been used to address the

distinct constructs of proactive and reactive aggression. Coefficient alphas indicated high reliability for the six subscales.

4. Teacher Impulsivity Scale. A teacher impulsivity scale described by White et al. (1994) was used to further assess the construct of behavioral impulsivity. This scale was constructed by adapting for teachers items from the CBCL (Achenbach, 1991a) (4 items) and the SRD (Elliot et al., 1985) (2 items). The six items – fails to finish things, impulsive or acts without thinking, demands must be met immediately, talks out of turn, wants to have things right away and impatient – are rated as not true, somewhat true, or often true. The coefficient alpha for this scale indicates high reliability and the scale is highly correlated with other measures of impulsivity.

Child Self-Report Scales

5. Youth Self-Report (YSR). The YSR (Achenbach, 1991c) is a multidimensional self-report scale designed for use by adolescents. The scale generates narrow-band and broad-band factors that parallel those generated by the CBCL and the TRF.

6. Self-Reported Delinquency Measure (SRD). The SRD (Elliot et al., 1985) a well-validated structured interview, was administered to the adolescent subjects. It assesses domains of overt and covert antisocial behavior, as well as substance abuse. Whereas child self-reports of oppositional and hyperactive behavior patterns generally yield under-reporting, self-report of covert antisocial behavior and delinquency has well-established validity. With regard to each antisocial or substance use behavior, the frequency and place of occurrence, as well as detailed information about the specific

acts, are systematically probed. Additionally, involvement with the police and court system are reviewed.

7. Eysenck Impulsiveness Scale (Eysenck, Easting & Pearson, 1984). This self-report measure of impulsive behavior consists of 23 items. White et al. (1994) modified the original British items in order to adapt the scale for American dialect and simplify the vocabulary. The adapted version generated reliability of .97 (White et al., 1994). Data support the validity of this scale, in that scores on this measure were significantly correlated with parent and teacher ratings of impulsivity, as well as measures of delinquency and its persistence over time.

Diagnostic Interviews

8. Diagnostic Interview Schedule for Children - Parent Version (DISC-P). The DISC-P, version 3.0 (Shaffer et al., 1997) is the newly revised version of this structured interview, which is administered to parents and generates DSM-IV diagnoses for children.

9. Diagnostic Interview Schedule for Children - Child Version (DISC-C). The DISC-C, version 3.0 (Shaffer et al., 1997) is the newly revised version of this structured interview, which is administered to the child and generates DSM-IV diagnoses. Although the validity of structured interviews administered to children is questionable below the age of 11 years, most data suggest that data derived from children in the age range of this follow-up are valid.

Cognitive/Academic

10. Wechsler Intelligence Scale for Children - III (WISC-III). The WISC-III (Psychological Corporation, 1991) was used to assess overall cognitive abilities. Like

its predecessor, the WISC-III yields separate Verbal, Performance and Full Scale IQ scores along with 12 independent subtest scores. However, it contains current normative data and updated test items. Subjects who are 17 years of age, and older, were administered the WAIS-III, in place of the WISC-III, as the maximum age of the WISC-III is 16 years, 11 months.

11. Wechsler Individual Achievement Test (WIAT). The WIAT (Psychological Corporation, 1992) is an individually administered achievement test battery that was normed on the same sample as the WISC-III. The WIAT contains subtests assessing various aspects of reading, spelling, writing and arithmetic skills. Due to time constraints, only the WIAT Screener, which consists of three standardized subtests that assess Basic Reading, Math Reasoning and Spelling, along with the Reading Comprehension subtest of the WIAT, was used for this study. These measures were used to assess overall academic achievement and to identify specific developmental disabilities.

Other Measures

12. Demographic Interview. A semi-structured interview designed to capture demographic information about the family was administered. This was used to supplement the initial portion of the DISC (Shaffer et al., 1997), which also gathers demographic information. Between these two sources, data were collected relevant to determining socioeconomic status of the families (e.g., education, occupation and income of the parents), family composition (who is living in the home), family structure (name and location of all family members), and extent of contact between children and parents not living in the home. Furthermore, the parent(s) provided information

regarding which, if any, treatment services the child and/or the family had received during the past year. Since sample retention was a major concern, a brief and informal method was used to assess services received in order to limit the time required to complete the follow-up evaluation.

13. Urine Toxicology Screen. A urine sample was collected from each adolescent and was screened for THC (a primary active ingredient in marijuana) metabolites, opiates, cocaine metabolite and methamphetamines. The urine screen (Status DS, manufactured for LifeSign) is sensitive to the use of numerous substances (cocaine, opiates, and amphetamines) during the past several days and is sensitive to THC metabolites (marijuana) 3 -10 days after smoking.

Summary Scores

After the follow-up evaluations were completed, the degree of physical aggression/assault, antisocial behavior, and substance use exhibited by each subject was assessed using all the information that had been collected. The presence/absence of these behaviors, their frequency and severity were independently determined by two clinicians who were each blind to all biological data from the baseline evaluations. Each behavior was rated on a frequency/severity scale of 1 to 9 on which 1 = the absence of significant behavior in that domain, 3 = infrequent minor behavior, 5 = frequent minor behavior or infrequent serious behavior, 7 = frequent serious behavior and 9 = persistent very serious behavior. A copy of the summary scale is attached in Appendix A.

In the area of physical aggression/assault, absence of significant behavior pointed towards no more than minor squabbles with peers or siblings. Minor behavior indicated the presence of physical fights with peers that did not result in real physical injury.

Altercations involving physical injury or weapon use and fights with adults were termed serious events. Finally, very serious events included assaults and those fights that resulted in serious physical injury.

For the domain of antisocial behavior, absence of significant behavior was defined as no more than typical adolescent indiscretions. Minor antisocial acts included: avoiding payment, begging for money, carrying a weapon without using it, curfew violation, cutting school/truancy, graffiti, hitchhiking, lying, minor vandalism/destruction of property, public disturbance, running away for a short duration of time, stealing of small monetary value, swearing and trespassing. Serious antisocial acts referred to burglary, setting fires with the intent to cause damage, major vandalism, stealing of high monetary value or stealing with confrontation of the victim, selling of stolen goods, drugs or sexual favors. Finally, very serious antisocial acts was defined as serious criminal behavior that would likely lead to incarceration.

Regarding substance abuse, absence of significant substance use was defined as no more than minor experimentation with cigarettes or alcohol. Minor substance use was viewed as the use of alcohol, cigarettes, marijuana or sniffing of household products beyond minor experimentation but less than abuse. Major substance use referred to the use of any drug that was not indicated as a minor substance. Finally, very serious substance use indicated abuse of major substances that caused impairment in functioning.

Behavior from age 14 through the time of the evaluation was considered for these outcome measures. When the parent, teacher, and/or proband disagreed regarding the frequency or severity of a behavior, the report of the most severe/frequent behavior

was accepted. Interrater reliability for the three scales was physical aggression/assault $r = .90$ ($p < .01$), antisocial behavior $r = .83$ ($p < .01$), and substance use $r = .93$ ($p < .01$). In cases where the raters differed by one or two points, the average of the two scores was used for data analysis. Those cases where the clinicians differed by more than two points were discussed and rated by consensus. This only occurred in three instances across two subjects. One subject of the 34 was not given a physical aggression/assault summary score due to the insufficient data to characterize his behavior on this dimension at follow-up.

Data Analyses

Hypothesis 1: It was hypothesized that aggressive children with a lower PRL response to the single oral dose of FEN at Time 1 would be more aggressive at outcome than the remainder of the participants. This hypothesis was tested using 2-way analyses of variance with levels of aggression and delta PRL at baseline used as independent variables and the summary scores for physical aggression/assault, antisocial behavior and substance use at follow-up used as dependent variables. Support for this hypothesis would be provided if the group of participants who were aggressive and exhibited relatively diminished 5-HT functioning at baseline showed a significantly higher degree of maladaptive behavior at outcome than the remaining participants.

It was further hypothesized that early neurochemical functioning would explain a portion of the variance in outcome unexplained by early aggression. This hypothesis was tested using multiple hierarchical linear regression analyses with the independent variables being aggression and peak delta PRL at initial assessment. The interaction between attenuated 5-HT functioning and early aggression was added as a third

predictor variable. The dependent measures were the summary scores for physical aggression/assault, antisocial behavior, and substance use at follow-up. Since considerable data indicate that early aggression is likely to predict later aggression, this hypothesis would be supported if the Time 1 measure of 5-HT function significantly contributed additional variance to the ability to predict aggression, antisocial behavior and substance use at follow-up. Furthermore, the presence of an interaction effect, indicating that diminished central 5-HT function is differentially predictive of outcome across children who were and were not aggressive at baseline, would support this hypothesis.

Hypothesis 2: It was hypothesized that the level of familial adversity at baseline would explain a significant portion of the variance in outcome that was not accounted for by early aggression and neurochemistry. Regarding the second hypothesis, hierarchical linear regression analyses were conducted to determine the extent to which familial factors contributed to poor outcome in children at risk for adolescent antisocial behavior, above and beyond the variance accounted for by biological and behavioral measures. The adversity index, which was compiled at Time 1, was used as the predictor for this analysis. The hypothesis would be supported if the level of familial adversity at baseline added predictive power for outcome above and beyond the contribution of early biological and behavioral indices.

Hypothesis 3: It was hypothesized that baseline hyperactivity/impulsivity symptomatology would be more predictive of outcome than inattention symptoms, beyond the contribution of early aggression. In order to determine the independent contribution of inattentive and hyperactive/impulsive symptoms in childhood to

behavioral outcome in adolescence, multiple hierarchical linear regression analyses were performed. Once the role of early aggression had been explained via regression analysis, the number of childhood inattentive and hyperactive/impulsive symptoms were added as independent variables. The contribution of the two domains of ADHD behaviors to adolescent outcome were ascertained and compared. This hypothesis would be supported if the level of inattention in childhood is less predictive of outcome than the degree of childhood impulsivity/hyperactivity.

RESULTS

Clinical re-evaluations were conducted on 34 of the 57 participants in the baseline study. Of the remaining 23 participants, two subjects contacted by the research team refused to participate in the follow-up study citing dissatisfaction with the results of their earlier participation and seven were located but did not respond to repeated telephone and mail requests for a re-evaluation. We were unable to locate 14 subjects of the initial sample after prolonged searches of computerized databases, telephone books, hospital records, and other sources. The participants seen for follow-up evaluations ranged in age from 14.6 to 18.4 years, with a mean (SD) age of 15.82 (.86) years, at the time of their assessment. They were re-evaluated on the average 6.68 (standard deviation = 1.09) years following their original evaluation.

Cognitive Characteristics: Intelligence scales were completed for 32/34 subjects seen at follow-up. The sample had a mean (SD) Full Scale IQ of 89.88 (13.33), with scores ranging from 60 to 117. The mean (SD) IQ score was 90.66 (14.16) on the Verbal scale and 90.78 (14.3) on the Performance Scale. Verbal IQs ranged from 63 to 117 and Performance IQs ranged from 59 to 125. Indices of academic achievement were obtained for 31/34 subjects seen for follow-up evaluations. Mean academic achievement in the areas of Reading, Spelling, Math Reasoning, and Reading Comprehension all fell between 89.84 and 92.52, with SDs from 16.0 to 17.58 (see Table 5).

Rating Scales: Numerous rating scales were used and reviewed by clinicians for the purpose of obtaining outcome summary scores for each participant. In order to further describe the sample, scores on the scales most pertinent to this dissertation (i.e.,

Attention, Delinquency, Aggression, Externalizing and Internalizing Behaviors) of the TRF, YSR and CBCL are reported herein. According to the self-report of 33 participants on the YSR, mean (SD) T scores were Attention = 55.82 (7.48), Delinquency = 61.61 (7.76), Aggression = 57.3 (8.69), Externalizing = 56.85 (10.78), and Internalizing = 46.48 (11.55). Parent report for 33 participants on the CBCL revealed mean (SD) scores of Attention = 66.15 (8.95), Delinquency = 62.18 (8.01), Aggression = 63.45 (10.15), Externalizing = 62.88 (9.81), and Internalizing = 55.18 (11.54). TRFs were distributed to three teachers for each participant. Twenty-one participants returned TRFs from at least one teacher, thirteen participants submitted TRFs from at least two teachers, and only four participants turned in forms from three teachers. Scores from all TRFs were averaged to provide the following mean scores: Attention = 60.21, Delinquency = 59.13, Aggression = 60.26, Externalizing = 58.92, and Internalizing = 52.47 (see Table 6).

Diagnostic Information: While a diagnostic interview, using the DISC and DSM-IV criteria was conducted with either the proband or parent/guardian for each participant, there were four probands who did not receive direct diagnostic interviews and one parent that was unavailable. Interviews conducted with the parents revealed that 54.5% of the sample (N = 18) met criteria for ADHD (11 met criteria for ADHD, Predominantly Inattentive Type, 2 met criteria for ADHD, Predominantly Hyperactive-Impulsive Type, and 5 met criteria for ADHD, Combined Type). Parents also reported that 42.4% of the sample (N = 14) met criteria for ODD and 18.2% (N = 6) met criteria for CD. Relative to the rates of DBDs reported by parents, a substantially lower prevelance of substance abuse and internalizing disorders were endorsed, such that

6.1% (N = 2) met criteria for an anxiety disorder, 3% (N = 1) met criteria for a mood disorder (Major Depressive Disorder), and 12.1% (N = 4) met criteria for one or more substance use disorders (see Table 7). The forms of substance abuse endorsed by the parents included Alcohol Abuse, Alcohol Dependence, Nicotine Dependence, Marijuana Abuse, and Marijuana Dependence.

Diagnostic interviews conducted with the probands revealed that 10.3% of the sample (N = 3) met criteria for ADHD (1 participant met criteria for each of the 3 categories of ADHD diagnoses: ADHD, Predominantly Inattentive Type; ADHD, Predominantly Hyperactive-Impulsive Type; and ADHD, Combined Type). Probands also reported that 6.9% of the sample (N = 2) met criteria for ODD and 24.1% (N = 7) met criteria for CD. Additionally, a relatively high prevalence of substance abuse and a substantially lower prevalence of internalizing disorders were endorsed by the participants, such that 6.9% (N = 2) met criteria for an anxiety disorder, none met criteria for a mood disorder, and 26.7% (N = 8) met criteria for one or more substance use disorders (see Table 7). The forms of substance abuse endorsed by the participants included Alcohol Abuse, Alcohol Dependence, Marijuana Abuse, and Marijuana Dependence. Possible anxiety disorders reported by parents and participants included Separation Anxiety Disorder, Post Traumatic Stress Disorder, Obsessive Compulsive Disorder, and Generalized Anxiety Disorder.

When collapsing the results of diagnostic interviews across parent and adolescent report, there was a low rate of agreement between respondents. There was only one participant who met criteria for a diagnosis of ADHD, Combined Type according to both parent and adolescent report. The same holds true for diagnoses of

ODD, Alcohol Abuse and Alcohol Dependence. In the case of CD, two participants exhibited sufficient symptomatology for a diagnosis according to both parent and adolescent report. Thus, Table 7 includes the rates for each of the disorders according to either parent or adolescent report. Based on diagnostic report of either proband or parent, 59% of the sample met diagnostic criteria for ADHD, 32% for CD, 44% for ODD, 12% for an anxiety disorder, 3% for a mood disorder and 32% for a substance use disorder.

Outcome Variables: The summary scores that were devised in the areas of aggression/physical assault, antisocial behavior and substance abuse served as outcome variables. Inter-rater reliability for the three outcome variables was reported within the Methods Section. Summary scores used for data analysis on the dimension of physical assault/aggression ranged from 1 to 8 with a mean (SD) of 3.78 (2.28). For the domain of antisocial behavior, scores used for data analysis ranged from 1.5 to 8.5 and had a mean (SD) of 4.56 (1.6). Finally, in the area of substance abuse, scores ranged from 1 to 6.5 and the mean (SD) = 2.8 (2.07).

In an attempt to validate the outcome measures developed for this dissertation, correlational analyses were conducted using the summary scores and parent and self-report ratings of aggression, delinquency, attention, externalizing and internalizing behaviors on the CBCL and YSR, respectively. The outcome measure for physical aggression/assault was positively associated with self-report of delinquency ($r = .51$, $p < .01$) and externalizing behavior ($r = .40$, $p < .05$) and parent ratings of aggression ($r = .44$, $p < .05$), delinquency ($r = .61$, $p < .01$) and externalizing behavior ($r = .50$, $p < .01$). Antisocial behavior summary score was positively correlated with self-report of

delinquency ($r = .62$, $p < .01$) and parent report of delinquency ($r = .66$, $p < .01$) and externalizing behavior ($r = .48$, $p < .01$). Finally, the substance abuse outcome measure was positively associated with self-report of delinquency ($r = .59$, $p < .01$) and externalizing behavior ($r = .43$, $p < .05$) and parent report of delinquency ($r = .50$, $p < .01$). For statistical properties of the summary scores, see Table 8.

Hypothesis #1: Several stages of data analysis were conducted in order to evaluate the contribution of the predictor variables (aggression and central 5-HT functioning at baseline) to the subjects' behavioral outcome in adolescence. First, correlational analyses were conducted with each of the outcome measures and the index of central 5-HT function at baseline. This analysis was conducted separately amongst those subjects who were considered aggressive at baseline and those who were viewed as non-aggressive at baseline and for the entire sample. Secondly, t-tests were conducted amongst the participants who were aggressive at baseline, comparing the participants with attenuated 5-HT function to the participants with enhanced 5-HT function on the three outcome variables. Thirdly, a two way analysis of variance (ANOVA) was conducted comparing the three outcome variables for four groups of participants: aggressive and low 5-HT function at baseline, aggressive and high 5-HT function at baseline, non-aggressive and low 5-HT at baseline, non-aggressive and high 5-HT at baseline. For the fourth stage of data analysis, multiple hierarchical linear regression analyses were conducted to evaluate the contribution of the predictor variables to the subjects' behavioral outcome in adolescence. The categorical rating of the presence or absence of aggression and delta PRL at initial assessment were used as independent variables.

When hierarchical linear modeling was conducted using dimensional variables for aggression, none of the models fit the data as close as the models that used the dichotomous variable for aggression. A separate hierarchical linear regression analysis was performed for each of the outcome measures of interest. In order to evaluate the contribution of an interaction effect, i.e., whether the index of early 5-HT function was differentially predictive of outcome depending upon the presence or absence of aggression in childhood, an interaction term was introduced to the hierarchical linear regression analyses as a third predictor variable.

Aggression/Physical Assault. Amongst the 17 subjects who were aggressive at baseline, delta PRL was inversely associated with the summary score for aggression/physical assault at follow-up. ($r = -.71$, $p = .001$) such that the aggressive subjects who had relatively low 5-HT functioning at baseline, showed higher levels of physical aggression at outcome. This correlation was not statistically significant amongst the 16 subjects who were not aggressive at time one ($r = -.39$, $p > .05$) (see Figure 2). The two correlations obtained for delta PRL and aggression/physical assault at follow-up were not significantly different ($z = 1.013$, $p = .16$). When the sample was studied in its entirety, i.e., not broken down based on the presence or absence of aggression at baseline, the correlation was similar to that obtained for the 16 subjects who were not aggressive at time one ($r = -.42$, $p < .05$) but reached statistical significance. Amongst the participants who were aggressive at baseline, those with relatively low delta PRL were shown to be more aggressive at outcome, compared to participants with relatively high delta PRL ($t = 2.65$, $p < .05$).

Figure 3 depicts the level of physical aggression/assault displayed at outcome by the participants who were and were not aggressive and had high or low 5-HT functioning at time one. Analysis of the outcome variable revealed a significant main effect for aggression, $F(1,33) = 16.43$, $p < .001$, such that physical aggression is more prominent at outcome in the subjects who were aggressive at baseline, than in those subjects who were not aggressive at baseline. Analysis also showed a significant main effect for 5-HT function $F(1,33) = 4.82$, $p < .05$, such that participants who exhibited relatively diminished 5-HT function at baseline showed a higher level of maladaptive behavior at outcome, than did the participants who displayed heightened 5-HT function at baseline. The 5-HT function x aggression interaction was not significant ($F(1,33) = 1.34$, $p = .26$).

The hierarchical linear regression model using delta PRL, presence/absence of aggressive behavior, and the interaction between aggressive behavior and 5-HT function at initial assessment as predictors was significant ($p < .001$) and accounted for 55% of the variance in the degree of physical aggression at outcome. Both the index of 5-HT function and presence/absence of aggression at initial assessment contributed significantly to this model ($p < .01$ for both predictors). Early aggression, which was introduced on the first step of the regression analysis, explained 28.4% of the variance in level of aggressive behavior during adolescence. Central 5-HT function in childhood was added on the second step of the regression analysis and accounted for an additional 22.5% of the variance seen in adolescent aggression. The third predictor variable, the interaction term, did not contribute significantly to the model and explained only an additional 3.7% of the variance in aggressive behavior at outcome ($p = .14$) (see Table

9). The direction of the interaction, however, was in the predicted direction, such that the index of 5-HT function tended to be a stronger predictor of poor outcome amongst those subjects who were aggressive at baseline. The index of early 5-HT function tended to contribute less to the outcome of those subjects who were not aggressive at baseline. It is noteworthy that the small N of those subjects seen for follow-up evaluations limited the statistical power for detection of an interaction effect.

Antisocial Behavior. Amongst the 18 subjects who were aggressive at time one, the summary score for antisocial behavior at outcome was significantly inversely correlated with delta PRL ($r = -.59$, $p = .01$). Thus, there was an inverse association between the index of 5-HT function at baseline and the level of antisocial behavior displayed at outcome amongst the subjects who were aggressive at the baseline evaluations. On the other hand, this correlation was not seen amongst those subjects who did not exhibit aggressive behavior at baseline ($r = -.05$, $p = .86$) (see Figure 4). The correlation between delta PRL and follow-up antisocial behavior was significantly larger amongst the participants who were aggressive at baseline relative to the correlation obtained amongst those participants who were not aggressive at baseline ($z = 1.66$, $p = .05$). When the sample was studied in its entirety, not broken down based on the presence or absence of aggression at baseline, the correlation did not reach statistical significance ($r = -.28$, $p = .11$). Amongst the participants who were aggressive at baseline, those with relatively low delta PRL tended to be more antisocial at outcome, compared to participants with relatively high delta PRL ($t = 2.06$, $p = .06$).

Figure 3 depicts the level of antisocial behavior displayed at outcome by the participants who were and were not aggressive and had high or low 5-HT functioning at

time one. Analysis of the outcome variable revealed a significant main effect for aggression, $F(1,34) = 8.47$, $p < .01$, such that antisocial behavior was more prominent at outcome in the subjects who were aggressive at baseline, relative to those subjects who were not aggressive at baseline. The main effect for 5-HT function $F(1,34) = 2.51$, $p = .12$ was not significant. The 5-HT function x aggression interaction was not significant ($F(1,34) = 1.25$, $p = .27$).

Hierarchical linear regression analysis was conducted with delta PRL and the dichotomous variable of presence/absence of aggression at baseline serving as predictors and the summary score for antisocial behavior serving as the outcome measure. Additionally, an interaction term was introduced into the regression, to analyze the interaction between early aggression and 5-HT function. The full model was significant ($p < .01$) and accounted for 34% of the variance in outcome. Early aggression, introduced as a predictor variable on the first step of the regression analysis, contributed significantly to the model ($p < .01$) and accounted for 18% of the variance in antisocial behavior at outcome. There was a trend for the index of central 5-HT function (the second variable introduced to the regression analysis) to contribute to the model ($p = .055$) and the level of early 5-HT function explained an additional 9.4% of the variance in adolescent antisocial behavior beyond that explained by early aggression. The interaction term, added as the third step to the regression analysis, approached significance ($p = .098$) and added 6.4% of predictive power, such that those subjects who were aggressive at baseline and exhibited relatively attenuated 5-HT function were at the highest risk for development of antisocial behavior during adolescence (see Table 10).

Substance abuse. The correlation between delta PRL levels at baseline and the summary score for drug abuse at outcome was not significant, regardless of the presence ($r = -.25$, $p = .35$) or absence ($r = .25$, $p = .35$) of aggression in the subjects (see Figure 5). When the sample was studied in its entirety, i.e., not broken down based on the presence or absence of aggression at baseline, the correlation did not reach statistical significance ($r = .02$, $p = .93$). Amongst the participants who were aggressive at baseline, those with relatively low delta PRL and those with relatively high delta PRL did not differ with regard to substance use at outcome ($t = -.06$, $p = .96$).

Figure 3 depicts the level of substance abuse displayed at outcome by the participants who were and were not aggressive and had high or low 5-HT functioning at time one. Analysis of the outcome variable did not reveal significant main effects for aggression ($F(1,32) = 2.29$, $p = .14$) or 5-HT function ($F(1,32) = .02$, $p = .90$). Furthermore, an interaction effect was not detected ($F(1, 32) = .001$, $p = .97$).

Hierarchical linear regression analysis was conducted with delta PRL and the dichotomous variable of absence/presence of aggression at baseline serving as predictors of degree of drug abuse at outcome. Once again, an interaction term was introduced into the model to analyze the interaction between early aggression and 5-HT function. The overall model was not significant ($p = .239$) and only accounted for 14% of the variance (see Table 11).

Hypothesis #2: Analyses were conducted to ascertain the extent to which early familial adversity contributed to behavioral expression at outcome, above and beyond the contribution of early biological and behavioral factors. Correlations between the index of familial adversity and the outcome scores for physical aggression/assault,

antisocial behavior and substance use, were not significant when the entire sample was used in the analyses. Amongst the participants who were aggressive and exhibited diminished 5-HT function at baseline, the correlations between the index of familial adversity and the outcome scores were not significant. Regarding physical aggression/assault $r = .20$ ($p = .67$, $N = 7$). With respect to antisocial behavior, $r = .54$ ($p = .17$, $N = 8$). Finally, in the area of substance use, $r = .67$ ($p = .14$, $N = 6$). The lack of statistical significance in these correlations may be attributable to the small sample size.

Amongst the participants who exhibited diminished 5-HT at baseline, irrespective of level of aggression, the correlation between baseline familial adversity and physical aggression at outcome was not significant ($r = -.18$, $p = .50$). The correlations between baseline familial adversity and the levels of antisocial behavior and substance use at outcome in these participants also did not reach statistical significance ($r = .22$, $p = .40$; $r = .40$, $p = .14$, respectively). The correlations between baseline familial adversity and outcome amongst the participants who exhibited enhanced 5-HT function at baseline, irrespective of level of aggression, were not significant. Regarding physical aggression/assault $r = -.007$, $p = .98$, for antisocial behavior $r = .04$, $p = .89$ and for substance use behavior $r = .09$, $p = .74$.

Hierarchical linear regression analysis was conducted with the adversity scores obtained at baseline, the categorical index of early aggression, and the measurement of childhood central 5-HT function serving as predictor variables for the three outcome scores. Regarding physical aggression/assault, the introduction of familial adversity to the model did not explain a significant amount of the variance unaccounted for by the other two independent variables and did not contribute significantly ($p = .503$) to the

overall model (see Table 12). After the contribution of early aggression on the first step of the regression analysis and central 5-HT function on the second step of the regression analysis, familial adversity only added .8% predictive power. Regression analysis performed with familial adversity as the only predictor of physical aggression/assault also did not reach significance ($p = .475$).

Similarly, regarding antisocial behavior, the addition of familial adversity as a third independent variable did not make a significant contribution ($p = .596$) to the overall model and only explained .7% of the variance beyond the first two independent variables ($p = .596$) in antisocial behavior at outcome (see Table 13). A regression analysis using familial adversity as the sole predictor of antisocial behavior was not significant ($p = .493$). In the area of substance abuse, familial adversity explained 5.2% of the variance remaining unaccounted for beyond the contribution of early maladaptive behavior (first step of the regression analysis) and 5-HT functioning (second step of the regression analysis). However, this was not a statistically significant change in the overall model ($p = .208$) (see Table 14). Finally, a regression analysis using familial adversity as the sole predictor of adolescent substance abuse was not significant ($p = .164$).

Hypothesis #3: It was hypothesized that early hyperactivity/impulsivity would make a greater contribution to behavioral outcome than early inattention. At baseline, the 34 subjects seen for follow-up exhibited a mean (SD) of 11.32 (3.87) symptoms of ADHD, according to DSM-III-R criteria. This included a mean (SD) of 4.15 (1.48) symptoms in the domain of inattention and a mean (SD) of 6.38 (2.26) symptoms in the areas of hyperactivity/impulsivity. Hierarchical linear regression analyses were

conducted using aggression and the number of inattention symptoms at baseline as predictors of the three outcome measures (see Table 15). Regarding physical aggression/assault, the regression model using early aggression and inattention symptomatology as predictors was significant ($p < .01$) and explained 29% of the variance. However, after accounting for early aggression, symptomatology in the domain of inattention only accounted for an additional .6% of the variance and did not contribute significantly ($p = .61$) to the overall model.

In the case of antisocial behavior, the regression model using the absence/presence of childhood aggression and the degree of inattention as independent variables was significant ($p < .01$) and explained 31% of the variance. Both early aggression ($p < .01$) and inattention ($p < .05$) contributed significantly to this regression model. After a portion (18.2%) of the variance in antisocial behavior at outcome was explained by early aggression, inattention symptoms in childhood explained an additional 12.8% of the variance.

Concerning substance abuse in adolescence, the regression model of early aggression and inattention as predictors of substance abuse in adolescence approached significance ($p = .07$) and accounted for 16.7% of the variance. There was a trend for early aggression to contribute to the overall model ($p = .08$) and it explained 8% of the variance in substance abuse at outcome. Number of inattention symptoms in childhood accounted for an additional 8.7% of the variance unexplained by early aggression and the contribution of inattentive symptomatology to the model approached significance ($p = .09$).

Hierarchical linear regression analyses were also conducted using the number of hyperactive/impulsive symptoms and the presence/absence of aggression in childhood as predictors of outcome in adolescence (see Table 16). Regarding physical aggression/assault in adolescence, the model of childhood aggression and hyperactivity/impulsivity was significant ($p < .01$) and explained 30.5% of the variance at outcome. Early aggression contributed significantly to this model ($p = .001$) and explained 28.4% of the variance in outcome. Insertion of hyperactivity/impulsivity on the second step of the model only accounted for an additional 2.1% of the variance ($p > .05$). With respect to antisocial behavior at outcome, the model of childhood aggression and hyperactivity/impulsivity was significant ($p < .01$) and explained 26.3% of the variance. While aggressive behavior explained 18.2% of the variance ($p < .05$), hyperactive/impulsive behavior added an additional 8.1% predictive power and this contribution to the model approached significance ($p = .07$). In the case of adolescent substance abuse, the model using early aggression and hyperactivity/impulsivity as predictors was not significant and neither independent variable explained a significant amount of the variance.

Hierarchical linear regression analyses were conducted using the total number of ADHD symptoms and the presence/absence of aggression in childhood as predictors of outcome in adolescence. Regarding physical aggression/assault in adolescence, the model of childhood aggression and total ADHD symptoms was significant ($p < .01$) and explained 30.1% of the variance at outcome. Early aggression contributed significantly to this model ($p = .001$) and explained 28.4% of the variance in outcome. Insertion of total ADHD symptoms on the second step of the model only accounted for an additional

1.8% of the variance ($p > .05$). With respect to antisocial behavior at outcome, the model of childhood aggression and total ADHD symptoms was significant ($p < .01$) and explained 29.2% of the variance. While aggressive behavior explained 18.2% of the variance ($p < .05$), total ADHD symptoms added an additional 11% predictive power and this contribution to the model was significant ($p < .05$). In the case of adolescent substance abuse, the model using early aggression and total ADHD symptoms as predictors approached significance ($p = .09$) and accounted for 15.4% of the variance in behavioral outcome. Early aggression accounted for 8% of the variance at outcome and total ADHD symptoms contributed an additional 7.3%.

Finally, hierarchical linear regression analyses were conducted to assess the contribution of the maintenance of ADHD symptomatology into adolescence to behavioral outcome. Childhood aggression and the number of inattentive or hyperactive/impulsive symptoms present at follow-up were used as predictor variables for the three outcome scores. Symptom counts at follow-up were based on parental report, due to the missing data from four proband diagnostic interviews and to maintain consistency with reliance on parental report for baseline symptoms. Inattention symptomatology at follow-up did not contribute to behavioral outcome in physical aggression/assault ($p = .908$), antisocial behavior ($p = .111$), or substance use ($p = .357$) beyond that already explained by early aggression. On the other hand, hyperactive/impulsive symptoms in adolescence contributed significantly to adolescent antisocial behavior ($p = .032$) and tended to contribute towards adolescent physical aggression/assault ($p = .091$) beyond the contribution of early aggression. Hyperactive/impulsive symptomatology at outcome did not account for a significant

portion of the variance in adolescent substance use ($p = .452$), beyond the variance accounted for by early aggression.

A comparison of the hierarchical linear regression models obtained using childhood aggression and inattention as independent variables, as opposed to the models derived using childhood aggression and hyperactivity/impulsivity as predictors indicates that the former models fit the data better. Regarding physical aggression/assault, while each model was significant, neither inattention nor hyperactivity/impulsivity made significant contributions above and beyond that of early aggression. In the case of antisocial behavior, both overall models achieved significance, while inattention contributed significantly to its model and there was only evidence of a trend towards significant contribution in the case of hyperactivity. Finally, the largest difference across models was seen in the area of substance abuse. Whereas the model using hyperactivity/impulsivity did not achieve significance, the regression model using inattention approached significance and there was a trend for inattentive symptomatology to contribute to this model. The opposite pattern was revealed when comparing the models obtained using childhood aggression and adolescent ADHD symptomatology. In this case, the models using childhood aggression and adolescent hyperactive/impulsive symptom counts were more predictive of outcome than models using childhood aggression and adolescent inattentive symptom counts.

DISCUSSION

This study is one of a limited number of follow-up studies of children for whom early neurochemical data were collected. To date, only one published study has examined the clinical characteristics of aggressive children who had earlier neurochemical evaluations and this involved only a two-year follow-up (Kruesi et al., 1992). The present results are derived from re-evaluation of 60% of the original study participants at an average of 6.7 years following their baseline evaluations. Despite a 40% attrition rate, this study provides important information on the relationship between childhood 5-HT function and adolescent behavior, given the paucity of literature on adolescent aggression (Farrington & Loeber, 2000), and the limited number and short duration of follow-up studies of individuals with early biochemical assessments.

Considerable evidence demonstrates the stability of aggression over the course of development and the relationship between childhood aggression and adolescent delinquent behavior (Brook et al., 1996; Brook, Whiteman & Finch, 1992; Kupersmidt & Coie, 1990; Olweus, 1979). The present findings are consistent with that body of literature and provide further support for the view that childhood aggression predicts the persistence of physical aggression and antisocial behavior into adolescence. Specifically, we found that participants who were aggressive in childhood exhibited significantly more physical aggression and antisocial behavior at outcome than did the participants who were not aggressive at baseline. The relationship between childhood physical aggression and adolescent behavior was further supported by the ability of childhood aggression to predict a significant portion of the variance in outcome for

behaviors in the domains of physical aggression/assault and antisocial behavior. With regard to adolescent substance use, the participants who were and were not aggressive in childhood did not significantly differ in their levels of substance use behavior in adolescence. However, there was a trend revealed for the ability of childhood aggression to predict substance use in adolescence.

Consistent with findings of other longitudinal studies, a portion of the participants who were aggressive in childhood persisted to poor outcome in adolescence and a portion of these children experienced a more positive outcome. In an attempt to further understand the combination of risk and protective factors that influenced the heterogeneity of participants' development, the role of early central 5-HT function was considered. The present results suggest that early 5-HT function helps predict the progression or reduction of physical aggression and, to a lesser degree, antisocial behavior, over time. Participants with diminished 5-HT function in childhood displayed higher levels of physical aggression in adolescence compared to children with relatively enhanced 5-HT function. However, children with relatively enhanced or diminished early 5-HT function did not differ in their levels of antisocial behavior or substance use at outcome. Early 5-HT function accounted for a significant portion of the variance in physical aggression/assault at outcome and tended to contribute towards the development of antisocial behavior at outcome. The degree of substance use behavior in adolescence that was explained by early 5-HT function was not statistically significant. When early 5-HT function did exhibit predictive power towards behavioral development (i.e., in the domains of physical aggression and antisocial behavior), the contribution was made in the portion of the variance left unexplained by childhood

aggression. Thus, neurochemical functioning in childhood acted as one of the determinants of adolescent behavior, independent of early aggression.

The relationship reported herein between early 5-HT function and behavioral outcome is in agreement with Kruesi et al.'s (1992) finding of an inverse relationship between baseline 5-HT function and behavior exhibited at two-year follow-up. Furthermore, the present findings are consistent with literature demonstrating an inverse relationship between 5-HT function and aggressive behavior in animals and human adults (Brown et al., 1982; Coccaro et al., 1989; Higley et al., 1992; Kraemer & Clarke, 1996; Lidberg et al., 1985; Linnoila et al., 1983; O'Keane et al., 1992; Soubrie, 1986). However, investigations of the relationship between central 5-HT function and behavior in children have yielded variable results that diverge from the typical inverse relationship seen in the literature on animals and human adults (Castellanos et al., 1995; Clarke et al., 1999; Halperin et al., 1994; Halperin et al., 1997a; Kruesi et al., 1990; Pine et al., 1997; Schulz et al., 2001; Stoff et al., 1992). The heterogeneity of aggressive children with respect to neurochemical functioning and outcome may be related and could account for the variability of results reported in children. As early 5-HT function has been shown to contribute to adolescent outcome above and beyond the contribution of early behavior, it is possible that distinct subgroups of aggressive children exist with enhanced or diminished 5-HT function that may vary in their developmental course. In support of this hypothesis, we found that aggressive children with diminished 5-HT function at baseline progressed to a higher degree of physical aggression and tended to exhibit more antisocial behavior at outcome than did those aggressive children with

enhanced 5-HT function at baseline. This difference was not observed in the level of substance use behavior at outcome.

It was further hypothesized that 5-HT function would be most predictive of outcome in aggressive children relative to non-aggressive children. The present data provide some support for the hypothesis regarding the differential contribution of 5-HT function to development in aggressive and non-aggressive children. Significant inverse correlations between early 5-HT function and adolescent levels of physical aggression and antisocial behavior were detected amongst the aggressive children but not amongst the non-aggressive children. (No significant correlations were detected in the realm of substance use). This suggests that the relationship between 5-HT function and adolescent behavior is mediated by the presence/absence of early aggression. However, the differences in outcome measures observed between participants with and without aggression and between those with relatively enhanced or diminished 5-HT function did not yield a significant interaction effect. Regarding the differential predictive power of early 5-HT function amongst aggressive and non-aggressive children, an interaction term used in regression analysis approached statistical significance in the realm of antisocial behavior, but did not achieve statistical significance with regard to outcome in the domains of physical aggression and substance use. It is possible that the inclusion of more participants would increase the statistical power for detection of interaction effects and provide greater support for this hypothesis.

Extensive research has identified numerous environmental factors that are associated with the development of aggression and delinquent behavior (Loeber et al., 1993). Furthermore, it has been demonstrated that, relative to independent

environmental factors, a combination of psychosocial risk/protective factors explain a larger portion of variance in behavioral development (Rutter et al., 1975). The specific combination of predictors studied (number of children in the home, number of adults in the home, socioeconomic status, and presence/absence of parental history of aggression or antisocial behavior) did not make a significant contribution to the explanation of the progression/reduction of maladaptive behavior beyond that accounted for by early aggression and neurochemical functioning. The divergence of the current findings from those reported in the literature may be due to the positively skewed distribution of adversity scores in this sample. The majority of the participants (61.8%) exhibited either zero or one risk factor on a scale of zero to four.

Marks et al. (1999) reported that the relationship between environmental adversity and behavioral development was manifested differently amongst participants depending upon the levels of 5-HT function at baseline. The association between psychosocial risk factors and outcome was reported to be strongest amongst participants with attenuated 5-HT function. However, in the present study, the relationship between environmental adversity and outcome did not achieve statistical significance regardless of the level of 5-HT function at baseline. The inability to replicate Marks et al.'s findings may be related to the small number of participants in each group when the current sample was categorized in this fashion.

Another prominent feature of this sample to consider in terms of development is diagnostic status. The majority of the participants (94%) presented with ADHD in childhood and therefore, like other children with ADHD, they are at high risk for poor long-term outcome. However, it is unclear what feature of the disorder, or common

comorbid difficulty, is most likely to account for the negative outcome seen in children with ADHD. Some authors have reported that it is both overactivity and inattention that act as risk factors for violence and antisocial behavior in adolescence (Taylor et al., 1996), while others have found that behavioral difficulties, such as aggression, that frequently co-occur with ADHD are responsible for the poor outcome seen in children with ADHD (Biederman et al., 1996). A third position is that overactivity, to the exclusion of inattention, is predictive of progression to maladaptive behavior in ADHD (Gagnon et al., 1995; Loeber et al., 1995). It was hypothesized that symptoms in the domain of overactivity/impulsivity would make a larger contribution to outcome than inattention symptomatology.

However, the hypothesis that early overactivity would be more predictive than early inattention of outcome was not supported in this study. After controlling for the contribution of early aggression, childhood overactivity/impulsivity did not explain a significant portion of the variance in outcome in the areas of physical aggression and substance use. Childhood hyperactivity/impulsivity tended to account for a portion of the variance in antisocial behavior unexplained by early aggression. On the other hand, after removing the variance explained by early aggression, childhood inattention predicted a significant amount of the remaining variance in antisocial behavior and tended to predict substance use. Relative to overactivity/impulsivity, early inattention functioned as the greater risk factor for negative outcome in children with ADHD.

When attempting to analyze the relationship between ADHD symptomatology and adolescent behavioral outcome, another approach was implemented using the level of ADHD symptomatology that had persisted into adolescence for the analyses. In this

case, the hypothesis was supported and the maintenance of hyperactive/impulsive symptomatology into adolescence was more predictive of outcome than continued inattentive symptomatology. Thus, when considering the relationship between ADHD symptomatology and outcome in adolescence it is necessary to differentiate between the contribution of childhood symptomatology as opposed to the influence of the symptoms that have persisted across childhood into adolescence. Furthermore, another factor in this relationship to consider is the correlation reported in the literature between aggression and overactivity. It is likely that the two predictor variables, aggression and overactivity, share variance that cannot be separated. When controlling for the contribution of early aggression, a portion of the variance that is explained by hyperactivity/impulsivity may be removed as well. Analyses regarding ADHD symptomatology in this sample should be interpreted with caution as 94% of the sample met diagnostic criteria for ADHD at baseline leading to a restricted range in number of symptoms. Furthermore, the distributions for total number of ADHD symptoms at baseline, as well as the distributions for hyperactive/impulsive symptoms and inattentive symptoms, were all negatively skewed.

In order to determine the best predictors of outcome in areas of adolescent behavior, multiple hierarchical linear regression analyses using different predictor variables were conducted for the three outcome measures. With regard to each index of outcome there is one model that fits the data best, i.e., the model that explained the greatest portion of the variance in the outcome variable in the most parsimonious fashion. The model with the best fit for prediction of physical aggression/assault in adolescence used the independent variables of early aggression and 5-HT function and

accounted for 51% of the variance. On the other hand, antisocial behavior in adolescence was best explained by early aggression and inattention, which predicted 31% of the variance at outcome. Although the model of early aggression and 5-HT function, combined with the interaction between these two variables, explained a third of the variance in antisocial behavior in adolescence, this model required three variables and only explained an additional 2% of variance beyond the two-predictor model of early aggression and inattention. Finally, in the area of substance use, the model using early aggression and inattention as predictor variables showed the best fit for the data and accounted for 17% of the variance.

There are some differences between the participants who were and were not seen for follow-up in this study that need to be taken into account. The participants who were not reevaluated had lower scores on measures of verbal academic achievement, tended to perform worse on an index of verbal intelligence, and tended to exhibit lower levels of 5-HT function at baseline, relative to the participants who were seen for follow-up. As evidence suggests that attenuated verbal skills (Farrington & Loeber, 2000) and diminished 5-HT function (Brown et al., 1982; Coccaro et al., 1989; Higley et al., 1992; Kraemer & Clarke, 1996; Lidberg et al., 1985; Linnoila et al., 1983; O'Keane et al., 1992; Soubrie, 1986) are associated with maladaptive behavior, it is possible that the participants who were not seen for follow-up represent a portion of the sample at greater risk for a negative outcome. However, there were no differences between those participants who were and were not seen for follow-up evaluations with regard to many additional risk factors, such as rates of environmental adversity. Furthermore, there were follow-up participants who proceeded to negative outcomes,

including psychiatric hospitalization and involvement with the juvenile justice system. Given the number of comparisons that were performed, several differences between the two groups were to be expected.

Amongst the participants who were seen for follow-up, there is evidence of a 10-point drop, on average, in Full Scale and Verbal IQ scores and a seven-point drop in Performance IQ scores from baseline to follow-up. This decline can be partially related to the change in instrument made across protocols, i.e. the switch from the WISC-R to the WISC-III. One would generally expect a decrease in intelligence scores when switching between these measurements of intellectual capacity due to an updating of the normative values (Wechsler, 1991). However, the 10-point decline in IQ scores is greater than expected due to measurement variability and thus may suggest intellectual decline in the participants over time. Yet, despite the drop in IQ scores, intellectual performance at follow-up remains within the average range of intellectual ability.

At follow-up, parents, teachers and probands completed ratings scales describing the behavior of the adolescents. Parents and probands also completed diagnostic interviews addressing symptomatology exhibited by the adolescents. Interestingly, both parents and teachers rated the participants as one-standard deviation above normal on scales of attention, aggression and delinquency while the probands rated their behavior on the attention and aggression scales as falling within normal limits. All raters were in agreement that a summary score for internalizing behaviors fell within normal limits. Regarding diagnostic information, parents and probands reported similarly low rates of internalizing disorders and a much higher proportion of externalizing disorders. Parents reported higher rates of ADHD and ODD than

probands, while probands reported a higher rate of substance use disorders than parents reported. Overall, similar to baseline reports, the participants exhibited low levels of internalizing difficulties, relative to higher rates of externalizing behavioral problems. Respondents were all in agreement with regard to levels of internalizing behaviors, while reports of externalizing behaviors differed across respondents.

Investigators of externalizing behaviors often comment on the difficulty of operationally defining human aggression and the research problems this creates (e.g., Barratt et al., 1997). The lack of a universally accepted method for measurement of aggression makes comparisons across studies particularly difficult. Rating scales that purport to tap aggression include an amalgam of oppositional behavior, verbal aggression, antisocial behavior, and actual physical aggression. Inaccurate measurement and disparity across reports provided by different respondents have created challenges for researchers attempting to study the relationship between neurobiology and aggressive behavior. The summary scales used in this study (see Appendix A) were designed to target the behaviors of interest in a precise manner, capture a full picture of the behaviors exhibited by the participants by collapsing the information that had been collected from various sources, as well as allow for the use of the gold standard within the field, clinical judgment. The method of using clinical best-estimate procedure to derive an overall rating of subject behavior has proven useful in earlier studies investigating the relationship between neurochemistry and behavior (Halperin et al., 1994). The summary scores devised for the purpose of this dissertation were shown to be associated with ratings of behavior at outcome by parents, teachers and self-report, supporting the validity of the scales. High inter-rater reliability was seen as well. As

expected, summary scores in the different behavioral dimensions (physical aggression/assault, antisocial behavior and substance use) were directly correlated with each other, excluding aggression and substance use which were not significantly associated with each other.

The present study has several strengths including multiple informants, multiple dependent measures, multi-ethnic representation within the sample and a longitudinal perspective. However, it also has clear limitations, such as the aforementioned issues of attrition and small sample size. While the large time window for follow-up used in this study is informative, it would also be useful to obtain data on clinical outcome at several shorter time-points. Such sampling would enable a better understanding of the developmental trajectory of aggressive and antisocial behavior, rather than the current work that presents views of childhood and adolescent behavior in isolation. More frequent follow-up may also assist in maintenance of the sample and reduce attrition.

An additional limitation of the present study is the inability to address gender differences. Given the absence of statistical outliers in the current data, the inclusion of one female amongst the participants in the follow-up evaluations is not likely to have altered the results obtained. The one female who was seen at follow-up was not aggressive at baseline and exhibited relatively enhanced 5-HT function (delta PRL = 24.32). Her behavioral outcome scores were a one for physical aggression/assault, two for antisocial behavior and one for substance use. Thus, her positive outcome in adolescence fits what would be predicted based on the hypotheses posited in this dissertation. Data from a pilot study of the neurochemistry of aggression in females did not report any differences between prepubertal aggressive boys and girls with regard to

an index of their 5-HT function (Koda et al., 1996). However, a large body of evidence attests to the differential manifestation of aggressive behavior across genders and Koda et al. found that the aggressive girls were less impulsive, and had higher Verbal IQs, than did the aggressive boys. Future research should include a larger number of females in order to address the different risk/protective factors for behavioral development between males and females.

Future prospective studies should also consider intervention that the participants receive and how the form and extent of treatment affect outcome. Insufficient information on treatment services was obtained in this study, partially due to the reliance upon self-report for treatment history over an average of a 6.68-year time-period. If this study had originally been designed as a longitudinal study, methods for collecting information on treatment services at regular intervals could have been established.

Reliance on self-report data was problematic in other areas of the study as well. While parental history of aggressive and antisocial behavior was assessed in this study, the information was collected via self-report on a semi-structured interview instrument. Self-report data are subjective in nature and prone to recall errors and response biases. Additionally, positive parental history reported in this study did not differentiate between manifestation of the targeted behavior during the parent's adulthood or childhood, or between the presence/absence of this parent in the child's home. Antisocial parents within the home environment and antisocial parents located outside of the home represent different degrees of risk for the proband's development. Future

research could distinguish between these finer aspects of parent history of antisocial or aggressive behavior.

Conclusions regarding the contribution of enhanced/diminished 5-HT function and its role in development cannot be made in this study due to the lack of clinical and healthy comparison groups. Aggressive behavior is present in numerous diagnostic groups and is not limited to children with ADHD. Consequently, any neurochemical abnormality associated with aggression would be more meaningful if it were present independent of diagnosis. The assignment of high and low categories to values of the index of 5-HT function is somewhat arbitrary, due to the absence of normative values for comparison. Furthermore, it must be noted that the PRL response to administration of FEN, used as an index of 5-HT function in this study, is an indirect measure of central 5-HT function. The invasive nature of direct measures of central neurochemical function presents challenges for use with minors in research.

The relationship between 5-HT function and aggressive behavior reported herein may vary as a function of age. Participants in the Kruesi et al. (1992) and Stoff et al. (1992) studies were older than the participants in studies where a positive association between 5-HT function and behavior was reported (Castellanos et al., 1995; Halperin et al., 1994; Pine et al., 1997). Thus, enhanced 5-HT function may be characteristic in younger children. Furthermore, Halperin et al. (1997a) reported that seven-nine year-old aggressive boys had an enhanced response to administration of FEN relative to non-aggressive boys. These group differences were not present in the nine to 11 year-old children. It is possible that developmental changes in 5-HT function may manifest themselves differently in children depending upon behavior. Questions dealing with

age-related changes in 5-HT function would require further assessment of central 5-HT function. Attempts to perform a second measurement of 5-HT function were not successful due to withdrawal of FEN from the market by the Food and Drug Administration and an inability to obtain a suitable pharmacological substitute that would not introduce measurement error beyond acceptable levels. Future research into the developmental trajectory of 5-HT function, in relation to behavior, would be most beneficial.

In summary, these data provide support for the first hypothesis tested in the present study. Participants who were aggressive and exhibited diminished 5-HT function at baseline were more aggressive at adolescent outcome, than were aggressive participants who exhibited enhanced 5-HT function at baseline. Furthermore, both early aggression and 5-HT function served as independent predictors of behavior at outcome. Regarding the second hypothesis, familial adversity did not account for a significant portion of the variance in behavior at outcome left unexplained by the contribution of early aggression and 5-HT function. Thus, the second hypothesis of this dissertation was not supported by the current findings. With respect to the third hypothesis, the findings were in the opposite direction from what had been predicted, i.e., baseline inattention symptoms were shown to have more predictive power with regard to outcome than did overactive/impulsive symptoms.

While these data shed some light on the developmental course of children with DBDs, the underlying mechanism(s) of aggression requires further study. Amongst children who are aggressive, the neurochemical factor of diminished 5-HT function may lead to disinhibited behavior and increase the likelihood of progression to further

maladaptive behavior. However, multiple pathways toward the development of aggression exist and are based on a myriad of individual, familial, environmental and neurochemical factors. It is clear from these data and the literature that no one risk or protective factor operates in isolation to determine the course of a child's development. Rather, it is the unique combination of these factors for any individual that may lead to the exhibition of aggression.

Although this study has provided evidence for early aggression and relatively diminished 5-HT functioning as risk factors towards negative outcome in adolescence, these findings are correlational in nature and cannot be used to comment on causality. Direct manipulation of early behavior and/or neurochemistry is required to make statements regarding causality but is not possible because of both logistic and ethical concerns. While the present findings do not support the contribution of environmental factors to behavioral development, an extensive literature indicates that a host of environmental factors are linked to the emergence of maladaptive behavior in children and adolescents. Additionally, an emerging literature in animals has begun to elucidate the impact that environmental factors may have on neurochemical functions. Again, direct manipulations of environmental stressors in an effort to assess their impact on central 5-HT function are clearly precluded due to ethical factors. Further, longitudinal studies examining naturally occurring changes in behavior and environment, in association with 5-HT function, could shed more light on this issue and uncover more risk and protective factors. Finally, technological advances in neuroimaging and genetics research have yielded two approaches that may help tease apart the biological and environmental contributions to the development of aggression behavior.

Table 1

Protocol for Clinical Evaluation at Follow-up

Behavior Rating Scales and Interviews

Completed by Parent:

Child Behavior Checklist (CBCL)

Self-Report:

Youth Self Report (YSR)
Self Report Delinquency Scale (SRD)
Eysenck Impulsiveness Scale

Completed by Teacher:

Teacher Report Form
Dodge Teacher Checklist of Social Behavior
Teacher Impulsivity Scale (6 Items)

Cognitive/Academic Measures:

Wechsler Intelligence Scale for Children - III (WISC-III)
[Wechsler Adult Intelligence Scale - III (WAIS-III)]
Wechsler Individualized Achievement Test (WIAT)

Structured Diagnostic Interviews:

Diagnostic Interview Schedule for Children - Parent Version (DISC-P)
Diagnostic Interview Schedule for Children - Youth Version (DISC-Y)

Other Measures:

Urine Toxicology Screen
Demographics/Services Rendered Interview

Table 2

Baseline sample characteristics of the participants who were and were not seen for follow-up

	Not Followed N = 23	Followed N = 34
	Mean (SD)	Mean (SD)
AGE	8.9 (1.2)	9.1 (1.2)
WISC-R VIQ*	93.8 (13.7)	100.7 (13.7)
WISC-R PIQ	97.6 (13.0)	97.7 (13.9)
WISC-R FSIQ	95.1 (12.6)	99.3 (12.3)
WRAT-R Reading**	80.3 (15.8)	94.3 (17.7)
WRAT-R Mathematics	93.7 (11.2)	94.8 (16.9)
WRAT-R Spelling**	79.3 (14.6)	93.2 (15.9)
CBCL Aggression	72.4 (12.7)	74.0 (12.5)
CBCL Delinquency	70.5 (10.1)	72.4 (8.0)
IOWA Aggression	8.2 (4.6)	7.9 (4.7)
IOWA I/O	11.6 (2.7)	10.9 (2.8)
DELTA PROLACTIN*	11.8 (5.8)	15.5 (8.3)

*$p < .10$, ** $p < .01$

Table 3

Diagnostic Status of the Sample at Baseline

Diagnosis	Not Followed N = 23	Followed N = 34	χ^2
Attention-Deficit/ Hyperactivity Disorder	20	32	.88
Conduct Disorder	5	11	.77
Oppositional Defiant Disorder	18	25	.17
Anxiety Disorder	9	9	1.02
Mood Disorder	3	3	.26

Table 4

Baseline characteristics of those participants seen for follow-up evaluations

	Not Aggressive N = 16		Aggressive N = 18	
	Mean	(SD)	Mean	(SD)
AGE	8.96	(1.18)	9.22	(1.31)
WISC-R VIQ	102.73	(13.51)	99.06	(13.97)
WISC-R PIQ	100.53	(13.19)	95.33	(14.32)
WISC-R FSIQ	101.80	(10.60)	97.17	(13.50)
WRAT-R Reading	94.50	(15.08)	94.18	(20.35)
WRAT-R Mathematics	98.44	(17.85)	91.41	(15.89)
WRAT-R Spelling	94.06	(14.20)	92.41	(17.81)
CBCL Aggression*	67.69	(9.67)	79.61	(12.20)
CBCL Delinquency	70.31	(7.14)	74.28	(8.53)
IOWA Aggression**	5.13	(4.26)	10.63	(3.46)
IOWA I/O	10.25	(2.38)	11.63	(3.12)
DELTA PROLACTIN	14.92	(8.56)	15.96	(8.34)
ENVIRONMENTAL RISK	1.25	(1.13)	1.39	(1.04)

*$p < .01$, ** $p < .001$

Table 5

Performance on Measures of Intelligence and Academic Achievement at Follow-Up (N = 34, 33 male, 1 female)

VARIABLE	MEAN(SD)
WISC III FSIQ	89.9 (13.3)
WISC III VIQ	90.7 (14.2)
WISC III PIQ	90.8 (14.3)
WIAT Reading	91.3 (17.6)
WIAT Math Reasoning	92.1 (16.0)
WIAT Spelling	89.8 (17.4)

Table 6

Scores on Rating Scales and Summary Outcome Measures at Follow-Up

(N = 34, 33 male, 1 female)

Measure	Mean (SD)
CBCL Aggression	63.45 (10.15)
CBCL Attention	66.15 (8.95)
CBCL Delinquency	62.18 (8.01)
TRF Aggression*	60.26
TRF Attention	60.21
TRF Delinquency	59.13
YSR Aggression	57.30 (8.69)
YSR Attention	55.82 (7.48)
YSR Delinquency	61.61 (7.76)
Summary Score: Physical Aggression/Assault	3.76 (2.26)
Summary Score: Antisocial Behavior	4.52 (1.61)
Summary Score: Substance Use	2.80 (2.07)

*Teacher Scores presented here represent summaries of forms completed by 1 – 3 teachers per participant.

Table 7

Diagnostic Status of the Sample at Follow-Up According to Parental and Self Report

Diagnosis	Parent Report N = 33	Self Report N = 30	Parent or Self Report N = 34
Attention-Deficit/ Hyperactivity Disorder	Combined = 5 Inattentive = 11 Hyperactive = 2	Combined = 1 Inattentive = 1 Hyperactive = 1	Combined = 5 Inattentive = 12 Hyperactive = 3
Conduct Disorder	6	7	11
Oppositional Defiant Disorder	14	2	15
Anxiety Disorder	2	2	4
Mood Disorder	1	0	1
Substance Use Disorder	4	8	11

Table 8

Intercorrelations Between Summary Scores, and Correlations with Rating Scales, at Outcome for 34 Participants

Scale	1	2	3	CBCL AGG	CBCL DEL	YSR AGG	YSR DEL
1. Aggression	--	.56**	.29	.44*	.61**	.32	.51**
2. Antisocial		--	.74**	.30	.66**	.32	.62**
3. Substance			--	.14	.50**	.34	.59**

*p < .05

**p < .01

Table 9

Summary of Hierarchical Regression Analysis for Variables Predicting Physical Aggression/Assault at Outcome (N= 33)

Variable	B	SE B	β
Step 1			
Aggression	2.41	.69	.53*
Step 2			
Aggression	2.63	.58	.58**
Serotonin	-.13	.04	-.48*
Step 3			
Aggression	4.32	1.24	.96*
Serotonin	-.13	.04	-.48*
Interaction	-.05	.04	-.42

Note. $R^2 = .28$ for Step 1; $\Delta R^2 = .23$ for Step 2 ($p < .01$); $\Delta R^2 = .04$ for Step 3

*$p < .01$, **$p < .001$

Table 10

Summary of Hierarchical Regression Analysis for Variables Predicting Antisocial Behavior at Outcome (N= 34)

Variable	B	SE B	β
Step 1			
Aggression	1.35	.51	.43**
Step 2			
Aggression	1.41	.49	.45***
Serotonin	-.06	.03	-.31**
Step 3			
Aggression	2.92	1.00	.92***
Serotonin	-.06	.03	-.30*
Interaction	-.05	.03	-.54*

Note. $R^2 = .18$ for Step 1; $\Delta R^2 = .09$ for Step 2 ($p \leq .05$); $\Delta R^2 = .06$ for Step 3 ($p < .10$)

*$p < .10$, **$p \leq .05$, ***$p < .01$

Table 11

Summary of Hierarchical Regression Analysis for Variables Predicting Substance Use at Outcome (N= 32)

Variable	B	SE B	β
Step 1			
Aggression	1.16	.71	.28
Step 2			
Aggression	1.16	.73	.29
Serotonin	-.003	.04	-.01
Step 3			
Aggression	3.01	1.54	.74*
Serotonin	-.002	.04	-.01
Interaction	-.06	.04	-.51

Note. $R^2 = .08$ for Step 1; $\Delta R^2 = .00$ for Step 2; $\Delta R^2 = .06$ for Step 3

*$p < .10$

Table 12

Summary of Hierarchical Regression Analysis for Variables Predicting Physical Aggression/Assault at Outcome (N= 33)

Step 1 and Step 2 are identical to those presented in Table 9

Variable	B	SE B	β
Step 3			
Aggression	2.62	.59	.58**
Serotonin	-.13	.04	-.47*
Environmental Risk	-.21	.31	-.09

Note. R^2 = .28 for Step 1; Δ R^2 = .23 for Step 2 ($p < .01$); ΔR^2 = .01 for Step 3

*$p < .01$, **$p < .001$

Table 13

Summary of Hierarchical Regression Analysis for Variables Predicting Antisocial Behavior at Outcome (N= 34)

Step 1 and Step 2 are identical to those in Table 10

Variable	B	SE B	β
Step 3			
Aggression	1.39	.49	.44**
Serotonin	-.06	.03	-.30*
Environmental Risk	.13	.23	.08

Note. $R^2 = .18$ for Step 1; $\Delta R^2 = .09$ for Step 2 ($p \leq .05$); $\Delta R^2 = .01$ for Step 3

*$p < .10$. **$p < .01$

Table 14

Summary of Hierarchical Regression Analysis for Variables Predicting Substance Use at Outcome (N= 32)

Step 1 and Step 2 are identical to those on Table 11

Variable	B	SE B	β
Step 3			
Aggression	1.07	.73	.26
Serotonin	-.06	.04	-.00
Environmental Risk	.44	.34	.23

Note. R^2 = .08 for Step 1; ΔR^2 = .00 for Step 2; ΔR^2 = .05 for Step 3

Table 15

Summary of Hierarchical Regression Analyses for Variables Predicting Outcome

Physical Aggression (N = 33) Step 1 is identical to Step 1 in Table 9

Variable	B	SE B	β
Step 2			
Aggression	2.44	.70	.54*
Inattention	.12	.24	.08

Note. $R^2 = .28$ for Step 1; $\Delta R^2 = .01$ for Step 2, *p < .01

Antisocial Behavior (N = 34) Step 1 is identical to Step 1 in Table 10

Variable	B	SE B	β
Step 2			
Aggression	1.43	.47	.45**
Inattention	.39	.16	.36*

Note. $R^2 = .18$ for Step 1; $\Delta R^2 = .13$ for Step 2 ($p < .05$), *p < .05, **p < .01

Substance Abuse (N = 32) Step 1 is identical to Step 1 in Table 11

Variable	B	SE B	β
Step 2			
Aggression	1.26	.69	.31*
Inattention	.40	.23	.30*

Note. $R^2 = .08$ for Step 1; $\Delta R^2 = .09$ for Step 2 ($p < .10$), *p < .10

Table 16

Summary of Hierarchical Regression Analyses for Variables Predicting Outcome

Physical Aggression (N = 33) Step 1 is identical to Step 1 in Table 9

Variable	B	SE B	β
Step 2			
Aggression	2.42	.69	.54*
Hyper/Impulsive	.15	.15	.15

Note. $R^2 = .28$ for Step 1; $\Delta R^2 = .02$ for Step 2, *p < .01

Antisocial Behavior (N = 34) Step 1 is identical to Step 1 in Table 10

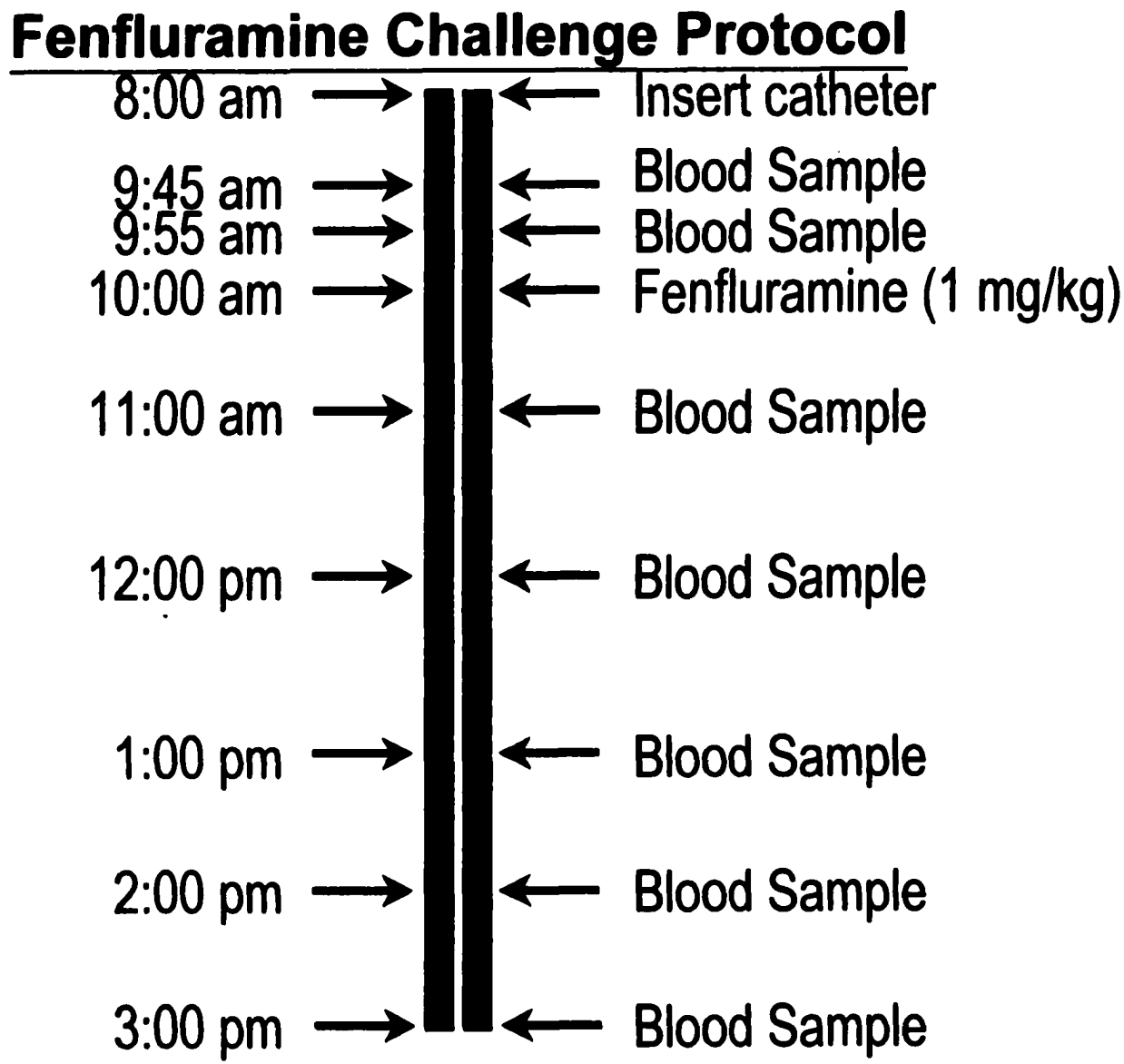
Variable	B	SE B	β
Step 2			
Aggression	1.35	.49	.43**
Hyper/Impulsive	.20	.11	.29*

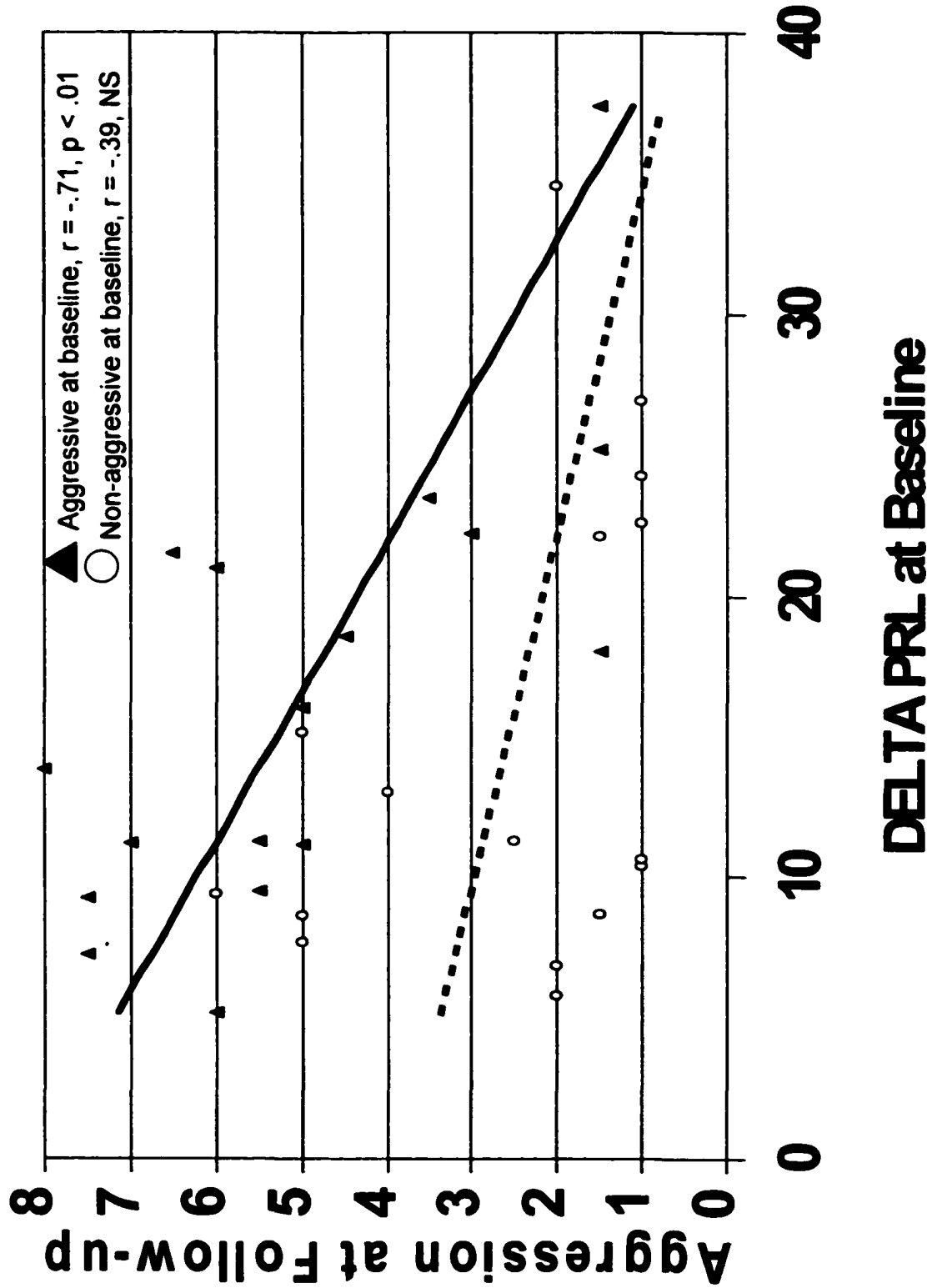
Note. $R^2 = .18$ for Step 1; $\Delta R^2 = .08$ for Step 2 (p < .10), *p < .10, **p < .05

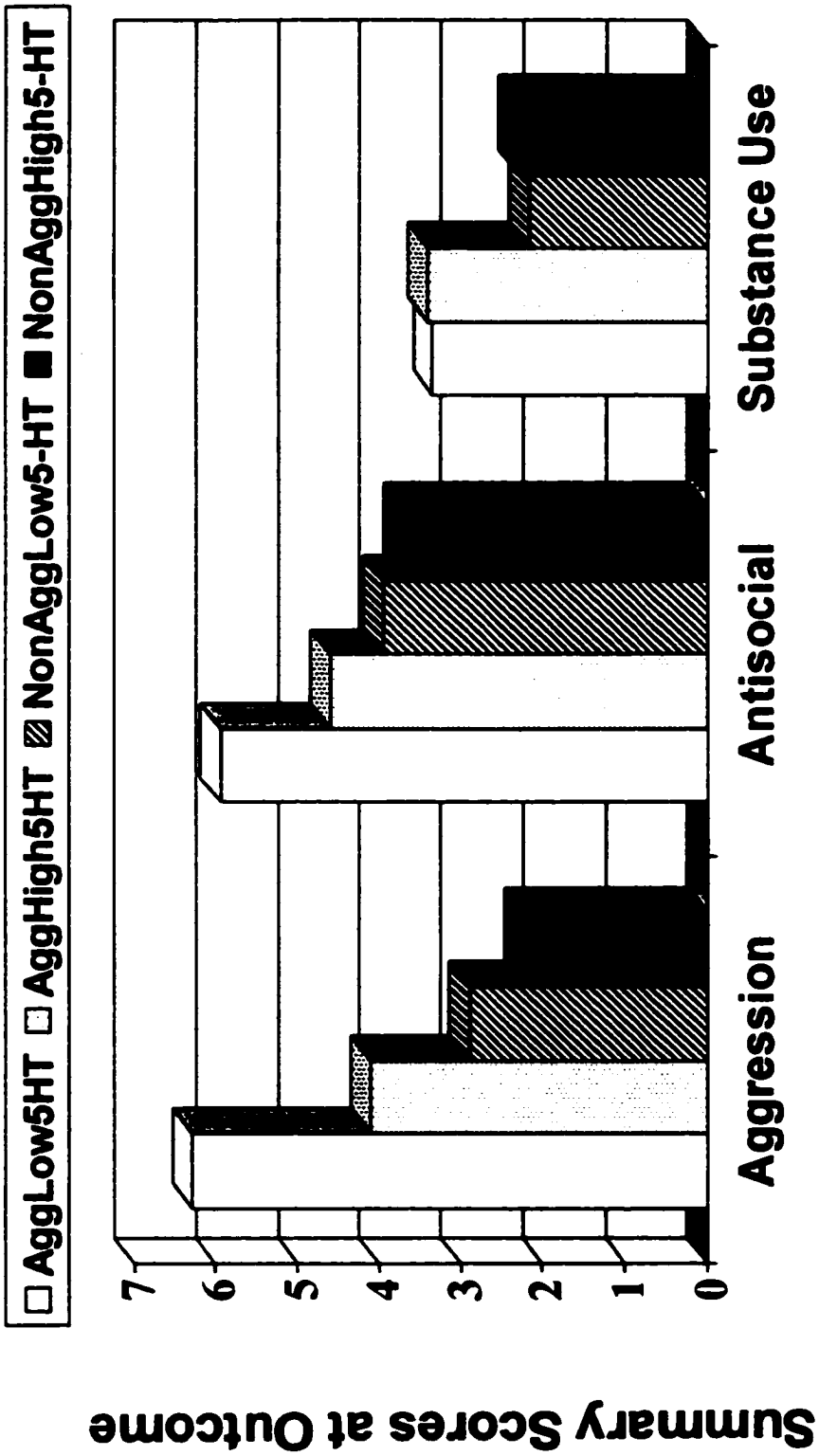
Substance Abuse (N = 32) Step 1 is identical to Step 1 in Table 11

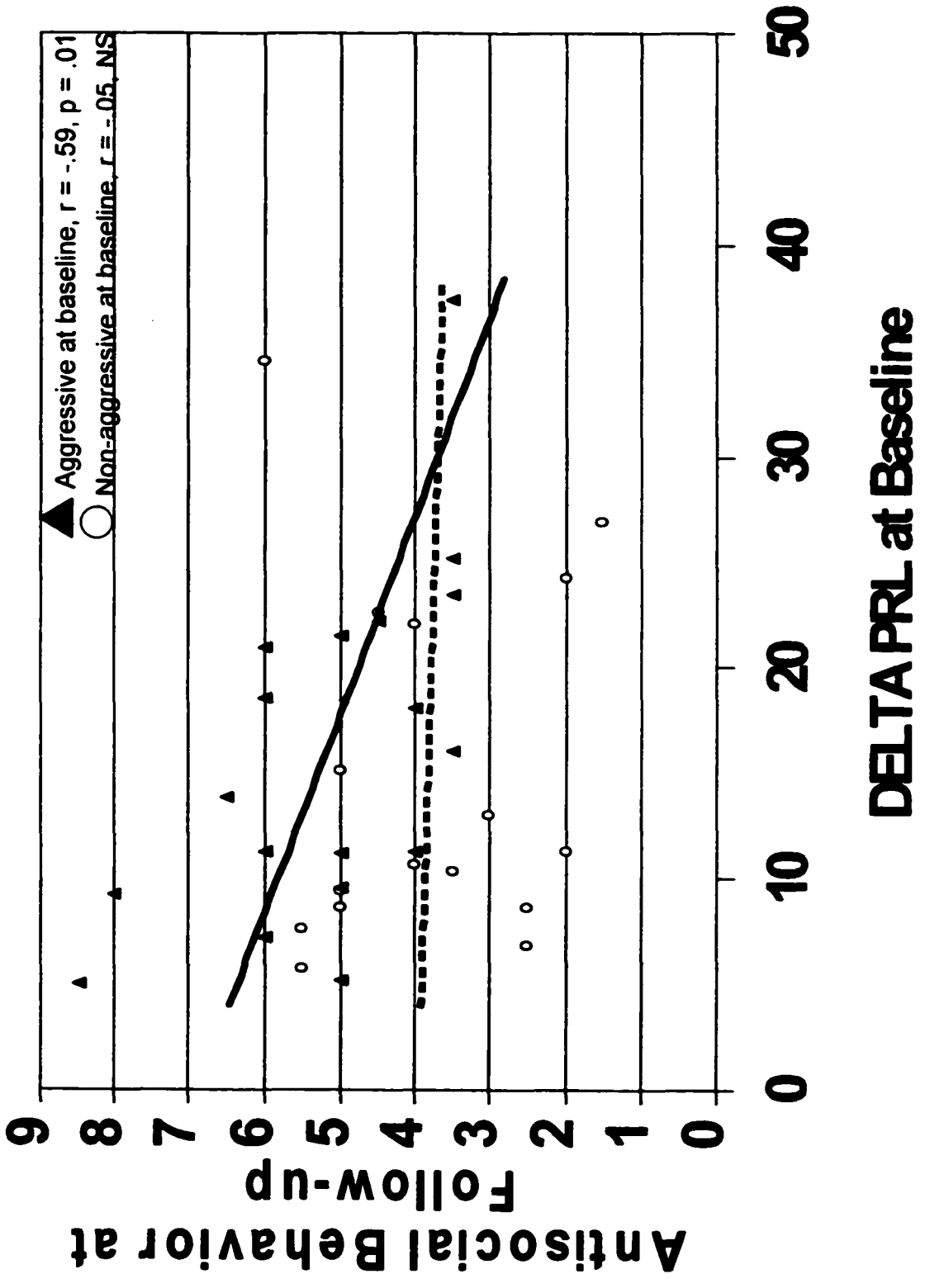
Variable	B	SE B	β
Step 2			
Aggression	1.18	.71	.29
Hyper/Impulsive	.18	.16	.20

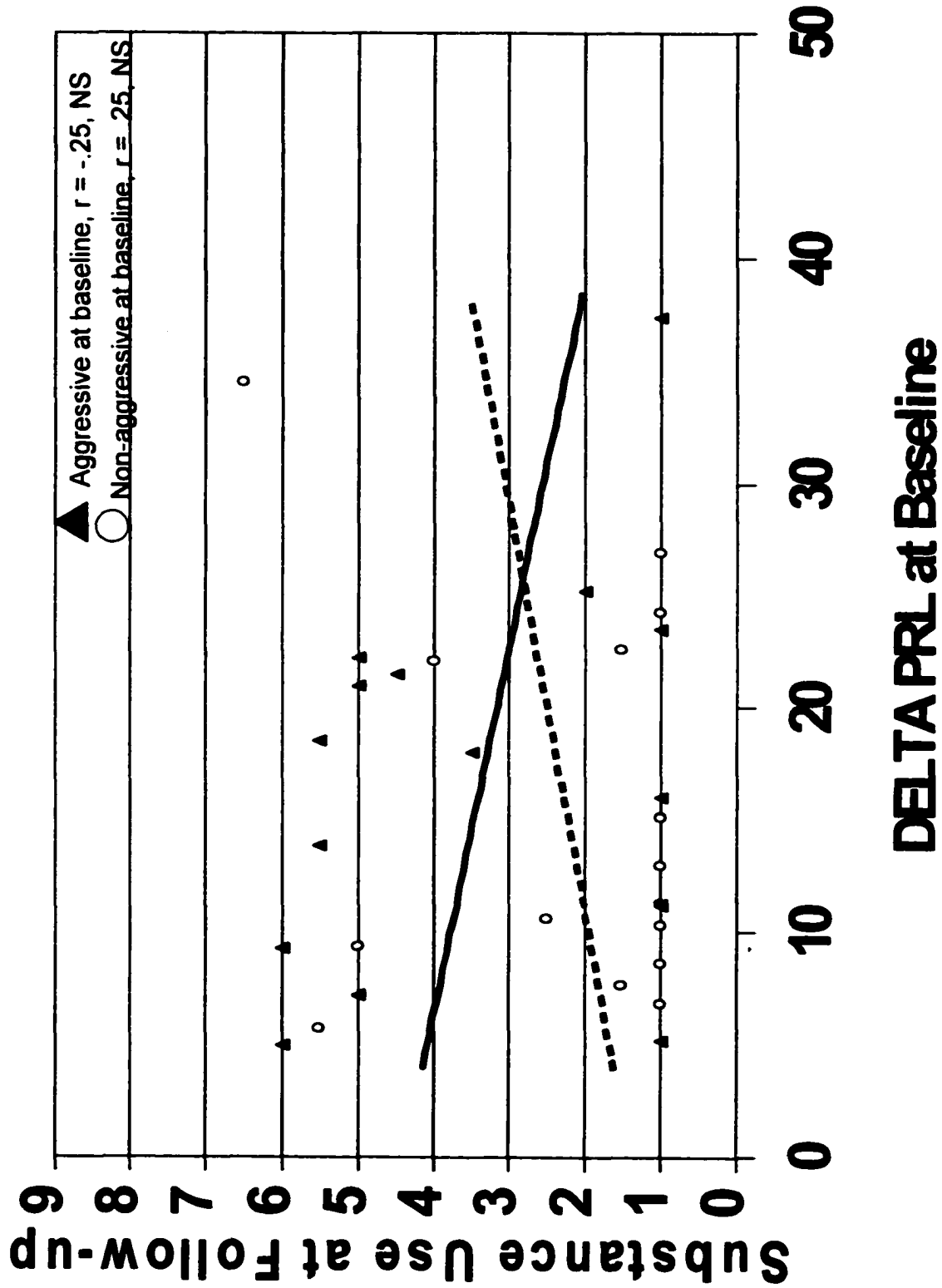
Note. $R^2 = .08$ for Step 1; $\Delta R^2 = .04$ for Step 2











Summary Scales for Data Analysis

Subject ID Number:_____ Rater Name:_____

Each domain should receive a score between 1 and 9. If a score can not be determined due to insufficient information, that domain should be coded "99." Consider behavior from age 14 through the current age. In case of disagreement between informants regarding frequency or severity of a behavior, the report of the **most** severe/frequent behavior should be counted for the summary score.

1	2	3	4	5	6	7	8	9
absence		infreq minor		freq minor/infreq serious		freq serious		persistent very serious

I. *PHYSICAL AGGRESSION/ASSAULT* **FINAL SCORE = _____**

KEY

- Absence of significant physical aggression = no more than minor squabbles w/ peers or siblings
- Minor fighting = physical fights with peers that result in no real physical injury
- Serious events = fights involving physical injury or weapon use. fights with adults are more likely to be considered "serious"
- Very serious events = those that result in serious physical injury

II. *ANTISOCIAL BEHAVIOR* **FINAL SCORE = _____**

KEY

- Absence of significant antisocial behavior = no more than typical adolescent indiscretions
- Minor antisocial acts = avoiding payment, begging $, carrying weapon w/out use, curfew violation, cutting school/truancy, graffiti, hitchhiking, lying, minor vandalism/destruction property, public disturbance, run away short duration, steal small value, swearing, trespassing
- Serious antisocial acts = burglary, fires that cause damage, major vandalism, stealing high value or with confrontation, selling: stolen goods, drugs, or sexual favors
- Very serious antisocial acts = serious criminal behavior that would likely lead to incarceration

III. *SUBSTANCE USE* **FINAL SCORE = _____**

KEY

- Absence of significant substance use = no more than minor experimentation with cigarettes or alcohol
- Minor substance use = alcohol, cigarettes, marijuana, sniffing household products
- Serious substance use = includes those drugs that were not indicated as minor
- Very serious substance use = abuse of major substance that causes impairment in functioning

TABLE OF ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine, serotonin
ADHD	Attention-Deficit/Hyperactivity Disorder
ANOVA	Analysis of Variance
ASPD	Antisocial Personality Disorder
CAS-P,T	Children's Aggression Scale – Parent and Teacher Versions
CBCL	Child Behavior Checklist
CD	Conduct Disorder
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTQ	Conners Teacher's Questionnaire
DBD	Disruptive Behavior Disorders
DISC	Diagnostic Interview Schedule for Children
DSM-III-R	Diagnostic and Statistical Manual, Third Edition Revised
DSM-IV	Diagnostic and Statistical Manual, Fourth Edition
FDA	Food and Drug Administration
FEN	Fenfluramine
IOWA	IOWA Conners Teacher's Questionnaire
IQ	Intelligence Quotient
MAO	Monoamine Oxidase
m-CPP	meta-chlorophenylpiperazine
Nor-FEN	nor-fenfluramine

ODD	Oppositional Defiant Disorder
PET	Positron Emission Tomography
PRL	prolactin
RIA	radio immuno assay
SD	standard deviation
SES	socioeconomic status
SRD	Self Report Delinquency Scale
SSRI	selective serotonergic reuptake inhibitors
THC	tetrahydrocannabinol
TRF	Teacher Report Form
VCR	videocassette recorder
WAIS-III	Wechsler Adult Intelligence Scale, Third Edition
WIAT	Wechsler Individualized Achievement Test
WISC-III	Wechsler Intelligence Scale for Children, Third Edition
WISC-R	Wechsler Intelligence Scale for Children, Revised
WRAT-R	Wide Range Achievement Test, Revised
YSR	Youth Self Report

BIBLIOGRAPHY

Achenbach T. M. (1991a). Manual for the Child Behavior Checklist 4/18 and 1991 Profile. Burlington, VT: University of Vermont.

Achenbach T. M. (1991b). Manual for the Teacher's Report Form and 1991 Profile. Burlington, VT: University of Vermont.

Achenbach T. M. (1991c). Manual for the Youth Self-Report and 1991 Profile. Burlington, VT: University of Vermont.

Alsobrook II, J. P., & Pauls, D. L. (2000). Genetics and violence. Juvenile Violence, 9, 765-776.

American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders, (4th Ed.). Washington, D. C.: author.

Anderson, J. C., Williams, S. M., McGee, R., & Silva, P. A. (1987). DSM-III disorders in preadolescent children: Prevalence in a large sample from the general population. Archives of General Psychiatry, 44, 69-76.

Arseneault, L., Tremblay, R. E., Boulerice, B., Seguin, J. R., & Saucier, J. (2000). Minor physical anomalies and family adversity as risk factors for violent delinquency in adolescence. American Journal of Psychiatry, 157, 917-923.

August, G. J., Realmuto, G. M., Joyce, T., & Hektner, J. M. (1999). Persistence and desistance of oppositional defiant disorder in a community sample of children with ADHD. Journal of American Academy of Child and Adolescent Psychiatry, 38, 1262-1270.

Barratt, E. S., Stanford, M. S., Kent, T. A., & Felthous, A. (1997). Neuropsychological and cognitive psychophysiological substrates of impulsive aggression. Society of Biological Psychiatry, 41, 1045-1061.

Beitchman, J. H., Inglis, A., & Schachter, D. (1991). Child psychiatry and early intervention: IV. The externalizing disorders. Canadian Journal of Psychiatry, 37, 245-249.

Biederman, J., Faraone, S. V., Milberger, S., Jetton, J. G., Chen, L., Mick, E., Greene, R. W., & Russell, R. L. (1996). Journal of American Academy of Child and Adolescent Psychiatry, 35, 1193-1204.

Biederman, J., Newcorn, J. H., & Sprich, S. (1991) Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety and other disorders. American Journal of Psychiatry, 148, 564-577.

Bird, H. R., Canino, G., Rubio-Stipec, M., & Gould, M. S. (1988). Estimates of the prevalence of childhood maladjustment in a community survey in Puerto Rico: The use of combined measures. Archives of General Psychiatry, 45, 1120-1126.

Birmaher, B., Stanley, M., Greenhill, L., Twomey, J., Gavrilescu, A., & Rabinovich, H. (1990.) Platelet imipramine binding in children and adolescents with impulsive behavior. Journal of American Academy of Child and Adolescent Psychiatry, 29, 914-918.

Bjork, J. M., Dougherty, D. M., Moeller, F. G., & Swann, A. C. (2000). Differential behavioral effects of plasma tryptophan depletion and loading in aggressive and nonaggressive men. Neuropsychopharmacology, 22, 357-369.

Blumensohn, R., Ratzoni, G., Weizman, A., Israeli, M., Greuner, N., Apter, A., Tyano, S., & Biegon, A. (1995). Reduction in serotonin $5HT_2$ receptor binding on platelets of delinquent adolescents. Psychopharmacology, 118, 354-356.

Brown, G. L., Ebert, M. H., Goyer, P. F., Jimerson, D. C., Klein, W. J., Bunney, W. E., & Goodwin, F. K. (1982). Aggression, suicide, and serotonin: Relationships to CSF amine metabolites. American Journal of Psychiatry, 139, 741-746.

Cadoret, R. J., & Cain, M. S. (1981). Environmental and genetic factors in predicting adolescent antisocial behavior in adoptees. The Psychiatric Journal of the University of Ottowa, 6, 220-225.

Cadoret, R. J., Leve, L. D., & Devor E. (1997). Genetics of aggressive and violent behavior. The Psychiatric Clinics of North America, 20, 301-322.

Cadoret, R. J., Yates, W. R., Troughton, E., Woodworth, G., & Stewart, M. (1995). Genetic-environmental interaction in the genesis of aggressivity and conduct disorders. Archives of General Psychiatry, 52, 916-924.

Cadoret, R. J., Yates, W. R., Troughton, E., Woodworth, G., & Stewart, M. A. (1996). An adoption study of drug abuse/dependency in females. Comprehensive Psychiatry, 37, 88-94.

Campbell, S. B., Shaw, D. S., & Gilliom, M. (2000). Early externalizing behavior problems: Toddlers and preschoolers at risk for later maladjustment. Developmental Psychopathology, 12, 467-488.

Castellanos, F. X., Elia, J., Kruesi, M. J. P., Gulotta, C. S., Mefford, I. N., Potter, W. Z., Ritchie, G. F., & Rapoport, J. L. (1995). Cerebrospinal fluid monoamine metabolites in boys with attention-deficit hyperactivity disorder. Journal of Psychiatry Research, 52, 305-316.

Cherek, D. R., & Lane, S. D. (1999). Effects of d,l-fenfluramine on aggressive and impulsive responding in adult males with a history of conduct disorder. Psychopharmacology, 146, 473-481.

Cherek, D. R., Moeller, F. G., Khan-Dawood, F., Swann, A., & Lane, S. D. (1999). Prolactin response to buspirone was reduced in violent compared to nonviolent parolees. Psychopharmacology, 142, 144-148.

Chiavegatto, S., Dawson, V. L., Mamounas, L. A., Koliatsos, V. E., Dawson, T. M. & Nelson, R. J. (2001). Brain serotonin dysfunction accounts for aggression in male mice lacking neuronal nitric oxide synthase. Proceedings of the National Academy of Sciences, 98, 1277-1281.

Clarke, R. A., Murphy, D. L., & Constantino, J. N. (1999) Serotonin and externalizing behavior in young children. Psychiatry Research, 19, 29-40.

Cleare, A. J., & Bond, A. J. (1997). Does central serotonergic function correlate inversely with aggression? A study using d-fenfluramine in healthy subjects. Psychiatry Research, 69, 89-95.

Coccaro, E. F. (1992) Impulsive aggression and central serotonergic system function in humans: an example of a dimensional brain-behavior relationship. International Clinical Psychopharmacology, 7, 3-12.

Coccaro, E. F., Berman, M. E., Kavoussi, R. J., & Hauger, R. L. (1996). Relationship of prolactin response to d-fenfluramine to behavioral and questionnaire assessments of aggression in personality-disordered men. Biological Psychiatry, 40, 157-164.

Coccaro, E. F., Gabriel, S. & Siever, L. J. (1990). Buspirone challenge: Preliminary evidence for a role for central 5-HT1a receptor function in impulsive aggressive behavior in humans. Psychopharmacological Bulletin, 26, 393-405.

Coccaro, E. F., Kavoussi, R. J., Cooper, T. B., & Hauger, R. L. (1997b). Central serotonin activity and aggression: Inverse relationship with prolactin response to d-fenfluramine, but not CSF 5-HIAA concentration, in human subjects. American Journal of Psychiatry, 154, 1430-1435.

Coccaro, E. F., Kavoussi, R. J., & Hauger, R. L. (1995). Physiological responses to d-fenfluramine and ipsapirone challenge correlate with indices of aggression in males with personality disorder. International Clinical Psychopharmacology, 10, 177-179.

Coccaro, E. F., Kavoussi, R. J., & Hauger, R. L. (1997). Serotonin function and antiaggressive response to fluoxetine: A pilot study. Biological Psychiatry, 42, 546-552.

Coccaro, E. F., Kavoussi, R. J., Hauger, R. L., Cooper, T. B., & Ferris, C. F. (1998). Cerebrospinal fluid vasopressin levels: Correlates with aggression and serotonin function in personality-disordered subjects. Archives of General Psychiatry, 55, 708-714.

Coccaro, E. F., Kavoussi, R. J., Trestman, R. L., Gabriel, S. M., Cooper, T. B., & Siever, L. J. (1997a). Serotonin function in human subjects: Intercorrelations among central 5-HT indices and aggressiveness. Psychiatry Research, 73, 1-14.

Coccaro, E. F., Siever, L. J., Klar, H. M., Maurer, G., Cochrane, K., Cooper, T. B., Mohs, R. C., & Davis, K. L. (1989). Serotonergic studies in patients with affective and personality disorders. Archives of General Psychiatry, 46, 587-599.

Coccaro, E. F., Silverman, J. M., Klar, H. M., Horvath, T. B., & Siever, L. J. (1994). Familial correlates of reduced central serotonergic system function in patients with personality disorders. Archives of General Psychiatry, 51, 318-324.

Cook, E. H., Stein, M. A., Ellison, T., Unis, A. S., & Leventhal, B. L. (1995). Attention deficit hyperactivity disorder and whole-blood serotonin levels: Effects of comorbidity. Psychiatry Research, 57, 13-20.

Cowen, P. J. (1993). Serotonin receptor subtypes in depression: Evidence from studies in neuroendocrine regulation. Clinical Neuropharmacology, 16, S6-S18.

Davis, B. M., Mathe, A. A., Mohs, R. C., Levy, M. I., & Davis, K. L. (1983). Effects of propantheline bromid on basal growth hormone, cortisol and prolactin levels. Psychoneuroendocrinology, 8, 103-107.

Davis, L. L., Clark, D. M., Kramer, G. L., Moeller, F. G., & Petty, F. (1999). D-fenfluramine challenge in posttraumatic stress disorder. Biological Psychiatry, 45, 928-930.

Dodge, K., Coie J., Terry, R., & Underwood, M. Teacher checklist of social behavior. Unpublished manuscript.

Dougherty, D.M., Bjork, J. M., Marsh, D. M., & Moeller, F. G. (1999). Influence of trait hostility on tryptophan depletion-induced laboratory aggression. Psychiatry Research, 88, 227-232.

Elliot, D. S., Huizinga, P., & Ageton, S. S. (1985). Explaining delinquency and drug use. Thousand Oaks, CA: Sage.

Eriksson, T., & Lidberg, L. (1997). Increased plasma concentrations of the 5-HT precursor amino acid tryptophan and other large neutral amino acids in violent criminals. Psychology and Medicine, 27, 477-478.

Esser, G., Schmidet, M. H., & Woerner, W. (1990). Epidemiology and course of psychiatric disorders in school-age children: Results of a longitudinal study. Journal of Child Psychology and Psychiatry, 31, 243-263.

Evans, J., Platts, H., Lightman, S., & Nutt, D. (2000). Impulsiveness and the prolactin response to d-fenfluramine. Psychopharmacology, 149, 147-152.

Eysenck, S. B. G., Easting, G., & Pearson, P.R. (1984). Age norms for impulsiveness, venturesomeness and empathy in children. Personality and Individual Differences, 5, 315-321.

Farrington, D. P., Gallagher, B., Morley, L., St. Ledger, R. J., & West, D. J. (1988). Are there any successful men from criminogenic backgrounds? Psychiatry, 51, 116-130.

Farrington, D. P., & Loeber, R. (2000). Epidemiology of juvenile violence. Juvenile Violence, 9, 733-748.

Fava, M., Vuolo, R. D., Wright, E. C., Nierenberg, A. A., Alpert, J. E., & Rosenbaum, J. F. (2000). Fenfluramine challenge in unipolar depression with and without anger attacks. Psychiatry Research, 94, 9-18.

Fergusson, D. M., Lynskey, M., T., & Horwood, L. J. (1996). Factors associated with continuity and changes in disruptive behavior patterns between childhood and adolescence. Journal of Abnormal Child Psychology, 24, 533-553.

Fishbein, D. H., Lozovsky, D., & Jaffe, J. H. (1989). Impulsivity, aggression, and neuroendocrine responses to serotonergic stimulation in substance abusers. Biological Psychiatry, 25, 1049-1066.

Gagnon, C., Craig, W. M., Tremblay, R. E., Zhou, R. M., & Vitaro, F. (1995). Kindergarten predictors of boys' stable behavior problems at the end of elementary school. Journal of Abnormal Child Psychology, 23, 751-766.

Gardner, D. L., Lucas, P. B., & Cowdry, R. W. (1990) CSF metabolites in borderline personality disorder compared with normal controls. Biological Psychiatry, 28, 247-254.

Goyette, C. H., Conners, C. K., & Ulrich, R. F. (1978). Normative data on revised Conners parents and teacher rating scales. Journal of Abnormal Child Psychology, 6, 221-236.

Grayson, R. H., Halperin, J. M., Sharma, V., Schwartz, S. T., Koda, V. H., & Newcorn, J. H. (1997). Changes in plasma prolactin and catecholamine metabolite levels following acute needle stick in children. Psychiatry Research, 69, 27-32.

Halperin, J. M., McKay, K. E., & Newcorn, J. H. (2002) Development, reliability, and validity of the Children's Aggression Scale – Parent Version. Journal of American Academy of Child and Adolescent Psychiatry, 41, 245-252.

Halperin, J. M., Newcorn, J. H., Kopstein, I., McKay, K. E., Schwartz, S. T., Siever, L. J., & Sharma, V. (1997b). Serotonin, aggression and parental psycopathology in children with attention-deficit hyperactivity disorder. Journal of American Academy of Child and Adolescent Psychiatry, 36, 1391-1398.

Halperin, J. M., Newcorn, J. H., Schwartz, S. T., Sharma, V., Siever, L. J., Koda, V. H., & Gabriel, S. (1997a). Age-related changes in the association between serotonergic function and aggression in boys with ADHD. Biological Psychiatry, 41, 682-689.

Halperin, J. M., Sharma, V., Siever, L. J., Schwartz, S. T., Matier, K., Wornell, G., & Newcorn, J. H. (1994). Serotonergic function in aggressive and nonaggressive boys with attention deficit hyperactivity disorder. American Journal of Psychiatry, 151, 243-248.

Handelsman, L., Holloway, K., Kahn, R. S., Sturiano, C., Rinaldi, P. J., Bernstein, D. P., Siever, L., Gabriel, S., & Cooper, T. B. (1996). Alcoholism: Clinical and Experimental Research, 20, 824-829.

Handelsman, L., Kahn, R. S., Sturiano, C., Rinaldi, P. J., Schmeidler, J. P., Bernstein, D. P., Siever, L., & Cooper, T. B. (1998). Hostility is associated with a heightened prolactin response to metachlorophenylpiperazine in abstinent cocaine addicts. Psychiatry Research, 80, 1-12.

Heinz, A., Higley, J. D., Gorey, J. G., Saunders, R. C., Jones, D. W., Homer, D., Zajicek, K., Suomi, S. J., Lesch, K., Weinberger, D. R., & Linnoila, M. (1998). In vivo association between alcohol intoxication, aggression and serotonin transporter availability in nonhuman primates. American Journal of Psychiatry, 155, 1023-1028.

Higley, J. D., King, Jr., S. T., Hasert, M. F., Champoux, M., Suomi, S. J., & Linnoila, M. (1996b). Stability of interindividual differences in serotonin function and its relationship to severe aggression and competent social behavior in rhesus macaque females. Neuropsychopharmacology, 14, 67-76.

Higley, J. D., & Linnoila, M. (1997). Low central nervous system serotonergiv activity is tritlike and correlates with impulsive behavior. A nonhuman primate model investigating genetic and environemental influences on nerurotransmission. Annals of New York Academy of Science, 836, 39-56.

Higley, J. D., Mehlman, P. T., Poland, R. E., Taub, D. M., Vickers, J., Suomi, S. J., & Linnoila, M. (1996a). CSF testosterone and 5-HIAA correlate with different types of aggressive behaviors. Biological Psychiatry, 40, 1067-1082.

Higley, J. D., Mehlman, P. T., Taub, D. M., Higley S. B., Suomi, S. J., Linnoila, M., & Vickers, J. H. (1992). Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. Archives of General Psychiatry, 49, 436-441.

Higley, J. D., Suomi, S. J., & Linnoila, M. (1991). CSF monoamine metabolite concentrations vary according to age, rearing, and sex, and are influenced by the stressor of social separation in rhesus monkeys. Psychopharmacology, 103, 551-556.

Hollingshead, A. B. (1975). Four factor index of social status. Unpublished manuscript, Department of Sociology, Yale University, New Haven, CT.

Huang, Y. Y., Grailhe, R., Arango, V., Hen, R., & Mann, J. J. (1999). Relationship of psychopathology to the human serotonin1B genotype and receptor binding kinetics in postmortem brain tissue. Neuropsychopharmacology, 21, 238-246.

Jastak, S., & Wilkinson, G. (1984). Wide Range Achievement Test – revised. Wilmington, DE: Jastak Associates, Inc.

Kashani, J. H., Beck, N. C., Hoeper, E. W., Fallahi, C. (1987). Psychiatric disorders in a community sample of adolescents. American Journal of Psychiatry, 144, 584-589.

Kavoussi, R. J., Liu, J., & Coccaro, E. F. (1994). An open trial of sertraline in personality disordered patients with impulsive aggression. Journal of Clinical Psychiatry, 55, 137-141.

Kellam, S. G., Ling, X., Merisca, R., Brown, C. H., & Ialongo, N. (1998) The effect of the level of aggression in the first grade classroom on the course and malleability of aggressive behavior into middle school. Developmental Psychopathology, 10, 165-185.

Kelso, J., & Stewart, M. A. (1986). Factors which predict the persistence of aggressive conduct disorder. Journal of Child Psychology and Psychiatry, 27, 77-86.

Kerr, M., Tremblay, R. E., Pagani, L., & Vitaro, F. (1997). Boys' behavioral inhibition and the risk of later delinquency. Archives of General Psychiatry, 54, 809-816.

Koda, V. H., Halperin, J. M., Newcorn, J. H., Schwartz, S. T., & McKay, K. E. (1996). Gender differences in the prolactin response to fenfluramine challenge in

children with disruptive behavior disorders. Annals of the New York Academy of Science, 794, 369-371.

Kolvin, I., Miller, F. J. W., Fleeting, M., & Kolvin, P. A. (1988). Social and parenting factors affecting criminal-offence rates: Findings from the Newcastle thousand family study. British Journal of Psychiatry, 152, 80-90.

Kraemer, G., & Clarke, A. S. (1996). Social attachment, brain function, and aggression. Annals of the New York Academy of Science, 794, 121-135.

Kraemer, G., Ebert, M. H., Schmidt, D. E., & McKinney, W. T. (1989). A longitudinal study of the effect of different social rearing conditions on cerebrospinal fluid norepinephrine and biogenic amine metabolites in rhesus monkeys. Neuropsychopharmacology, 2, 175-189.

Krebs, H. A., Cheng, L. K., & Wright G. J. (1984). Determination of fenfluramine and norfenfluramine in plasma using a nitrogen sensitive detector. Journal of Chromatography, 310, 412-417.

Kruesi, M. J. P., Hibbs, E. D., Zahn, T. P., Keysor, C. S., Hamburger, S. D., Bartko, J. J., & Rapoport, J. L. (1992). A 2-year prospective follow-up study of children and adolescents with disruptive behavior disorders. Archives of General Psychiatry, 49, 429-435.

Kruesi, M. J. P., Rapoport, J. L., Hamburger, S., Hibbs, E., Potter, W. Z., Lenane, M., & Brown, G. (1990). Cerebrospinal fluid monoamine metabolites, aggression and impulsivity in disruptive behavior disorders of children and adolescents. Archives of General Psychiatry, 47, 419-426.

Kupersmidt, J. B., & Coie, J. D. (1990). Preadolescent peer status, aggression, and school adjusment as predictors of externalizing problems in adolescence. Child Development, 61, 1350-1362.

Lidberg, L., Tuck, J. R., Asberg, M., Scalia-Tomba, G. P., & Bertilsson, L. (1985). Homicide, suicide, and CSF 5-HIAA. Acta Psychiatry of Scandinavia, 71, 230-236.

Linnoila, M., DeJong, J., & Virkkunen, M. (1989). Family history of alcoholism in violent offenders and impulsive fire setters. Archives of General Psychiatry, 46, 613-616.

Linnoila, M., Virkkunen, M., Scheinin, M., Nuutila, A., Rimon, R., & Goodwin, F. K. (1983). Low cerebrospinal fluid 4-hydroxyindoleacetic acid concentrations differentiates impulsive from nonimpulsive. Life Science, 33, 2609-2614.

Lipsey, M. W. & Derzon, J. H. (1998). Predictors of violent or serious delinquency in adolescence and early adulthood: A synthesis of longitudinal research. In R. Loeber & D. P. Farrington (Eds.), Serious and violent juvenile offenders: Risk factors and successful interventions (pp. 86-105). Thousand Oaks, CA: Sage Publications Inc.

Livingston, R. L., Dykman, R. A., & Ackerman, P. T. (1990). The frequency and significance of additional self-reported psychiatric diagnoses in children with attention deficit disorder. Journal of Abnormal Child Psychology, 18, 465-478.

Loeber, R. (1982). The stability of antisocial and delinquent child behavior: A review. Child Development, 53, 1431-1446.

Loeber, R. & Farrington, D. P. (2000). Young children who commit crime: Epidemiology, developmental origins, risk factors, early interventions, and policy implications. Developmental Psychopathology, 12, 737-762.

Loeber, R., Green, S. M., Keenan, K., & Lahey, B. B. (1995). Which boys will fare worse? Early predictors of the onset of conduct disorder in a six-year longitudinal study. Journal of American Academy of Child and Adolescent Psychiatry, 34, 499-509.

Loeber, R., & Hay, D. (1997). Key issues in the development of aggression and violence from childhood to early adulthood. Annual Review of Psychology, 48, 371-410.

Loeber, R., Wung, P., Keenan, K., Giroux, B., Stouthamer-Loeber, M., Van Kammen, W. B., & Muughan, B. (1993). Developmental pathways in disruptive child behavior. Development and Psychopathology, 5, 103-133.

Loney, J., Kramer, J., & Milich, R. (1981). The hyperkinetic child grows up: Predictors of symptoms, delinquency and achievement at follow-up. In Gadow, K. D., & Loney, J. (Eds.), Psychosocial aspects of drug treatment for hyperactivity (pp. 381-416). Boulder Co.: Westview Press.

Loney, J., & Milich, R. (1982). Hyperactivity, inattention and aggression in clinical practice. Advances in Developmental Behavioral Pediatrics, 3, 113-147.

MacDonald, V. M. & Achenbach, T. M. (1996). Attention problems versus conduct problems as six-year predictors of problem scores in a national sample. Journal of American Academy of Child and Adolescent Psychiatry, 35, 1237-1246.

Manuck, S. B., Flory, J. D., Ferrell, R. E., Denk, K.M., Mann, J. J., & Muldoon , M. F. (1999). Aggression and anger-related traits associated with a polymorphism of the tryptophan hydroxylase gene. Biological Psychiatry, 45, 603-614.

Manuck, S. B., Flory, J. D., McCaffery, J. M., Matthews, K. A., Mann, J. J., & Muldoon, M. F. (1998). Aggression, impulsivity, and central nervous system serotonergic responsivity in a nonpatient sample. Neuropsychopharmacology, 19, 287-299.

Marks, D. J., Newcorn, J. H., McKay, K. E., Koda, V. H., Himelstein, J., Schulz, K. P., Bonafina, M. A., & Halperin, J. M. (1999). Childhood aggression: The interaction between biological risk and psychosocial adversity. Scientific Proceedings of the Annual Meeting of the American Academy of Child and Adolescent Psychiatry, 15, 119.

Mcbride, P. A., Tierney, H., DeMeo, M., Chen, J. S., & Mann, J. J. (1990). Effects of age and gender on CNS serotonergic responsivity in normal adults. Biological Psychiatry, 27, 1143-1155.

McKay, K. E., Halperin, J. M., Grayson, R., Hall S., Peracchio, N. & Newcorn, J. H. (1993). The children's aggression scale: Parent and teacher versions. Scientific Proceedings of the Annual Meeting of the American Academy of Child and Adolescent Psychiatry, 9, 49.

McKay, K. E., Newcorn, J. H., Schultz, K., Kopstein, I., Schwartz, S. T., & Halperin, J. M. (1995). Serotonin, aggression, and family psychopathology in ADHD boys. Scientific Proceedings of the Annual Meeting of the Amreican Academy of Child and Adolescent Psychiatry, 11, 111.

Miles, D. R. & Carey, G. (1997). Genetic and environmental architecture of human aggression. Journal of Personality and Social Psychology, 72, 207-217.

Moeller, F. G., Allen, T., Cherek, D. R., Dougherty, D. M., Lane, S., & Swann, A. C. (1998). Ipsapirone neuroendocrine challenge: Relationship to aggression as measured in the human laboratory. Psychiatry Research, 81, 31-38.

Moeller, F. G., Dougherty, D. M., Swann, A. C., Collins, D., Davis, C. M., & Cherek, D. R. (1996). Tryptophan depletion and aggressive responding in healthy males. Psychopharmacology, 126, 97-103.

Moss, H. B., Yao, J. K., & Panzak, G. L. (1990). Serotonergic responsivity and behavioral dimensions in antisocial personality disorder with substance abuse. Biological Psychiatry, 28, 325-328.

New, A. S., Gelernter, J., Yovell, Y., Trestman, R. L., Nielsen, D. A., Silverman, J., Mitropoulou, V., & Siever, L. J. (1998). Tryptophan hydroxylase genotype is associated with impulsive-aggression measures: A preliminary study. American Jounal of Medical Genetics, 81, 13-17.

New, A. S., Trestman, R. L., Mitropoulou, V., Benishay, D. S., Coccaro, E., Silverman, J., & Siever, L. J. (1997). Serotonergic function and self-injurious behavior in personality disorder patients. Psychiatry Research, 69, 17-26.

Nielsen, D. A., Goldman, D., Virkkunen, M., Tokola, R., Rawlings, M.S., & Linnoila, M. (1994). Suicidality and 5-hydroxyindolacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Archives of General Psychiatry, 51, 34-38.

O'Keane, V., Moloney, E., O'Neill, H., O'Connor, A., Smith, C., & Dinan, T. G. (1992). Blunted prolactin responses to d-fenfluramine in sociopathy. British Journal of Psychiatry, 160, 643-646.

Olivier, B., & Mos, J. (1992). Rodent models of aggressive behavior and serotonergic drugs. Progess in Neuro-Psychopharmacology and Biological Psychiatry, 16, 847-870.

Olivier, B., Mos, J., van Oorschot, R., & Hen, R. (1995). Serotonin receptors and animal models of aggressive behavior. Pharmacopsychiatry, 28, 80-90.

Olweus, D. (1979). Stability of aggressive reaction patterns in males: A review. Psychology Bulletin, 86, 852-857.

Pagani, L., Boulerice, B., Vitaro, F., & Tremblay, R. E. (1999). Effects of poverty on academic failure and delinquency in boys: A change and process model approach. Journal of Child Psychology and Psychiatry, 40, 1209-1219.

Pesonen, U., Koulu, M., Bergen, A., Eggert, M., Naukkarien, H., Virkkunen, M., Linnoila, M., & Goldman, D. (1998). Mutation screening of the 5-hydroxytryptamine7 receptor gene among Finnish alcoholics and controls. Psychiatry Research, 77, 139-145.

Pick, L. H., Halperin, J. M., Schwartz, S. T., & Newcorn, J. H. (1999). A longitudinal study of neurobiological mechanisms in boys with attention-deficit hyperactivity disorder: Preliminary findings. Biological Psychiatry, 45, 371-373.

Pihl, R. O., Young, S. N., Harden, P., Plotnick, S., Chamberlain, B., & Ervin, F. R. (1995). Acute effect of altered tryptophan levels and alcohol on aggression in human males. Psychopharmacology, 119, 353-360.

Pine, D. S., Coplan, J. D., Wasserman, G. A., Miller, L. S., Fried, J. E., Davies, M., Cooper, T. B., Greenhill, L., Shaffer, D., & Parsons, B. (1997). Neuroendocrine with aggressive behavior and adverse rearing. Archives of General Psychiatry, 54, 839-846.

Pliszka, S. R., Rogeness, G. A., Renner, P., Sherman, J., & Broussard, T. (1988). Plasma neurochemistry in juvenile offenders. Journal of American Academy of Child and Adolescent Psychiatry, 27, 588-594.

Psychological Corporation. (1974). The Wechsler Intelligence Scale for Children – revised. New York: author.

Psychological Corporation. (1991). The Wechsler Intelligence Scale for Children- third edition. New York: author.

Psychological Corporation (1992). The Wechsler Individual Achievement Test. New York: author.

Pulkkinen, L. (1987). Offensive and defensive aggression in humans: A longitudinal perspective. Aggressive Behavior, 13, 197-212.

Rhee, S. H. & Waldman, I. D. (2002). Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. Psychology Bulletin, 128, 490-529.

Roeling, T. A. P., Veening, J. G., Kruk, M. R., Peters, J. P. W., Vermelis, M. E. J., & Nieuwenhuys, R. (1994). Efferent connections of the hypothalamic "aggression area" in the rat. Neuroscience, 59, 1001-1024.

Rowland, N. E., & Carlton, J. (1986). Neurobiology of an anorectic drug: fenfluramine. Progress and Neurobiology, 27, 13-62.

Rutter, M., Cox, A., Tupling, C., Berger, M., & Yule, W. (1975). Attainment and adjustment in two geographical areas, 1: The prevalence of psychiatric disorders. British Journal of Psychiatry, 126, 493-509.

Satterfield, J. H. & Schell, A. (1997). A prospective study of hyperactive boys with conduct problems and normal boys: Adolescent and adult criminality. Journal of American Academy of Child and Adolescent Psychiatry, 36, 1726-1735.

Schulz, K. P., Newcorn, J. H., McKay, K. E., Himelstein, J. Koda, V. H., Siever, L. J., Sharma, V., & Halperin, J. M. (2001) Relationship between central serotonergic function and aggression in prepubertal boys: Effect of age and attention-deficity/hyperactivity disorder. Psychiatry Research, 14, 1-10.

Shaffer, D. (1997) The NIMH Diagnostic Interview Schedule for Children, Version 4 (DISC-4).

Shaffer, D., Fisher, P., Piacentini, J., Schwab-Stone, M., & Wicks, J. (1989). Diagnostic Interview Schedule for Children (DISC-2.1P) – Parent version. New York: New York State Psychiatric Institute.

Shaikh, M. B., De Lanerolle, N.C., & Siegel, A. (1997). Serotonin 5-HT_{1A} and 5-$HT_{2/1C}$ receptors in the midbrain periaqueductal gray differentially modulate defensive rage behavior elicited from the medial hypothalamus of the cat. Brain Research, 765, 198-207.

Siegel, A., Roeling, T. A., Gregg, T. R., & Kruk, M. R. (1999). Neuropharmacology of brain-stimulation-evoked aggression. Neuroscience Biobehavioral Review, 23, 359-389.

Siever, L. J., Buchsbaum, M. S., New, A. S., Spiegel-Cohen, J., Wei, T., Hazlett, E. A., Sevin, E., Nunn, M., & Mitropoulou, V. (1999). d,l-Fenfluramine response in impulsive personality disorder assessed with [18F] fluorodeoxyglucose positron emission tomography. Neuropsychopharmacology, 20, 413-423.

Soloff, P. H., Meltzer, C. C., Greer, P. J., Constantine, D., & Kelly, T. M. (2000). A fenfluramine-activated FDG-PET study of borderline personality disorder. Biological Psychiatry, 47, 540-547.

Soubrie, P. (1986). Reconciling the role of central serotonin neurons in human and animal behavior. Behavioral Brain Science, 9, 319-364.

Spencer, T., Biederman, J., & Wilens, T. (1999). Attention-deficit/hyperactivity disorder and comorbidity. Pediatric Clinics of North America, 46, 915-927.

Stahl, S. M. (1985). Platelets as pharmacologic models for the receptors and biochemistry of monoaminergic neurons. In Longenecker, G. L.(Ed.), The platelets: physiology and pharmacology (pp. 307-339). New York: Academic Press.

Stanley, B., Molcho, A., Stanley, M., Winchel, R., Gameroff, M. J., Parsons, B., & Mann, J. J. (2000). Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. American Journal of Psychiatry, 157, 609-614.

Stoff, D. M., Pasatiempo, A. P., Yeung, J., Cooper, T. B., Bridger, W. H. & Rabinovich, H. (1992). Neuroendocrine responses to challenge with dl-fenfluramine and aggression in disruptive behavior disorders of children and adolescents. Psychiatry Research, 43, 263-276.

Stoff, D. M., Pollock, L., Vitiello, B., Behar, D., & Bridger, W. H. (1987). Reduction of (^{3}H)-imipramine binding sites on platelets of conduct-disoriented children. Neuropsychopharmacology, 1, 55-62.

Summers, C. H., & Greenberg, N. (1995). Activation of central biogenic amines following aggressive interaction in male lizards, Anolis carolinensis. Brain Behvioral Evolution, 45, 339-349.

Szatmari, P., Offord, D. R., & Boyle, M. H. (1989). Ontario child healthy study: Prevalence of attention deficit disorder with hyperactivity. Journal of Child Psychology and Psychiatry and Allied Disciplines, 30, 219-230.

Taylor, M. B., Chadwick, O., Heptinstall, E., & Danckaerts, M. (1996). Hyperactivity and conduct problems as risk factors for adolescent development. Journal of American Academy of Child and Adolescent Psychiatry, 35, 1213-1226.

Unis, A. S., Cook, E. H., Vincent, J. G., Gjerde, D. K., Perry, B. D., Mason, C., & Mitchell, J. (1997). Platelet serotonin measures in adolescents with conduct disorder. Biological Psychiatry, 42, 553-559.

Virkkunen, M., Eggert, M., Rawlings, R., & Linnoila, M. (1996). A prospective follow-up study of alcoholic violent offenders and fire setters. Archives of General Psychiatry, 53, 523-529.

Vitaro, F., Gendreau, P. L., Tremblay, R. E., & Oligny, P. (1998). Reactive and proactive aggression differentially predict later conduct problems. Journal of Child Psychology and Psychiatry, 39, 377-385.

Wallander, J. L. (1988). The relationship between attention problems in childhood and antisocial behavior eight years later. Journal of Child Psychology and Psychiatry, 29, 53-61.

Wechsler, D. (1991). Manual of the Wechsler Intelligence Scale for Children – III San Antonio, TX: Psychological Corporation.

Westergaard, G. C., Suomi, S. J., Higley, J. D., & Mehlman, P. T. (1999). CSF 5-HIAA and aggression in female macaque monkeys: Species and interindividual differences. Psychopharmacology, 146, 440-446.

Wetzler, S., Kahn, R. S., Asnis, G. M., Korn, M., & van Praag, H. M. (1991). Serotonin receptor sensitivity and aggression. Psychiatry Research, 37, 271-279.

White, J. L., Moffitt, T.E., Caspi, A., Bartusch, D. J., Needles, D. J., & Loeber, M. S. (1994). Measuring impulsivity and examining its relationship to delinquency. Journal of Abnormal Psychology, 103, 192-205.

Yeh, S., Fricke, R. A., & Edwards, D. H. (1996). The effect of social experience on serotonergic modulation of the escape circuit of crayfish. Science, 271, 366-369.