Gender Differences in the Neuropsychology

of Childhood Aggression

by

Vivian Huhn Koda

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

1999

UMI Number: 9917667

UMI
300 North Zeeb Road
Ann Arbor, MI 48103

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.

1/26/99
Date

Jeffrey M. Halperin, Ph.D.
Chair of Examining Committee

1/27/99
Date

Joseph Glick, Ph.D.
Executive Officer, Psychology

Richard J. Bodnar, Ph.D.
Gail A. Wasserman, Ph.D.
Supervisory Committee

The City University of New York

Abstract

Gender Differences in the Neuropsychology

of Childhood Aggression

by

Vivian Huhn Koda

Adviser: Jeffrey M. Halperin

The goal of this dissertation was to examine gender differences in cognitive, neuropsychological, behavioral and biological correlates of aggressive behavior in prepubertal children. Girls and boys between seven and ten years of age, exhibiting aggressive or disruptive behaviors, participated in this research. An aggression rating was determined based upon parent ratings of aggression on the Child Behavior Checklist (CBCL/4-18) (Achenbach, 1991). Children were designated as aggressive if CBCL Aggression scores were ≥ 70; scores ≤ 69 resulted in nonaggressive group placement. Two groups of girls (12 aggressive and 12 nonaggressive) and two equal-sized groups of boys were matched for age and the CBCL Aggression scale score.

Cognitive assessment revealed that aggressive girls had significantly higher Verbal IQ (VIQ) scores than aggressive boys. Relative to their non-aggressive counterparts, aggressive girls had higher VIQ scores, but aggressive boys had lower VIQ scores. Aggressive girls academically outperformed all other groups of children. A Continuous Performance Test revealed significantly lower impulsivity among girls compared to boys. Thus, normal intelligence, academic competence and stronger behavioral control differentiated aggressive girls from impulsive, cognitively impaired aggressive boys.

History of psychopathology in first and second degree relatives showed a greater prevalence of Internalizing difficulties in families of boys than girls. Although just short of significance, a greater incidence of antisocial behavior was found in fathers of aggressive boys compared to fathers of aggressive girls.

Demographic data revealed a greater prevalence of family adversity among aggressive boys as compared to all other groups. Aggressive boys were most often reared in single parent homes, with more children per household, and had parents with the lowest levels of education. In contrast, aggressive girls were most often from dual-parent homes, with fewer children per household, and had parents with the highest education levels.

There were no differences on neurobiological measures as a function of aggression or gender.

The findings of this research are consistent with an extensive literature indicating that aggressive boys are characterized by physical aggression, cognitive difficulties, and a wide array of psychosocial liabilities. However, this pattern does not hold up in the clinically referred aggressive girls in this study.

Acknowledgments

This research was funded by a grant from the Marie Keese LeLash Foundation, Inc., through the Research Foundation of the City University of New York, for which I am most grateful. I want to thank Dr. Jeffrey Halperin, for countless hours of hard work, guidance and counsel, for patience above and beyond the call, and, most especially, for the opportunity to learn from him. Without Dr. Halperin, this dissertation would not have been possible. So, too, I wish to thank Dr. Richard Bodnar, and Dr. Gail Wasserman, for graciously giving of their expertise and time, and for helping me to sharpen my research focus. Thanks, also, to Dr. Jeffrey Newcorn, and Dr. Hilary Gomes, for their insightful critiques and gratefully received reassurances. I also want to thank my colleagues, without whom the journey would have been far more difficult, much less interesting, and quite void of comic relief. Of course, I give heartfelt thanks to my family for putting up with and sustaining me throughout this process; my lovely sister, Patricia, for always knowing what to say, and when to say it; my daughter, Jennifer, for her inspiring courage; and, my son, Daniel, for his humor and unyielding belief. Most of all, I thank my husband, Richard, whose encouragement and support never, never wavered.

This work is dedicated to the memory of my parents.

Table of Contents

List of Tables

List of Figures

Introduction

An extensive literature indicates that aggressive children are differentiated from nonaggressive children by several factors including the presence of cognitive deficits and psychosocial adversity, high incidence of psychopathology in family members, and possible deficits in central serotonergic function. However, this literature is based nearly exclusively on research conducted with male samples, while the phenomenology and correlates of aggression in females have not been systematically studied. Although some substrates of aggression may be similar across genders, differences in the manifestation of aggression suggest contradistinctions in underlying mechanisms. This study assessed cognitive, family, psychosocial and neurobiological distinctions in clinic referred prepubertal girls and boys as a function of the presence or absence of aggressive behavior. It was hypothesized that:

1. As compared to aggressive boys, aggressive girls would be significantly less impulsive, as measured by neuropsychological testing, and have fewer, if any, verbal deficits;
2. As compared to non-aggressive children, as well as aggressive boys, aggressive girls would have an increased incidence of aggressive/antisocial behavior in their first and second degree relatives;
3. Adverse home/family environmental factors will be more frequent among aggressive boys as compared to aggressive girls and nonaggressive girls and boys;
4. Aggressive girls would have a greater FEN-induced PRL response than aggressive boys, reflecting gender-related differences in serotonergic responsivity.

Phenomenon of Aggression in Young Females

Aggression in females, that is, the commission of an act with the intent to inflict harm on another person, is not typically physical in manifestation as it is in males. Rather, females more frequently enlist indirect means to accomplish a harmful outcome. The subversive and covert behaviors presumed to be more stereotypically female are not readily accessible to observational investigation and, therefore, by their nature, are likely to be under-represented in identified samples. Furthermore, in view of the differences in female and male aggression, it is possible that this maladaptive behavior pattern is associated with distinct psychiatric disorders in the two genders, and with different underlying mechanisms and outcome. To properly assess gender differences in aggression, it is incumbent upon researchers to more thoroughly investigate and describe female aggression.

The differences between male and female aggressive behaviors have been broadly dichotomized into *direct* versus *indirect* modes of aggression ever since these categories were initially proposed by Buss (1961). Direct aggression is typically confrontational in nature and often involves physical contact. In contrast, indirect aggression has been described as social manipulation in which the aggressor manipulates others and is thus able to avoid retaliation. Indirect aggression often involves using manipulations such as gossip, becoming friends with another as revenge, or telling the other one's secrets to a third person. Whereas direct aggression is commonly seen in boys, indirect aggression is far more typical of girls (Lagerspetz, Björkqvist, & Peltonen, 1988; Björkqvist, Lagerspetz, & Kaukiainen, 1992; Lagerspetz & Björkqvist, 1992). These studies demonstrated that indirect aggression in girls emerges in adolescence and remains the predominant mode of aggression throughout the late teenage years. As stated by Hood (1996), girl's aggression derives from hurtful intentions to damage the target psychologically and socially in that most important social setting of adolescence, the peer group. Using different terminology, other studies have characterized girls' aggression as predominantly *covert* (Cairns, Perrin & Cairns, 1985; Loeber & Schmaling, 1985), or *instrumental* (i.e., aggression that is intended to gain a reward or advantage for the aggressor) as opposed to *overt* or *hostile* (i.e., inflicting pain or injury without an apparent benefit or advantage for the aggressor) (Feshbach, 1970; Hartup, 1974). Overt, direct physical aggression is not considered to be typical of female aggressive behavior.

One form of indirect aggression, *relational* aggression, has been hypothesized to be typical of girls (Crick and Grotpeter, 1995). According to Crick and Grotpeter (1995), girls are more likely to harm peers through purposeful manipulation and damage of their peer relationships, whereas boys are more likely to harm peers through *overt* aggression, that is, harming others through physical aggression, verbal threats, or intimidation. They found that girls were significantly more relationally aggressive than were boys, and suggested that the higher use of relational aggression among girls is to hinder the generation or maintenance of close, intimate connections with others, goals that are particularly important to girls. They also suggested that the degree of aggressiveness exhibited by girls has been underestimated because the forms of aggression relevant to girls' peer groups have not been assessed.

The reported lower prevalence and severity of female aggression has often been attributed to early differential socialization (Bandura, 1965; Eagley & Steffen, 1986; Perry & Bussey, 1979). Presumably, girls learn not to display physical aggression because it is considered to be an unacceptable behavior, while boys learn that male aggressiveness is appropriate and, in many circumstances, expected. A study of normative beliefs about aggression in school-age children revealed that boys' approval of aggression was significantly higher than girls, but that children's aggression approval scores did not consistently relate to their actual aggressive behavior as measured by self-report, teacher ratings and peer nominations (Huesmann, Guerra, Miller, & Zelli, 1991). It was thought that the lack of relationship between girls' aggression approval scores and aggressive behavior may have been due to a floor effect, with low scores on both measures. Huesmann and colleagues (1991) suggested that while gender differences in normative beliefs about aggression emerge at an early age, they are of limited value in explaining early gender differences in aggressive behavior. Crick and Dodge (1994) proposed that the less common overtly aggressive girls and relationally aggressive boys may be more at risk for social-psychological maladjustment than relationally aggressive girls and overtly aggressive boys because of the non-normative nature of their behavior. Children who engaged in these atypical forms of aggression were shown to be significantly more maladjusted than children who engaged in gender normative forms of aggression and children who were nonaggressive (Crick, 1997).

The presence of aggressive behavior has frequently been associated with the Disruptive Behavior Disorders (DBDs) of childhood, and particularly with Oppositional-Defiant Disorder (ODD) and Conduct Disorder (CD). (A list of terms used throughout this study is presented in Appendix A). Several studies have examined the representation of girls in the DBDs. Prevalence rates, as reported in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994), indicate that ODD occurs in 2% - 16% of school- age children. According to DSM-IV, ODD is more prevalent in males than in females before puberty, but rates are similar after puberty. A somewhat different picture is presented by an epidemiological study in which ODD is reported to have virtually the same prevalence and age pattern in girls and boys (Cohen et al. 1993). This investigation found low levels of ODD among 10- and 11-year-olds, rising to high levels among 13-16-year-olds and a sharp fall off in prevalence thereafter (Cohen, et al., 1993).

Gender differences also characterize CD, with male and female prevalence rates ranging from 6% - 16% and 2% - 9%, respectively (APA, 1994). Epidemiological studies have found differences in prevalence rates of CD, with some reporting much higher rates of CD in boys than girls (Anderson, Williams, McGee & Silva, 1987; Offord, et al., 1987), and others finding roughly equivalent rates (Kashani et al., 1987; Leslie, S., 1974). Cohen et al. (1993) suggest that reporting age-specific prevalence rates partially reconciles these differences. They report overall CD to be twice as prevalent in boys than in girls, but boy's prevalence was highest in the youngest group (10 - 13), declining over ages 10 - 20, in contrast to girls who showed an increase in prevalence to a peak age of 16, followed by a sharp decline.

Further complexity in the identification and characterization of aggression in girls occurs as a result of differences between clinic and nonreferred populations. Clinic populations have been shown to be more impaired, more likely to have comorbid disorders, and less likely to include prepubertal girls (Goodman, Lahey, Fielding, Dulcan, Narrow, & Regier, 1997). Further, gender differences reported in clinic settings may reflect a moderating effect of the referral source. A recent study of gender differences in children and adults with ADHD reported that there was a trend for girls with relatively more severe ratings of hyperactivity, conduct disorder, or inattention to be referred earlier than were boys (Arcia & Conners, 1998). It may be that referral bias results in over-representation of more atypically aggressive girls in clinic samples.

Thus, important questions remain as to whether clinic-referred aggressive girls are as impaired as their male counterparts; in what measures are they similar, and in what ways are they significantly different. Significant differences in measures would suggest gender-differentiated diagnosis and treatment, whereas close similarity would argue for a single diagnosis and treatment process which would be appropriate for both sexes.

Stability of Aggression

An initial consideration in the assessment of gender differences in children's aggression is at what stage of development such differences become manifest. Secondly, are these gender-differentiated behaviors characterized by stability or change? During the decade between 1970 and 1980, a burgeoning interest in aggressive behavior engendered numerous studies, and sparked a debate on the etiology of aggression, arguing either biological determination or socialization effects.

Early studies (Barrett, 1979; Terman & Tyler, 1954; Whiting & Edwards, 1973) and reviews (Hyde, 1984; Maccoby & Jacklin, 1974) of gender differences in aggression generally concluded that in children, as in adolescents and adults, males are more aggressive than females. Maccoby and Jacklin (1974), found that aggressive behaviors were sex differentiated early in development, before age 6, and probably as early as age 2. Since these sex differences were found before socialization pressures differentially influenced the expression of aggression between the sexes, they concluded that the prevalence of male over female aggression manifested a biological predisposition for male aggressive behavior. Tieger (1980), disputed the hypothesis of biological causation of aggression, stating that gender differences were consistently observable only after the age of 5, and that in pre-schoolers, gender differences were smaller and nonsignificant. He suggested that gender differences became greater after the age of 5, as a result of cumulative socialization experiences.

Hyde's (1984) meta-analysis examined gender differences in aggression, with the purpose of estimating the magnitude of gender differences in aggression, that is, the amount of variation in the population accounted for by female-male differences. Hyde found a modest negative association between age of subjects and the magnitude of gender differences. In contrast to Tieger's (1980) findings, gender differences were larger among preschoolers than among older subjects. Hyde cautioned, however, that such age-related findings were often confounded by the kind of aggression measured. For example, while preschoolers are typically measured on physical aggression, studies in college-age subjects often measure different constructs of aggression, such as the willingness to shock another individual.

Later studies of aggressive behavior in toddlers did not find gender differences until age 4 or 5 (Achenbach, Edelbrock, & Howell, 1987; Rose, Rose & Feldman, 1989), nor were gender differences found in toddlers in object-related aggression (Zahn-Waxler, Ianotti, Cummings & Denham, 1990). Similarly, a prevalence study of problem behaviors in 2 to 3-year-old Dutch children revealed no significant differences due to gender or age (Koot & Verhulst, 1991).

It is well established that the development of abnormally aggressive behavior in young boys portends aggressive, delinquent and antisocial behavior which is persistent (Olweus, 1979; Loeber, 1982; Magnusson & Bergman, 1988). However, the few longitudinal investigations which have assessed gender differences have produced inconsistent findings, leaving open the question of stability in young females. A longitudinal study of children from 8 - 19 years of age, showed moderately greater stability in girls than boys (Eron, Huesmann, Lefkowitz, & Walder, 1972), while others have found less stability in girls (Olweus, 1981; Huesmann, Eron, Lefkowitz, & Walder, 1984) or, stability in boys only (Roff & Wirt, 1984). Gender differences in the stability of aggression among young children will be considered in the following section.

Toddlers. Problem behaviors of 1 ½- to 2-year old girls and boys interacting in play groups were observed and coded, as were the reactions of their peers and care givers (Fagot, 1984). Aggressive behavior (hitting, taking objects, verbal assaults) in boys showed high stability over a one-year period ($r = .78$, $p < .001$), while girl's aggression was far less stable ($r = .23$, $p < .05$). The two-year assessment showed boy's continued stability, while girls' scores were no longer significant. The pattern of reactions that children received from peers and care givers was consistent with the stability of the problem behaviors: Boy's aggression received a response 81% of the time, while girls received responses to their aggressive acts only 24% of the time. Thus, behaviors that received attention were maintained (boy's aggression), while those which were ignored (girl's aggression) tended to drop out. Another assessment of toddlers in a daycare setting (Crother, Bond & Rolf, 1981) revealed a greater frequency of externalizing behavior in boys than girls, and a different developmental pattern. Boys' initiation of fights increased from age 2 to 4, and then decreased at age 5; in girls, initiating fights steadily decreased in frequency from age 2 through 5.

Keenan and Shaw (1994) found stability of aggression in children 18 to 24 months of age, assessed during play segments of varying levels of stress, from *none* (free-play), to *mild* (cleaning up toys), to *high* (taking toys away or being left with another caretaker). Global ratings for girls were moderately stable, and for boys were significant. Moderate short-term stability was found, particularly for unprovoked aggression occurring in low or mildly stressful situations. Aggression during high-stress situations (provoked) at 18 months was not significantly correlated with later aggression. Thus, correlations from 18 to 24 months of age were very strong for the toddlers who demonstrated pervasive aggression at 18 months. Another perspective may be that "provoked" aggression, in this study, represents a developmentally normal frustration response for an under-2-year-old child, whereas "unprovoked" represents a more trait-like, irritable/aggressive style of responding.

Children & Adolescents. Several longitudinal studies have recruited children of grade school age who were then evaluated at 3-to-4-year intervals, spanning pre- and post-pubertal development. A Finnish study (Pitkänen-Pulkkinen, 1981; Pulkkinen, 1987), found that peer nominated aggressiveness, first measured at age 8 and re-examined at 14 years of age, was as stable for girls as for boys ($r = 0.37$ for both sexes). Self-ratings of aggression at the age of 26, were correlated with the early peer-nominated aggression ratings at age 8, with the correlation of stability being higher for females than males.

Teacher and self-rated aggression in a group of children examined in the 4th grade and re-assessed a year later in 5th grade, found short-term stability of aggression to be the same for highly aggressive girls and boys (Cairns & Cairns, 1984). However, a later examination of this cohort showed that while the stability of girl's aggressiveness from the 4th to the 8th grade was as high as the boy's, in the 9th grade girl's aggressiveness was correlated less highly with early aggressiveness than the boy's.

School age children (grades 1,4, and 7) were recruited for assessment of aggressive and antisocial behaviors and social withdrawal through the Concordia Longitudinal Risk Project (Schwartzman, Ledingham, & Serbin, 1985). Separate equal-sized samples of girls and boys were assessed every three years (Serbin, Schwartzman, Moskowitz, & Ledingham, 1991). Early patterns of aggression were found to be stable at the third-year follow up (Moskowitz, Schwartzman & Ledingham, 1985), and 6 years after initial identification, at which time gender differences were emerging (Moskowitz & Schwartzman, 1989). While the adolescent aggressive group had the most psychiatric and nonpsychiatric medical problems overall, the aggressive females were receiving more medical treatment than the other groups of adolescent girls and more than the adolescent aggressive males. Data gathered in the oldest cohort, in their late teens to middle twenties, revealed striking sex differences in criminal behavior (Moskowitz, Crawley, & Schwartzman, 1989). Aggressive males were far more likely to commit (or at least be caught committing) a criminal offense than the aggressive females (45.5% and 3.8% respectively).

Relatively little is known about the predictors of antisocial and aggressive behavior in girls. However, the little that is known suggests that the presence of childhood behavioral disorders is associated with poor outcome in girls as well as boys (Robins & Price, 1991). Girls with a history of CD are at greater risk for substance abuse, and an increased rate of psychiatric disorders as adults, greater than that seen in males. Further, exhibiting conduct problems before age 15, predicted only externalizing diagnoses in men, while in women, early conduct problems also predicted internalizing diagnoses of depressive, somatization and anxiety disorders.

Overall, longitudinal studies provide evidence of gender similarities in the stability of aggression between girls and boys from toddlers through late childhood. Adolescents showed equal stability of aggression for girls and boys to age 16, at which time correlations with early aggression decreased and psychiatric problems emerged for girls. The profile that develops from prevalence, stability and outcome measures of aggressive behavior is one of greater gender similarity in childhood, followed by profound post-pubertal sex-differentiated changes.

Cognitive Factors

Associations between deficits in cognitive functioning and antisocial behavior have been shown in epidemiological and clinical samples. Low IQ in adolescents has been associated with antisocial behavior (Berger, Yule, & Rutter, 1975; Kandel et al., 1988; Lynam, Moffitt & Stouthamer-Loeber, 1993; White, Moffitt, & Silva, 1989) and aggression (Huesmann, Eron, Lefkowitz, & Walder, 1984; Kellam, Branch, Agrawal, & Ensminger, 1975). Huesmann et al., (1984) investigated the relative correlation of the stability of IQ to the stability of aggression in a 22-year longitudinal study. A moderate negative correlation between IQ and aggression at 8 years of age was shown in girls and boys ($r = -0.32$, $r = -0.27$, respectively). The relation of early to later aggression was independent of the IQ/aggression correlation at age 8, which suggested to Huesmann and colleagues that the effect of IQ on aggression has taken place before age 8, and that subsequent changes in aggressive behavior are not affected by IQ.

Proponents of causal hypotheses of the relationship between deficits in cognitive functioning and antisocial behavior, have suggested that conduct problems in the classroom impede the child's ability to learn, or, alternatively, that cognitive difficulties propel the child toward behavior disorder, largely in response to academic failure and poor coping skills. CD occurring subsequent to academic difficulties would be consistent with theories espoused by Hirschi and Hindelang (1979), and Buikhuisen (1987), that learning deficits produce antisocial behavior through the experience of school failure. Robins (1991) has suggested that both CD and school failure may have their origins in poor cognitive functioning. Alternatively, cognitive deficits and antisocial, aggressive behaviors may be linked to yet a third variable.

As in other correlates of antisocial behavior, few studies of cognitive and neuropsychological differences include an adequate number of girls for separate assessment and comparison. The Dunedin, New Zealand, longitudinal investigation of health, development and behavior, did address gender issues and found that neuropsychological deficits were associated with delinquency in a cohort of 13 year old girls and boys in (Moffitt & Silva, 1988). Although deficits were found in verbal skills, visuospatial-motor integration, and auditory verbal memory, there were no gender differences found in IQ or any other cognitive measures. The failure to find an interaction between gender and delinquency in relation to neuropsychological measures is consistent with previous studies that have examined gender differences (Andrew, 1982; Brickman, McManus, Grapentine, & Alessi, 1984). No evidence was found for a delinquency-related deficit in executive function, which, Moffitt and Silva (1988) suggested, may have reflected use of measures that lacked specificity for frontal lobe function. Conduct disorder and frontal lobe impairment have been attributed to a disinhibition deficit associated with frontal lobe functions.

A study comparing conduct disordered male adolescents with matched controls revealed that CD boys performed more poorly on measures sensitive to frontal lobe dysfunction (conceptual perseveration, poorly sustained attention, and impaired sequencing on memory and motor tasks), but not on other cognitive measures specified as non-frontal (Lueger & Gill, 1990). Frontal lobe function has been hypothesized to be a neurobiological correlate of hyperactive and aggressive behaviors associated with Attention Deficit Hyperactivity Disorder (ADHD), and violence in adults (Mattes, 1980; Raine & Buchsbaum, 1996). There have been no similar studies in females.

Later studies conducted exclusively in boys further assessed executive functioning in relation to aggressive behaviors. Deficits in verbal problem solving and reasoning were found in a sample of antisocial adolescents (Moffitt, 1993) and deficits in executive function were found in a study of delinquency (Moffitt, 1990). Another study conducted with adolescent boys demonstrated that tests of executive function had the strongest association with physically aggressive behavior, over and above tests of verbal learning, cerebral dominance, and incidental spatial learning (Séguin, Pihl, Harden, Tremblay, & Boulerice, 1995).

The association between reading disability (RD) and behavior problems has been well examined (McGee, Share, Moffitt, Williams, & Silva, 1988; Rutter & Yule, 1970; Cantwell & Baker, 1991), although a consensus as to temporal or causal relationship has not been established. As in the argument surrounding CD and cognitive difficulties, some would suggest that behavior problems precede and lead to RD by interfering with the learning process, or that RDs lead to the experience of failure and thus foment behavioral difficulties, or, thirdly, that there are other variables common to both factors (Rutter & Yule, 1970). Bruck (1989) suggested that the strength of the association between RD and behavior problems was mediated by gender. A study of children's reading and behavior problems, while not supporting a causal relationship between the two disabilities, revealed that children experiencing both difficulties had the worst outcome, suggesting that behavior problems may exacerbate reading delay (Smart, Sanson, & Prior, 1996). Sex differences were noted in this study, with two-thirds of boys having comorbid RD and behavior problems, while two-thirds of RD girls had no behavior problems, suggesting gender-specificity in the pathways leading to RD.

The investigation of cognitive and neuropsychological deficits associated with antisocial and aggressive behaviors is made somewhat more complex when assessment includes children and adolescents with comorbid ADHD. Moffitt (1990) found that delinquent boys with comorbid ADD had significantly lower mean Verbal IQ scores and more neuropsychological deficits, including deficits in executive function, than delinquents without comorbid ADD. Carlson, Tamm, & Gaub, 1997), examined gender differences in children with ADHD, ODD, and co-occurring ADHD/ODD (ADHD-C). Ratings of aggression were higher in boys than in girls in the ADHD-C and ODD groups. Girls with ODD alone were rated as more appropriate and less attentive, but more socially impaired than boys with ODD.

Inattention and hyperactivity in childhood are said to be stronger correlates of academic problems than aggression, however, by adolescence, antisocial behavior and delinquency are associated with underachievement (Hinshaw, 1992). Aggression and frequent school absences are significant predictors of early school withdrawal (Kupersmidt & Coie, 1990), and the presence of aggressive behavior in combination with poor academic achievement is highly predictive of school dropout in both sexes (Cairns, Cairns, & Neckerman, 1989). 47% of girls and 82% of boys who were identified as having high levels of aggression and poor academic performance in seventh grade, dropped out of school before completing 11th grade. The early dropout rate for those students with the combination of high aggression and low academic performance ranged between 45% and

71%, whereas the rate for nonaggressive and academically competent students ranged between 1% and 8%.

Cognitive abilities, both verbal and spatial, have been shown, through family, twin and adoption studies, to be one of the most heritable domains of behavior (Plomin & Craig, 1997). Twin and adoption studies have also shown as much genetic influence on school achievement as on cognitive abilities. Reading disability, one of the most prevalent specific cognitive disabilities, has also been shown to run in families, and convergent study findings suggest that reading deficits are substantially due to genetic factors. The complex associations between aggression, cognitive functioning, and academic competence may have quite different family and environmental antecedents when viewed from a gender perspective.

Family Psychopathology

Findings of an increased incidence of aggressive or antisocial behavior among relatives of aggressive children support a role for familial transmission in the development of childhood aggression. High rates of aggressive behavior, antisocial personality disorder and sociopathy have been documented among first degree relatives of conduct disordered and aggressive children relative to non-aggressive children (Biederman et al., 1987; Faraone, Biederman, Keenan, & Tsuang, 1991; Frick et al.,1992). It is also important in considering family influences to note that stability of aggressive and antisocial behaviors within families has been well established across generations (Eron & Huesmann, 1990).

Heredity-environment analyses allow assessment of the relative contributions of genes and environment to aggressive behavior. Twin and adoption studies provide the research vehicle for separating genetic and environmental variance of aggressive and antisocial behavior . An underlying assumption in twin studies is that genetic influences are more highly correlated in identical (monozygotic - MZ) twins, than in fraternal (dizygotic - DZ) twins. Adoption studies, in which the adoptee lives away from biological relatives, provide an opportunity to examine both the effects of family environment and heritable effects attributed to biological relatives with whom the adoptee has had little or no contact. Studies have variously demonstrated greater genetic influences (Cadoret, Yates, Troughton, Woodworth & Stewart, 1995; Eaves, et al., 1997), while others have shown greater influences of family environment (DiLalla & Gottesman, 1989; Rutter, et al., 1990). The question of age-related gender differences of heritable or experiential influences has been addressed in several studies.

Twin/Adoption Studies. Studies of problem behaviors in samples of pre-school-age twins, though few in number, have consistently shown greater shared environmental influences, as compared to genetic influences, which are not gender-differentiated (Loehlin, 1992; Van den Oord, Verhulst, & Boomsma, 1996; Schmitz, Cherny, Fulker & Mrazek, 1994). This is consistent with other observations that juvenile symptoms of Antisocial Personality Disorder are influenced by shared environmental factors, whereas genetic influences may be stronger in later-onset symptomatology (Lyons et al., 1995).

Among older children and adolescents (8 - 16 years of age), shared environmental influences have been found to be significant only for ODD, whereas marked genetic influences were shown for CD (Eaves et al., 1997). Overall, there was no evidence in this sample that different genetic or environmental factors affect girls and boys, although

Eaves and colleagues suggest that the relative contribution of genes and environment may differ significantly between the sexes. In support of this hypothesis, an adoption study in 10 to 15-year olds in the Netherlands, found genetic influences in aggressive behaviors which were gender-differentiated: genetic influences were greater for boys and shared environmental influences were greater in girls (Van den Oord, Boomsma & Verhulst, 1994).

Studies of child and adolescent disruptive and aggressive behaviors conducted retrospectively in adult twins have found substantial genetic contribution to the liability for developing CD (Slutske et al., 1997). The magnitude of additive genetic influences (each of many genes contributing to the expression of the behavioral trait) was equal in women and men. Shared environmental influences were important only in women. Although the overall effect of the shared environment in this investigation was not significant, the effect of the era in which the individual grew up significantly contributed to the variation in the liability to develop CD, possibly reflecting sociocultural changes which lead to increased risk for antisocial behaviors in youth. One could speculate that the effects of sociocultural change may subtly increase girl's risk of CD more than boy's. For example, increased participation by females in activities, work and social situations which were once exclusively populated by males have removed constraints on female conduct which previously may have directly and/or indirectly protected girls from high risk situations.

Sex differences in the heritability of criminality and alcoholism were evaluated in the Stockholm Adoption Study (Sigvardsson, Cloninger, Bohman, & von Knorring, 1982). The genetic influence for criminality was found to be significant and qualitatively the same in males and females. Petty criminality (without alcohol abuse) was more common in adopted men than in adopted women (4.5% v 1.8%). However, the risk of petty criminality in the biologic parents of criminal women was significant (50% v 21%), and was more than double that of their male counterparts. Thus, the genetic predisposition to criminality was usually more severe in affected women than men. That is, the threshold in liability for development of criminality was higher in women than in men in reference to antisocial personality disorder.

Heritability of irritable impulsiveness was studied in twins reared together and apart (Coccaro, Bergeman, & McClearn, 1993), utilizing data gathered for the Swedish Adoption/Twin Study of Aging (SATSA), (Bergeman, Plomin, McClearn, Pedersen, & Friberg, 1988; Pedersen, Plomin, McClearn, & Friberg, 1988; Plomin, Pedersen, McClearn, Nesselroade, & Bergeman, 1988). Results revealed a significant genetic component, but not a shared environmental influence, for both "lack of assertiveness/aggression" and "impulsive irritability." There was no significant influence of shared rearing environment nor significant effects of age, gender, or age-by-gender interaction for either construct.

Family history was assessed to discern possible gender-differentiated relationships between psychopathology in first and second degree relatives and aggressive behaviors in prepubertal children. Several twin and adoption studies have shown genetic influence on aggressive behavior in children of antisocial parents to be small or insignificant (Cadoret & Stewart, 1991; Loehlin, 1992; Schmitz, Cherny, Fulker & Mrazek, 1994). Another twin study finding important genetic influences in problem behaviors in toddlers, found no significant gender differences in aggression ratings (Van den Oord, Verhulst, & Boomssma, 1996). The absence of findings of gender differences is consistent with Loehlin's (1992) meta-analysis of twin studies in toddlers. Among older children and adolescents, however, preliminary analyses from a twin study of genetics and developmental psychopathology in 8- to 16-year-olds have provided estimates of heritability of greater than 50% (Eaves et al., 1997).

Although findings in twin and adoption studies depict genetic influences as predominant in the transmission of aggressive and antisocial behaviors, heritability cannot account for all of the variance and thus provides the strongest evidence in support of environmental influences. An association between an array of family factors and aggressive and antisocial behaviors in children has been demonstrated in the literature.

Family Adversity

Specific variables of the family (home) environment as a predictor of children's antisocial behaviors (e.g. parental psychopathology, substance abuse/alcoholism, marital discord, separation/divorce and economic hardship) have been examined in adoption studies comparing biological and adoptive backgrounds. Though relatively few twin/adoption studies have specifically examined gender differences in aggressive and antisocial behaviors, vis-a-vis these influences, an increasing number of studies have begun to provide convergent information elucidating these issues.

A genetic predisposition to antisocial behavior was demonstrated in adoptees, 10 years of age to adult, (Cadoret & Cain, 1980) and significant sex differences were found in the environmental predictor variables. Males were more vulnerable than females to the adverse environmental effects of psychiatric conditions in adoptive parents or siblings, or divorce in adoptive parents. The adverse environmental variable was a nonsignificant negative predictor in females, which was suggested to be indicative of a higher threshold for environmental stress in females. Both sexes appeared equally vulnerable to the effects of long-term institutional care. Cadoret and Cain (1980) suggest that long-term care, as a form of discontinuous mothering in which adoptees fail to form any attachment, may predispose males to more antisocial behaviors. In females, however, the long-term effect could manifest differently, at a later age, such as in mothering skills. Although there was no significant interaction of sex-by-biologic predictors in the total sample, when the sample was divided by sex, the genetic influence on antisocial behavior was greater in females than in males. Having an antisocial 1st or 2nd degree relative was a significant biological predictor in females only. The one significant genetic predictor in males was having an alcoholic 1st or 2nd degree relative. Thus, males were vulnerable to adverse environmental conditions, and were biologically predisposed to antisocial behavior by alcoholism in a relative. On the other hand, females antisocial behavior had a greater genetic component and no significant environmental influence.

The effect of adverse adoptive home environment on male and female adoptees' conduct disorder, adult antisocial behavior, and aggressivity was investigated in adults between 18 and 47 years of age (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995). Adverse home environment was assessed by: marital problems or separation/divorce/ in adoptive parents; alcohol or other drug abuse and/or dependence in a parent; depression or anxiety condition in a parent; and other psychopathologic condition in a parent (e.g. conduct disorder and somatization). An adverse home environment independently predicted increased adult antisocial behaviors. Adverse home environment increased aggressivity and CD in adoptees in the presence of, but not in the absence of genetic predisposition. There were no significant gender differences in genetic, environmental or genetic-environmental interaction effects. It is suggested that antisocial personality disorder interacts with the adverse adoptive home environment to increase aggressivity and CD in adoptees.

In this overview, genetic influences were found to be greater than environmental influences in the etiology of antisocial behavior in both females and males. Gender differences were not found to be significant in preschoolers. However, as this is an under-investigated age group, opportunities for comparisons are limited. The magnitude of genetic influences on antisocial behavior did not vary significantly between females and males in 6 of 8 studies reviewed. Gender differences in environmental influences reflected a vulnerability of males to adoptive family stressors which was not seen in females, suggesting a higher threshold in women to environmental risk. Risk of criminality in the biologic parents of criminal women was shown to be more than double that of males, suggesting that the threshold of genetic risk for development of criminal behavior is higher in women than in men. Lastly, it was demonstrated that adverse home environment increased CD only with concomitant genetic predisposition.

Serotonin Function

The role of the serotonin system in the development and expression of aggression has been extensively investigated and is well supported in both animal and human literature. This literature has consistently indicated that low serotonergic function is associated with increased levels of aggressive behavior (Coccaro et al., 1989; Higley, Mehlman, Poland, Taub, Vicker, et al., 1996; Kruesi et al., 1990; Linnoila, Virkkunen, Scheinen, Nuutila, Rimon & Goodwin, 1983). Yet, unitary explanations have generally given way to models of dynamic interrelationships of biological and environmental factors in aggressive behavior. Current investigations of the neurobiological bases of aggression have proceeded within this context. The following sections provide a brief review of serotonin's role in neural development and an overview of empirical evidence of a relationship between aggression and serotonergic function.

Serotonin (5-HT) cells are among the earliest cells to develop in the fetal brain. Studies in rats show that the time during which development of the brain occurs is also the time at which serotonin levels are highest, turnover is most rapid, and receptors are highest in number (Whitaker-Azmitia, Shemer, Caruso, Molino, & Azmitia, 1990). Serotonin regulates the development of the 5-HT neuron itself, and it has been suggested that 5-HT serves as a developmental regulator for other neuronal types. In the immature brain, serotonin astroglial cells regulate brain development by providing a template for neurons to grow along, and by producing growth-regulating factors which are released by astrocytes through stimulation of the 5-HT_{1A} receptor (Whitaker-Azmitia et al. 1990). Thus, it is proposed that astroglial 5-HT_{1A} receptors are involved in selection of correct synapses and removal of excess or incorrect ones.

Serotonergic neurons comprise the most expansive neuronal network in the mammalian brain (Jacobs, Wilkinson &, Fornal, 1990). The serotonergic system is involved in many functions such as the control of emotional behavior, sleep and wakefulness, endocrine function, appetite, body temperature, blood pressure and perception of pain (Gothert, 1992). The activity of the serotonergic neurons is closely tied to the sleep-wake-arousal cycle, with highest firing rate during active waking and arousal, intermediate level of discharge during quiescent states and slow wave sleep, and virtual silence during rapid-eye-movement sleep. Brain serotonergic neurons display a slow, highly regular, and frequently clocklike spontaneous activity which may be endogenous, as is if driven by an internal pacemaker (Jacobs et al., 1990). Noting that the tonic activity of serotonergic neurons appears to vary in a stereotypical manner in association with behavioral state, and not specifically in association with any process, Jacobs and colleagues suggest that the primary role of serotonergic neurons in physiology and behavior may be to coordinate the activity of target structures in conjunction with the organism's level of behavioral arousal.

In parallel with their capacity for sensitizing tonic and repetitive motor activities in the brainstem and spinal cord, serotonin neurons are thought to dampen somatosensory processing throughout the CNS, possibly through concerted actions of noradrenergic and serotonergic mechanisms (Baumgarten & Grozdanovic, 1995). It is hypothesized, therefore, that serotonin-mediated dampening of sensory processing and responsiveness occurs throughout the CNS and is associated with the serotonin-modulated latency to responding ("waiting capacity"). It is further hypothesized that central serotonergic function serves to mediate control over irrelevant, distracting or irritating sensory stimulation and premature responding, that is, impulsivity.

<u>5-HT Studies in Aggression</u>

Understanding of the role of serotonin in aggression has been advanced through the development of animal models of aggressive behavior and experimental differentiation of the functional roles of 5-HT receptor subtypes.

<u>Animal Studies - Rodents</u>. An inhibitory role of serotonin was proposed by Soubrie (1986), through experiments demonstrating that impairment of serotonergic transmission in rodents resulted in compromised ability to tolerate a delay before responding, that is, reduced latency to respond or premature (impulsive) responding.

A comparison of the effects of serotonergic drugs on resident-intruder and maternal aggression (MA) suggested that these two forms of aggression in female and male rodents share similar neuroanatomical and neurochemical substrates because of the similarity in many behavioral effects (Olivier and Mos, 1992). 5-HT agonist drugs differentially affecting serotonergic transmission and 5-HT receptor subtypes were found to reduce offensive aggression, supporting a general inhibitory role of serotonin for male and female aggression in rats. Sex-related discrepancies were seen with the use of fluvoxamine, a 5-HT reuptake blocker, in which females showed a dose-dependent decrease in aggression while male's aggression was non-specifically inhibited only at the highest dose. The behavioral profiles of 5-$HT_{1A/B}$ and 5-HT_{1B} agonists were the most specific in both female and male rodents on the basis of these comparison studies.

Saudou, et al., (1994) investigated intermale aggressiveness of resident "knockout" mice (lacking 5-HT_{1B} receptors) when exposed to an intruder. The knockout mice exhibited markedly intensified and rapid onset aggressive behavior when confronted with a wild-type intruder. It was observed that the 5-HT_{1B} knockout mice were not only more aggressive, but possibly more impulsive than their heterozygous litter mates or wild-type mice.

The resident-intruder paradigm was used to study the effects in female mice of the administration of amiflamine, a selective monoamine oxidase inhibitor of MAO-type A, the enzyme that predominantly metabolizes 5-HT (Wallian, Brain, & Haug, 1993). Amiflamine (FLA 336) was administered to investigate whether it would reduce spontaneous attack by female mice on same sex intruders. When FLA 336 was administered to both resident and intruder females or only to the resident female, it acutely suppressed aggression, decreasing attacks on the intruder females and increasing attack latencies.

Animal Studies - Nonhuman Primate. Findings in several species of monkeys have provided evidence for a negative correlation between 5-HT and aggressive behavior, consistent with the general inhibitory role for serotonin in aggression as seen in rodents.

A series of studies in rhesus monkeys examining age, rearing and sex differences in the relationship of serotonin and aggression, has contributed significantly to the understanding of aggressive behavior in nonhuman primates (Higley, Suomi, & Linnoila, 1991; 1992; Higley, Mehlman, Taub, Higley, Suomi, et al., 1992; Higley, King, Hasert, Champoux, Suomi, & Linnoila, 1996; Higley, Mehlman, Poland, Taub, Vickers, et al., 1996). Developmental changes in 5-HT and catecholamine activity were assessed over the first two years of life in female and male rhesus monkeys that had been reared in one of two conditions; anxiety producing peer-only groups, or mother-infant dyads (Higley, et al., 1991). Animals were studied at 6, 18 and 50 months of age, and each monkey underwent a series of four 4-day social separations. Prior to and during the first and fourth separations, CSF was assayed for 5-HIAA, HVA, and MHPG, the metabolites of serotonin, dopamine, and norepinephrine, respectively. Serotonin was the neurotransmitter most affected by age, rearing and sex. There was a significant age-related decline across all three ages. Peer-only (PO) reared subjects had higher levels of 5-HIAA than the mother-infant dyad reared subjects, but this difference was present in males only; PO females seemed relatively unaffected by this rearing condition. PO rearing had a similar effect on MHPG concentrations which were elevated in both comparisons. Higley et al. (1991) suggest that increased levels of anxiety and fearfulness seen in PO-reared monkeys reflect increased activation of both the serotonin and norepinephrine systems. The effects of separation on CSF 5-HIAA and MHPG concentrations were consistent with this interpretation. There were initial increases over the baseline for both metabolite concentrations. The MHPG concentrations remained increased throughout the separations; however, the increases in 5-HIAA concentrations largely returned to baseline by the fourth week. Higley and colleagues suggest that the discontinuity in 5-HIAA levels could reflect a sensitization mechanism, that is, repeated separations may have produced increased levels of despair which may be associated with low levels of 5-HIAA.

Similar findings resulted from the chronic administration of fenfluramine in 4 male vervet monkeys which produced dose-related decreases in CSF 5-HIAA, and significantly increased human-directed aggression and aggression toward a conspecific (Raleigh, Brammer, Ritvo, Geller, McGuire, & Yuwiler, 1986). Both the physiological and behavioral measures were reversible after termination of FEN treatment. Raleigh and colleagues suggest that the decrease in CSF-5-HIAA is consistent with hyperstimulation of postsynaptic receptors, since it had been demonstrated (Peroutka and Snyder, 1980) that chronic treatment with drugs which enhance 5-HT neurotransmitter function down regulates 5-HT_2 receptor sites.

Interindividual stability of CSF monoamine concentrations was assessed in two groups of female rhesus macaques across time, and between baseline and stressful conditions (Higley et al., 1996). The relationship between social dominance ranking and 5-HT functioning was also examined. Female macaques were placed in groups with one or two adult males. An unfamiliar female was added to each group in the fifth week. CSF monoamine metabolites, NE, and behavioral data were collected for 6 months, and data characterizing spontaneous aggressive behavior were collected for an additional year. Stressors of group placement or addition of a unfamiliar female resulted in increases of each of the metabolites above baseline. Across the study, 5-HIAA was most consistently elevated above baseline. Interindividual differences in CSF concentrations of the monoamine metabolites and NE were highly stable over time, both during baseline and stressful conditions. Females with low CSF 5-HIAA exhibited higher rates of *spontaneous (overt) aggression* involving physical fighting, chasing, or lunging. CSF NE was also negatively correlated with rates of aggression. In contrast, *competitive aggression*, elicited encounters used to maintain social dominance ranking, were not correlated with either CSF 5-HIAA or NE. Competitive aggression is less severe, restrained aggression shown in typical daily encounters between macaques. Females with above average CSF 5-HIAA prior to or following group formation were more likely to attain and maintain high social dominance ranking than females with below average CSF 5-HIAA. Thus, CNS monoamine functioning in adult rhesus female macaques was said to be trait like, showing a predisposition in the response of 5-HT and the catecholamines. It is also suggested that these findings support a role for serotonin in controlling impulses that regulate aggression.

Adult Males - Aggression and Violence. An inverse relationship has generally been shown between aggressive, antisocial behavior and central serotonergic function in adult males. This literature has relied primarily upon two approaches to measuring central 5-HT function; 1) assessment of CSF 5-HIAA, and 2) neuroendocrine challenge procedures such as measuring the prolactin response to fenfluramine challenge. Appendix B reviews the rationale and scientific data supporting the validity of the fenfluramine challenge for assessing central serotonergic function.

Reduced prolactin response to fenfluramine challenge has been demonstrated in impulsive aggressive personality disordered patients, and in patients with Major Depressive Disorder with a history of suicide attempts (Coccaro, et al., 1989). Additionally, reduced 5-HT function in personality disordered males was associated with the presence of impulsive personality traits in first degree relatives (Coccaro, Silverman, Klar, Horvath, & Siever, 1994). In contrast, a positive relationship was revealed between fenfluramine-related prolactin response and elevated aggressive/impulsive behavior in drug abusers (Fishbein, Lozovsky, & Jaffe, 1989). This discrepant result may reflect prior cocaine use or the history in this sample of multiple drug abuse. Central serotonergic function as measured by CSF 5-HIAA concentrations in males has also provided evidence of a negative correlation between 5-HT function and aggression in personality disordered patients with and without a history of suicide attempts (Brown, Goodwin, Ballenger, Goyer, & Major, 1979), as well as in borderline personality disorder (Brown, Ebert, Goyer, Jimerson, Klein, et al.,1982). Among impulsive/violent offenders, males who had attempted suicide had the lowest CSF 5-HIAA levels compared to non-attempters (Linnoila, Virkkunen, Scheinen, Nuutila, Rimon, & Goodwin, 1983). Similarly, low CSF 5-HIAA concentrations were associated with impulsivity, aggressiveness and high CSF testosterone among alcoholic, violent offenders and fire setters (Virkkunen, Rawlings, Tokala, Poland Guidotti, et al., 1994).

Assessment of serotonergic function and aggressiveness is rarely undertaken in healthy individuals. One such study in normal adults assessed the relationship of 5-HT function and measures of trait aggression and hostility in women and men, using prolactin and cortisol response to fenfluramine challenge (Cleare & Bond, 1997). In males, there were significant inverse correlations between 5-HT mediated cortisol responses and scores on trait aggression and hostility inventories. There were no similar correlations found in females. The study did not find a significant relation between aggressive parameters and the serotonin mediated PRL responses. Females had higher Δ PRL responses than males. Thus, an inverse relationship between serotonergic activity and increased trait aggression in healthy males, but not in healthy females is modestly supported in this study. The authors suggest that failure to find a significant relationship between aggression and serotonergic function may, in part, reflect failure to control for menstrual cycle phase which increases variance in the sample, and a limited spread of aggression scores, with few subjects scoring above a low aggressive range.

Adult Females - Self-directed Aggression and Depression. To my knowledge, there are no studies which have examined the relationship of central serotonergic function and aggression exclusively in adult female populations, and females are under-represented in aggression studies which include both males and females. Investigative research in serotonergic function in women has focused primarily on mood disorder, self-injury and suicidality. To relate this focus of investigation in females to similar research in male populations, one may consider assessment of impulsive behavior and central serotonergic function. Low 5-HT activity has been postulated to be a trait marker for impulsive behavior in general, including suicide (Neilsen, Goldman, Virkunnen, Tokola, Rawlings, & Linnoila 1994), and has been associated with self-directed aggression in suicide attempters and victims (Asberg, Schalling, Traksman-Bendz, & Wagner, 1987; Mann, Arango, Marzuk, & Reis, 1989). The relationship of central serotonergic function and mood disorder, suicidality, impulsiveness and aggression, as examined in women, will be reviewed in the following section.

Self-mutilative behavior (SMB) which is defined as repetitive, direct physical self-harm without conscious suicidal intent, is most commonly found in young female patients with personality disorders (Herpertz, 1995; Pattison & Kahan, 1983; Winchel & Stanley, 1991). SMB is thought to be a specific form of inwardly directed aggressiveness. A further distinction has been made between *impulsive* and *premeditated* self-harming actions (Herpertz, Steinmeyer, Marx, Oidtmann, & Saß, 1995). The significance of aggression and impulsivity for self-mutilative behavior in women was examined using the fenfluramine challenge procedure. A group of women with MDD (suicide attempters and nonattempters), and normal controls were also assessed. All patient groups showed a blunted prolactin response to FEN compared to controls (Herpertz et al., 1995). Prolactin response was most reduced in patients with a high measure of impulsivity and aggressiveness. Ratings of aggression revealed that self-directed hostility was higher among depressives with a history of suicide attempt. Measures of aggression did not distinguish between impulsive and pre-meditated self-mutilators, as had been expected. Depressives without a history of suicide attempt presented with the lowest measures of impulsivity and aggressiveness and had the highest prolactin response among the four groups of patients.

Self-directed aggression as a feature of personality disorders, was investigated through fenfluramine challenge in female and male patients with personality disorder (New et al., 1997). It was found that patients with a history of self-mutilation or suicide had blunted prolactin and cortisol responses to fenfluramine compared to those with no history of either suicide attempt or SMB who showed the highest PRL response to FEN. The patients who displayed a severe form of self-directed aggression, engaging in both suicide attempts and self-mutilation had the most marked serotonergic abnormality, having the most blunted responses to FEN. It is interesting to note that in the analysis of variance, only self-mutilation as a single factor tended to predict a blunted FEN-induced PRL response. Subjects with a history of self-directed aggression also had a history of outward directed aggression. Overall, women had higher and more variable responses to fenfluramine challenge than men. Though only 2 women in the study engaged in both suicide attempts and self-mutilation, a pattern similar to that seen in men was observed in women. The women who did not have a history of suicide attempts or self-mutilation exhibited more robust responses to fenfluramine compared to women who engaged in both behaviors.

Child and Adolescent Boys - Aggression. Studies of the relationship of aggression and serotonergic function in children have focused nearly exclusively on boys. Aggression, but not impulsivity, was negatively correlated with CSF 5-HIAA concentrations in a group of children and adolescents (27 boys; 2 girls) with mixed disruptive behavior disorder diagnoses (Kruesi, Rapoport et al., 1990). The absence of significant negative correlations between 5-HIAA and measures of impulsivity was suggested as being related to the restricted range of impulsivity within the group, since cognitive and personality measures did not differ between the disruptive patients and the contrast group. A two-year follow up (Kruesi, Hibbs et al., 1992), demonstrated that the inverse correlation between CSF 5-HIAA and aggression remained significant such that earlier 5-HIAA predicted later aggression. An association between 5-HIAA and suicide attempts was not found. In contrast to the negative relationship between CSF 5-HIAA and aggression found by Kreusi and colleagues (1990, 1992), a positive correlation between CSF-5-HIAA and aggressivity was found in a sample of markedly hyperactive ADHD boys (Castallanos et al., 1994). It is possible that diagnostic differences in the two samples contributed to the opposite findings. CSF HVA was positively correlated with several measures of hyperactivity. Castellanos and colleagues (1994) suggest that, given high correlations found between CSF HVA and 5-HIAA in their sample, increased CSF HVA was dominating the relationship between the two monoamines.

Fenfluramine challenge has also produced varied results in the investigation of aggression in boys. No differences were found in prolactin response to FEN challenge in a heterogeneous group of boys with DBDs compared to a group of normal controls (Stoff, Pasatiempo, Yeung, Cooper, Bridger, & Rabinovich, 1992). In contrast, a study in 7 - 11 year old boys showed aggressive children with ADHD had a significantly larger prolactin response to FEN than nonaggressive children (Halperin, et al., 1994). An attempt to replicate these findings of significantly greater prolactin response to fenfluramine in aggressive versus nonaggressive boys was initially unsuccessful (Halperin, et al., 1997). However, when the subjects were divided into two age groups (<9.1 or >9.1), younger aggressive boys had a significantly greater fenfluramine-induced PRL response than younger nonaggressives. No such difference was found in the older age group, which may indicate that enhanced PRL response to FEN in aggressive children becomes blunted at a later age. A positive correlation between prolactin response to FEN and aggression has also been demonstrated in brothers ($\bar{x}$ age 10.0 yrs.) of convicted delinquents (Pine et al., 1997). Previously, this research group had demonstrated associations between low evaluation scores from home observations (higher scores given to healthier environments), and disruptive psychiatric symptoms (Wasserman, Miller, Pinner, & Jaramillo, 1996). Thus, rearing environment was also assessed, resulting in a positive correlation between PRL and maladaptive parent-child patterns (Pine et al.,1997).

Child and Adolescent Girls - Depression. No studies of aggression and its relationship to serotonergic functioning have previously been conducted exclusively in prepubertal or adolescent girls. As in the adult female population, young girls are more likely to be represented in investigations of mood disorder. Depression in children and adolescents with comorbid disruptive disorders has been associated with poor outcome, more suicide attempts, and higher incidence of criminality in adulthood (Harrington, Fudge, Rutter, Pickles,& Hill,1990;1991; Puig-Antich et al., 1989). The temporal relationship between decreasing disruptive behavior, pubertal changes, and emerging mood disorders in females, compared with relatively stable antisocial behavior in males, suggests that during the transitional period between early childhood and adolescence, in those individuals with predisposing serotonergic dysfunction, interactions between neurotransmitters and neurohormones may influence behavioral outcome differentially in girls and boys. In this context, a study of neurohormonal functioning in prepubertal and adolescent girls with major depressive disorder is of interest.

L-5-HTP challenge in prepubertal children demonstrated significantly greater PRL secretion among depressives relative to normal controls (Ryan et al., 1992). Girls with MDD had higher PRL secretion than boys with MDD, and significantly greater PRL secretion than normal girls. Normal girls had lower PRL secretion than normal boys. However, MDD boys had no significant difference in AUC or peak PRL secretion compared with normal boys. Thus, PRL hypersecretion was seen in depressed girls, but not in depressed boys compared to same-sex controls. Prepubertal suicidal depressed children were not different from their nonsuicidal depressed counterparts in hormonal response to serotonergic challenge.

The 24-hour pattern of prolactin secretion, without serotonergic challenge, was investigated in adolescents with MDD and in normal controls (Waterman et al., 1994). Neither the pattern nor the amount of prolactin secretion was significantly different between groups. However, there were significant gender differences. Girls secreted more prolactin than boys, but no significant gender-by-diagnosis interactions were found. Findings that basal PRL secretion appears normal in early-onset depression, whereas L-5-HTP stimulated prolactin secretion is abnormal, are postulated to reflect different types or sites of neural dysregulation in the pathophysiology of early onset depressive disorders.

In summary, an inverse relationship between serotonergic function and aggression is generally reported among adult males. Studies of aggression and serotonergic dysfunction have not been conducted in female populations, although several lines of research suggest that findings in males may generalize to females. Blunted FEN-related PRL response was seen in all patient groups in self-harming behavior and depression in adult females. PRL response has been related to severity of disorder, such that combining a history of suicide or impulsivity with other pathology may be associated with diminished PRL responsivity. Studies of children's FEN-induced PRL responses in relation to aggressive behavior have produced equivocal results. CSF-5HIAA has been both negatively and positively related to aggressive and antisocial behavior in boys. Enhanced PRL response to FEN has been demonstrated in relation to aggression in ADHD boys in some, but not all, studies. Thus, serotonergic mechanisms are implicated in aggressive behavior in children and adults, but the direction of the relationship is not certain. Investigations of serotonergic function and aggression in girls have not been conducted.

However, a study in children (Waterman et al, 1994) demonstrated a greater fenfluramine-induced PRL release in girls than in boys. While an inverse relationship between serotonergic activity and aggression has been demonstrated in adolescent boys (Kruesi, Rappoport et al, 1990; Halperin et al., 1994; Pine et al., 1997), a similar relationship has not been demonstrated in girls. However, low 5-HT activity has been associated with MDD in prepubertal girls (Ryan, 1992).

Summary

Taken together, the data presented indicate that aggressive behavior may manifest differently in girls and boys. Whereas a substantial literature indicates that aggressive behavior in boys is associated with overt, physically assaultive behavior, impulsivity, cognitive deficits and psychosocial deprivation, girl's aggression is considered to be relational, that is, inflicting harm by covert social manipulation intended to cause damage to the individual within their peer group. Girl's aggression is thought to be more controlled (less impulsive) than their male counterparts. However, less is known regarding the cognitive/neuropsychological functioning of aggressive girls or about their experience of psychosocial adversity.

This study was designed to examine correlates of aggressive behavior in prepubertal girls and boys to determine if the characterization of aggressive behavior developed in the literature, which is based primarily upon male samples, also characterizes aggressive behavior in girls. If aggressive girls and boys are found to be comparable on measures of cognitive, neuropsychological, behavioral and serotonergic function, it would be likely that the symptoms represent the same disorder and underlying mechanisms. If, however, aggressive girls and boys are found to differ on most measures, it would support the hypothesis that aggression in girls is different from that seen in boys and may represent a different disorder with implications for diagnosis and treatment.

__Hypotheses__

1. Studies consistently report verbal processing and language deficits in impulsive aggressive children and adults (Hinshaw, 1992; Barratt, Stanford, Kent & Felthous, 1997). Yet, unlike behavioral manifestations of aggression typically seen in males, female aggression is described as controlled and reflective, resulting in social wounding of the target. **It is therefore hypothesized that as compared to aggressive boys, aggressive girls will be found to be significantly less impulsive, as measured by neuropsychological testing, and as having fewer, if any, verbal deficits.**

2. A role for the familial transmission of aggressive and antisocial behavior is supported by findings of high rates of aggressive behavior, antisocial personality disorder and sociopathy among first degree relatives of conduct disordered and aggressive children relative to non-aggressive children (Biederman et al., 1987; Frick et al., 1992). The lower rate of aggressive behavior in girls has prompted investigators (Cloninger, Reich & Guze, 1975; Sigvardsson et al., 1982) to posit that females require higher levels of biological predisposition in order for them to manifest aggressive behavior. **Therefore, it is hypothesized that as compared to non-aggressive children, as well as aggressive boys, aggressive girls will have an increased incidence of aggressive/antisocial behavior in their first and second degree relatives.**

3. Heritability cannot account for all of the variance in twin and adoption studies of

aggressive and antisocial behaviors, thus allowing for evidence in support of environmental influences. An array of potentially adverse family circumstances, such as marital discord, absence of a parent and limited available resources, have been examined for influence upon the manifestation of aggression and antisocial behavior among children and adolescents. As in other areas of aggression research, females have infrequently been included in adequate numbers for analysis and comparison. Significant gender differences have been found in environmental predictors of aggression in subjects from 10 to adult, showing males to be more vulnerable than females to the effects of family adversity such as psychiatric illness and divorce (Cadoret & Cain, 1980). **It is therefore hypothesized that adverse home/family environmental factors will be more frequent among aggressive boys as compared to aggressive girls and nonaggressive girls and boys.**

4. The association of the serotonergic system and the manifestation of aggression and antisocial behavior has been extensively investigated in both animal and human literature. Animal literature has demonstrated an inhibitory role of serotonin (reducing impulsive or aggressive responding) in rodents (Soubrie, 1986; Olivier & Mos, 1992) and non-human primates (Higley et al, 1991;1992;1996; Raleigh et al., 1986). An inverse relationship between impulsive aggressive behavior and central serotonergic function has also been demonstrated in several samples of males (Brown et al., 1979; Coccaro et al., 1989; Linnoila et al, 1983; Virkkunen et al, 1994). While no similar studies of aggression have been conducted in females, among women with Major Depressive Disorder (MDD), serotonin was most reduced in patients with high levels of impulsivity and aggressiveness (Herpertz et al., 1995). Studies examining the relationship of 5-HT to aggression in

children have used nearly exclusively male samples and have generated conflicting results (Castellanos et al. 1995; Halperin et al. 1994; 1997; Kruesi et al. 1990; 1992; Pine et al. 1997; Stoff et al. 1992). Pilot data from this study (Koda et al., 1996) demonstrated a greater fenfluramine-induced PRL response in prepubertal girls compared to boys. It is possible that this increased 5-HT response is related to decreased impulsivity in girls relative to boys. **Therefore, it is hypothesized that aggressive girls will have a greater FEN-induced PRL response than aggressive boys in this prepubertal sample, reflecting gender-related differences in serotonergic responsivity.**

Methods

Subject Screening & Initial Assessment

Girls and boys between seven and ten years of age, who were reported to exhibit varying degrees of aggressive or disruptive behaviors, were recruited to participate in this research. Children who had been brought by parents or legal guardians to the Division of Child and Adolescent Psychiatry of the Mount Sinai Medical Center for evaluation and treatment of behavioral difficulties were screened to determine their interest in and appropriateness for the study. Referrals were also received through school personnel (guidance counselors, school psychologists, principals, etc.) at the request of parents of school children who are experiencing academic and social difficulties, as well as though community service agency officials who are familiar with the quality of the evaluations conducted by the child study research team. Parents also contacted the child study unit directly, having learned of the study from friends or family members. Most of the boys were from the immediate urban area contiguous to the Mount Sinai Medical Center. While many of the girls were also from this area, several were from other New York Boroughs, and from communities in New Jersey, and Westchester County, New York.

All children were initially screened for acceptance into the study using parent ratings on the Child Behavior Checklist/4 - 18 (CBCL). If a child appeared likely to meet criteria for aggressive behavior, an evaluation was conducted to determine the child's eligibility for the study. All subjects were of prepubertal status (Tanner Stage I or II) by parent report. Children were excluded if they 1) had a chronic medical illness or were currently taking systemic medication; 2) had a diagnosed neurological disorder; 3) had a

Full Scale IQ below 70; 4) had a diagnosis of schizophrenia, autism, pervasive developmental disorder or a chronic tic disorder; 5) were not attending school; or 6) were not English speaking (child and parent). Approval by the Mt. Sinai Institutional Review Board (IRB) as well as parent consent and patient assent were obtained prior to September 1997.

Subject Matching

Girls and boys who scored two standard deviations above the mean on the CBCL Aggression Scale were designated as aggressive (CBCL Aggression score ≥70) and those with a CBCL Aggression score ≤69, as nonaggressive. Girls who met inclusion criteria were matched by age (± 6 months) and CBCL Aggression Subscale score (± 5 points) to boys drawn from a larger ongoing study of children with disruptive behavior disorders under, the direction of Jeffrey M. Halperin, Ph.D. This procedure resulted in two groups of girls, aggressive (N = 12) and non-aggressive (N = 12) closely matched for age and CBCL Aggression score to two groups of aggressive (N = 12) and non-aggressive (N = 12) boys (see Table I).

TABLE I	AGE (years)			CBCL Aggression Score	
	N	$\bar{x}$	sd	$\bar{x}$	sd
All Girls	24	9.08	1.28	69.42	11.83
All Boys	24	9.24	1.29	70.00	11.88
Aggressive Girls	12	8.96	1.50	79.25	5.74
Aggressive Boys	12	9.11	1.54	79.75	6.33
Nonaggressive Girls	12	9.20	1.07	59.58	6.97
Nonaggressive Boys	12	9.37	1.04	60.25	6.89

In addition to the CBCL parent ratings obtained during the initial screening and acceptance into the study, all children received further clinical/behavioral, cognitive and neurobiological assessment. Family history and demographic information were also obtained for each child.

Clinical/Behavioral Assessment

Diagnostic Interview Schedule for Children (DISC). The revised Diagnostic Interview Schedule for Children (DISC) (Shaffer, Fisher, Piacentini, Schwab-Stone, & Wicks, 1989), is a highly structured interview that can be reliably administered by a trained non-clinical interviewer. Separate interviewers, who were blind to the child's probable group placement, interviewed the parent(s) using the full DISC. The child's teacher was interviewed by telephone using the Disruptive Disorders Module of the DISC. A combination of the parent and teacher interviews was used to determine whether inclusion and exclusion criteria were satisfied.

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 I/O (inattentive/overactive) and A (aggressive) scales of the IOWA allow for some distinction between these two symptom profiles. The Conduct, Hyperactivity, Inattention/Passivity Factors and Hyperactivity Index provide further discrimination of behaviors. Normative data for the IOWA are available for a sample of 608 (293 boys and 315 girls) elementary school children (Pelham, Milich, Murphy, & Murphy, 1989).

__**Child Behavior Checklist (CBCL) 1991.**__ The revised CBCL (Achenbach, 1991) is a 113-item checklist that is completed by parents. The CBCL generates standardized T-scores for a broad range of behavioral dimensions including hyperactivity, aggression, and delinquency and has been found to be highly reliable. Normative data are available for 1,200 (619 girls, 581 boys) 4-11 year-old, and for 2,368 (604 girls, 564 boys) 12-18 year-old, nonhandicapped subjects. The CBCL aggression scores are based upon identical items, but separate norms for boys and girls.

__**Children's Aggression Scale - Teacher Version (CAS-T)**__ The CAS-T (McKay, Halperin, Grayson, Hall, Perochio, et al., 1993) was designed to evaluate the presence of verbal aggression, aggression toward objects or animals, physical aggression toward people, and use of weapons in children. Unlike previous teacher "aggression" scales, such as the IOWA Conners, which primarily assess oppositional and defiant behavior, this scale was designed to assess the frequency and severity of aggressive acts. Normative data have been collected for 324 children on the CAS-T, which generates a separate dimensional measure in each domain of aggression that it assesses. The CAS-T was completed by the child's current teacher as well as her/his teacher from the prior academic year.

__**Children's Aggression Scale - Parent Version (CAS-P)**__ The CAS-P (McKay et al., 1993) was designed to evaluate the presence of verbal aggression, aggression toward objects or animals, physical aggression towards people and use of weapons in children. This scale was designed to assess the frequency and severity of aggressive acts. The CAS-P distinguishes between aggression in and outside of the home, and also distinguishes between aggression directed against children versus aggression directed against adults. These distinctions are particularly important for assessing aggressive traits in children, since fighting with siblings at home is common in children who would otherwise be considered non-aggressive. Preliminary findings for this scale indicate that scores in several domains discriminate between ADHD children with and without comorbid conduct disorder.

Cognitive Assessment

Wechsler Intelligence Scale for Children - III (WISC-III). The WISC-III (The Psychological Corporation, 1991) was used to assess general cognitive abilities. The WISC-III is a well-normed standardized intelligence test that yields separate Verbal, Performance and Full Scale IQ scores along with 12 independent subtest scores. A child was accepted into the study only if she/he received a Full Scale IQ of 70 or higher, which placed her/him above the Mildly Mentally Retarded range.

Wechsler Individual Achievement Test (WIAT). The WIAT (The Psychological Corporation, 1992), was used as an overall test of academic achievement. The test battery contains several subtests assessing various aspects of reading, spelling, writing and arithmetic skills. Due to time constraints, however, the WIAT Reading Comprehension subtest and the WIAT Screener were used in this study. The WIAT Screener consists of three well-normed and standardized subtests that assess Basic Reading, Math Reasoning and Spelling in approximately 15-20 minutes.

Continuous Performance Test (CPT). A Continuous Performance Test (Halperin, Wolf, Pascualvaca, et al., 1988; Halperin, O'Brien, Newcorn et al., 1990;

Halperin, Sharma, Greenblatt, & Schwartz, 1991), was used to obtain objective measures of impulsivity, dyscontrol and inattention. Letters are presented on a computer screen with a 1.5-second interstimulus interval. The child is told to respond (to press the space bar) when she or he sees an "A" followed by an "X". A total of 400 letters are presented and the task lasts approximately 12 minutes. The inattention score is computed by summing misses and X-only errors with reaction times above the mean hit reaction time. The measure of impulsivity consists of the number of A-not-X errors plus A-only errors with reaction times above 1.25 seconds. The measure of dyscontrol consists of the remaining false alarms that are not included in the other measures. Although the exact significance of dyscontrol errors is not clear, it is thought to reflect a general "fidgetiness" and not to represent either inattention or impulsivity.

Family History Assessment

Family history of psychiatric symptomatology was assessed using a semi-structured interview administered either to the child's mother, both parents together, or another relative with whom the child lived. The interviewer systematically queried about symptom domains that each family member may have experienced as a child (where appropriate) and as an adult. When a positive response was elicited, additional probes were used to determine whether the problem caused impairment. Since full criteria for disorders could not be reliably ascertained, endorsement of impairment in any one symptom domain was considered to be indicative of a positive history. Problem areas assessed were 1) ADHD symptoms (i.e., inattention, fidgetiness); 2) Aggressive behaviors (i.e., persistent fighting, causing injury to others, use of weapons, destruction of property);

3) Substance abuse (i.e., alcohol and drugs); 4) Antisocial behaviors (i.e., stealing, fire-setting, trouble with the law); 5) Internalizing symptoms (i.e., excessive worrying, depression); 6) Psychotic symptoms (i.e., hallucinations, delusions, paranoia); and 7) Cognitive Impairment (i.e., learning problems, slower than others, history of special education). Data were obtained for 91 parents, 160 grandparents, and 261 aunts and uncles, for a total of 512 first and second degree adult relatives. Data for siblings were not included because most were below the age of risk for many of the domains assessed.

Demographic Assessment

Information as to the child's home environment was obtained through an interview with the parent or primary caregiver. The interviewer followed a questionnaire ascertaining information as to number of family members, non-family members and number of children residing in the home; parents' marital status; amount of contact child had with each parent (daily, weekly, monthly, yearly, no contact); educational status of parents; and, job status and description of employment for parents.

Neurobiological Assessment.

An index of central 5-HT function is the prolactin (PRL) response to acute challenge with the 5-HT releaser/uptake inhibitor fenfluramine (FEN) (Quattrone et al., 1978). The magnitude of this PRL response has been found to distinguish between aggressive and non-aggressive ADHD children (Halperin et al., 1994), aggressive and non-aggressive siblings of adjudicated adolescents (Pine et al., 1997), and between aggressive and non-aggressive personality disordered (Coccaro et al., 1989), and substance abusing (Fishbein et al., 1989) adults. FEN is a centrally-acting pharmacological agent which releases endogenous stores of 5-HT, blocks re-uptake of synaptic 5-HT, and stimulates post-synaptic 5-HT receptors, directly and indirectly (Rowland & Carlton, 1986). The resultant enhancement of central 5-HT activity is reflected in a robust dose-dependent rise in plasma PRL levels (Lewis & Sherman, 1985).

Subjects were free of medications for at least four weeks prior to the FEN challenge and were maintained on a low monoamine diet for three days prior to the study. The protocol was begun after an overnight fast, at 8 am, with insertion of an indwelling intravenous catheter (kept open with normal saline) into a forearm vein. Subjects remained awake, supine and fasting until 3 pm. Samples of blood for baseline plasma PRL were obtained at 9:45 and at 9:55 am (-15 and -5 min.). Using double blind procedures in 9 girls, FEN, 1 mg/kg, or placebo (PLA), were administered orally at 10 am (0 min). In all other subjects only FEN, 1 mg/kg, was administered. Post- FEN/PLA samples of plasma PRL were obtained hourly until 3 pm. All samples were placed immediately on ice until centrifugation within two hours. After separation, samples remained frozen until assayed by RIA (Davis, Mathe, Mohs, Levy, 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 used as the measure of maximal PRL responsiveness to the 5-HT challenge. A VCR and videotapes were available to the child for entertainment, and a researcher was present throughout the procedure.

Post-FEN samples for plasma FEN and nor-fenfluramine (Nor-FEN) 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 was placed immediately on ice until centrifugation within two hours. After separation, plasma was frozen at -20°C until assay by gas-chromatography with electrical detection (Krebs, Chens, & Wright, 1984). The lower limit of sensitivity is 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 Tom Cooper, at the Nathan Kline Institute for Psychiatric Research.

Studies in adults (Coccaro et al., 1989; McBride et al., 1989), adolescents (Stoff et al., 1992), and children (Halperin et al, unpublished) have shown that the robust PRL enhancement following a FEN challenge is due to the medication, and that a placebo challenge only minimally alters plasma PRL. Yet, this has not been demonstrated in female children. Therefore, with nine girls, the double blind placebo challenge described above was employed. This provided an ascertainment of non-specific neuroendocrine changes that may occur in young girls in response to the non-pharmacological aspects of the procedure. Further placebo challenge was not conducted as it would have imposed additional time commitment and inconvenience upon the children and their families and further discomfort upon the child, and was thus not ethically justified. Test-retest reliability for the PRL response to FEN has been shown to be good in prepubertal children when the two trials were separated by one week (Stoff, Pasatiempo, Yeung, Bridger, & Rabinovich, 1992), and two-year stability coefficients in children (Pick et al, 1998) were found to be comparable to those reported using more invasive measures of 5-HT function in primates (Higley et al., 1996; Kraemer & Clarke, 1996). The two challenge procedures were separated by one week and the order was counterbalanced, such that half received the FEN challenge first and half received PLA first.

A single 1 mg/kg dose of FEN in children is unlikely to cause any side effects. Higher doses for up to 9 months have been used experimentally to treat autistic children (Beisler, Tsai, & Stiefel, 1986; Yarbrough et al., 1987) and for 3 weeks in ADHD children (Donnelly et al., 1989). During these trials mild side effects such as sleep disturbances, weight loss and irritability were occasionally reported. One child developed a rash, and was terminated from a study. No side effects were reported after a single dose.

Data Analysis

Cognitive Data. Gender differences in measures of intellectual functioning (WISC-III) were assessed using a two-way factorial analysis of variance (ANOVA). Academic achievement as measured on the WIAT, and CPT measures of Impulsivity, Dyscontrol and Inattention were also examined using two-way ANOVA. When appropriate, post hoc analysis was performed using Tukey's HSD.

Clinical/Behavioral Data. Differences in the presence of childhood psychiatric disorders, as determined by the DISC, in aggressive and nonaggressive girls and boys, was examined using general loglinear analysis for categorical variables. Examination of standardized residuals was used to interpret significant interaction effects. Gender differences in aggressive and nonaggressive children in behavioral ratings of the IOWA CTQ and the CAS-P and CAS-T, were examined using two-way factorial ANOVA, with two independent variables (Gender and Aggression Status). Post hoc analyses of significant interactions were conducted using Tukey's HSD.

Family History Data. The incidence of psychopathology in first and second degree relatives among aggressive and nonaggressive girls and boys was examined using a two-way analysis of variance (ANOVA) and post hoc Tukey's HSD when appropriate.

Demographic Data. General loglinear analysis was used to examine relationships between categorical home environmental variables (e.g. marital status, parent's years of education completed, parent's employment status, and child-parent contact), and aggressive and nonaggressive behavior in girls and boys. Significant interaction effects were interpreted by examination of standardized residuals. Two-way factorial analysis of variance (ANOVA) was used to examine differences among aggressive and nonaggressive girls and boys in total numbers of children and family members living in the households of children in this study.

Neurobiological Data. Gender differences in the PRL response to FEN challenge in aggressive and nonaggressive children were assessed using a three-way mixed analysis of covariance, controlling for plasma medication level, with two between group variables (Gender and Aggression Status), and one within group variable (Time). There were seven time points (2 pre- and 5 post-FEN administration). A two-way analysis of covariance (ANCOVA) controlling for peak medication, was used to examine peak Δ PRL (peak PRL minus the combined baseline PRL) response to FEN, the two independent variables being Gender and Aggression Status (as determined by CBCL aggression ratings).

RESULTS

Cognitive Distinctions

Associations between gender and aggression and aspects of cognitive functioning were assessed using measures of overall intellectual function, academic achievement, and a laboratory measure of inattention and impulsivity. The Wechsler Intelligence Scale for Children - III (WISC-III, The Psychological Corporation, 1991), and the Wechsler Individual Achievement Test (WIAT, The Psychological Corporation, 1992) were used to assess intellectual and academic functioning. Objective measures of inattention, impulsivity, and dyscontrol were obtained using The Continuous Performance Test (CPT), (Halperin, et al., 1991)

Group differences among the cognitive measures were assessed using two way factorial analysis of variance (ANOVA). There were no main effects on the WISC-III Verbal IQ for Gender (F = 2.97, df 1,44, p = .10) or Aggression Status (F = 1.28, df 1, 44, p = .26). There was, however, a significant Aggression Status × Gender interaction effect for Verbal IQ (F = 4.99, df 1,44, p = .03). Post hoc analysis revealed that aggressive girls scored significantly higher on VIQ than aggressive boys, but there was no significant difference between nonaggressive girls and boys on this measure (**Figure 1**). There were no main effects or interaction effects for Performance IQ or FSIQ, although FSIQ interaction effect (F = 3.76, df 1,44, p =.059) approached significance.

Dimensional assessment of cognitive function using Pearson product-moment correlation showed that among boys, but not among girls, parent ratings of delinquent behavior (CBCL Delinquency scores), were negatively correlated with

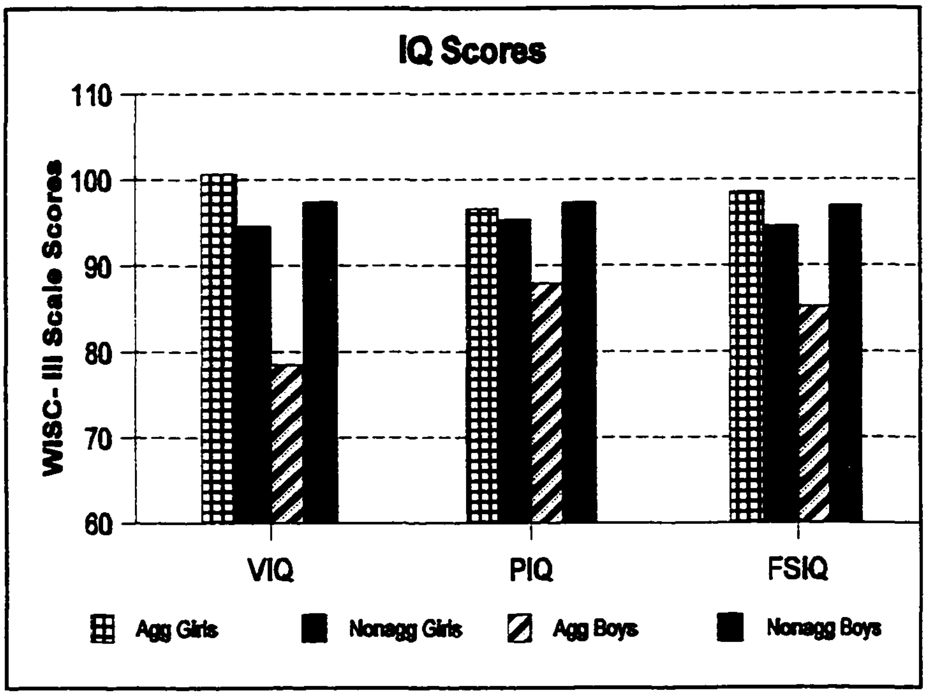


Figure 1. IQ scores in 7 - 10 year-old girls and boys. Aggressive girls (N = 12), nonaggressive girls (N = 12), aggressive boys (N = 12), nonaggressive boys (N = 12).

both FSIQ ($r = -0.54, p = 0.01$) and PIQ ($r = -0.44, p = 0.03$). FSIQ among the boys was also negatively correlated with CBCL Aggression ($r = -.040, p = 0.05$). Teacher ratings of aggression (IOWA - Aggression) and conduct problems (IOWA - Conduct) were not associated with measures of general intellectual ability in either girls or boys.

As shown in **Table 2**, analysis of academic achievement measures produced significant main effects for Gender on all subtests of the Wechsler Individual Achievement Test (WIAT) and significant Gender × Aggression Status interaction effects for all subtests except spelling. The Reading Decoding test of the WIAT, did not result in a significant main effect for Aggression Status (F = .586, df 1,43, $p = .45$), however, there was a significant main effect for Gender (F = 9.96, df 1,43, $p =.003$) and a significant

Table 2. Psychometric Characteristics of Aggressive and Nonaggressive Children

	Aggressive Girls (N=12)		Nonaggressive Girls (N=12)		Aggressive Boys (N=12)		Nonaggressive Boys (N=12)			
Variable	$\bar{x}$	sd	$\bar{x}$	sd	$\bar{x}$	sd	$\bar{x}$	sd	F	
WISC-III										
VIQ	100.67	19.39	94.50	14.54	78.50	26.67	97.33	14.26	4.99*	A♀>A♂
PIQ	96.50	15.10	95.25	12.66	87.92	15.55	97.25	14.80	n.s.	
FSIQ	98.50	14.77	94.50	13.55	85.25	12.81	96.92	14.75	n.s.	
WIAT										
Reading	106.64	15.27	93.50	17.42	82.75	14.35	88.58	14.37	9.96‡ 4.45*	♀ > ♂ A♀>A♂
Reading Comp	104.91	15.24	94.64	12.34	79.44	10.16	86.17	11.82	17.93‡ 4.82*	♀ > ♂ A♀>A♂
Spelling	103.09	13.40	95.50	16.53	82.33	11.73	85.83	13.97	13.58‡	♀ > ♂
Mathematics	99.09	8.63	95.83	9.64	84.25	13.97	96.42	9.26	5.03‡ 6.18*	♀ > ♂ A♀>A♂
CPT										
Impulsivity	4.58	4.10	4.17	4.63	13.25	10.55	10.42	13.31	8.17‡	♀ > ♂
Dyscontrol	6.17	5.77	12.50	8.17	23.33	19.67	17.42	17.93	7.24‡	♀ > ♂
Inattention	9.42	8.23	10.08	4.93	12.25	7.53	9.33	8.02	n.s.	

*Interaction Effect: Gender × Aggression Status, $p < .05$; ‡ Gender Main Effect, $p < .05$; A = Aggressive

Gender × Aggression Status interaction (F = 4.45, df 1, 43, $p = .04$). Post hoc analysis revealed significantly higher reading ability scores in aggressive girls ($\bar{x}$ 106.64) than in aggressive and nonaggressive boys ($\bar{x}$ 82.70 and $\bar{x}$ 88.58, respectively). Nonaggressive girls ($\bar{x}$ 93.50) did not differ significantly from any of the other groups. Similarly, on the Reading Comprehension subtest, while there was no main effect for Aggression Status (F = .284, df 1,39, $p = .60$), a significant main effect was produced for Gender (F = 17.93, df 1,39, $p < .001$) and a significant interaction effect for Gender × Aggression Status (F = 4.82, df 1,39, $p = .03$). Post hoc analysis showed significantly higher reading comprehension scores for aggressive girls ($\bar{x}$ 104.91) compared to aggressive and nonaggressive boys ($\bar{x}$ 79.44 and $\bar{x}$ 86.17, respectively). As in Reading Decoding, nonaggressive girls ($\bar{x}$ 94.64) did not differ significantly from any other group.

Achievement tests of spelling resulted in a significant main effect for Gender only (F = 13.58, df 1, 43, p = .001) with girls scoring higher than boys. There was no main effect for Aggression Status (F = .22, df 1,43, p = .64) or interaction effect for Gender × Aggression Status (F = 1.83, df 1,43, p = .18).

Analysis of the mathematics subtest did not result in a main effect for Aggression Status (F = 2.22, df 1,43, p = .14), but there was a significant main effect for Gender (F = 5.03, df 1,43, p = .03), and a significant Gender × Aggression Status interaction effect (F = 6.18, df 1,43, p =.02). Aggressive boys ($\bar{x}$ 84.25) had significantly lower mathematics achievement scores than aggressive girls ($\bar{x}$ 99.09) and nonaggressive boys ($\bar{x}$ 96.42).

Dimensional assessment of academic achievement using Pearson product-moment correlation, showed that parent ratings of delinquency (CBCL Delinquency scores) were inversely related to WIAT- Reading Comprehension scores, in boys only (r = - 0.63, p < 0.01), and with WIAT-Spelling (r = - 0.42, p = 0.05), only in girls.

Analysis of Continuous Performance Test scores revealed a significant main effect for Gender on the measure of Impulsivity (F = 8.173, df 1,44, p =.006), reflecting lower scores for girls ($\bar{x}$ 4.38) compared to boys ($\bar{x}$ 10.79). There was no main effect for Aggression Status (F = 0.39, df 1,44, p = .54), nor was there a significant Gender × Aggression Status interaction effect for Impulsivity (**Figure 2**).

A significant main effect for Gender (F = 7.24, df 1,2, p <.01) was also found on CPT Dyscontrol (believed to capture fidgetiness), on which girls scored lower than boys.

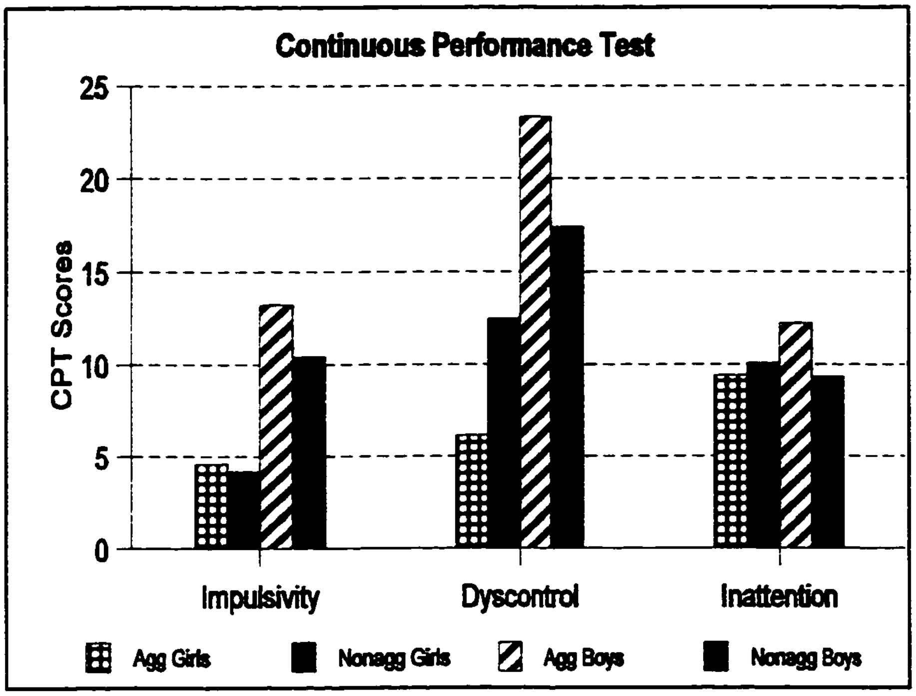


Figure 2. CPT scores in 7 - 10 year-old girls and boys. Aggressive girls (N = 12), nonaggressive girls (N=12), aggressive boys (N = 12), nonaggressive boys (N = 12).

There was no main effect for Aggression Status (F = 0.003, df 1,44, p = .96), nor interaction effect for Gender × Aggression Status (F = 2.23, df 1,44, p = .14). CPT-Inattention results showed no main effects for Gender (F = .245, df 1,44, p = .623) or Aggression Status (F = .285, df 1,44, p = .596), nor an interaction effect for Gender × Aggression Status (F = .723, df 1,44, p = .40).

Dimensional assessment of CPT measures of inattention, impulsivity and dyscontrol, using Pearson product-moment correlation, showed that among boys only, teacher ratings of aggressive behavior (IOWA-Aggression) and conduct problems (IOWA- Conduct) negatively correlated with CPT Inattention measures (r = - 0.52, p = 0.01, for both). There were no significant correlations between parent ratings and CPT measures.

Overall, significant interactions for measures of academic achievement and verbal ability indicate that, whereas aggressive boys have verbal and academic difficulties relative to non-aggressive boys, aggressive girls have better skills relative to non-aggressive girls. CPT results revealed girls to be significantly less impulsive than boys and to exhibit less fidgetiness. Both categorical and dimensional analyses show greater cognitive difficulties associated with aggression in boys, but not in girls, although the nature of cognitive impairment is somewhat different.

Childhood Psychiatric Disorder Distinctions

Structured interviews with parents, using the Diagnostic Interview Schedule for Children (DISC) version 2.1 (Shafer et al., 1989), provided information on gender differences in the development of childhood psychiatric disorders in aggressive and non-aggressive children. General Loglinear Analysis for categorical variables was used to examine associations among gender, aggression, and the Disruptive Behavior Disorders (**Figure 3**). There was a significant three-way interaction effect for Aggression Status × Gender × ADHD ($\chi^2 = 40.33$, $p < .001$). All aggressive girls and boys in this sample had diagnosed ADHD, and ADHD was present in all but one of the nonaggressive boys. Nonaggressive girls had the least incidence (41.7%) of ADHD.

General Loglinear analysis also revealed a significant three-way interaction of Aggression Status × Gender × ODD ($\chi^2 = 29.54$, $p < .001$). All aggressive girls and all but one aggressive boy (91.7%) had diagnosed ODD. Nonaggressive boys had somewhat

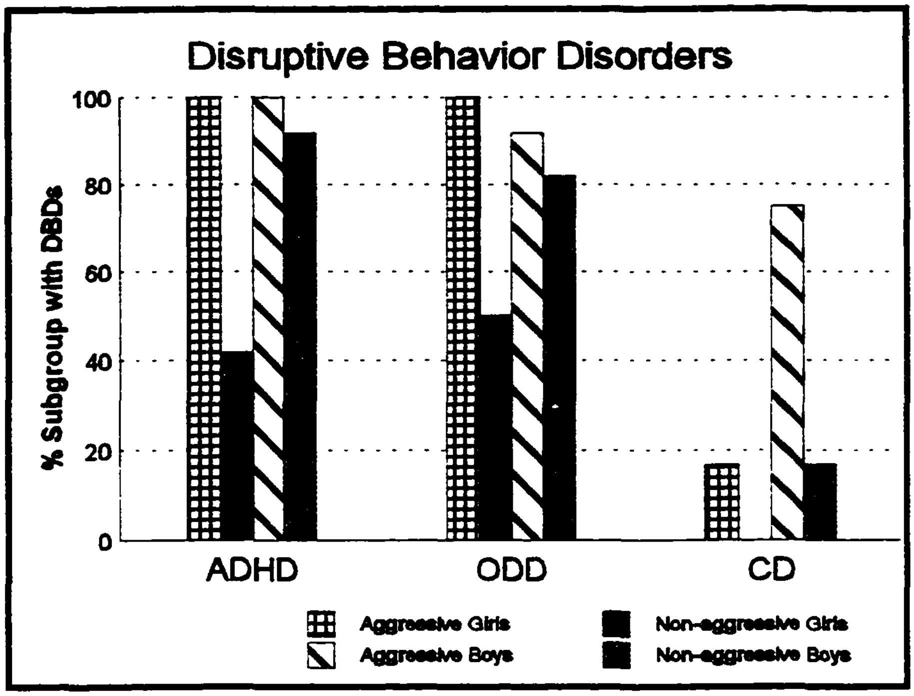


Figure 3. Diagnostic Interview Schedule for Children (DISC), v.2, DBDs in children (N = 48).

less ODD (81.8%) and nonaggressive girls had the least reported ODD (50%). Conduct Disorder was found in 27% of the children. There was a significant three-way interaction effect for Aggression Status × Gender × CD ($\chi^2 = 29.32, p < .001$). Aggressive boys had the highest incidence of CD (75%), while nonaggressive girls had no reported CD. Aggressive girls and nonaggressive boys (16.7% for each subgroup) were alike in the reported incidence of CD.

Aggressive girls were represented equally with aggressive boys in diagnosed ADHD, and ODD, but were more like nonaggressive boys in the incidence of CD. Nonaggressive girls were least represented in diagnosed DBDs. Most children had been referred to this study due to disruptive behaviors. Thus, the high incidence of DBDs is a result of the referral process.

General Loglinear Analysis did not reveal significant differences among the children for either Major Depressive Disorder (MDD) ($\chi^2 = 2.78, p = .60$) or Dysthymic Disorder (DD) ($\chi^2 = 2.85, p = .58$). There was one reported case each of DD and MDD in aggressive girls, and a single reported case of MDD in aggressive boys. All other children were without diagnosed mood disorder.

Differences of gender and aggression status and comorbidity of anxiety disorders were assessed using General Loglinear Analysis. There was a significant interaction effect for Aggression Status × Gender × Overanxious Disorder of Childhood/Generalized Anxiety Disorder (OAD/GAD) ($\chi^2 = 33.21, p < .001$). 13.3% of all children were reported to have symptomatology consistent with a diagnosis of OAD/GAD. The greatest incidence of diagnosed OAD/GAD (33.3%) was reported among aggressive girls. There was no reported OAD/GAD among nonaggressive girls. Aggressive and nonaggressive boys (9.1% and 8.3%, respectively) each had a single reported case of OAD/GAD. There was a significant interaction effect for Aggression Status × Gender × Separation Anxiety Disorder (SAD) ($\chi^2 = 27.09, p < .001$). Among the 15.2% of the children reported to suffer from SAD, aggressive boys had the highest reported incidence (33.3%), compared to nonaggressive boys (8.3%), and aggressive or nonaggressive girls (8.3% and 10%, respectively).

The children in this study were assessed dimensionally using the IOWA Conners Teacher Questionnaire (IOWA). The IOWA CTQ (Loney and Milich, 1982), is comprised of factors for Conduct Problems, Hyperactivity, and Inattention-Passivity, as well as scales which allow distinctions between symptom profiles for hyperactive (I/O scale) and aggressive (A scale) disorders, and a Hyperactivity Index which selects children with both hyperactive and aggressive disorders. Two-way factorial analysis of variance of the Conners Teacher Questionnaire ratings revealed significant main effects for Gender for all factors and scale scores, but no significant main effects for Aggression Status nor significant interaction effects (**see Table 3**). Thus, the significant main effects for Gender for Conduct factor (F = 13.40, df 1,42, *p* = .001), Hyperactivity factor (F = 8.68, df 1,42, *p* =.005), Inattention/Passivity factor (F = 7.55, df 1,42, *p* = .009), Hyperactivity Index (F 13.95, df 1,42, *p* = .001), the Iowa Inattention/ Overactivity scale (F = 11.08, df 1,42, *p* = .002), and the Iowa/Aggression scale (F = 13.59, df 1,42, *p* = .001), reflect the teachers' perceptions of a greater degree of behavioral difficulties for boys than girls.

The Children's Aggression Scales - Parent Version (CAS-P), and Teacher Version (CAS-T), assess the frequency and severity of aggressive acts in five domains, distinguishing between aggression in the home as compared to aggression in the school environment. Parental aggression ratings (CAS-P) produced significant main effects for Aggression Status on three of five measures, with no significant main effects for Gender or Interaction effects (**Table 3**). Thus, parental ratings resulting in significant main effects of Aggression Status for Verbal Aggression (F = 12.39, df 1,39, *p* = >001), Aggression Against Objects and Animals (F = 11.03, df 1,40, *p* = .002), and Provoked Physical Aggression (F = 11.69, df 1,40, *p* = .001) differentiated prepubertal behaviors by level of aggression but not by gender of the child. However, parental ratings of Unprovoked Unprovoked (Initiated) Aggression yielded significant main effects for Aggression Status (F = 19.71, df 1,40, *p* <.001), and Gender (F = 4.63, df 1,40, *p* = .04), with no significant

Table 3. Behavior Ratings in Girls and Boys (7 - 10 yrs of age)

	Aggressive Girls N = 12		Nonaggressive Girls N = 12		Aggressive Boys N = 12		Nonaggressive Boys N = 12		Effect (Gender ¶) (Aggression†) (Interaction‡)	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	F	Sig.
IOWA CTQ										
Conduct[1]	1.47	0.88	0.92	0.77	2.00	0.55	1.94	0.68	13.40	.001¶
Hypfacto[1]	1.90	0.52	1.26	0.87	2.11	0.58	2.23	0.71	8.68	0.01¶
Inatten/Pass[1]	1.30	0.59	1.41	0.95	1.98	0.51	1.89	0.69	7.55	0.01¶
Hypindex[1]	1.77	0.57	1.27	0.77	2.15	0.53	2.19	0.50	13.95	.001¶
Iowa I/O[2]	9.36	3.59	6.75	4.14	11.73	2.61	11.25	3.60	11.08	<.01¶
Iowa Agg[2]	6.82	4.67	3.33	3.65	9.27	2.83	9.00	3.84	13.59	.001¶
CAS -P[3]										
Verbal	8.50	5.03	4.25	3.44	11.32	5.47	5.66	4.15	12.39	.001†
Object/Animal	2.03	1.53	0.60	1.05	3.26	2.43	1.35	1.48	11.03	.002†
Provoked Phys	3.25	1.87	1.75	1.68	4.75	1.86	2.10	2.35	11.69	.001†
Initiated Phys	2.73	2.73	0.49	0.75	4.31	2.21	1.41	1.26	4.63 19.71	0.04† .001¶
Use of weapon	0.00	0.00	0.04	0.14	0.26	0.31	0.00	0.00	4.43 9.71	0.05¶ .003‡
CAS-T[3]										
Verbal	3.00	2.92	1.96	2.70	5.67	1.79	3.09	2.07	5.31 4.91	0.03¶ 0.03†
Object/Animal	0.58	0.53	0.22	0.65	1.79	1.00	0.79	0.71	14.96 8.18	.001¶ .007†
Provoked Phys	1.01	1.11	0.55	1.20	2.32	1.44	1.18	1.13	5.90 4.08	0.02¶ 0.05†
Initiated Phys	0.74	1.16	0.43	1.35	2.20	1.55	1.22	1.07	7.37	0.01¶

[1]Scores : 0 "not at all", 1 "just a little", 2 "pretty much", and 3 "very much" averaged to get factor score.

[2]Based on two five-item subscales derived from the Conners Teacher Rating Scale (Conners, 1969).

[3]Scores range from 0 "never", to 4 "most days".

interaction effect (F = .32, df 1,40, p = .58). Aggressive boys had significantly higher ratings of initiated aggression than nonaggressive boys, and aggressive girls had significantly higher ratings of provoked aggression than nonaggressive girls. However, aggressive boys did not receive significantly greater ratings of initiated aggression than aggressive girls. Analysis of Aggression Involving a Weapon resulted in a significant main effect for Gender (F = 4.33, df 1,40, p = .05), but not for Aggression Status (F = 3.84, df 1,40, p =.057). A significant interaction effect (F = 9.71, df 1,40, p = .003), reflected greater use of weapons in aggressive boys than in nonaggressive boys, with no use of weapons reported in either aggressive or nonaggressive girls.

Results of the two-way factorial analysis of the CAS- T differed from those of the parent version in that significant main effects were found both for Gender and for Aggression Status in three of the five domains. Analysis of Verbal Aggression resulted in significant main effects for both Gender (F = 5.31, df 1,38, p = .03), and Aggression Status (F = 4.91, df 1,38, p =.03), with aggressive boys rated as more verbally aggressive than all other groups, but significantly greater than nonaggressive girls only. Aggressive girls and nonaggressive boys were rated as nearly equal in verbal aggression. There was no significant interaction effect (F = .964, df 1,38, p = .33). Analysis of Aggression Against Objects and Animals produced significant main effects for Gender (F = 14.26, df 1,37, p = .001) and Aggression Status (F = 8.18, df 1,37, p = .007), but no significant interaction effect (F = 1.98, df 1,37, p = .17). Aggressive boys showed significantly greater levels of aggression against objects and animals than all other groups. Analysis of Provoked Physical Aggression also resulted in significant main effects for Gender (F =

5.90, df 1,38, p = .02) and Aggression Status (F = 4.08, df 1,38, p = .05), but no significant interaction effect (F = .787, df 1,38, p = .38). Provoked physical aggression was significantly greater in aggressive boys than in nonaggressive girls only. Initiated Physical Aggression analysis produced a significant main effect for Gender (F = 7.37, df 1,38, p =.01), but there was no main effect for Aggression Status (F = 2.31, df 1,38, p = .14), and no significant interaction effect (F = .717, df 1,38, p = .40). Initiated physical aggression was greater in boys than girls. There were no teachers who reported having knowledge of children's use of weapons.

Family History Distinctions

The relationship of family psychopathology to the expression of aggression in children was investigated in this study through parent interviews assessing problem areas including aggressive and antisocial behaviors, internalizing symptoms, substance abuse, ADHD, cognitive impairment and psychotic symptomatology. Data for siblings were not included in this study because most siblings were below the age of risk for many of the domains assessed. Data were obtained for 91 parents, 160 grandparents and 261 aunts and uncles for a total of 512 first and second degree relatives.

Two-way analysis of variance (ANOVA) of the incidence of first and second degree relatives with a history of Internalizing difficulties produced a significant main effect for Gender (F = 6.84, df 1,42, p = .01), with greater prevalence of internalizing difficulties reported in the families of boys than in the families of girls. There was no main effect for Aggression Status (F = 2.50, df 1,42, p = .12), nor interaction effect of Gender × Aggression Status (F = .155, df 1,42, p =.70). There were no other significant findings based upon measures of family psychopathology including all first and second degree relatives, although incidence of cognitive difficulties approached significance for Aggression Status (F = 3.85, df, 1,42, p =.056). Although just short of significance, nearly twice the incidence of antisocial behavior was reported in the fathers of aggressive boys as compared to the fathers of aggressive girls (F = 3.99, df 1,42, p =.052). Thus, gender differences were found in just one symptom domain (Internalizing disorder) when all family members were included, and in antisocial behavior among fathers (see **Table 4**). In all other domains assessed, influence of family history of psychopathology upon aggressive behavior was not found to be statistically significant and did not differentially influence aggressive behavior in girls and boys.

Table 4. Family Psychopathology

Percentage of 1st and 2nd Degree Relatives With History of Disorder						
	Aggressive Girls	Nonagg Girls	Aggressive Boys	Nonagg Boys	F ratio	Sig.
Antisocial Behavior (Father's)	0.12	0.15	0.23	0.12	3.99	0.052
Internalizing	0.17	0.08	0.27	0.22	6.84‡	0.01
Cognitive Difficulties	0.10	0.09	0.19	0.06	3.85	0.056

‡ Gender Main Effect

Dimensional assessment of family history of psychopathology, using Pearson product-moment correlation, showed that by parent ratings (CBCL - Delinquency), delinquent behavior among boys was positively correlated with a family history of aggressive behavior ($r = 0.65, p = 0.001$), antisocial behavior ($r = 0.50, p = 0.02$), and that both CBCL - Delinquency and CBCL - Aggression were positively correlated with a family history of cognitive difficulties ($r = 0.50, p = 0.02$; $r = 0.60, p < 0.01$, respectively). Among the girls, CBCL- Aggression was positively correlated with a family history of ADHD ($r = 0.46$, $p = 0.03$) and Thought Disorder ($r = 0.52$, $p = 0.01$), whereas CBCL - Delinquency was positively correlated with a family history of Internalizing Disorder ($r = 0.42$, $p = 0.05$). Teacher ratings of aggression (IOWA-Aggression) and conduct problems (IOWA-Conduct) significantly covaried with family psychopathology only among the girls, with higher ratings of girl's aggression and conduct problems covarying with greater incidence of Thought Disorder among family members ($r = 0.45$, $p = 0.03$; $r = 0.42$, $p = 0.05$, respectively). Thus, the general trend in dimensional analysis was for increased aggression in boys to be associated with a family history of aggressive/antisocial behavior and cognitive difficulties. In contrast, aggression in girls was more closely associated with ADHD, Thought Disorder and Internalizing Disorder.

Demographic Distinctions

An assessment of the child's home environment was obtained through interviews with parents ascertaining the following: number of family members living in the child's home; parents' marital status; amount of contact child had with parents; educational, and job status of parents.

General Loglinear Analysis of categorical variables was used to examine differences among aggressive behavior, gender and home environmental variables (see **Table 5**). Overall, fewer children were reared in dual-parent homes (28.3%) than in single parent homes. There was a significant interaction effect for Aggression Status × Marital Status ($\chi^2 = 13.22$, $p = 0.04$) and Gender × Marital Status ($\chi^2 = 12.44$, $p = 0.05$).

Aggressive boys had the lowest incidence (9.1%) of dual-parent homes, and aggressive girls had the highest (45.5%).

Table 5. Demographic Information in Aggressive and Nonaggressive Girls and Boys Age 7 - 10 years

	% Total Sample	% Aggressive Girls	% NonAgg Girls	% Aggressive Boys	% NonAgg Boys
Marital Status					
Married	28.3	45.5	25.0	9.1	33.3
Not Married	71.7	54.5	75.0	90.9	66.7
Paternal Contact					
Daily	35.4	41.7	33.3	25.0	41.7
Weekly - No Contact	64.6	58.3	66.7	75.0	58.3
Maternal Contact					
Daily	85.1	91.7	91.7	63.6	91.7
Weekly - No Contact	14.9	8.3	8.3	36.4	8.3
Paternal Education					
H.S. Grad or >	81.1	100.0	80.0	66.7	77.8
< H.S. Education	18.9	0.0	20.0	33.3	22.2
Maternal Education					
H.S. Grad or >	78.0	100.0	83.3	50.0	80.0
< H.S. Grad	22.0	0.0	16.7	50.0	20.0
Paternal Employment					
Employed	62.2	87.5	30.0	44.4	90.0
Unemployed	37.8	12.5	70.0	55.6	10.0
Maternal Employment					
Employed	43.2	45.5	25.0	30.0	72.7
Unemployed	56.8	54.5	75.0	70.0	27.3

The potential influence of marital status on children's behavior was assessed using independent samples t-tests of parent ratings of delinquency (CBCL-Delinquency) and teacher ratings of conduct problems (IOWA - Conduct). Among the boys, being raised in single-parent families was associated with significantly higher parent ratings of delinquency ($t = 2.75$, $p = 0.01$) compared to boys raised dual-parent homes. In contrast, teachers rated boys from dual-parent homes as having greater conduct problems than boys from single-parent homes ($t = 2.16$, $p = 0.04$).

Three measures of paternal influence in the home environment were examined. Among the girls and boys in this study, less than half (35.4%) had daily contact with their father. Of these children, aggressive boys had the least opportunity for interaction with their father, followed by nonaggressive girls (33.3%) and aggressive girls and nonaggressive boys (41.7% for each). There was a significant interaction effect for Aggression Status × Gender × Father's Education Level ($\chi^2 = 19.69$, $p = 0.003$). Aggressive boys had the highest incidence of fathers with less than high school education (33.3%), while aggressive girls had the highest incidence of fathers with high school or better education (100%). Dimensional analysis using Spearman rank order correlation, showed a tendency for less education among the fathers to covary with higher rates of CBCL - Delinquency ($r_s = -0.44$, $p = 0.06$) and CBCL-Aggression ($r_s = -0.38$, $p = 0.11$), among the boys only.

There was also a significant interaction effect for Father's Employment Status × Aggression Group ($\chi^2 = 14.45$, $p = 0.03$). 62.2% of fathers in this sample were employed. The highest rates of employment were found among nonaggressive boys (90%) and aggressive girls (87.5%). The lowest rate of employment was found in fathers of nonaggressive girls (30%). Using independent samples *t*-tests, father's employment status ($t = 2.10$, $p = 0.05$) was found to be significant, relative to parent ratings of girl's aggression (CBCL-Aggression). Higher rates of father's employment was associated with higher rates of aggression among the girls, but not among the boys.

Mother's frequency of contact with child, education and job status were also examined using General Loglinear Analysis. There was a significant interaction effect for Aggression Status × Gender × Mother's Frequency of Contact ($\chi^2 = 29.10$, $p < .001$). 14.9% of the sample had less than daily contact with their mother, and of those children having infrequent contact with their natural mother, aggressive boys (36.4%) had the least contact compared to all three other groups (8.3% for each). Mother's level of education was also found to be associated with aggression status and gender. There was a significant interaction effect for Aggression Status × Gender × Mother's Education ($\chi^2 = 21.40$, $p = .002$). The mothers of 22% of the children in this sample had less than a high school education. Aggressive boys had the greatest incidence of low-education-status maternal parent (50%), compared to 20% for nonaggressive boys, 16.7% for nonaggressive girls, and 0% incidence in aggressive girls. While 56.8% of the mothers of children in this sample were unemployed, there were no significant differences regarding maternal employment status.

The number of family members living in a household was examined using two-way factorial analysis of variance (ANOVA). Analysis of the total number of children living in a household did not result in main effects for Aggression Status ($F = 0.59$, $p = 0.45$) or Gender ($F = 1.9$, $p = 0.18$). However, there was a significant interaction effect for Aggression Status × Gender ($F = 8.47$, $p = 0.006$), reflecting significantly more children in households of aggressive boys than aggressive girls. Similarly, analysis of the total members of a household did not produce significant main effects for Aggression Status (F = 0.32, $p = 0.57$) or Gender (F = 0.04, $p = 0.85$), but there was a significant interaction effect for Aggression Status × Gender (F = 4.31, $p = 0.04$), reflecting more family members per households of aggressive boys.

Dimensional assessment of family adversity using Pearson product-moment correlation, showed that among the boys, a greater number of children per household was associated with higher parental ratings of aggression ($r = 0.41$, $p = 0.05$). (See summary of correlational data below, **Table 6**.)

Table 6. Correlations of Behavioral Ratings with Cognitive Measures, Family Psychopathology and Family Adversity.

Parent Ratings				**Teacher Ratings**			
CBCL Delinquency		**CBCL Aggression**		**Iowa Conduct**		**Iowa Aggression**	
Variable	*r*	Variable	*r*	Variable	*r*	Variable	*r*
Cognitive Measures*							
♂FSIQ/PIQ	- 0.45	♂FSIQ	- 0.40				
♂Reading	- 0.69						
♀ *Spelling*	- 0.42			♂Inattention	- 0.52	♂Inattention	- 0.52
Family Psychopathology*							
♂Aggressive	0.65						
♂Antisocial	0.50						
♂Cognitive	0.50	♂Cognitive	0.60				
♀ *Internalizing*	0.42	♀ *ADHD*	0.46				
		♀ *Thought Dx*	0.52	♀ *Thought Dx*	0.42	♀ *Thought Dx*	0.45
Family Adversity*							
♂ Father's Education	- 0.44	♂ Father's Education	- 0.38				
		♂ # Children	0.41				
♂# Adults	- 0.49	♀ # *Adults*	0.47			♀ # *Adults*	0.51

♂ In boys only; ♀ In girls only; * $p < .05$

However, higher parental ratings of delinquent behavior covaried with having fewer numbers of adults per household ($r = -0.49$, $p = 0.02$). In contrast to boys, whose greater behavioral difficulties were associated with single–parent homes, among the girls, both parent ($r = 0.47$, $p = 0.02$) and teacher ($r = 0.51$, $p = 0.01$) ratings of aggression were positively correlated with a larger total number of adults per household. Thus, the general trend of associations is for increased circumstances of adversity in the home environment to be associated with higher rates of aggression among boys only.

Neurobiological Distinctions

Central 5-HT function in prepubertal children was assessed by measuring the prolactin (PRL) response to fenfluramine (FEN) challenge. While experimental stringency would suggest conducting separate FEN and placebo challenges in all children in this study, in adults (Coccaro et al., 1989; McBride, Anderson, Hertzig, Sweeney, Kream, et al., 1989), adolescents (Stoff et al., 1992), and children (Halperin et al., unpublished data), studies indicate that PRL does not change in response to placebo challenge. To ensure that the PRL response in girls in this study was directly related to the administration of FEN, a subsample of girls (N = 9) was administered both active and placebo challenges. As shown in **Figure 4**, FEN caused a significant increase in PRL relative to placebo. Placebo did not result in a significant elevation in PRL, as compared to baseline, at a any time point. Two-way (Time × Drug) repeated measures analysis of variance yielded significant main effects for Time ($F = 6.56$, df 6, 48, $p < .001$), Drug ($F = 9.03$, df 1,8, $p = .017$), and a significant Time × Drug interaction ($F = 8.61$, df 6, 48, $p < .001$). Further

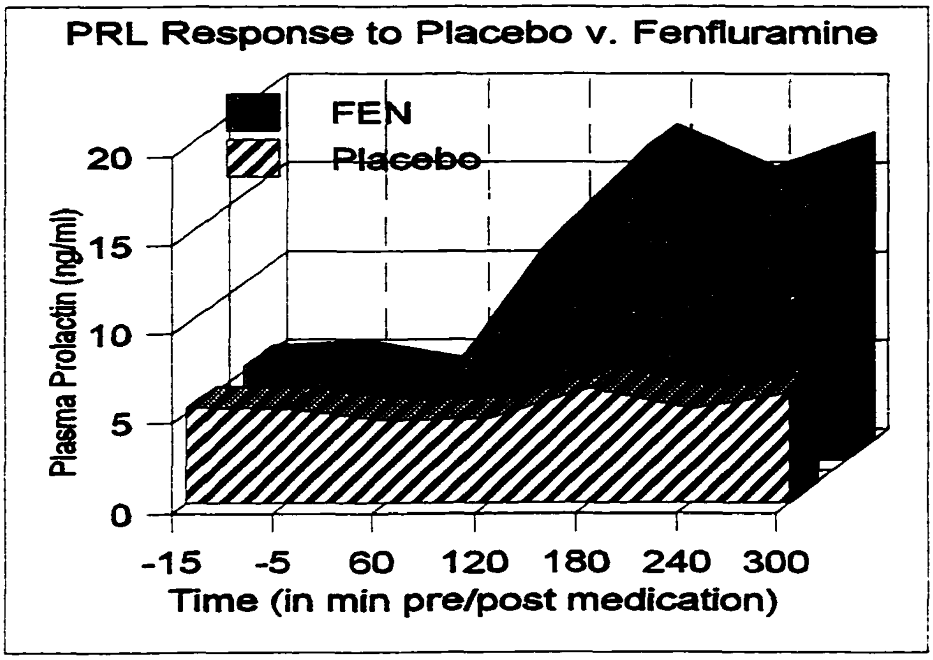


Figure 4. PRL response to 1 mg/kg FEN and Placebo in 9 girls (7 - 10-year-olds).

placebo challenges were not conducted as they would have added significantly to the time commitment required of the children and their families, and to the discomfort of the child.

Prior to assessing the PRL response to FEN challenge, it was important to determine whether any groups differed with regard to absorption and metabolism of fenfluramine. Changes in plasma fenfluramine and its active metabolite norfenfluramine were analyzed using three-way mixed analysis of variance conducted with two between group variables (Gender and Aggression Status) and one within group variable (Time). Analysis of plasma fenfluramine (**Figure** 5) produced a significant main effect for Gender ($F = 4.23$, df 1,34, $p = .047$), reflecting higher plasma fenfluramine levels for girls compared to boys over all 5 time points post fenfluramine administration. There was no significant main effect for Aggression Status ($F = 0.14$, df 1,34, $p = .71$). There was a

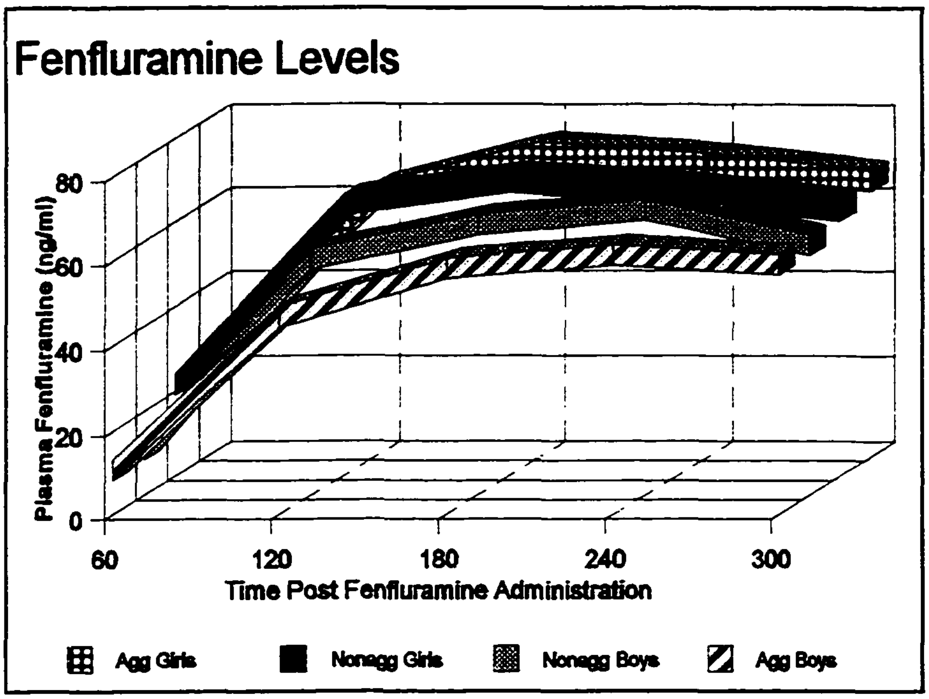


Figure 5. Fenfluramine levels in children. (Aggressive girls N = 9; nonaggressive girls N=10; aggressive boys N = 9; nonaggressive boys N = 10).

significant main effect for Time (F = 168.65, df 4, 136, p <.001), but no interaction effect for Gender × Aggression Status × Time (F = .31, df 4,136, p = .87).

Analysis of plasma norfenfluramine (**Figure 6**) resulted in a significant main effect for Time (F = 245.93, df 4, 136, p <.001) and an interaction effect for Aggression Status × Time (F = 2.81, df 4,136, p =.028) accounted for by a consistently lower level of plasma norfenfluramine in aggressive boys and girls compared to nonaggressive boys and girls which was significant at the fourth time point post-FEN. There were no interaction effects for Gender × Time (F = .77, df 4, 136, p = .54) or Gender × Aggression Status × Time (F = .82, df 4, 136, p = .52). There were no main effects for Gender (F = .68, df 1, 34, p = .41), Aggression Status (F = 3.09, df 1,34, p = .09) or Gender × Aggression Status interaction (F = 1.10, df 1,34, p = .30).

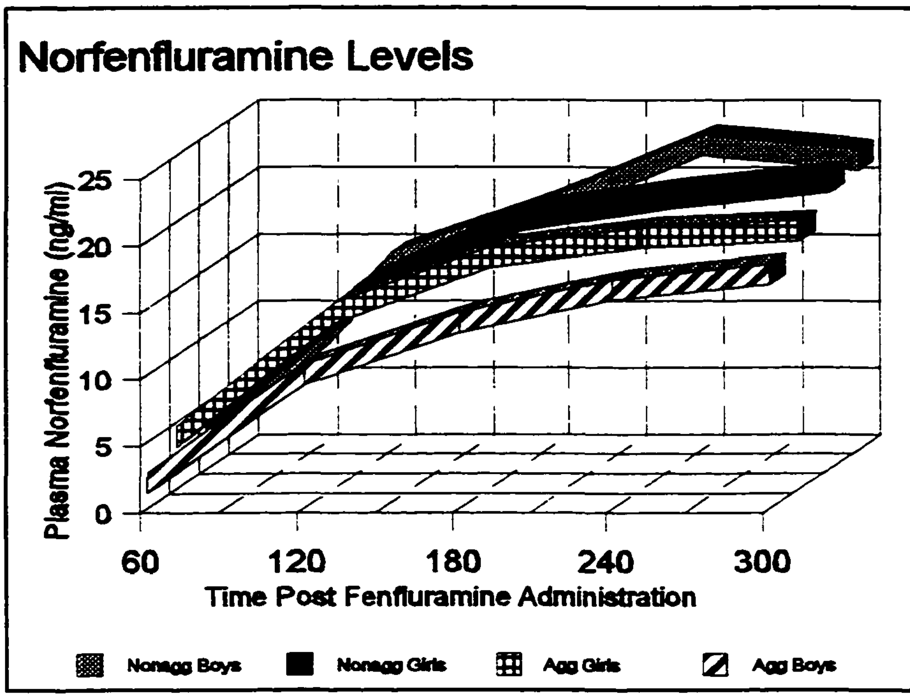


Figure 6. Norfenfluramine levels in children. (Aggressive girls N=9; nonaggressive girls N=10; aggressive boys N=9; nonaggressive boys N=10).

Prolactin response to fenfluramine challenge as a function of gender and aggression status, was analyzed with medication, an index of the subjects' plasma fenfluramine/norfenfluramine levels, as a covariate (**Figure** 7). Three-way mixed analyses of variance were conducted, with two between group variables (Gender and Aggression Status) and one within group variable (Time). There were no main effects for Gender ($F = .23$, df 1,33, $p = .64$) or Aggression Status ($F = .00$, df 1,33, $p = .95$) and no interaction effect for Gender × Aggression Status ($F = .18$, df 1,33, $p = .67$). There was a significant main effect for Time ($F = 5.05$, df 6, 203, $p < .001$), but there were no significant interaction effects for Gender × Time ($F = 1.00$, df 6,203, $p > .42$), Aggression Status × Time ($F = 1.45$, df 6, 203, $p > .19$), nor Gender × Aggression Status × Time ($F = 1.11$, df 6, 203, $p > .35$).

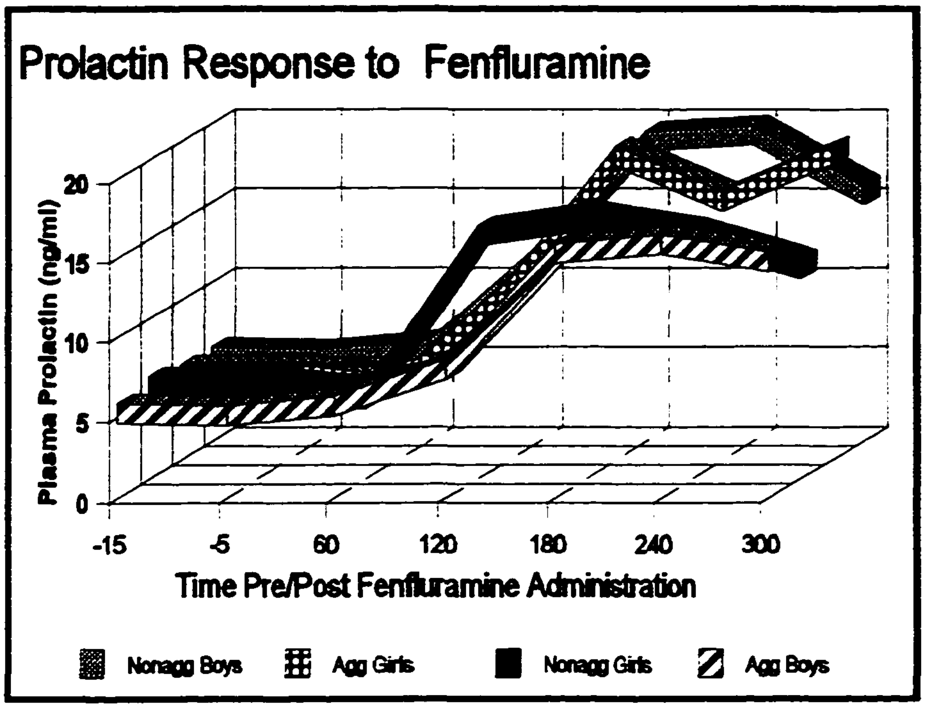


Figure 7. Prolactin response to 1 mg/kg fenfluramine in children. (Aggressive girls N = 9; nonaggressive girls N = 10; aggressive boys N = 9; nonaggressive boys N = 10)

Peak Δ PRL response to FEN was examined using a two-way analysis of covariance (ANCOVA) (Aggression Status × Gender) controlling for peak medication (**Table 7**). There were no significant main effects for Aggression Status (F = .057, df

Table 7. Comparison of Biological Measures

	Aggressive Girls (N = 9)		Nonaggressive Girls (N = 10)		Aggressive Boys (N = 9)		Nonaggressive Boys (N = 10)	
Variable	$\bar{x}$	s.d.	$\bar{x}$	s.d.	$\bar{x}$	s.d.	$\bar{x}$	s.d.
Prolactin								
Baseline (ng/ml)	5.38	1.64	5.79	2.39	5.18	1.10	5.20	1.39
Peak (ng/ml)	22.63	13.80	20.01	10.49	17.81	5.24	20.72	8.11
Peak Δ (ng/ml)	17.26	13.23	14.23	9.01	12.63	4.48	15.52	8.40
Peak Medication	93.44	16.47	91.60	14.34	80.44	16.61	91.30	17.61

1,2, $p = .81$), Gender (F = .04, df 1,2, $p = .84$) or Aggression Status × Gender (F = .491, df 1,2, $p = .49$). Thus, FEN-induced prolactin secretion did not vary significantly as a function of gender or aggression status.

Discussion

Aggression and violence have a tremendously negative impact upon society, inflicting severe financial cost and human suffering. The term aggression comprises a complex array of interdependent behaviors which have internal and external environmental influences. Although violent behavior is most commonly associated with males, recent data indicate that aggression and violence perpetrated by juvenile females have steadily increased at a rate greater than that in male juvenile offenders (Snyder & Sickmund, 1996). Furthermore, considerable data suggest that aggression in males and females is manifested differentially, such that males engage primarily in overt physical aggression, whereas females more often engage in indirect relational aggression. Yet, the literature examining neurologic, cognitive, psychosocial and family correlates of aggressive behavior have focused almost exclusively on male samples, leaving unexamined the question as to whether aggressive behaviors in females have similar correlates.

This dissertation was designed to assess gender differences in neurobiological, cognitive, behavioral and psychosocial correlates of aggression in prepubertal girls and boys. Overall, the results indicate that most factors which have previously been found to characterize aggressive boys were born out by the findings of this study. However, the patterns underlying aggressive behaviors in the girls were often quite different.

Cognitive Findings

Neuropsychological assessment revealed several gender differences with regard to aggressive behavior. Most notably, there was a significant Gender x Aggression interaction for Verbal IQ (VIQ). Relative to their non-aggressive counterparts, aggressive boys had lower VIQ scores, but aggressive girls had higher VIQ scores. The finding of lower VIQ in aggressive boys is consistent with a sizeable literature indicating lower verbal abilities in a wide array of aggressive male samples. However, in contrast, the aggressive girls in this sample showed no evidence of verbal or language-related deficiencies. Consistent with this finding in the verbal domain, aggressive boys, but not aggressive girls, were characterized by deficits in most academic areas. Notably, there was some degree of selectivity of cognitive deficits in that the groups did not differ in Performance IQ (PIQ).

Several investigators have hypothesized causal links between behavioral disturbance and learning problems in children. These hypotheses variously suggest that either early learning and language problems result in increased behavioral disturbance as the child experiences greater failure in school, or that behavioral disturbance interferes with learning and leads to academic underachievement. Robins (1991) suggests that both behavioral disturbance and school failure develop from poor cognitive functioning, while others, who consider bidirectional models to be inadequate in explaining the complexity of behavior and learning, posit reciprocal, multifactorial causal models (Ohman & Magnusson, 1987).

The results of this study suggest that the relationship between aggression and learning is different across the genders. Whereas previous hypotheses have attempted to link chronic academic failure and heightened aggressive behavior in boys, this link has been less apparent in girls. The findings from this study do not support a causal relationship between academic failure and aggressive behavior in girls. However, the classification of aggressive and non-aggressive behavior in this study was based upon parent reports. It is noteworthy that unlike the aggressive boys, the aggressive girls in this study. were not perceived as extremely aggressive by their teachers. The behavioral disturbance of aggressive girls in this sample was less apparent in the classroom setting and may therefore be less likely to impact on the acquisition of verbal/academic skills. It may also be that among the girls, aggressive behaviors are not integral with academic difficulties, and do not share a common etiology. Aggressive girls in this sample appear to have better-developed verbal skills. This may lead to more socially manipulative aggressive behaviors, while boys's verbal limitations may heighten a general level of frustration, and lead to more overt physical confrontation. This hypothesis is consistent with prospective data indicating higher school achievement as well as higher career orientation in verbally aggressive girls compared to physically aggressive girls (Pulkkinen, 1992). Cluster analysis of the prospective data suggested that girls' aggressiveness may have combined with school problems or been apart from them, but only in the former case was girls' aggressive behavior predictive of negative outcomes..

Continuous Performance Tests of impulsivity, dyscontrol and inattention showed significantly greater impulsivity and dyscontrol (fidgetiness) among boys compared to girls in this group, with aggressive boys having the highest impulsivity scores (nearly 2 standard deviations above the norm). It is this striking difference between behavioral control and normal verbal intelligence versus extreme impulsivity and cognitive impairment which clearly differentiated the aggressive girls from the aggressive boys. This is consistent with research suggesting that language is an underlying variable in both disruptive behavior problems and academic underachievement (Hinshaw, 1992). Verbal skills have long been held to organize and mediate behavior (Luria, 1959;1961; Vygotskii, 1962). Children with language processing difficulties may be at a significant disadvantage in controlling impulsive, disruptive behaviors. A study of language impairment and behavioral characteristics in psychiatrically disturbed children showed that 52.6% of the sample met criteria for language impairment (Cohen, Davine, Horodezky, Lipsett, & Isaacson, 1993). Those children who had previously undiagnosed language impairments, were rated as having the most serious problems with aggression and delinquency. Whereas the behavior of the impulsive/aggressive boys in this study sample may reflect deficits in the verbal domain, the controlled/aggressive girls appear to utilize their language skills to develop and implement strategies to navigate their social and academic environment.

Family History Findings

Family history of psychopathology in first and second degree relatives did not support the hypothesized greater incidence of aggression/antisocial behavior among the family members of aggressive girls as compared to aggressive boys. Although just short of significance, when examined in fathers alone, antisocial behavior was found to be higher among fathers of aggressive boys compared to fathers of aggressive girls. The relative absence of psychopathology among the total sample of first and second degree relatives of aggressive children in this study is inconsistent with evidence of high rates of antisocial behavior among relatives of aggressive children (Biederman et al, 1987; Frick et al, 1992). This lack of a difference may have been due to the limitations of sample size. Additionally, in many cases, the parent who provided family history data often expressed difficulty in giving an accurate and thorough report of the family history of an absent spouse, as well as information specific to the spouse. Thus, it is probable that pertinent data are missing from the family history of pathology.

Family Adversity Findings

The data examining the association of home environment with aggressive behaviors supported the hypothesis of more frequent occurrence of adverse home/family environmental factors among aggressive boys as compared to aggressive girls and nonaggressive girls and boys. Aggressive boys were most often reared in single parent households, had mothers and fathers with less education than parents of other children in this study, and had the least contact with their natural mother. Aggressive boys were also found to be living in homes having more children per household than other children in this study. In sharp contrast, aggressive girls were most often reared in dual-parent households, had mothers and fathers with the most education, and were living in homes with the fewest children per household. The findings in aggressive girls of family environmental advantage relative to other children in this study are difficult to interpret. The advantages that they share – more intact families, better educated parents, and less competition for resources (fewer siblings) may reflect unknown sampling characteristics. Among the aggressive girls, 4 out of twelve were from communities outside of the metropolitan New York City area, compared to 1 child among the nonaggressive girls, and none among aggressive and nonaggressive boys. From this perspective, it is possible that community characteristics uniquely influenced findings of family environmental stability among aggressive girls.

It is also possible that, as compared to girls who are clinically-referred for non-aggressive psychiatric problems (as were the non-aggressive children in this study), aggressive girls have more advantageous environmental backgrounds. Further, It may be that, unlike in boys, psychosocial adversity leads to internalizing difficulties in girls. Without having a normal control group it is difficult to determine whether the aggressive girls in this study were truly "advantaged," or whether they came from "average" homes.

Serotonergic Findings

Examination of gender differences in serotonergic function did not support the hypothesis that prepubertal aggressive girls would have a greater FEN-induced PRL response than aggressive boys and thus does not support a gender-differentiated serotonergic responsivity. As compared to placebo, FEN generated a significant increase in plasma PRL levels. However, the magnitude of the PRL increase did not differ as a function of aggression or gender, and there was no gender by aggression interaction.

The cumulative literature of recent years which examines serotonergic function in preadolescent boys, as well as information from the larger data set from which boys for this study were drawn, suggest that no systematic differences in 5-HT function distinguish aggressive from nonaggressive boys. Some studies have found evidence of reduced serotonergic function in aggressive boys (Kruesi et al. 1990; 1992), others have found evidence of increased serotonergic function in aggressive boys (Castellanos et al. 1995; Halperin et al. 1994; Pine et al. 1997), and still others have found no differences between aggressive and non-aggressive boys (Halperin et al. 1997; Stoff et al. 1992). Consequently, at this time, the question of increased (or decreased) 5-HT function in aggressive girls and boys is a less relevant question. More importantly, in view of the consistent findings of low 5-HT function in aggressive animals and adult males, the significance of varying levels of 5-HT function in children needs to be uncovered. Preliminary analyses raise the possibility that among aggressive children, low 5-HT function may have prognostic significance since, in boys, it is associated with increased familial risk for aggressive/antisocial behavior (Halperin et al. 1997). Exploration of this hypothesis, which would require subgroup analyses, are not possible given the small sample in this study.

Among girls, as compared to boys, central 5-HT function may uniquely co-vary with neurohormonal influences throughout development to mediate behavioral responses. An imbalance in the 5-HT-neurohormonal relationship in girls may result in a relatively broad spectrum of age-related behavioral disorders. Thus, it may be important to prospectively examine 5-HT function among aggressive, non-aggressive and normal control groups of girls, rather than to focus on gender-related differences in 5-HT function.

Limitations of Research

The primary limitation of this research is the small sample size, which not only limited statistical power, but also precluded post-hoc subgroup analyses. The limited sample size is attributable to two factors. First, the invasive nature of the neuroendocrine challenge makes recruitment for such studies quite difficult. While the challenge does not pose significant risk to the children, many parents are reluctant to have their child take a non-therapeutic medication (i.e., fenfluramine) and many children do not want to undergo the needle-stick required for the blood draws. In addition, the low clinic referral rate of aggressive girls contributed to the difficulty in gathering a larger research sample. While there was no difficulty in finding aggressive boys, prepubertal girls who meet criteria for significant aggression are difficult to find.

Another important limitation related to the nature of the sample studied. It is often stated that children drawn from clinical settings are not representative of children in the general population (Goodman et al., 1997), but are more impaired, less competent, and more likely to have comorbid disorders. In this study, the high incidence of DBDs in aggressive girls and boys and nonaggressive boys, as well as a significantly greater incidence of Generalized Anxiety Disorder among aggressive girls and Separation Anxiety among aggressive boys, is consistent with the higher comorbidity associated with clinically referred populations.

Thus, population-based, epidemiological samples are frequently preferable for studies of disorders among youth. However, it is extremely difficult (if not impossible) to conduct this type of biological research in an epidemiologically valid sample. Families of non-referred children, to whom there is little benefit in their participation, will not enroll in studies requiring the administration of medicine on serial blood draws. Furthermore, the lower incidence of identified disruptive antisocial behaviors among females in the general population would necessitate initial screening of thousands of female subjects. Therefore, the findings of this research should be interpreted with the caveat that they may not generalize to all aggressive and non-aggressive girls and boys in the population. This difficulty is particularly evident in the cognitive and psychosocial findings in this study, where the aggressive girls seemed to have advantages over the other groups. Nevertheless, the sample in this study is likely to be representative of families seeking clinical treatment, and as such may have important clinical implications. It has been suggested that behaviorally disruptive and aggressive girls get referred for evaluation and treatment earlier than their male counterparts. While this may represent a socio-cultural bias or intolerance toward such behaviors in female children, it may indicate unique problems within the family that lead to referral, and may not, in fact, indicate true aggression in the child. However, ratings of children's aggression by parent, also hold up by teacher ratings, although aggression is characterized differently.

Group placement and identification of aggressive behavior was also a thorny issue in conducting this research. Unlike research in adults, where patients are the informants, valid self-reports are difficult to obtain from children. As an alternative in this study, parent ratings of aggression on the CBCL were used for group placement of aggressive and nonaggressive girls and boys. It is difficult to know the extent to which the perceptions of the parents reflect true aggression in their children. The widely acknowledged discordance between parent and teacher ratings of aggression ratings was seen in this study, with parents more consistently rating children as aggressive. While teachers were consistent in their ratings of aggressive boys, there was more variability in their assessment of aggressive girls, rating them as similar to nonaggressive boys in verbal and provoked aggression.

Future Research Directions

Significant cognitive differences between girls and boys were found in this study.

An exceptionally high level of impulsivity combined with poor verbal abilities differentiated the aggressive boys from self-controlled, intellectually competent aggressive girls. Further investigation of this outcome is important in understanding the behavioral similarities, differences and underlying mechanisms of aggression in girls and boys. Prospective studies of gender similarities and differences in aggressive and antisocial behaviors, encompassing the peripubertal, adolescent and early adult years, are necessary to document developmental course and long-term outcome. Community-based samples, including aggressive, nonaggressive and normal controls should be recruited to minimize possible error due to sampling characteristics. The assessment of aggression should be expanded to include indirect, relational aggression, in addition to physical aggression. Additionally, determination of aggression status should be validated by parent, teacher and clinician ratings, as well as by peer nominations. Neuropsychological testing of working memory, shifting sets, impulsivity and problem solving, as well as tests of social skills, would contribute to a clearer understanding of the cognitive abilities and deficits in aggressive children and adolescents. Importantly, the development of age and gender-specific criteria to facilitate longitudinal studies is an integral and necessary part of future investigative work.

Summary and Conclusions

As initially hypothesized, the data presented in this study are consistent with the literature indicating that aggressive boys are characterized by overt, physical aggression, cognitive difficulties, and family adversity. However, in girls, aggressive behavior manifests very differently. Aggressive girls were not impulsive, were cognitively and academically competent, and did not experience similar levels of family adversity. Thus, it is likely that there are different underlying determinants for aggression in girls and boys. It is also suggested that aggressive behavior in girls is not unidimensional. It is likely, therefore, that long-term outcome may differ not only across genders but also among girls whose manifestations of aggression require differential diagnosis and treatment strategies.

Appendix A

List of Terms

ADHD	Attention Deficit/Hyperactivity Disorder
CAS-T/P	Children's Aggression Scale- Teacher and Parent Versions
CBCL	Achenbach Child Behavior Checklist - 1991
CD	Conduct Disorder
CPT	Continuous Performance Test
DBD	Disruptive Behavior Disorders
DD	Dysthymic Disorder
DISC	Diagnostic Interview Schedule for Children
FEN	Fenfluramine
5-HT	Serotonin
5-HIAA	5-hydroxyindoleacetic acid; metabolite of serotonin
IOWA-CTQ	Iowa Conners Teacher Questionnaire
MDD	Major Depressive Disorder
NOR-FEN	Norfenfluramine; metabolite of fenfluramine
OAD/GAD	Overanxious Disorder of Childhood/Generalized Anxiety Disorder
ODD	Oppositional Defiant Disorder
PRL	Prolactin
SAD	Separation Anxiety Disorder
WIAT	Wechsler Individual Achievement Test
WISC-III	Wechsler Intelligence Scale for Children - III

Appendix B

Fenfluramine Challenge Procedure

Neurotransmitters such as serotonin influence the hormonal regulation of secretions in the hypothalamic-pituitary-adrenal axis (HPA). Serotonin is thought to modulate prolactin (PRL) release, secreted from the anterior pituitary via neuronal projections from the dorsal raphe nuclei (Van de Kar & Bethea, 1982). While PRL is primarily under tonic dopamine inhibitory control via DA_2 receptors on the pituitary lactotrophs (Tuomisto & Mannisto, 1985), 5-HT is stimulatory and was thought to act indirectly since there are no 5-HT receptors on the pituitary lactotrophs (Lamberts & MacLeod, 1978). The stimulatory effect of 5-HT on the release of PRL in the HPA has led to assessment of central serotonergic function through peripheral hormone measures.

The prolactin response to pharmacological challenge with dl-fenfluramine hydrochloride (Pondimin), which brings about a dose dependent increase in plasma PRL, has been used as an indirect method for evaluating central serotonergic activity. Fenfluramine (FEN) enhances serotonergic transmission by stimulating release of endogenous serotonin from the presynaptic neuron and by blocking serotonin reuptake (Borroni, Ceci, Garattini, & Mennini, 1983; Garatinni, Mennini, & Samanin, 1987) and serotonin's active metabolite norfenfluramine directly stimulates 5-HT receptors. The PRL response to fenfluramine was proposed as reflecting the functional status of both pre- and postsynaptic serotonergic neurons, providing a measure of net serotonergic responsivity in the hypothalamic-pituitary axis (Quattrone, DiRenzo, Schettini, Tedeschi, & Scopacasa, 1978). For many years, d,l-fenfluramine was considered the most specific serotonergic probe (Cowen & Anderson, 1985). It was later shown, however, that it also causes the release of noradrenaline and dopamine, although at doses higher than those affecting 5-HT (Invernizzi, Bereta, Garatinni & Saminin, 1986). D-fenfluramine is a more 5-HT-specific agent, lacking the catecholamine effects of racemic d,l-fenfluramine. Data indicate, however, that the effects of d,l-fenfluramine and d-fenfluramine on prolactin release are virtually identical (Coccaro, Kavoussi & Hauger, 1994). Indirect stimulation of postsynaptic receptors via increased hypothalamic release of serotonin (Van de Kar, 1991) and direct activation of postsynaptic receptors by serotonin's active metabolite norfenfluramine (McCann, Hatzidimitriou, & Ricaurte, 1996) have both been proposed as serotonergic mechanisms mediating FEN-induced PRL release. Studies have variously implicated **5-HT**$_{1A}$ (Aguilar, Ranchal, Aguilar, & Pinilla, 1993; Palazidou, Stephenson, Butler, Coskeran, Chambers & McGregor, 1995), **5-HT**$_2$ (Goodall, Cowen, Franklin & Silverstone, 1993; Park & Cowen, 1995), **5-HT**$_{2A}$ (Lacau-Mengido, Libertun & Becú-Villalobos, 1996), and **5-HT**$_{2C}$ (Lacau-Mengido et al., 1996; McCann, Hatzidimitriou & Ricaurte, 1996) receptors.

References

Achenbach, T.M., Edelbrock, C., & Howell, C. (1987). Empirically -based assessment of the behavioral/emotional problems of 2-3 year old children. Journal of Abnormal Child Psychology, 15, 629-650.

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

Aguilar, E., Ranchal, A., Aguilar, R., & Pinilla, L. (1993). Gonadotropin and prolactin secretion in prepubertal female rats treated with 8-hydroxy-2-(di-n-propylamino) tetralin. Journal of Neural Transmission, 94, 165-173.

Albert, D.J., Jonik, R.H., & Walsh, M.L. (1992). Interaction of estradiol, testosterone, and progesterone in the modulation of hormone-dependent aggression in the female rat. Physiology and Behavior, 52, 773-779.

Allen, S.J., Benton, J.S., & Goodhardt, M.J.e.a. (1983). Biochemical evidence of selective nerve cell changes in the normal ageing human and rat brain. Journal of Neurochemistry, 41, 256-265.

American Psychiatric Association. (1987). Diagnostic and Statistical Manual of Mental Disorders. (Third ed.). Washington,D.C.: American Psychiatric Association.

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

Anastasi, A. (1988). Psychological issues in intelligence testing. In Anonymous, Psychological Testing. (pp. 336-370). New York: Macmillan Publishing Company.

Andrew, J.M. (1982). Memory and violent crime among delinquents. Criminal Justice and Behavior, 9, 364-371.

Angold, A., & Costello, E.J. (1995). The Child and Adolescent Psychiatric Assessment. Psychological Medicine, 25, 755-762.

Archer, J. (1991). The influence of testosterone on human aggression. British Journal of Psychology, 82, 1-28.

Arnold, A.P., & Breedlove, S.M. (1985). Organization and activational effects of sex steroids on brain and behavior: A reanalysis. Hormones and Behavior, 19, 469-498.

Asberg, M., Schalling, D., Traksman-Bendz, L., & Wagner, A. (1987). Psychobiology of suicide, impulsivity, and related phenomena. In H. Y. Meltzer (Ed.), Psychopharmacology: Third Generation of Progress. (pp. 655-688). New York: Raven Press.

Atkins, M.S., & Stoff, D.M. (1993). Instrumental and hostile aggression in childhood disruptive behavior disorders. Journal of Abnormal and Child Psychology, 21, 165-178.

Åsberg, M., Bertilsson, L., Tuck, D., Cronholm, B., & Sjöqvist, F. (1973). Indoleamine metabolites in the crebrospinal fluid of depressed patients before and during treatment with nortriptyline. Clinical Pharmacology and Therapeutics, 14, 277-286.

Bandura, A. (1965). Influence of models' reinforcement contingencies on the acquisition of imitative responses. Journal of Personality and Social Psychology, 1, 589-595.

Barrett, D.E. (1979). A naturalistic study of sex differences in children's aggression. Merrill-Palmer Quarterly, 25, 193-207.

Baumgarten, H.G., & Grozdanovic, Z. (1995). Psychopharmacology of central serotonergic systems. Pharmacopsychiatry, 28(Supplement), 73-79.

Beach, F.A. (1971). Hormonal factors controlling the differentiation, development, and display of copulatory behavior in the ramstergig and related species. In E. Toback, L. Aronson, & E. Shaw (Eds.), Biopsychology of Development. (pp. 249-296). New York: Academic Press.

Becú, D., & Libertun, C. (1982). Comparative maturation of the regulation of prolactin and thyrotropin by serotonin and thyrotropin-releasing hormone in male and female rats. Endocrinology, 110, 1879-1884.

Behar, D., & Stewart, M.A. (1984). Aggressive conduct disorder: The influence of social class, sex and age on the clinical picture. Journal of Child Psychology and Psychiatry and Allied Disciplines, 25(1), 119-124.

Beisler, J.M., Tsai, L.Y., & Stiefel, B. (1986). The effects of fenfluramine on communication skills in autistic children. Journal of Autism and Developmental Disorders, 16, 227-233.

Bennett, J.P., Enna, S.J., Bylund, D.B., Gillin, J.C., Wyatt, R.J., & Snyder, S.H. (1979). Neurotransmitter receptors in frontal cortex of schizophrenics. Archives of General Psychiatry, 36, 927-934.

Bergeman, C.S., Plomin, R., McClearn, G.E., Pedersen, N.L., & Friberg, L.T. (1988). Genotype-environment interaction in personality development: Identical twins reared apart. Psychology and Aging, 3, 399-406.

Bethea, C.L. (1993). Colocalization of progestin receptors with serotonin in raphe neurons of macaque. Neuroendocrinology, 57, 1-6.

Bettencourt, BA., & Miller, N. (1996). Gender differences in aggression as a function of provocation: A meta-analysis. Psychological Bulletin, 119(3), 422-447.

Björkqvist, K., Österman, K., & Kaukiainen, A. (1992). The development of direct and indirect aggressive strategies in males and females. In K. Björkqvist & P. Niemelä (Eds.), Of mice and women: aspects of female aggression. (pp. 51-63). San Diego: Academic Press, Inc.

Björkqvist, K., Lagerspetz, K.M., & Kaukiainen, A. (1992). Do girls manipulate and boys fight? Developmental trends regarding direct and indirect aggression. Aggressive Behavior, 18

Blanchard, R.J., & Blanchard, D.C. (1977). Aggressive behavior in the rat. Behavioral Biology, 21, 197-224.

Borroni, E., Ceci, A., Garattini, S., & Mennini, T. (1983). Differences between D-Fenfluramine and D-norfenfluramine in serotonin presynaptic mechanisms. Journal of Neurochemistry, 40, 891-893.

Botchin, M.B., Kaplan, J.R., Manuck, S.B., & Mann, J.J. (1993). Low versus high prolactin responders to fenfluramine challenge: Marker of behavioral differences in adult male cynomolgus macaques. Neuropsychopharmacology, 9(2), 93-99.

Bradley, P.B., Engel, G., Feniuk, W., Fozard, J.R., Humphrey, P.P., Middlemiss, D.N., Mylecharane, E.J., Richardson, B.P., & Saxena, P.R. (1986). Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. Neuropharmacology, 25, 563-576.

Brain, P.F. (1979). Hormones and Aggression. Montreal: Eden Press.

Brickman, A.S., McManus, M.M., Grapentine, W.L., & Alessi, N. (1984). Neuropsychological assessment of seriously delinquent adolescents. Journal of the American Academy of Child Psychiatry, 23, 453-457.

Broida, J., & Svare, B. (1982). Postpartum aggression in C57BL/6J and DBA/2J mice: experiential and environmental influences. Behavioural and Neural Biology, 3, 76-83.

Brooks-Gunn, J., & Warren, M.P. (1989). Biological contributions to affective expression in young adolescent girls. Child Development, 60, 372-385.

Brown, G.L., Goodwin, F.K., Ballenger, J.C., Goyer, P.F., & Major, L.F. (1979). Aggression in humans. Correlates with cerebrospinal fluid amine metabolites. Psychiatry Research, 1, 131-139.

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.

Bruck, D. (1989). Prevalence and etiology of learning-disabled children's adjustment problems. In J. J. Dumont & H. Nakken (Eds.), Learning Disabilties: Vol.2: Cognitive, social and remedial aspects. (pp. 73-86). Amsterdam, The Netherlands: Swets & Zeitlinger.

Bucht, G., Adolfsson, R., Gottfries, C.G., Roos, B.-E., & Winblad, B. (1981). Distribution of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in human brain in relation to age, drug influence, agonal status and circadian variation. Journal of Neural Transmission, 51, 185-203.

Buikhuisen, W. (1987). Cerebral dysfunctions and persistent juvenile delinquency. In S. A. Mednick & T. E. Moffitt (Eds.), The Causes of Crime: New Biological Approaches. (pp. 168-184). New York: Cambridge University Press.

Buss, A.H. (1961). The Psychology of Aggression. New York: Wiley.

Cadoret, R.J., & Cain, C. (1980). Sex differences in predictors of antisocial behavior in adoptees. Archives of General Psychiatry, 37, 1171-1175.

Cadoret, R.J., & Stewart, M.J. (1991). An adoption study of attention deficit, hyperactivity and aggression and their relationship to antisocial personality disorder. Comprehensive Psychiatry, 32, 73-82.

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

Cairns, R.B., & Cairns, B.D. (1984). Predicting aggressive patterns in girls and boys: A developmental study. Aggressive Behavior, 10, 227-242.

Cairns, R.B., Perrin, J.E., & Cairns, B.D. (1985). Social structure and social cognition in early adolescence: Affiliative patterns. Journal of Early Adolescence, 5, 339-355.

Cairns, R.B., Cairns, B.D., & Neckerman, H.J. (1989). Early school dropout: Configurations and determinants. Child Development, 60(6), 1437-1452.

Cantwell, D.P., & Baker, L. (1991). Association between attention deficit-hyperactivity disorder and learning disorders. Journal of Learning Disabilities, 24, 88-95.

Castellanos, F.X., Elia, J., Kreusi, M.J., Gulotta, C.S., Mefford, I.N., Potter, W.Z., Ritchie, G.F., & Rapoport, J.L. (1994). Cerebrospinal fluid monoamine metabolites in boys with Attention-Deficit Hyperactivity Disorder. Psychiatry Research, 52, 305-316.

Cleare, A.J., Murray, R.M., & O'Keane, V. (1996). Reduced prolactin and cortisol responses to d-fenfluramine in depressed compared to healthy matched control subjects. Neuropsychopharmacology, 14, 349-354.

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., 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., Bergeman, C.S., & McClearn, G.E. (1993). Heritability of irritable impulsiveness: A study of twins reared together and apart. Psychiatry Research, 48, 229-242.

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.

Coccaro, E.F., Kavoussi, R.J., & Hauger, R. (1994). PRL and HVA responses to D- and D,L-fenfluramine in humans. Biological Psychiatry, 35, 644

Cohen, P., Cohen, J., Kasen, S., Velez, C.N., Hartmark, C., Johnson, J., Rojas, M., Brook, J., & Streuning, E.L. (1993). An epidemiological study of disorders in late childhood and adolescence: I. Age- and gender-specific prevalence. Journal of Clinical Psychology and Psychiatry, 34(6), 851-867.

Conners, C.K. (1969). A teacher rating scale for use in drug studies with children. American Journal of Psychiatry, 126, 884-886.

Constantino, J.N., Grosz, D., Saenger, P., Chandler, D.W., Nandi, R., & Earls, F.J. (1993). Testosterone and aggression in children. Journal of the American Academy of Child and Adolescent Psychiatry, 32(6), 1217-1222.

Convit, A., Douyon, R., Yates, K.F., Smith, G., Czobar, P., deAsis, J., Vitral, J., Camus, L., & Volavka, J. (1996). Frontotemporal abnormalities and violent behavior. In D. M. Stoff & R. B. Cairns (Eds.), Aggression and Violence. (pp. 169-194). Mahwah: Lawrence Erlbaum Associates.

Cowen, P.J., & Anderson, I.M. (1985). 5-HT neuroendocrinology: changes during depressive illness and antidepressant drug treatment. In J. F. Deakin (Ed.), The Biology of Depression. (pp. 71-90). London: Gaskell.

Cowen, P.J., & Charig, E.M. (1987). Neuroendocrine responses to intravenous tryptophan in major depression. Archives of General Psychiatry, 44, 958-966.

Crick, N., & Grotpeter, J.K. (1995). Relational aggression, gender, and social-psychological adjustment. Child Development, 66, 710-722.

Crick, N.R., & Dodge, K.A. (1994). A review and reformulation of social-information-processing mechanisms in children's social adjustment. Psychological Bulletin, 115, 74-101.

Crick, N.R. (1997). Engagement in gender normative versus nonnormative forms of aggression: Links to social-psychological adjustment. Developmental Psychology, 33(4), 610-617.

Crowther, J.H., Bond, L.A., & Rolf, J.E. (1981). The incidence, prevalence, and severity of behavior disorders among preschool-aged children in day care. Journal of Abnormal Child Psychology, 9(1), 23-42.

Cummings, E.M., Hollenbeck, B., Iannotti, R.J., Radke-Yarrow, M., & Zahn-Waxler, C. (1986). Early organization of altruism and aggression: developmental patterns and individual differences. In C. Zahn-Waxler, E. M. Cummings, & R. J. Iannotti (Eds.), Altruism and Aggression: Biological and Social Origins. (pp. 165-188). Cambridge: Cambridge University Press.

Cummings, E.M., Iannotti, R.J., & Zahn-Waxler, C. (1989). Aggression between peers in early childhood: Individual continuity and developmental change. Child Development, 69, 887-895.

Dabbs, J.M., Jurkovic, G.J., & Frady, R.L. (1991). Salivary testosterone and cortisol among late adolescent male offenders. Journal of Abnormal Child Psychology, 19(4), 469-478.

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

De Ruiter, A.J., Feitsma, L.E., Keijser, J.N., Koolhaas, J.M., van Oortmerssen, G.A., & Bohus, B. (1993). Differential perinatal testosterone secretory capacity of wild house mice testes is related to aggressiveness in adulthood. Hormones and Behavior, 27, 231-239.

Deakin, J.F., Pennell, I., Upadhyaya, A.J., & Lofthouse, R. (1990). A neuroendocrine study of 5HT function in depression: evidence for biological mechanisms of endogenous and psychosocial causation. Psychopharmacology, 101, 85-92.

DeBold, J.F., & Miczek, K.A. (1981). Sexual dimorphism in the hormonal control of aggrssive behavior of rats. Pharmacology Biochemistry and Behavior, 14(Suppl. 1), 89-93.

DiLalla, L.F., & Gottesman, I.I. (1989). Heterogeneity of causes for delinquency and criminality: Lifespan perspectives. Development and Psychopathology, 1, 339-349.

Donnelly, M., Rapoport, J.L., Potter, W.Z., Oliver, J., Keysor, C.S., & Murphy, D.L. (1989). Fenfluramine and dextroamphetamine treatment of childhood hyperactivity. Archives of General Psychiatry, 46, 205-212.

Eagley, A.H., & Steffen, V.J. (1986). Gender and aggressive behavior: A meta-analytic review of the social psychological literature. Psychological Bulletin, 100, 309-330.

Eaves, L.J., Silberg, J.L., Meyer, J.M., Maes, H.H., Simonoff, E., Pickles, A., Rutter, M., Neale, M.C., Reynolds, C.A., Erickson, M.T., Heath, A.C., Loeber, R., Truett, K.R., & Hewitt, J.K. (1997). Genetics and developmental psychopathology, 2: the main effects of genes and environment on behavioural problems in the Virginia twin study of adolescent behavioral development. Journal of Child Psychology and Psychiatry, 38(8), 965-980.

Ehrhardt, A.A. (1975). Prenatal hormone exposure and psychosexual differentiation. In E. J. Sachar (Ed.), Topics in Psychoendocrinology. New York: Grune & Stratton.

Ehrhardt, A.A., Grisanti, G.C., & Meyer-Bahlburg, H.F. (1977). Prenatal exposure to medroxyprogesterone acetate (MPA) in girls. Psychoneuroendocrinology, 2, 391-398.

Eron, L.D., Huesmann, L.R., Lefkowitz, M.M., & Walder, L.O. (1972). Does television violence cause aggression? American Psychologist, 27, 253-263.

Fagot, B.I. (1984). The consequents of prolem behavior in toddler children. Journal of Abnormal Child Psychology, 12(3), 385-396.

Feshbach, N.D. (1964). Sex differences in children's modes of aggressive responses towards outsiders. Merrill-Palmer Quarterly, 15, 249-258.

Feshbach, S. (1970). Aggression. In P. Mussen (Ed.), Carmichael's manual of child psychology. (pp. 159-259). New York: Wiley.

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.

Fleming, J.E., & Offord, D.R. (1990). Epidemiology of childhood depressive disorders: A critical review. Journal of the American Academy of Child and Adolescent Psychiatry, 29(4), 571-580.

Forest, M.G. (1989). Physiological changes in circulating androgens. Pediatric Adolescent Endocrinology, 19, 104-109.

Foresta, C., Indino, M., & Scandellari, C. (1987). Role of gonadal steroids in the serotoninergic control of prolactin secretion in men. Clinical Endocrinology, 26, 601-607.

Frodi, A., Macaulay, J., & Thome, P.R. (1977). Are women always less aggressive than men? A review of the experimental literature. Psychological Bulletin, 84, 634-660.

Gaddum, J.H., & Picarelli, Z.P. (1957). Two kinds of tryptamine receptor. British Journal of Pharmacology, 12, 323-328.

Gandelman R., Simon, N.G., & McDermott, N.J. (1979). Prenatal exposure to testosterone and its percursors influences morphology and lateral behavioral responsiveness to testosterone of female mice. Physiology and Behavior, 23, 23-26.

Garattini, S., Mennini, T., & Samanin, R. (1987). From fenfluramine racemate to *d*-fenfluramine. Annals of the New York Academy of Science, 499, 156-166.

Ge, X., Best, K.M., Conger, R.D., & Simons, R.L. (1996). Parenting behaviors and the occurrence and co-occurrence of adolescent depressive symptoms and conduct problems. Developmental Psychology, 32(4), 717-731.

Ghiraldi, L.L., Plonsky, M., & Svare, B.B. (1993). Postpartum aggression in mice: The role of ovarian hormones. Hormones and Behavior, 27, 251-268.

Goodall, E.M., Cowen, P.J., Franklin, M., & Silverstone, T. (1993). Ritanserin attenuates anorectic, endocrine, and thermic responses to d-fenfluramine in human volunteers. Psychopharmacology, 112, 461-466.

Goy, R.W., & Goldfoot, D.A. (1975). Neuroendocrinology: animal models and problems of human sexuality. Archives of Sexual Behaviors, 4, 405-420.

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

Göthert, M. (1992). 5-hydroxytryptamine receptpors. Arzneim-Forsch./Drug Reserach, 42(I), 238-246.

Halperin, J.M., Wolf, L.E., Pascualvaca, D.M., Newcorn, J.H., Healey, J.M., O'Brien, J.D., Morganstein, A., & Young, J.G. (1988). Differential assessment of attention and impulsivity in children. Journal of the American Academy of Child and Adolescent Psychiatry, 27, 326-329.

Halperin, J.M., O'Brien, J.D., Newcorn, J.H., Healey, J.M., Pascualvaca, D.M., Wolf, L.E., & Young, J.G. (1990). Validation of hyperactive, aggressive, and mixed hyperctive/aggressive disorders in children: A research note. Journal of Child Psychology and Psychiatry and Allied Disciplines, 31, 455-459.

Halperin, J.M., Sharma, V., Greenblatt, E., & Schwartz, S.T. (1991). Assessment of the continuous performance test: reliability and validity in a nonreferred sample. Psychological Assessment: Journal of Consulting and Clinical Psychology, 3, 603-608.

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(2), 243-248.

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

Hampel, R., & Selg, H. (1975). FAF-Fragebogen zur Erfassung von Aggresivitätsfaktoren (Inventory for the Assessment of Factors of Aggressiveness). Hogrefe: Göttingen.

Harrington, R., Fudge, H., Rutter, M., Pickles, A., & Hill, J. (1990). Adult outcomes of child and adolescent depression: I. Psychiatric status. Archives of General Psychiatry, 47, 465-473.

Harrington, R., Fudge, H., Rutter, M., Pickles, A., & Hill, J. (1991). Adult outcome of childhood and adolescent depresion II. Links with antisocial disorders. Journal of the American Academy of Child and Adolescent Psychiatry, 30, 434-439.

Hartup, W.W. (1974). Aggression in childhood: Developmental perspectives. American Psychologist, 29, 336-341.

Heninger, G.R., Charney, D.S., & Sternberg, D.E. (1984). Serotonergic function in depression: prolcatin response to intravenous tryptophan in depressed patients and healthy subjects. Archives of General Psychiatry, 41, 398-402.

Herpertz, S., Steinmeyer, S.M., Marx, D., Oidtmann, A., & Saß, H. (1995). The significance of aggression and impulsivity for self-mutilative behavior. Pharmacopsychiatry, 28(Supplement), 64-72.

Herpertz, S. (1995). Self-injurious behavior: psychopathological and nosological characteristics in subtypes of self-injurers. Acta Psychiatrica Scandinavia, 91, 57-68.

Hetherington, E.M. (1985). Long-term effects of divorce and remarriage on the adjustment of children. Journal of the American Academy of Child and Adolescent Psychiatry, 24(5), 518-530.

Hewitt, J.K., Silberg, J.L., Neale, M.C., Eaves, L.J., & Erickson, M.T. (1998). The analysis of parental ratings of children's behavior using LISREL. Behavior Genetics, 22, 293-317.

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

Higley, J.D., Suomi, S.J., & Linnoila, M. (1992). A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. Biological Psychiatry, 32, 127-145.

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

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

Hines, M. (1982). Prenatal gonadal hormones and sex differences in human behavior. Psychological Bulletin, 92, 56-80.

Hirschi, T., & Hindelang, M.J. (1977). Intelligence and delinquency: a revisionist review. American Sociological Review, 42, 571-587.

Hood, K.E. (1996). Intractable tangles of sex and gener in women's aggressive development: An optimistic view. In D. M. Stoff & R. B. Cairns (Eds.), Aggression and Violence: Genetic, Neurobiological, and Biosocial Perspectives. (pp. 309-335). Mahwah, New Jersey: Lawrence Erlbaum.

Hoving, K., Wallace, J., & LaForme, G. (1979). Aggression during competition: Effects of age, sex and amount and type of provociation. Genetic Psychology Monographs, 99, 251-289.

Huesmann, L.R., Eron, L.D., Lefkowitz, M.M., & Walder, L.O. (1984). Stability of aggression over time and generations. Developmental Psychology, 20(6), 1120-1134.

Humphrey, P.P., Hartig, P., & Hoyer, D. (1993). A proposed new nomenclature for 5-HT receptors. Trends in Pharmacol Science, 14, 233-236.

Hyde, J.S. (1984). How large are gender differences in aggresion? A developmental meta-analysis. Developmental Psychology, 20(4), 722-736.

Invernizzi, R., Berettera, C., Garattini, S., & Samanin, R. (1986). D- and l-isomers of fenfluramine differ markedly in their interaction with brain serotonin in rat. European Journal of Pharmacology, 120, 9-15.

Jacobs, B.L., Wilkinson, L.O., & Fornal, C.A. (1990). The role of brain serotonin. A neuophysiologic perspective. Neuropsychopharmacology, 3(5/6), 473-479.

Johnson, E.O., Arria, A.M., Borges, G., Ialongo, N., & Anthony, J.C. (1994). The growth of conduct problem behaviors from middle childhood to early adolescence: Sex differences and the suspected influence of early alcohol use. Journal of Studies on Alcohol, 56, 661-671.

Jurik, N., & Winn, R. (1990). Gender and homicide: A comparisonof men and women who kill. Violence and Victims, 5, 236

Kandel, E., Mednick, S.A., Kirkegaard-Sorensen, L., Hutchings, B., Knop, J., Rosenberg, R., & Schulsinger, F. (1988). IQ as a protective factor for subjects at high risk for antisocial behavior. Journa of Consulting and Clinical Psychology, 56, 224-226.

Keenan, K., & Shaw, D.S. (1994). The development of aggression in toddlers: A study of low-income families. Journal of Abnormal Child Psychology, 22(1), 53-77.

Kempf, E., Puglisi-Allegri, S., Cabib, S., Schleef, C., & Mandel, P. (1984). Serotonin levels and turnover in different brain areas of isolated aggressive or non-aggressive strains of mice. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 8, 365-371.

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 Sciences, 794, 369-371.

Koot, H.M., & Verhulst, F.C. (1991). Prevalence of problem behavior in Dutch children aged 2-3. Acta Psychiatrica Scandinavia, 83(Supplement 367), 1-37.

Kovacs, M., Paulauskas, S., Gatsonis, C., & Richards, C. (1988). Depressive disorders in chldhood III. A longitudinal study of comorbidity with and risk for conduct disorders. Journal of Affective Disorders, 15, 205-217.

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

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

Kreusi, M.J., 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. Prediction by cerebrospinal fluid 5-hydroxyindoleacetic acid, homovanillic acid, and autonomic measures. Archives of General Psychiatry, 49, 429-435.

Lacau-Mengido, I.M., Libertun, C., & Becú-Villalobos, D. (1996). Different serotonin receptor types participate in 5-hydroxytryptohphan-induced gonadotropins and prolactin release in the female infantile rat. Neuroendocrinology, 63, 415-421.

Lagerspetz, K.M., Björkqvist, K., & Peltonen, T. (1988). Is indirect aggression typical of females? Gender differences in aggressiveness in 11- to 12-year-old children. Aggressive Behavior, 14, 403-414.

Lagerspetz, K.M., & Björkqvist, K. (1992). Indirect aggression in girls and boys. In L.R.Huesmann (Ed.), Aggressive Behavior: Current Perspectives. New York: Plenum.

Lamberts, S.W., & MacLeod, R.M. (1978). The interaction of serotonergic and dopaminergic systems on prolactin secretion in the rat. Endocrinology, 103, 287-295.

Langlais, P.J., Walsh, F.X., Bird, E.D., & Levy, H.L. (1985). Cerebrospinal fluid neurotransmitter metabolites in neurologically normal infants and children. Pediatrics, 75, 580-586.

Lauder, J.M. (1990). Ontogeny of the serotonergic system in the rat: serotonin as a developmental signal. Annals of the New York Academy of Science, 604, 297-313.

Lehman, M.N., & Adams, D.B. (1977). A statistical and motivational analysis of the soical behaviours of the male laboratory rat. Behaviour, 61, 238-275.

Levy, A.D., Li, Q., Rittenhouse, P.A., & Van de Kar, L.D. (1993). Investigation of the role of 5-HT_3 receptors in the secretion of prolactin, ACTH and renin. Neuroendocrinology, 58, 65-70.

Lewis, D.O., Yeager, C.A., Cobham-Portorreal, C.S., Klein, N., Showalter, C., & Anthony, A. (1991). A follow-up of female delinquents: Maternal contribution to the perpetuation of deviance. Journal of the American Academy of Child and Adolescent Psychiatry, 30, 197-201.

Lidow, M.S., Goldman-Rakic, P.S., & Rakic, P. (1991). Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proceedings of the National Academy of Science, 88, 10218-10221.

Linnoila, M., Virkunen, M., Scheinin, M., Nuutila, A., Rimon, R., & Goodwin, F.K. (1983). Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Science, 33, 2609-2614.

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

Loeber, R., & Schmaling, K.B. (1985). Empirical evidence for overt and covert patterns of antisocial conduct problems: A meta-analysis. Journal of Abnormal Child Psychology, 13, 337-352.

Loehlin, J.C. (1992). Genes and Environment in Personality Development: Individual Differences and Development. Thousand Oaks: Sage Publications, Inc.

Loney, J., & Milich, R. (1982). Hyperactivity, inattention and aggression in clinical practice. Advances in Devel Behav Pediat, 3, 113-147.

Luine, V.N., Renner, K.J., Frankfurt, M., & Azmitia, E.C. (1984). Facilitated sexual behavior reversed and serotonin restored by raphe nuclei transplanted into denervated hypothalamus. Science, 20, 1436-1439.

Lynam, D.R., Moffitt, T.E., & Stouthamer-Loeber, M. (1993). Explaining the relation between IQ and delinquency: Class, race, test motivation, school failure, or self-control? Journal of Abnormal Psychology, 102, 187-196.

Lyons, M.J., True, W.R., Eisen, S.A., Goldberg, J., Meyer, J.M., Faraone, S.V., Eaves, L.J., & Tsuang, M.T. (1995). Differential heritability of adult and juvenile antisocial traits. Archives of General Psychiatry, 52, 906-915.

Maccoby, E.E., & Jacklin, C.N. (1974). The Psychology fo Sex Differences. Stanford: Stanford Univeristy Press.

Maccoby, E.E., & Jacklin, C.N. (1980). Sex differences in aggression: A rejoinder and reprise. Child Development, 51, 964-980.

Magnusson, D., & Bergman, L.R. (1988). A pattern approach to the study of pathways from childhood to adulthood. In L. N. Robins & M. Rutter (Eds.), Straight and devious pathways from childhood to adulthood. Cambridge: Cambridge University Press.

Mann, J.J., Arango, V., Marzuk, P.M., & Reis, D.J. (1989). Evidence for the 5-HT hypothesis of suicide: A review of post-mortem studies. British Journal of Psychiatry, 155(Suppl 8), 7-14.

Mann, J.J., McBride, P.A., Malone, K.M., DeMeo, M., & Kendler, K.S. (1995). Blunted serotonergic responsivity in depressed inpatients. Neuropsychopharmacology, 13(1), 53-64.

Martin, C.A., Milich, R., Martin, W.R., Hartung, C.M., & Haigler, E.D. (1997). Gender differences in adolescent psychiatric outpatient substance use: Associated behaviors and feelings. Journal of the American Academy of Child and Adolescent Psychiatry, 36(4), 486-494.

Mattes, J.A. (1980). The role of frontal lobe dysfunctin in childhood hyperkinesis. Comprehensive Psychiatry, 21, 358-369.

McBride, P.A., Anderson, G.M., Hertzig, M.E., Sweeney, J.A., Kream, J., Cohen, D.J., & Mann, J.J. (1989). Serotonergic responsivity in male young adults with autistic disorder. Archives of General Psychiatry, 46, 213-221.

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.

McBurnett, K., Lahey, B.B., & Frick, P.J.e.al. (1991). Anxiety, inhibition, and conduct disorder in children: II. Relation to salivary cortisol. Journal of the American Academy of Child and Adolescent Psychiatry, 30, 192-196.

McCann, U.D., Hatzidimitriou, G., & Ricaurte, G.A. (1996). Prolactin response to fenfluramine is independent of serotonin release. European Journal of Pharmacology, 312, R-1-R-2

McGee, R., Share, D., Moffitt, T.E., Williams, S., & Silva, P.A. (1988). Reading disability, behavior problems and juvenile delinquency. In D. H. Saklofske & S. B. Eysenck (Eds.), Individual differences in children and adolescents. (pp. 158-171). London: Hodder & Stoughton.

McKay, K., Halperin, J.M., Grayson, R., Hall, S., Peraochio, N., & Newcorn, J.H. The Children's Aggressions Scale: parent and teacher versions. In Anonymous. Scientific Proceedings of the Annual Meeting of the American Academy of Child & Adolescent Psychiatry: Vol. 9. American Academy of Child & Adolescent Psychiatry.

Meyer-Bahlburg, H.F., Grisanti, G.C., & Ehrhardt, A.A. (1977). Prenatal effects of sex hormones on human male behavior: Medroxyprogesterone acetate (MPA). Psychoneuroendocrinology, 2, 383-390.

Meyer-Bahlburg, H.F., & Ehrhardt, A.A. (1980). Neurobehavioral effects of prenatal origin: Sex hormones. In R. H. Schwarz & S. J. Yaffe (Eds.), Drugs and Chemical Risks to the Fetus and Newborn. (pp. 93-107). New York: Alan R. Liss.

Meyer-Bahlburg, H.F., & Ehrhardt, A.A. (1982). Prenatal sex hormones and human aggression: A review, and new data on progestogen effects. Aggressive Behavior, 8, 39-62.

Moffitt, T.E., & Silva, P.A. (1988). Neuropsychological deficit and self-reported delinquency in an unseleted birth cohort. Journal of the American Academy of Child and Adolescent Psychiatry, 27, 233-240.

Moffitt, T.E. (1990). The neuropsychology of juvenile delinquency: A critical review. In M. Tonry & N. Morris (Eds.), Crime and justice: A review of research. (pp. 99-169). Chicago: University of Chicago Press.

Moffitt, T.E. (1993). The neuropsychology of conduct disorder. Development and Psychopathology, 5, 135-151.

Moskowitz, D.S., Schwartzman, A.E., & Ledingham, J.E. (1985). Stability and change in aggression and withdrawal in middle childhood and eqrly adolescence. Journal of Abnormal Psychology, 94(1), 30-41.

Moskowitz, D.S., & Schwartzman, A.E. (1989). Life paths of aggressive and withdrawn children. In D. M. Buss & N. Cantor (Eds.), Personality psychology: Recent trends and emerging directions. (pp. 99-114). New York: Springer-Verlag.

Moskowitz, D.S., Crawley, M., & Schwartzman, A.E. Adult criiminal activity among adolescents who were aggressive or withdrawn. (1989). Anonymous. New Orleans: American Psychological Association.

Moyer, K.E. (1968). Kinds of aggression and their physiological basis. Communications in Behavioral Biology, 2, 65-87.

Moyer, K.E. (1976). The psychobiology of aggression. New York: Harper & Row.

Munaro, N.I. (1978). The effect of ovarian steroids onhypothalamic 5-hydroxytryptamine neuronal activity. Neuroendocrinology, 26, 270-276.

New, S.A., Trestman, R.L., Mitropoulou, V., Benishay, D.S., Coccaro, E.F., Silverman, J.M., & 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, R., & Linnoila, M. (1994). Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Archives of General Psychiatry, 51, 34-38.

O'Keane, V., O'Hanlon, M., Webb, M., & Dinan, T. (1991). d-Fenfluramine/prolcatin response throughout the menstrual cycle: evidence for an oestrogen-induced alteration. Clinical Endocrinology, 34, 289-292.

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

Olweus, D. (1979). Stability of aggressive reaction patterns in males: A review. Psychological Bulletin, 86, 852-875.

Olweus, D. (1981). Continuity in aggressive and withdrawn, inhibited behaviour patterns. Psychiatry and Social Science, 1, 141-159.

Paikoff, R.L., Brooks-Gunn, J., & Warren, M.P. (1991). Effects of girls' hormonal status on depressive and aggressive symptoms over the course of one year. Journal of Youth and Adolescence, 20(2), 191-215.

Palazidou, E., Stephenson, J., Butler, J., Coskeran, P., Chambers, S., & McGregor, A.M. (1995). Evidence for 5-hydroxytryptamine$_{1A}$ receptor involvement in the control of prolcatin secretion in man. Psychopharmacology, 119, 311-314.

Pan, J.-T., & Yang, I.C.-H. (1996). Central administration of 8-OH-DPAT and mCPP stimulates prolactin secretion in ovariectomized, estrogen-treated rats: lack of an effect on tuberoinfundibular dopaminergic neuron activity. Life Sciences, 58, 1189-1194.

Park, S.B., & Cowen, P.J. (1995). Effect of pindolol on prolactin response to D-fenfluramine. Psychopharmacology, 471-474.

Park, S.B., Williamson, D.J., & Cowen, P.J. (1996). 5-HT neuroendocrine function in major depression: prolactin and cortisol responses to D-fenfluramine. Psychological Medicine, 26, 1191-1196.

Pattison, E.M., & Kahan, J. (1983). The deliberate self-harm syndrome. American Journal of Psychiatry, 140, 867-872.

Pearson, J., Ialongo, N., Hunter, A.G., & Kellam, S. (1994). Family structure and aggressive behavior in a population of urban elementary school children. Journal of the American Academy of Child and Adolescent Psychiatry, 33, 540-548.

Pedersen, N.L., Plomin, R., McClearn, G.E., & Friberg, L.T. (1988). Neuroticism, extraversion, and related traits in adult twins reared apart and reared together. Journal of Personality and Social Psychology, 55, 950-957.

Pelham, W.E., Milich, R., Murphy, D.A., & Murphy, H.A. (1989). Normative data on the IOWA Conners Teacher Rating Scale. Journal of Clinical Child Psychology, 3, 259-262.

Peroutka, S.J., & Syder, S.H. (1979). Multiple serotonin receptors: differential binding of (^{3}H)hydroxytryptamikne, (^{3}H)lysergic acid diethylamine and (^{3}H)spiperone. Molecular Pharmacology, 16, 687-699.

Perry, D.G., & Bussey, K. (1979). The social learning theory of sex differences: imitation is alive and well. Journal of Personality and Social Psychology, 37, 1699-1712.

Petersen, A.C., Compas, B.E., Brooks-Gunn, J., Stemmler, M., Ey, S., & Grant, K.E. (1993). Depression in adolescence. American Psychologist, 48, 155-168.

Phoenix, C., Goy, R., Gerall, A., & Young, W. (1959). Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology, 65, 369-382.

Pick, L.H., Halperin, J.M., Schwartz, S.T., & Newcorn, J.H. (1998). A longitudinal study of neurobiological mechanisms in boys with attention-deficit hyperactivity disorder: preliminary findings. Biological Psychiatry, In Press

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 response to fenfluramine challenge in boys;associations with aggressive behavior and adverse rearing. Archives of General Psychiatry, 54, 839-846.

Pitkänen-Pulkkinen, L. (1981). Long-term studies on the characteristics of aggressive and non-aggressive juveniles. In P. F. Brain & D. Benton (Eds.), Multidisciplinary approaches to aggression research. Amsterdam: Elsevier North-Holland Biomedical Press.

Plomin, R., Pedersen, N.L., McClearn, G.E., Nesselroade, J.R., & Bergeman, C.S. (1988). EAS temperaments during the last half of the life span: Twins reared apart and twins reared together. Psychology and Aging, 3, 43-50.

Poe-Yamagata, E., & Butts, J.A. (1996). Female Offenders in the Juvenile Justice System: Statistics Summary. Office of Juvenile Justice and Delinquency Prevention, U.S. Department of Justice.

Price, L.H., Charney, D.S., Delgado, P.L., & Heninger, G.R. (1991). Serotonin function and depression: neuroendocrine and mood responeses to intravenous L-tryptophan in depressed patients and healthy comparison subjects. American Journal of Psychiatry, 148, 1518-1525.

Puig-Antich, J., Goetz, D., Davies, M., & et al. (1989). A controlled family history study of prepubertal major depressive disorder. Archives of General Psychiatry, 46, 406-418.

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

Quattrone, A., DiRenzo, G.F., Schettini, G., Tedeschi, G., & Scopacasa, F. (1978). Increased plasma prolactin levels induced in rats by *d*-fenfluramine: Relation to central serotonergic stimulation. European Journal of Pharmacology, 49, 163-167.

Quay, H.C. (1986). Classification. In H. C. Quay & J. S. Werry (Eds.), Psychopathological Disorders of Childhood. (pp. 1-34). New York: Wiley.

Quay, H.C. The psychobiology of undersocialized aggressive conduct disorder: Presidential address. (1991). Anonymous. Costa Mesa,CA: Society for Research in Child and Adolescent Psychopathology.

Radke-Yarrow, M., Zahn-Waxler, C., & Chapman, M. (1983). Children's prosocial dispositions and behavior. In P. Mussen (Ed.), Carmichael's Manual of Child Psychology. (pp. 470-545). New York: Wiley & Sons.

Raine, A., & Buchsbaum, M. (1996). Violence, Brain Imaging, and Neuropsychology. In D. M. Stoff & R. B. Cairns (Eds.), Aggression and Violence. (pp. 195-217). Mahwah: Lawrence Erlbaum Associates.

Raleigh, M.J., Brammer, G.L., Ritvo, E.R., Geller, E., McGuire, M.T., & Yuwiller, A. (1986). Effects of chronic fenfluramine on blood serotonin, cerebrospinal fluid metabolites, and behavior in monkeys. Psychopharmacology, 90, 503-508.

Reinisch, J.M. (1974). Fetal hormones, the brain, and human sex differences; a heuristic, integrative review of the recent literature. Archives of Sexual Behaviors, 3, 51-90.

Rejeski, W.J., Brubaker, P.H., Herb, R.A., Kaplan, J.R., & Koritnik, D. (1988). Anabolic steroids and aggressive behavior in cynomolgus monkeys. Journal of Behavioral Medicine, 11, 95-105.

Robins, L.N. (1978). Sturdy childhood predictors of adult outcome: replications from longitudinal studies. Psychological Medicine, 8, 611-622.

Robins, L.N. (1990). Conduct Disorder. Child Psychology and Psychiatry, 32, 193-212.

Robins, L.N., & Price, R. (1991). Adult disorders predicted by childhood conduct problems: Results from the NIMH epidemiologic Catchment Area Project. Psychiatry, 54, 116-131.

Roff, J.D., & Wirt, R.D. (1984). Childhood aggression and social adjustment as antecedents of delinquency. Journal of Abnormal and Child Psychology, 12, 111-126.

Rose, R.M., Holaday, J.W., & Bernstein, I.S. (1971). Plasma testosterone, dominance rank and aggressive behaviour in male rhesus monkeys. Nature, 231, 366-368.

Rose, S.L., Rose, S.A., & Feldman, J.F. (1989). Stability of behavior problems in very young children. Development and Psychopathology, 1, 5-19.

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

Rutter, M., & Yule, W. (1970). Reading retardation and antisocial behavior: The nature of the association. In M. Rutter, J. Tizard, & K. Whitmore (Eds.), Education, Health and Behavior. (pp. 240-255). London: Longmans.

Rutter, M., Macdonald, H., Le Couterur, A., Harrington, R., Bolton, P., & Bailey, A. (1990). Genetic factors in child psychiatric disorders:II. Empriical findings. Journal of Child Psychology and Psychiatry, 1, 39-83.

Ryan, N.D., Birmaher, B., Perel, J.M., Dahl, R.E., Meyer, V., Al-Shabbout, M., Iyengar, S., & Puig-Antich, J. (1992). Neuroendocrine response to L-5-hydroxytrptophan challenge in prepubetal major depression: Depressed vs normal children. Archives of General Psychiatry, 49, 843-851.

Sandnabba, N.K. (1992). Aggressive behavior in female mice as a correlated characteristic in selection for aggressiveness in male mice. In K. Björkqvist & P. Niemelä (Eds.), Of Mice and Women: Aspects of Female Aggression. (pp. 367-379). New York: Academic Press.

Saudou, F., Amara, D.A., Dierich, A., LeMeur, M., Ramboz, S., Segu, L., Buhot, M.-C., & Hen, R. (1994). Enhanced aggressive behavior in mice lacking 5-HT_{1B} receptor. Science, 265, 1875-1878.

Scerbo, A.S., & Kolko, D.J. (1994). Salivary testosterone and cortisol in disruptive children: relationship to aggressive, hyperactive, and internalizing behaviors. Journal of the American Academy of Child and Adolescent Psychiatry, 33(8), 1174-1184.

Schaal, B., Tremblay, R.E., Soussignan, R., & Susman, E.J. (1996). Male testosterone linked to high social dominance but low physical aggression in early adolescence. Journal of the American Academy of Child and Adolescent Psychiatry, 34(10), 1322-1330.

Schmitz, S., Cherny, S.S., Fulker, D.W., & Mrazek, D.A. (1994). Genetic and environmental influences on early childhood behavior. Behavior Genetics, 24(1), 25-34.

Schonfeld, I.S., Shaffer, D., O'Connor, P., & Portnoy, S. (1988). Conduct disorder and cognitive functioning: testing three causal hypotheses. Child Development, 59, 993-1007.

Schwartzman, A.E., Ledingham, J.E., & Serbin, L.A. (1985). Identification of children at risk for adult schizophrenia: A longitudinal study. International Review of Applied Psychology, 34, 363-380.

Serbin, L.A., O'Leary, K.D., Kent, R.H., & Tonick, I.J. (1973). A comparison of teacher response to the preacademic and problem behaviors of boys and girls. Child Development, 44, 796-804.

Serbin, L.A., Schwartzman, A.E., Moskowitz, D.S., & Ledingham, J.E. (1991). Aggressive, withdrawn, and aggressive/withdrawn children in adolescence: Into the next generation. In D. J. Pepler & K. H. Rubin (Eds.), The Development and Treatment of Childhood Aggression. (pp. 55-69). Hillsdale: Erlbaum.

Séguin, J.R., Pihl, R.O., Harden, P.W., Tremblay, R.E., & Boulerice, B. (1995). Cognitive and neuropsychological characteristics of physically aggressive boys. Journal of Abnormal Psychology, 104(4), 614-624.

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.

Sigvardsson, S., Cloninger, C.R., Bohman, M., & von Knorring, A.L. (1982). Predisposition to petty criminality in Swedish adoptees III. Sex differences and vallidation of the male typology. Archives of General Psychiatry, 39, 1248-1253.

Sijbesma, H., Schipper, J., De Kloet, E.R., Mos, J., Van de Kar, L.D., & Olivier, B. (1991). Postsynaptic 5-HT_1 receptors and offensive aggression in rats: a combined behavioral and autoradiographic study with eltoprazine. Pharmacology Biochemistry and Behavior, 38, 447-458.

Slutske, W.S., Heath, A.C., Dinwiddie, S.H., Madden, P.A., Bucholz, K.K., Dunne, M.P., Statham, D.J., & Martin, N.G. (1997). Modeling genetic and environmental influences in the etiology of Conduct Disorder: A study of 2,682 adult twin pairs. Journal of Abnormal Psychology, 106(2), 266-279.

Smart, D., Sanson, A., & Prior, M. (1996). Connections between reading disability and behavior problems: Testing temporal and causal hypotheses. Journal of Abnormal Child Psychology, 24(3), 363-383.

Soubrie, P. (1986). Reconciling the role of central serotonin neuronsin human and animal behavior. The Behavioual and Brain Sciences, 9, 319-364.

Spielberger, C.D. (1988). State-Trait Anger Expression Inventory (STAXI Professional Manual). New York: Psychological Assessment Reserouces.

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, 277-285.

Stoff, D.M., Pasatiempo, A.P., Yeung, J.H., Cooper, T.B., Bridger, W.H., & Rabinovich, H. (1992). Test-retest reliability of the prolactin and cortisol responses to D,L-fenfluramine challenge in disruptive behavior disorder. Psychiatry Research, 42, 65-72.

Terman, L.M., & Tyler, L.E. (1954). Psychological Sex Differences. In L. Carmichael (Ed.), Manual of Child Psychology. New York: Wiley.

The Psychological Corporation. (1991). The Wechsler Intelligence Scale for Children. (Third ed.). New York: The Psychological Corporation.

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

Tieger, T. (1980). On the biological basis of sex differences. Child Development, 51, 943-963.

Törk, I. (1990). Anatomy of the serotonergic system. Annals of the New York Academy of Sciences, 600, 9-35.

Tuomisto, J., & Mannisto, P. (1985). Neurotransmitter regulation of anterior pituitary hormones. Pharmacologial Review, 37, 249-332.

U.S.Department of Justice, B.o.J.S. (1996). Sourcebook of Criminal Justice Statistics 1996. Washington,D.C.: US Government Printing Office.

Ulrich, U., Nowara, I., & Rossmanith, W.G. (1994). Serotonergic control of gonadotophin and prolactin secretion in women. Clinical Endocrinology, 41, 779-785.

Urban, R.J., & Veldhuis, J.D. (1991). A selective serotonin reuptake inhibitor, fluoxetine hydrochloride, modulates the pulsatile secretion of prolactin in postmenopausal women. American Journal of Obstetrics and Gynecology, 164, 147-152.

Vaden-Kiernan, N., Ialongo, N., Pearson, J., & Kellam, S. (1995). Household family structure and children's aggressive behavior: A longitudinal study of urban elementary school children. Journal of Abnormal and Child Psychology, 23(553), elementary school children. Journal of Abnormal and Child Psychology, 23(553), 568

Valzelli, L., Bernasconi, S., & Garattini, S. (1981). p-Chloro-phenylalanine-induced muricidal aggression in male and female laboratory rats. Neuropsychobiology, 7, 315-320.

Van-Goozen, S.H., Cohen-Kettenis, P.T.G.L.J., Frijda, N.H., & Van-de-Poll, N.E. (1995). Gender differences in behaviour: activating effects of cross-sex hormones. Psychoneuroendocrinology, 20(4), 343-363.

Van de Kar, L. (1991). Neuroendocrine pharmacology of serotonergic (5-HT) neurones. Annual Review of Pharmacology and Toxicology, 31, 289-320.

Van de Kar, L.D., & Bethea, C.L. (1989). Pharmacological evidence that serotonergic stimulation of prolactin release is mediated via the dorsal raphe nucleus. Neuroendocrinology, 35, 225-230.

van den Oord, E.J., Boomsma, D.I., & Verhulst, F.C. (1994). A study of problem behaviors in 10- to 15-year-old biologically related and unrelated international adoptees. Behavior Genetics, 24(3), 193-205.

van den Oord, E.J., Verhulst, F.C., & Boomsma, D.I. (1996). A genetic study of maternal and paternal ratings of problem behaviors in 3-year-old twins. Journal of Abnormal Psychology, 105(3), 349-357.

Vergnes, M., Depaulis, A., Boehrer, A., & Kempf, E. (1988). Selective increase of offensive behavior in the rat following intrahypothalamic 5,7-DHT-induced serotonin depletion. Behav Brain Reserach, 29, 85-91.

Virkunen, M., Rawlings, R., Tokola, R., Poland, R.E., Guidotti, A., Nemeroff, C., Bissette, G., Kallogeras, K., Karonen, S.-L., & Linnoila, M. (1994). CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. Archives of General Psychiatry, 51, 20-27.

von Knorring, A.L., Oreland, L., Haggendal, J., Magnusson, T., Almay, B., & Johansson, F. (1986). Relationship between platelet MAO activity and concentrations of 5-HIAA and HVA in cerebrospinal fluid in chronic pain patients. Journal of Neural Transmission, 66, 37-46.

Wallian, L., Brain, P.F., & Haug, M. (1993). Aggression in female mice: contrasting effects of amiflamine (FLA 336), a selective and reversible MAO-type A inhibitor. Physiology and Behavior, 54, 411-414.

Wasserman, G.A., Miller, L.S., Pinner, E., & Jaramillo, B. (1996). Parenting predictors of early conduct problems in urban high risk boys. Journal of the American Academy of Child and Adolescent Psychiatry, 35, 1227-1236.

Waterman, G.S., Dahl, R.E., Birmaher, B., Ambrosini, P., Rabinovich, H., Williamson, D.E., Novacenko, H., Nelson, B., Puig-Antich, J., & Ryan, N.D. (1994). The 24-hour pattern of prolactin secretion in depressed and normal adolescents. Biological Psychiatry, 35, 440-445.

Whitaker-Azmitia, P.M., Shemer, A.V., Caruso, J., Molino, L., & Azmitia, E.C. (1990). Role of high affinity serotonin receptors in neuronal growth. Annals of the New York Academy of Science, 604, 315-331.

White, J.L., Moffitt, T.E., & Silva, P.A. (1989). A prospective replication of the protective effects of IQ in subjects at high risk for juvenile delinquency. Journal of Consulting and Clinical Psychology, 57, 719-724.

White, J.L., Moffitt, T.E., Caspi, A., Bartusch, D.J., Needles, D.J., & Stouthamer-Loeber, M. (1994). Measuring impulsivity and examining its relationship to delinquency. Journal of Abnormal Psychology, 103(2), 192-205.

Whiting, B., & Edwards, C.P. (1973). Cross-cultural analysis fo sex differences in the behavior of children aged three to eleven. Journal of Social Psychology, 91, 171-188.

Winchel, R., & Stanley, M. (1991). Behavior: a review of the behavior and biology of self-mutilation. American Journal of Psychiatry, 148, 306-317.

Yarbrough, E., Santat, U., Perel, I., Webster, C., & Lombardi, R. (1987). Effects of fenfluramine on autistic individuals residing in a state developmental center. Journal of Autism and Developmental Disorders, 17, 303-314.

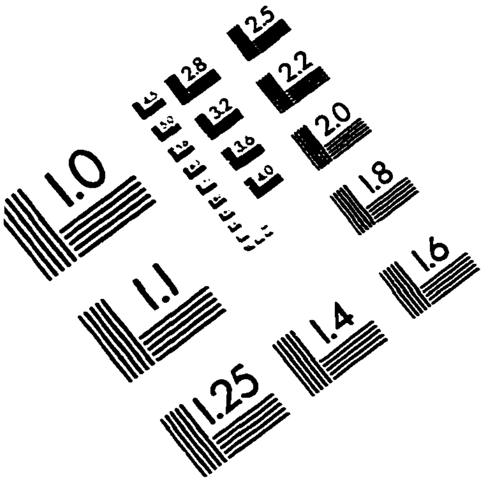
Young, W., Goy, R., & Phoenix, C. (1964). Hormones and sexual behavior. Science, 143, 212-218.

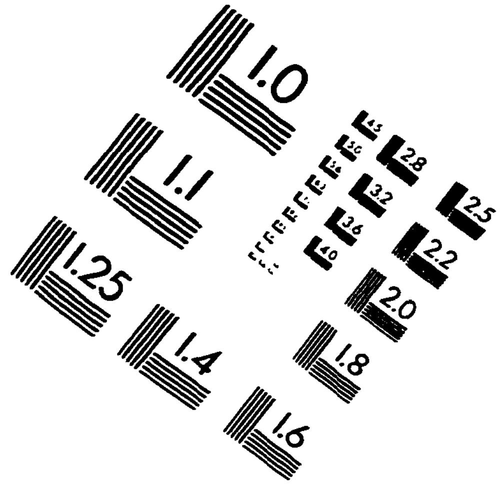
Zahn-Waxler, C., Ianotti, R.J., Cummings, E.M., & Denham, S. (1990). Antecedents of problem behaviors in children of depressed mothers. Development and Psychopathology, 2, 271-291.

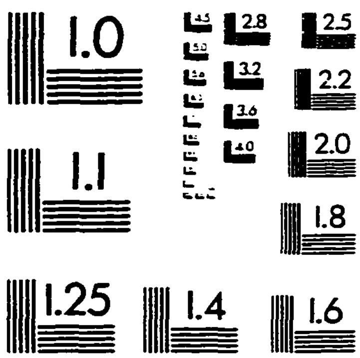
Zahn-Waxler, C. (1993). Warriors and worriers: gender and psychopathology. Development and Psychopathology, 5, 79-89.

Zoccolillo, M. (1993). Gender and the development of conduct disorder. Development and Psychopathology, 5, 65-78.

IMAGE EVALUATION TEST TARGET (QA-3)

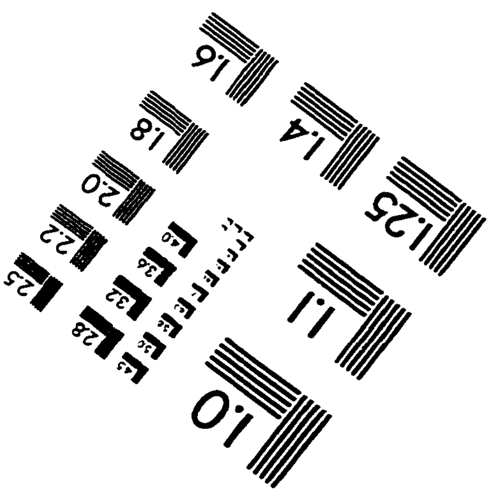


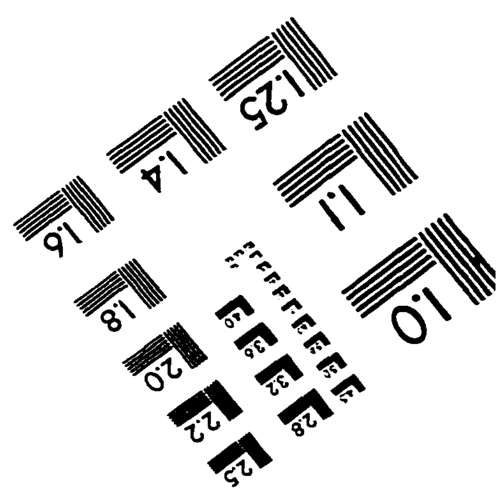




150mm

6"





APPLIED IMAGE . Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989