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SEROTONERGIC FUNCTION AND IMPULSIVITY IN  
MALE PATHOLOGICAL GAMBLERS

by

CONCETTA M. DECARIA

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

1995

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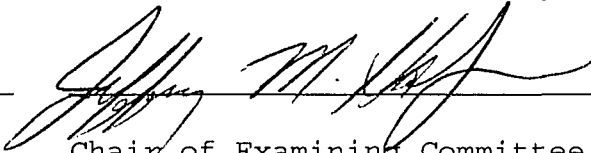
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This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

SEROTONIN FUNCTION AND IMPULSIVITY  
IN MALE PATHOLOGICAL GAMBLERS

by

Concetta M. DeCaria

Advisor: Jeffrey Halperin, PhD

A randomized, double-blind, placebo-controlled m-chloro-phenylpiperazine (m-CPP) challenge procedure was conducted to assess central serotonergic (5-HT) function in 10 male pathological gamblers relative to 10 male nonreferred controls. Selected psychometric measures were employed to assess constructs of impulsivity previously found in pathological gamblers. The relationship between 5-HT function and impulsivity in pathological gamblers was investigated. Results indicated that: 1) male pathological gamblers had a significant increase in prolactin release at

180 and 210 minutes following oral m-CPP (0.5 mg/kg), but not after placebo administration, relative to controls; 2) pathological gamblers had a significantly increased m-CPP "high" response compared to placebo "high" response, relative to controls; and 3) there was no relationship between the challenge measures (i.e., m-CPP prolactin levels and "high" ratings) and the neuropsychological/phenomenological measures (i.e., Matching Familiar Figures Test - Impulsivity-Reflectivity Index scores, Porteus Maze Test Q scores, or Barratt Impulsiveness Scale factor scores). These findings suggest that 5-HT abnormalities may be present in male pathological gamblers as evidenced by 5-HT postsynaptic receptor hypersensitivity (i.e., enhanced prolactin response to m-CPP and enhanced euphorogenic ["high"] response to m-CPP). Further, there does not appear to be a relationship between 5-HT postsynaptic receptor hypersensitivity and selected neuropsychological and phenomenological constructs of impulsivity in male pathological gamblers.

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## INTRODUCTION

Pathological gambling (PG) is a highly disabling and understudied disorder which is progressive and chronic. Although a major public health problem due to its poor outcome and devastating effects on families, pathological gambling remains a neglected disorder with few controlled studies of causes or treatment. Moreover, high rates of suicide attempts among pathological gamblers (Ciarrocchi & Richardson, 1989; Custer & Custer, 1978; Lesieur, 1988; Linden, Pope, & Jones, 1986; Livingston, 1974; McCormick, Russo, Ramirez, & Taber, 1984; Moran, 1969) underscore the critical need for further research in this field.

Little is currently known about the behavioral and neurobiological mechanisms that underlie pathological gambling. PG is characterized as a disorder of impulse control. While impulsivity per se has been highlighted as an important dimensional construct of pathological gambling, it is also present in other disorders. Neurobiological studies of impulsive disorders have regarded neurotransmitter function as an important measure of the pathophysiology associated with these disorders. A

reliable, positive relationship between serotonergic (5-HT) dysfunction and impulsive behavior has been reported (Asberg, Traskman, & Thoren, 1976; Brewerton, Murphy, & Jimerson, 1991; Brown, Goodwin, Ballenger, Goyer, & Major, 1979; Coccaro, Siever, Kavoussi, & Davis, 1989; Fishbein, Lozovsky, & Jaffe, 1989; Halperin et al., 1994; Hollander et al., 1994; Linnoila et al., 1983; Meltzer, Perline, Tricou, Lowy, & Robertson, 1984; Traskman, Asberg, Bertilsson, & Sjostrand, 1981). One safe and reliable method of investigating 5-HT receptor function has been the pharmacological challenge test (Mueller, Murphy, & Sunderland, 1986; Mueller, Sunderland, & Murphy, 1985). Challenge procedures utilize 5-HT agents to stimulate neuroendocrine and behavioral responses in patients and nonreferred controls as a means of assessing 5-HT receptor function.

In this dissertation, randomized, double-blind, placebo-controlled challenges with the 5-HT agent m-chlorophenylpiperazine (m-CPP) were conducted to assess 5-HT receptor function in male pathological gamblers relative to sex matched nonreferred controls. Neuropsychological and

phenomenological assessments were administered to identify constructs of impulsivity in male pathological gamblers. The relationship between 5-HT receptor function and constructs of impulsivity in pathological gamblers was explored.

#### HISTORICAL BACKGROUND:

A review of the history of gambling provides the basis for better understanding the relationship between societal attitudes toward legal and illegal gambling practices and the development of gambling opportunities. Increased opportunity has been associated with increased rates of gambling and increased prevalence of pathological gambling. Although categorization of pathological gambling as a psychiatric disorder is a recent phenomenon, descriptive accounts suggest that vulnerable individuals have been devastated by such activity throughout history.

#### Ancient History:

Historical records show that gambling existed as early as 4000 years ago, in China, circa 2300 B.C. A gaming board was recovered in the excavations of the city of Ur, believed

to be used by Chaldean tribesmen around the year 2000 B.C. Egyptians played the 'Game of Robbers', tau, in which chance was sometimes used to decide the fate of people who committed crimes. In India, legalization and taxation of gambling were recorded as early as 321 B.C. (Ashton, 1969; Quinn, 1890; Starkey, 1964; Steinmetz, 1969). In Greece and Rome, gambling thrived although it was against the law. The Greeks were considered skillful gamblers, and the Roman emperors, avid gamblers. Dice games were reported to be popular in Rome, with the earliest forms of dice believed to be made from knuckle bones of sheep or goats. Loaded dice were found in the ruins of Pompeii. Further, a form of lottery was played by the Romans as entertainment when they dined (Commission on the Review of the National Policy Toward Gambling, 1976). Thus, many of the games employed today have roots extending back to ancient times.

#### European History:

By the 13th century, playing cards first appeared in England and France. The first public lottery was believed to be held in L'Ecluse, France in 1420 to raise money for fortifications. Gambling continued to flourish for several

centuries. In 1775, Paris gambling houses were licensed and profits were contributed to hospitals (Ashton, 1969; Persius, 1823; Quinn, 1890; Steinmetz, 1969).

The French influenced the gambling habits of the British aristocracy even though the British invented many of their own games of chance. Eventually, gambling became popular with the lower-class British people. Lotteries were held in England in the 1600's to provide funds for the water system in London. Similarly, the British Museum was financed by lotteries (Ashton, 1969; Cotton, 1674; Lucas, 1930; Quinn, 1890; Sergeant, 1931; Steinmetz, 1969).

Horseracing was originally known as a gentleman's sport in the mid-1600's, but quickly became a popular gambling sport. By 1667, the first official race track, which became a gambling mecca, was established by Charles II. As in ancient times, corruption infiltrated the racing industry. Horseracing was rigged from its inception. Jockeys were bribed, "ringers" ran races under other horses names, and horses were forced to give poor performances so that future odds could be increased (Ashton, 1969; Cotton, 1674; Quinn,

1890; Sergeant, 1931; Steinmetz, 1969). These practices have endured to the present time.

Illegal gambling dens existed throughout the major urban areas in England in the 1700's, protected by the averted eyes of law enforcers. These gambling houses often operated as restaurants or bars with hidden areas for gambling. Some of the most popular games included roulette and "faro", a game in which bets were placed on cards drawn from a dealing box (Ashton, 1969; Cotton, 1674; Quinn, 1890; Sergeant, 1931; Steinmetz, 1969). However, despite the permissiveness and pervasiveness of gambling throughout that time, many people opposed these practices and were outspoken about their sentiments.

#### American History: The Early Years

Gambling in the United States originated with the American Indians, prior to the European settlement. They were known to gamble with straws and sticks in games similar to card games (Chafetz, 1960). Subsequently, the Spanish, French, and English settlers contributed to the development of gambling in America, importing their card games (Asbury, 1938; Bender, 1938; Chafetz, 1960; Ezell, 1960; Quinn,

1890). The colonists introduced the moral and legal debates about gambling similar to the fierce discussions in Europe.

In the 1600's, differences in the attitudes toward gambling were striking, with contrasting views between New England and the south. In New England, the Puritans were vehemently opposed to gambling. Within ten years following the landing of the Mayflower, a stringent anti-gambling law was passed. Lotteries, dice and cards were banned in Massachusetts and Connecticut in the 1670's. In contrast, gaming was accepted in the southern colonies where many of the settlers were aristocrats. By 1700, horseracing became a very popular sport in the south, with the best track located in Virginia. New York became a gambling center after the Dutch left, where horseracing and cock-fighting were popular (Chafetz, 1960).

Lotteries were a source of controversy in American history. On one hand, they played a significant role in the economic development in the colonies through the 1800's. Since they provided a stable source of revenue and voluntary taxation, most citizens and religious groups approved of lotteries. On the other hand, however, in time, the system

was abused and was used for personal gain. Moreover, it was perceived as a system which exploited the poor. As a result, by the mid-1700's, lotteries were banned in Massachusetts, New York, Connecticut and Pennsylvania (Chafetz, 1960). Thus, although lotteries initially provided an important source of economic development, by the time of the Revolution, the lottery was in decline (Ezell, 1960).

After the Revolutionary War, the lottery again became a popular source of revenue, and an alternative to increasing taxes. From 1790 to 1860, 23 of the 33 states utilized lotteries as a means of raising funds. Proceeds were directed toward public and private resources such as hospitals, orphanages, transportation systems, communication systems, libraries, churches and historical societies. Interestingly, universities such as Harvard, Columbia, and Brown were partially funded by lotteries. Lottery management company methods served as precursors to management techniques used in later developing major U.S. corporations, banks and brokerages. The Chase Manhattan Bank and the National Bank of New York were established by

individuals who previously managed lotteries (Ezell, 1960). From the mid-1800's through the first few decades of the 1900's, lotteries were on the decline due to an unfavorable economy as well as public opinion related to associated criminal practices.

Although lotteries were banned during this time in America, other forms of gambling were thriving. Gambling was most frequently found in cities considered the 'New Frontier' such as New Orleans, St. Louis and San Francisco. New Orleans was the original host (Quinn, 1890), and the first gambling houses were established there. Although certain houses catered to the rich, most gamblers became integrated into the New Orleans underworld.

Gambling spread from New Orleans to New York and Washington (1830's to 1840's), then to the West Coast at the time of the gold rush (1849). Riverboat gambling emerged and contributed to the development of gambling meccas wherever the riverboat docked along the Mississippi and Ohio rivers. Cities such as Cincinnati, St. Louis and Chicago became major gambling arenas along the rivers. New York remained the Northeastern mecca (Commission on the Review of

the National Policy Toward Gambling, 1976). Western gambling havens included Denver, Kansas City and San Francisco (Asbury, 1933).

American History: The 20th Century

Gambling continued to thrive openly until the beginning of World War I, at which time it was driven underground and operated by organized crime. These organizations developed to protect themselves from the law as well as from like-minded competitors. Gambling displaced bootlegging as the primary business in the underworld. Three infamous men who typified this period were New Yorkers Arnold Rothstein, Al Capone, and Meyer Lansky, all first generation Americans (Commission on the Review of the National Policy Toward Gambling, 1976).

In the 1930's, the Depression, as well as the termination of Prohibition, affected the illegal gambling industry. The Depression hastened efforts for legalization of gambling in various states. As a result, eighteen states legalized horseracing (Cook, 1961). In 1931, casino gambling was legalized in Nevada (Turner, 1965). The ending of Prohibition also left illegal gambling as the primary

economic resource for organized crime. In cities such as New York, Chicago and New Orleans, gambling was morally accepted by the public, similar to the attitudes toward drinking alcohol. Further, gambling was regarded as a way of giving some relief to the human condition as the Depression continued. Consequently, illegal casinos, horseracing, numbers, sports betting, and slot machines soon flooded the industry (Hammer, 1973). Bribery of politicians and police also allowed illegal gambling to perpetuate.

During the 1940's, illegal gambling soared. Approximately six billion dollars were spent by the public each year on illegal gambling, a figure greater than the combined profits of General Motors, General Electric, U.S. Steel and 100 other major manufacturers (Havemann, 1952). By the end of the 1940's, 57% of the population gambled, a 12% increase from the mid-1940's, according to a Gallup Poll. Moreover, legal gambling in Nevada became an extremely successful venture.

The population of gamblers continued to increase during the 1950's. In New Orleans, Louisiana (Time-Life, Inc., 1958) as well as Biloxi, Mississippi (Time-Life, Inc.,

1951), casinos operated openly along with horseracing and sports betting. In northern New Jersey, gambling casino's were available to wealthy Manhattanites (Berger, 1952). Although requests for reform of gambling were attempted, the public, the police, and the politicians were not willing to respond (Wagner, 1972).

As time went on, further attempts were made to enlighten the public about the impact of organized crime on gambling and on society, but ultimately, longterm effects were insignificant. Although public awareness and concern regarding the relationship between illegal gambling and organized crime increased following the open hearings of the Kefauver investigation (Report of the Special Senate Committee to Investigate Organized Crime in Interstate Commerce, 1951), the government's response to the committee's recommendations was limited as well as ineffective (President's Commission on Law Enforcement and Administration of Justice, 1967).

Throughout the 1960's, the overall situation remained essentially the same. Whereas legal gambling was still limited, illegal gambling continued to grow more than ever.

Numbers and sports betting increased as bookmaking continued to become commonplace in most cities (Coggins, 1966).

Organized crime remained a strong force, resistant to law enforcement. In 1970, the Commission to Investigate Alleged Police Corruption, the Knapp Commission, found that corruption was pervasive throughout law enforcement agencies. Police received payoffs from gambling revenues in exchange for their protection. Further, the Knapp Commission found that the judiciary failed to support gambling laws. From 1967 to 1970, nearly 10,000 arrests were made. Only 10% of those arrested were actually indicted and less than 1% were convicted. For those convicted, sentences were nominal (Knapp Commission Report on Police Corruption, 1973). Thus, with this type of network operating, gambling regulation was not apparent.

During the last two decades, availability of legal and illegal gambling has escalated. Although continuous attempts have been made to deflate the impact of organized crime on the gaming industry, it is obvious that the roots of this system have been firmly planted. It is unlikely that illegal gambling will disappear in the near future.

Moreover, as ongoing debates about legalization of gambling continue to take place, wherever possible, new gambling opportunities will develop.

In sum, gambling appears to be a fairly universal activity, spanning across the globe and throughout time. Economics and revenue created by both legal and illegal gambling sources have played significant roles in shaping and reshaping societal attitudes toward gambling.

During stressful or lean times, as was observed during wartime or economic depression, tolerance of gambling increased, impacting upon political and legal actions. Gambling may have generally served as an antidote for loneliness or boredom, and perhaps had the greatest impact on those most vulnerable toward addiction to such activity.

Shifting attitudes toward intolerance and prohibition of gambling seemed to be related to the recognition of corrupt practices, perceived as debasing the work ethic and limiting legitimate economic development. Religious and moral issues centered around the destruction of the family and of the individual at risk.

Nonetheless, economics and the generation of revenue through legal and illegal sources appeared to most powerfully impact upon the cost-benefit ratio of the legalization of gambling. As a result, the recognition of pathological gambling as an important public health issue has been limited. Adequate resources needed for the development of effective treatment for pathological gambling have not yet become available. After 4000 years, investigations regarding the mechanisms that may underlie pathological gambling are just beginning to be conducted. This dissertation reflects such an effort.

#### CLINICAL DESCRIPTION AND DEFINITION

As a psychiatric disorder, pathological gambling may be difficult to identify and diagnose, and is frequently overlooked in clinical settings. Clinically, pathological gamblers may present as having affective symptomatology and/or substance abuse problems, since these conditions often co-occur with PG (Lesieur & Blume, 1990; Lesieur, Blume, & Zoppa, 1986). Moreover, impulsive behaviors associated with Axis II disorders, such as borderline and

antisocial personality disorders, may be also present, and may overshadow symptomatology related to PG. Further, symptoms and behaviors specifically related to pathological gambling, which may have important implications for treatment, are often denied or hidden by the gambler. Consequently, pathological gambling may be overlooked and underdiagnosed.

Pathological gambling was first recognized as a distinct entity by the psychiatric community in the United States in 1980 (American Psychiatric Association, 1980). At that time, pathological gambling was first officially categorized as an impulse control disorder in the DSM-III (1980). Diagnostic criteria included both 1) a failure to resist the urge to gamble, and 2) increased gambling associated with increased levels of stress which may either be relieved by gambling or from which pleasure is felt (American Psychiatric Association, 1980).

The categorization of pathological gambling was changed to an "Impulse Control Disorder Not Elsewhere Classified" in the DSM-III-R (American Psychiatric Association, 1987, pp. 324-325). Essential features included: 1) failure to resist

the urge to gamble, 2) increased thoughts, urges, and gambling activity during stressful periods, 3) disruption of personal, familial, or vocational endeavors, and 4) intensification of gambling resulting from problems originated by gambling (American Psychiatric Association, 1987). One significant change in diagnostic criteria from the DSM-III to the DSM-III-R was that antisocial personality disorder was no longer considered a differential diagnosis. In the DSM-III-R, if both disorders were present, they were both to be diagnosed since they often co-occur.

In the most recent edition (1994), the DSM-IV continued to classify pathological gambling as an "Impulse-Control Disorder Not Elsewhere Classified" (American Psychiatric Association, 1994, pp. 615-618). Pathological gambling, therefore, has been classified in the same category as intermittent explosive disorder, kleptomania, pyromania, and trichotillomania. "The essential feature of Impulse-Control Disorders is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others" (American Psychiatric Association, 1994, p. 615). More specifically, the essential feature of

pathological gambling is the constantly recurring gambling behavior that is maladaptive (i.e., loss of judgment and excessive gambling), in that personal, familial and/or vocational endeavors are disrupted (American Psychiatric Association, 1994).

DSM-IV diagnostic criteria for pathological gambling are:

"A. Persistent and recurrent maladaptive gambling behavior as indicated by five (or more) of the following:

- (1) is preoccupied with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)
- (2) needs to gamble with increasing amounts of money in order to achieve the desired excitement
- (3) has repeated unsuccessful efforts to control, cut back, or stop gambling
- (4) is restless or irritable when attempting to cut down or stop gambling

- (5) gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety, depression)
- (6) after losing money gambling, often returns another day to get even ("chasing" one's losses)
- (7) lies to family members, therapist, or others to conceal the extent of involvement with gambling
- (8) has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling
- (9) has jeopardized or lost a significant relationship, job or educational or career opportunity because of gambling
- (10) relies on others to provide money to relieve a desperate financial situation caused by gambling.

B. The gambling behavior is not better accounted for by a Manic Episode" (American Psychiatric Association, 1994, p. 618).

Thus, since it was first listed in the DSM-III, pathological gambling has been consistently classified as a disorder of impulse control in which the impulse or urge to

gamble is persistent and maladaptive, disrupting vital relationships and activities of daily living.

#### EPIDEMIOLOGY

Two nationwide surveys estimated the prevalence of PG in the general population. An American national survey suggested that 68% of the general population participated in some form of gambling, and that 0.77% of American adults are considered probable pathological gamblers (Commission on the Review of the National Policy Toward Gambling, 1976). In England, estimates of PG range from 0.2% (Dickerson, 1974) to 1% (Royal Commission on Gambling, 1976-1978).

Prevalence estimates of probable PG from state surveys range from 1.2% to 3.4%, with increased rates in states which provide increased opportunity for legal gambling (Commission on the Review of the National Policy Toward Gambling, 1976; Culleton, 1985; Sommers, 1988; Volberg, 1990; Volberg & Steadman, 1988, 1989).

The DSM-IV prevalence estimates of pathological gambling range from 1-3% (American Psychiatric Association, 1994).

Prevalence estimates of PG in the general population

differ from estimates of a treatment-seeking population. In one study, six month estimates of pathological/probable pathological gamblers in treatment programs at three sites in New York state were compared to six month estimates of pathological/probable pathological gamblers from a general population New York state survey. In the statewide survey of the general population, relative to those in treatment programs, there were higher rates of pathological/probable pathological gamblers who were female (36% vs 7%, respectively), younger (less than 30 years old) (38% vs 18%, respectively), and non-Caucasian (43% vs 9%, respectively) (Volberg & Steadman, 1988). Many individuals who may benefit from treatment may not be aware of the available resources, especially since few specialized facilities are available and effective treatment methods are not yet clearly indicated.

Female pathological gamblers clearly represent an understudied and underserved group, since females comprise approximately one-third of pathological gamblers (Lesieur, 1988). Interestingly, 14% of the female gamblers' fathers and 4% of their mothers were also pathological gamblers. As

such, familial influence may be an important predictor of the development of pathological gambling.

Pathological gambling among adolescents and young adults has been on the rise. Prevalence estimates of PG among high school students range from 1.7%-3.6% (Ladouceur & Mireault, 1988) to 5.7% (Lesieur & Klein, 1987). In the U.K., approximately 50% of the members of Gamblers Anonymous (GA) were adolescents and young adults, almost exclusively gambling on fruit machines (slot machines) (Moody, 1989). Estimates of PG among college students range from 4% to 6% (Frank, 1988; Lesieur & Klein, 1987).

Thus, prevalence estimates of PG highlight the heterogeneity among pathological gamblers, the differences in demographics between estimates made from the general population and those made in relation to those who seek treatment, increased occurrence associated with increased opportunity, and increased rate of adolescent pathological gambling. Since most pathological gamblers begin their gambling career during adolescence (Custer, 1982; Livingston, 1974), early identification and intervention are critical.

### CLINICAL PROFILE

Distinctive behaviors, perceptions and traits are characteristic of pathological gamblers. Characteristics apparent during the early stages of PG include: 1) preoccupation with gambling; 2) excessive gambling; 3) spontaneous and solitary gambling; 4) securing special "gambling money;" 5) fantasies of success; 6) increased risk tolerance; 7) egotism; and 8) denial that gambling behavior could be a problem (Taber, 1980). Other common characteristics associated with PG throughout the lifespan include: 1) maintaining gambling as a primary interest to the exclusion of other interests; 2) continuation of gambling while winning and failure to stop while losing; 3) apparent lack of understanding of the consequences of the self-defeating behavior, associated with optimism and a belief that winning is inevitable; and 4) subjective experience of excitement and tension just prior to the outcome of a wager (Bergler, 1943). Thus, it would appear that these irrational beliefs, misperceptions and maladaptive behaviors perpetuate gambling behavior.

Comorbid psychiatric symptoms and disorders further complicate the clinical profile of a pathological gambler. In particular, an increase in affective symptomatology and substance abuse disorders have been found among pathological gamblers. Based on the Symptom Check List (SCL-90), a 90-item self-report scale, pathological gamblers were found to have elevated depression scale scores, whereas low scores were found on obsessive-compulsiveness, sensitivity, anxiety and phobia scales when compared to healthy control subjects (Derogatis, 1977). Likewise, on the Beck Depression Inventory, elevated depression scores were found among pathological gamblers (Lyons, 1984). On the Minnesota Multiphasic Personality Inventory (MMPI), pathological gamblers were found to have elevated scores on the depression and psychopathy subscales (Bolen, Caldwell, & Boyd, 1975; Graham & Lowenfeld, 1986; Moravec & Munley, 1983).

Depressive symptoms such as hopelessness and suicidality have also been found among pathological gamblers (Linden et al., 1986). Estimates of suicide attempts range from 17% to 24% (Ciarrocchi & Richardson, 1989; Custer & Custer, 1978;

Lesieur, 1988; Livingston, 1974; Moran, 1969). Younger patients are more likely to have suicidal tendencies and major depressive disorders (McCormick et al., 1984).

Among in-patients hospitalized for pathological gambling, 76% met criteria for a major depressive disorder, 38% were hypomanic, 8% were manic, 2% were diagnosed with schizoaffective disorder, depressed type, and 8% had no comorbid disorder (McCormick et al., 1984). Among out-patient samples, 28% met criteria for major depressive disorder, 24% had bipolar disorder, and 28% had anxiety disorders (Linden et al., 1986). For those who were depressed, onset of pathological gambling preceded onset of depression in 86% of the inpatients and in 72% of the out-patients. This suggests that for the majority of pathological gamblers, depression may develop either as a response to the loss of stimulation that occurs when gambling during the earlier course of the disorder or in response to the series of negative life events that occur as the course of the disorder progresses. The psychological mechanisms that underlie this disorder may differ for those who develop depression prior to the onset of

pathological gambling. Gender differences may also play an important role in this regard (see CLINICAL COURSE). This distinction may also have important implications for approach to treatment.

An atypical finding in which very few PG in-patients were concurrently diagnosed with mood disorders was also described (Lesieur & Blume, 1990). The lack of depressive symptomatology may have been influenced by the non-structured clinical interviews used in this study relative to structured interviews used in the other studies. As a result, depression may have been underdiagnosed. These divergent findings highlight the need to carefully assess the presence of depression by means of a valid and reliable diagnostic instrument in association with pathological gambling.

In addition to affective symptomatology, high rates of comorbid substance abuse and dependency further complicate the clinical profile of many pathological gamblers. For example, 9% of in-patient substance abusers were diagnosed as pathological gamblers (Lesieur et al., 1986) and 17% of alcohol abusers had gambling problems (Haberman, 1969).

Conversely, 47% of in-patient pathological gamblers (McCormick et al., 1984) and 52% of Gamblers Anonymous members (Linden et al., 1986) were alcohol/drug abusers. Of note, among a sample of female pathological gamblers, 28% had alcoholic fathers and 5% had alcoholic mothers (Lesieur, 1988). Thus, there appears to be a strong relationship between pathological gambling and substance abuse.

Finally, pathological gamblers may also experience dissociative-like states, similar to that experienced by alcohol abusers and compulsive overeaters (Jacobs, 1989). Pathological gamblers were compared to social gamblers on measures of dissociative states during or shortly after gambling. Dissociative measures included: 1) trance-like experiences; 2) feeling 'outside oneself' and watching oneself; 3) perception of altered identity; and 4) 'memory blackouts' (Jacobs, 1984). Overall, dissociative states were experienced more than twice as frequently in pathological gamblers compared to social gamblers. Increased life stressors are associated with extensive gambling and were associated with a higher rate of frequency. It has been hypothesized that dissociative

states may be linked to increased sympathetic arousal, and that gambling may precipitate physiological and neurochemical changes that contribute to the manifestation of these states (Jacobs, 1982).

Thus, there appears to be a core of irrational beliefs, maladaptive behaviors, and comorbid symptoms that contribute to the clinical profile of the pathological gambler.

#### CLINICAL COURSE

One prominent model of the clinical course of pathological gambling was the Three-Phase Model which included: 1) the Winning Phase; 2) the Losing Phase; and 3) the Desperation Phase (Custer & Milt, 1985). This original model was revised, incorporating gender specificity and social dimensions (Lesieur & Blume, 1990; Rosenthal, 1986a, 1989a), resulting in a more comprehensive theoretical model.

The Four-Phase Model of the clinical course of pathological gambling includes: 1) the Winning Phase; 2) the Losing Phase; 3) the Desperation Phase; and 4) the Giving-Up Phase. In the Winning Phase (Phase 1), male gamblers

associate gambling skills with initial successes, especially if they experience a "big win." Early losses may be either ignored or viewed as having occurred by chance. These types of irrational beliefs regarding the locus of control of gambling outcome become reinforced during this phase of the clinical course. There is also an increase in preoccupation with gambling and amount of money wagered. Female gamblers tend to experience Phase 1 gambling in one of two ways: 1) as an anesthetic, to escape from life's problems (i.e., as in a dissociative state) (Jacobs, 1988; Lesieur, 1988), and 2) as a means of seeking action, often initially experiencing a "big win."

The Losing Phase, Phase 2, begins when gambling takes place in an attempt to recover losses produced by irrational gambling. The gambler often gambles alone. The frequency and the amount of gambling increases. Lying and deceit begin to take place. Disruption of personal, familial, social, occupational and financial interests occur. It is during this phase that the gambler seeks-out family members for a "bailout."

The Desperation Phase, Phase 3, is characterized by a drastic change in behavior. This phase could be viewed as an addictive phase. Involvement in illegal activities such as forgery, fraud, theft or embezzlement occur in an attempt to sustain gambling activity. The gambler becomes restless and irritable, and at times, may even become abusive to family members. Most all other activities and interests are ignored. At this point, eating and sleeping habits deteriorate. Often suicidal thoughts occur and sometimes suicide attempts are made.

During the Giving-Up Phase, Phase 4, the pathological gambler comes to the realization that gambling no longer serves the purpose of winning back losses. The gambler realizes that the debts are so outrageous, that he/she will never be able to recover them (Rosenthal, 1989a). Gambling occurs merely for the reinforcement of the excitement that may be induced, with little concern whether there are wins or losses. Suicidality is also associated with this phase for certain pathological gamblers. By contrast, initiation of the recovery process may also begin at this point for

pathological gamblers who either have adequate coping skills or who have been directed toward some type of treatment.

In addition to this descriptive model of the clinical course of PG, distinct factors which may precipitate heavy gambling in a social gambler, or hasten the intensity of gambling in a pathological gambler have been identified. These factors include a number of life stressors such as: 1) substance use or abuse; 2) death or divorce; 3) birth of a child; 4) threat or actual physical trauma; and 5) success or failure in an occupational setting (Bolen & Boyd, 1968; Boyd & Bolen, 1970). Any one of these life stressors may contribute to the exacerbation of symptoms at a particular point in time. However, for the pathological gambler, the course is chronic, with increasingly devastating consequences as the disorder progresses. Several theories have been proposed in an attempt to explain why pathological gamblers continue to gamble, despite the consequences.

#### THEORETICAL PERSPECTIVES

Psychoanalytic, psychodevelopmental, cognitive, behavioral and physiological theories of pathological

gambling have emerged. Each of these perspectives has its own merits and limitations. An integrative approach toward understanding the underlying mechanisms of this disorder may be most useful.

### Psychoanalytic Theories

Early psychoanalytic theorists associated gamblers with masochism, anal fixation and compulsive personality traits (Von Hattingberg, 1914). Freud (1928) viewed gambling as self-punishment to rid the guilt experienced for having negative feelings about one's father. Freud also described gambling as a desire for excitement and as an expression of addictive behavior based on a compulsion to masturbate. Further, gambling has been theorized to represent a rebellion against parental authority (Bergler, 1943), a mechanism to alleviate depression (Greenson, 1947; Israeli, 1935), and an expression of omnipotence (Bergler, 1957; Greenson, 1947; Rosenthal, 1986a, 1986b). Psychoanalytic studies of pathological gambling have been criticized for their shortcomings, such as small and selected samples as well as untestable assertions (Allcock, 1986). Albeit,

these early ideas have provided a conceptual basis for current thinking.

### Psychodevelopmental Theories

The childhood backgrounds of pathological gamblers have often been associated with a high incidence of family dysfunction (Taber, McCormick, & Ramirez, 1987) which interferes with identity formation. Childhood and adolescent development is often marked by intense feelings of low self-esteem, inadequacy and inferiority, along with a deep sense of parental rejection. These perceptions may predispose an individual toward development of addictive behavior (Jacobs, 1989), as well as personality disorders and characterological features, as is often found in pathological gamblers (McCormick, Taber, & Kreudelback, 1989).

According to the developmental model, during the process of normal development within the first years of life, trust and consistency exist and differentiation between self and parents occur. Eventually, a separate identity develops, incorporating the identification of self and others, encompassing both 'good' and 'bad' dimensions (Rinsely,

1989). Impairment in the child's development of an integrated identity may occur if the environment supplies neither consistency nor a basis for trust. As such, the child may not be able to appropriately soothe oneself in an attempt to manage associated tensions and anxieties. Consequently, 'splitting' between 'good'/'bad' self and others may manifest as a defense mechanism.

For pathological gamblers, the act of gambling may provide a means of developing a sense of self-esteem and internal comfort. Excitement may function as a substitute for hope. Furthermore, gambling may provide a means of avoiding the fear of abandonment and rejection, as well as a way of attaining grandiose fantasies (Rugle, 1993). Consequently, maladaptive personality traits may manifest in adulthood, such as those observed in DSM-IV Axis II borderline, narcissistic and antisocial personality disorders. Borderline personality traits such as emotional lability, idealization/ devaluation, boredom intolerance, and identity disintegration often characterize treatment-seeking gamblers (Rugle, 1991). Narcissistic features such as omnipotence, grandiosity, exaggerated desire for

attention and admiration (as a defensive mechanism against rejection and emptiness) have also been frequently described in PG (Taber, 1983). Additionally, antisocial personality characteristics have been identified among pathological gamblers, and include impulsivity, conflict with authority, and rebelliousness (Custer & Custer, 1978; Graham & Lowenfeld, 1986; Taber, 1983).

Personality disorders are described as "enduring patterns of inner experience and behavior that deviate markedly from the expectations of the individual's culture, are pervasive and inflexible, have an onset in adolescence and early adulthood, are stable over time, and lead to distress or impairment" (American Psychiatric Association, 1994, p. 629). These lifelong characteristics are often difficult to treat and significantly change. As such, pathological gambling may manifest as a result of underlying developmental deficits associated with distinct Axis II personality traits and disorders. Furthermore, PG is also frequently associated with comorbid Axis I disorders (i.e., affective disorders and substance abuse), which may also

develop and co-occur as a result of the pathological gambler's family history and developmental pathogenesis.

### Cognitive Theories

According to cognitive theories, development of cognitive structures reflects the evolution of a belief system which is influenced by neurophysiological functions and heavily determined by the environment and learning (Rugle, 1993). In pathological gamblers, this maladaptive belief system precipitates irrational, illogical thinking and decision making, which in turn, impacts upon the development of negative affect and impulsivity (Gilovitch, 1983; Ladouceur, Gaboury, Dumont, & Rochette, 1988; McCormick & Taber, 1988).

Ineffective cognitive structures in PG are generally associated with expectancies, beliefs about self-efficacy, and locus of control (Gilovitch, 1983; Griffiths, 1990). Most of these erroneous perceptions significantly contribute to the development and maintenance of gambling (Ladouceur, 1990). Losses are often attributed to chance or irrational external factors, whereas wins are frequently associated with special skills or other attributes of the gambler

(Gilovitch, 1983). These types of erroneous percepts are typically associated with Phase I and Phase II of gambling. However, unless mediation occurs, these irrational beliefs may always remain part of a pathological gambler's belief system and may compound additional motivating factors that prompt ongoing gambling activity (as may be seen in Phase III or IV of gambling).

One of the most successful methods of measuring cognitive dimensions has been the "thinking aloud method" (Gaboury & Ladouceur, 1989). Using this model, gamblers were asked to verbalize their thoughts, impressions and images that occurred while gambling. More than 80% of the gamblers expressed irrational thoughts and perceptions regarding certain aspects of gambling, regardless of the type of gambling activity. Perceptions relating to variables other than chance were expressed. These variables included responses related to cause-and-effect, "near misses," superstitious behavior, inappropriate attributions and personal control (Ladouceur, 1990).

Psychological mechanisms of the "near miss" were examined, revealing that "near misses" have the same

reinforcing properties as "wins" (Reid, 1986). This mechanism could be viewed as cognitive conditioning via secondary reinforcement. The "near miss" may also function as a partial reinforcement mechanism since it may reinforce some of the beliefs and perceptions about the choices which turn out to be correct. Slot machines and lotteries are designed to produce a greater than chance number of "near misses." The reinforcing quality of the "near miss" can be quite powerful, especially for the pathological gambler, who may be in a primed state of arousal, as well as vulnerable to a host of irrational beliefs.

Irrational perceptions of self-efficacy (i.e., the belief that one has adequate coping skills) has also been described as characteristic in pathological gamblers. Coping methods are associated with confidence levels and an estimation of the likelihood of succeeding in a particular situation. Pathological gamblers' coping methods are often consistent with those associated with the learned helplessness model. As such, irrational self-blaming and an assumption that life's problems are unsolvable contribute to the ineffective coping strategies, decreasing self-efficacy.

Helplessness, hopelessness, depression and anxiety may manifest as a result of these irrational beliefs (Beck, Rush, Shaw, & Emery, 1979; Burns, 1980; Ellis, 1975). Consequently, pathological gamblers may choose addictive behaviors such as gambling and substance abuse as coping mechanisms (McCormick & Taber, 1988) which correspond to the impulsivity and negative affect observed in PG (McCormick, 1987).

Implications of the impact of cognitive structure on gambling behavior are clear. Erroneous percepts may contribute to the development and maintenance of gambling behavior. Reinforcing mechanisms include behavioral conditioning and the associated physiological arousal. These mechanisms operate in an organism which appears to be simultaneously seeking facilitation and regulation of stimulation and arousal.

#### Optimum Level of Stimulation Model

The Optimum Level of Stimulation Model suggests that every individual has an optimum level of arousal at which one feels well and functions most effectively (Zuckerman, 1979). Arousal may include autonomic as well as cortical

arousal, regulated by environmental stimulation. Increased or decreased levels of stimulation may be sought in an effort to maintain homeostasis. The pathological gambler's search for a continuous increase in arousal may occur intermittently and over time (Zuckerman, 1969). Further, "withdrawal symptoms" (e.g., irritability; restlessness) may develop as a result of gambling cessation and decreased levels of arousal.

Interestingly, this model offers an explanation for continued gambling once intermittent reinforcement patterns have been extinguished. As such, gambling sessions often continue until all of one's money is gone. There are several factors that account for why gambling is so resistant to extinction, despite increased negative consequences (Jacobs, 1982, 1984). First, there is a significant positive reinforcement factor which occurs early in the gambler's career. This reinforcement results in the production of pleasurable feelings in a person who otherwise feels particularly low and deprived. Second, extremely strong associations have occurred by the extensive repetitions of behavior, both in reality and in fantasy.

Third, the most critical factor refers to the near phobic avoidance of the return to, and maintenance of the initial dysregulated resting state. The contrast may be so dramatic that it further reinforces the behavior. Thus, the pathological gambler may continuously experience the pull toward levels of arousal that only further reinforces the self-defeating behavior which initially precipitated the cycle.

#### Gambling as an Addiction

Pathological gambling is often viewed as an addiction (i.e., an inability to reduce or stop the use of a "substance" resulting in personal, physical, social and/or occupational impairment).

The phenomenological link between gambling and addiction is evident when comparing DSM-IV criteria for PG and substance use disorders. Criteria for the latter include tolerance (Dickerson, 1984), dependence (Moran, 1970), and withdrawal (Wray & Dickerson, 1981). In PG, tolerance develops when the amount or the frequency of the wager increases in order to sustain the desired level of excitement. Withdrawal is associated with restlessness and

irritability that may manifest if unable to gamble.

Dependence develops when the gambler: 1) makes larger wagers than intended; 2) makes continuous efforts to decrease gambling; 3) continues to gamble in an effort to regain losses; 4) does not participate in usual social or occupational activities in order to gamble.

Two factors are associated with increased vulnerability toward the development of an addiction. First, a dysregulated physiological resting state (either aroused or depressed), and second, a childhood feeling of inadequacy (Jacobs, 1986). Onset may occur by chance when a person with these predisposing factors is confronted by the addictive stimulus. Dependence may develop over time to guard against anticipation of anxiety or painful realities, alleviating stress (Jacobs, 1982, 1984). Addictive behavior is also associated with increased levels of tension prior to engaging in the addictive activity, and a sense of relief following the activity. For the pathological gambler, like the substance abuser, a strong sense of pleasure and a release of tension accompany completion of the behavior, at least in the initial stages of the disorder

(Moran, 1970). As such, the gambling behavior itself may be regarded as the addictive substance which reduces the tension and anxiety (Anderson & Brown, 1984).

Thus, these overlapping variables underscore that which makes identification and treatment difficult for pathological gamblers.

#### Behavior Completion Model

The behavior completion model emphasizes that a neural network is associated with the activation of a particular stimulus that has been previously associated with a particular behavior (McConaghy, 1980). Once the stimulus begins to activate the system, the behavior pattern must be completed. An interruption of this process is experienced as a stressor that is interpreted as a noxious event. This model may be applicable to PG, since gambling activity is not usually stopped in the middle of a string of losses or of wins. If so, the gambler may experience increased tension (i.e., the noxious event) which would then be relieved by completion of the behavior. (This model may also be applicable to compulsive behavior and rituals as experienced in obsessive-compulsive disorder).

The actual completion of the gambling behavior usually occurs when the availability of all possible financial resources (in that setting and during that episode) have been tapped. To a social gambler, a win, fatigue, or the closing of the facility may terminate the gambling episode. To a pathological gambler, a win may only further prolong the gambling episode. Moreover, neither fatigue nor the closing of a gambling establishment may facilitate termination of gambling behavior in a pathological gambler. The search often continues until the all of the money is gone.

Thus, the behavior completion model provides one perspective regarding the resistance to extinction often observed in pathological gamblers.

#### Model of Operant Conditioning

A model of operant conditioning describes factors associated with the development and maintenance of gambling. Most pathological gamblers have a significant win early in their career (Custer and Milt, 1985). According to this model, it is the variable reinforcement schedule that drives the pathological gambler to continue gambling (Bolen & Boyd,

1968). The exposure and availability increase the probability of the development of pathological gambling. The arousal associated with the gambling activity becomes the reinforcing agent, since after the initial stages of gambling, winning money becomes a secondary factor.

Each of these theoretical models offers an insightful view toward understanding the development, maintenance, and refractory nature of pathological gambling. Collectively, the complexity of the underlying mechanisms of PG underscores the difficulty in treating pathological gamblers.

### TREATMENT

Few treatment options and facilities currently exist for the pathological gambler. Psychoanalysis, behavior and cognitive therapy, self-help groups, and pharmacotherapy have been available for the treatment of PG. However, the effectiveness of these treatments is uncertain since most treatment studies have been based on case reports, and very few controlled treatment outcome studies have been conducted. Further, investigations of long-term efficacy

are limited. As such, development of effective treatment for pathological gambling is in its infancy. Findings from neurobiological studies of pathological gambling, as proposed in this dissertation, may help elucidate the pathophysiology of this disorder, which in turn may lead to controlled pharmacological treatment studies.

#### Psychoanalytic Treatment

The earliest reports of treatment come from the psychoanalytic literature. Most of the studies which report good outcome are based on single-case studies (Commess, 1960; Eissler 1950; Harkavy, 1954; Harris, 1964; Linder, 1950; Reider, 1960; Simmel, 1920). Many of these psychoanalysts employed treatment methods based on Freud's (1928) perspective. Freud postulated that gamblers gamble not for money, but for the arousal, and may actually wish to lose. This desire to lose may be related to a son's ambivalence toward his father. Feelings of guilt associated with the love-hate relationship toward one's father may be relieved by punishing oneself, and thus, losing when gambling.

Another psychoanalytic perspective from which other case reports of successfully treated pathological gamblers have been described relates to the narcissistic personality organization and related defense mechanisms. Simmel (1920) focused on his patient's narcissistic fantasies, particularly the denial of both dependency needs and feelings of inadequacy. More recently, psychodynamic treatment continues to focus on primary problems which include self-regulation and identity formation (Livingston, 1974; Rosenthal, 1986b; Roston, 1961; Taber, 1982).

Further, omnipotence has been regarded as a critical factor that needs to be understood and addressed in order to successfully treat pathological gamblers (Rosenthal, 1986a, 1986b). The grandiosity and the illusion of controlling events which cannot be controlled and to predict outcome of future events are the basis for the omnipotence found in pathological gamblers according to this perspective.

Reports of successful treatment have also been described in larger sample sizes (Bergler, 1957), however, methodological flaws, including biased sampling, lack of

outcome criteria, and inadequate assessment of follow-up, contribute to questionable results (Allcock, 1986).

### Behavioral Treatment

Behavioral methods have been frequently used in treatment. From this perspective, gambling is viewed as a learned behavior that can be treated with counter conditioning. Aversive therapy has been the method most commonly employed (Victor & Cruz, 1967) to reach the goal of behavior therapy, which is the total abstinence of gambling. Importantly, most of the behavioral treatment studies have not been controlled, comparative studies. Instead, these investigations were small sample or single-case studies, which primarily used aversive therapy techniques.

Albeit, outcome studies have shown some success at one year follow-up. In one study, treatment with electric shocks were given at a variable interval schedule to three patients watching a film on gambling or playing a poker machine. Two of the three patients were reportedly abstinent at one year follow-up, and although the third relapsed, he responded to a second treatment trial (Barker & Miller, 1968). Other studies using aversive therapy techniques

indicated that five of fourteen patients (Seager, 1970) and eight of twelve patients were abstinent at one year follow-up (Koller, 1972). In a single case study, one gambler, who was a horserace bettor, received a series of 675 random shocks during 45 ten-minute sessions throughout a two-week period (Goorney, 1968). This patient was successfully treated, and at a one year follow-up, there was no resumption of gambling. Although these results show some indication of the efficacy of aversive therapy in the treatment of PG, it is currently seldomly used due to ethical reasons.

Combinations of various behavioral interventions have also been used with some apparent success. Interventions included self-administered shock, behavior substitution, time-out from family, self-recording of the gambling activity (Cotler, 1971), direct punishment, mildly aversive stimuli (rubber band snapping) and covert desensitization (Greenberg & Rankin, 1982). Imaginal desensitization has also been used. With this method, patients visualized themselves in a gambling situation that they've experienced. While remaining relaxed, they then

visualized leaving the situation without having gambled.

Interestingly, imaginal desensitization was found to be more effective in decreasing gambling urges and levels of anxiety than aversive therapy (McConaghy, Armstrong, Blaszczynski, & Allcock, 1983). Whereas pathological gamblers practice what they should do during imaginal desensitization, they learn what they should not do during aversive therapy.

#### Cognitive Treatment

Cognitive therapy has been used with some success in the treatment of pathological gambling. These techniques focus on the arousal associated with gambling, perpetuated by irrational verbalizations. Preliminary results from one study using cognitive restructuring showed a decrease in the frequency of gambling and associated irrational verbalizations (Ladouceur, 1990). Perceptions which associated gambling success to variables other than chance formed the basis of these irrational verbalizations. Illusion of control contributes to inappropriate percepts pertaining to cause-and-effect relationships, personal attributions, and superstitious behavior in reference to winning. In this preliminary study, cognitive restructuring

included seven components: 1) behavior analysis; 2) dispensing information about gambling; 3) feedback regarding accuracy of beliefs; 4) identification of irrational thoughts; 5) awareness training to identify irrational thoughts while gambling; 6) comprehension of reasoning behind irrational thoughts; 7) adaptation of changes from irrational thoughts to rational thoughts. Three of four social gamblers and two of three pathological gamblers decreased the frequency of their gambling. Overall, following cognitive restructuring, subjects decreased irrational verbalizations from 92% at baseline to 16% at a three month follow-up. Consequently, rational verbalizations increased from 8% at baseline to 84% at follow-up. The cognitive restructuring method appears to have potential for the treatment of PG. Further investigation is needed.

#### Self-Help Groups

Self-help groups have been available to nearly all gamblers seeking this type of support. According to the Gamblers Anonymous model, gambling is viewed as a progressive illness which can be stopped. Retrospective

studies show a drop-out rate up to 70% within the first year (Stewart & Brown, 1988), and overall drop-out rates ranging from 75% to 90% (Moody, 1990). Eight percent of Gamblers Anonymous members reported total abstinence at a one-year follow-up and 7% at a two-year follow-up (Brown, 1985). Success rates are minimal and reliability of outcome measures are questionable. It appears that self-help groups do not address the treatment needs of a large proportion of those who are seeking help for pathological gambling.

#### In-Patient Treatment

In-patient treatment and rehabilitation programs have emerged since the early 1970's (Glen, 1976; Taber, 1981). These programs are modeled after in-patient treatment programs for the rehabilitation of substance abusers. Outcome studies have shown that approximately 55% of patients reported abstinence at one-year follow-up (Russo, Taber, McCormick, & Ramirez, 1984; Taber, McCormick, Russo, Adkins, & Ramirez, 1987). However, since these results are based on studies which are not controlled, it is difficult to say whether or not spontaneous recovery occurred and contributed to the reported success rates from these groups.

Of note, in one study, it was found that those who reported abstinence also reported decreased depression, increased financial stability, increased quality of interpersonal relationships, and an increased likelihood to participate in Gamblers Anonymous or other treatment programs (Russo et al., 1984). In another study, 18% of the patients who were abstinent reported a significant increase in familial and occupational stability, but were still significantly depressed. These findings suggest that for some of the pathological gamblers, depression may be associated with the consequences of gambling, and for others, gambling may be a consequence or attempt to deal with depression.

#### Pharmacotherapy

There is very little research on the efficacy of pharmacotherapy in pathological gambling. One report, on the use of lithium carbonate, demonstrated mild success for gamblers who also suffered from an affective disorder (Moskowitz, 1980). In a single case report, possible efficacy of a serotonin reuptake blocker, clomipramine, was demonstrated (Hollander, Frenkel, DeCaria, Trungold, & Stein, 1992). During the double-blind placebo-controlled

trial of clomipramine, the patient continued to gamble during the initial 10-week placebo phase, whereas gambling discontinued during the 10-week clomipramine phase. Following the double-blind study, the patient was treated with clomipramine for an additional 28 weeks. With the exception of a short relapse at week 17, (death of a family member occurred at this time), she remained in complete remission. Further, three additional PG patients were treated with a 10 week trial of clomipramine, achieving substantial improvement in their actual gambling behavior (Hollander & DeCaria, unpublished observations).

These reports offer a glimpse at the possibility of treating pathological gambling with medications that act on the central serotonergic system. These types of studies underscore the need for investigating the underlying neurobiological mechanisms associated with PG and the development of well-defined and controlled clinical trials.

#### PERSONALITY PROFILE: DIMENSIONAL VARIABLES

Identifying personality traits of pathological gamblers helps to discern morbid risk, pathophysiology, and treatment

outcome. Yet the available data are generally inconsistent and difficult to compare. Heterogeneity of gaming preferences, sample size and selection, varied assessment scales, and an overall paucity of available research in this area contribute to the difficulty in generalizing findings. Although there are a few distinct dimensions that appear to be consistently described in the PG literature, they are not always consistently supported. These dimensions include: 1) impulsivity; 2) sensation-seeking; 3) depression; and 4) extroversion.

Impulsivity per se is one symptom dimension that is frequently associated with pathological gambling (McCormick, 1987; Millon, 1983; Swyhart, 1976), but is also present in other disorders. The DSM classification has been based primarily on behavioral observations and phenomenology (where findings have been inconsistent). Thus, there is a great need to incorporate associated neurobiological and neuropsychiatric factors with phenomenology. This integration may further enhance the development of classification, diagnosis, and treatment of pathological gamblers.

Elevated scores reflecting higher levels of impulsivity have been found on the Barratt Impulsiveness Scale (Swyhart, 1976), the California Personality Inventory (McCormick, Taber, Kreudelback, & Russo, 1987), and the Millon Multiaxial Inventory (Millon, 1983). However, in one study, using the Barratt Impulsiveness Scale, no significant differences were found between pathological gamblers and normal controls (Allcock & Grace, 1988). The relationship between neurobiological measures and constructs of impulsivity in PG will be assessed in this dissertation.

Although pathological gamblers have been described as sensation-seeking (Custer, 1982), some studies do not support this view. The Zuckerman Sensation-Seeking Scale Form Y has been used to measure: 1) Thrill and Adventure Seeking (tendency toward physical and dangerous activities); 2) Experience Seeking (characterized by changes in lifestyles and cognitive stimulation; 3) Disinhibition (preferring social activities and gambling); and 4) Boredom Susceptibility (repetitive acts difficult to tolerate). Pathological gamblers scored significantly lower on the Thrill and Adventure Seeking Scale, the Experience Seeking

Scale (Blaszczynski, Wilson, & McConaghy, 1986), as well as the sensation-seeking scale total score (Blaszczynski et al., 1986; Carrasco, Saiz-Ruiz, Moreno, Hollander, & Lopez-Ibor, 1994), relative to normal controls. Additionally, Tri-Dimensional Personality Questionnaire (TPQ) (Cloninger, 1987) Harm Avoidance Scale scores were significantly higher among pathological gamblers compared to normal controls (Carrasco et al., 1994). Thus, rather than sensation-seeking behavior, it has been suggested that affective disturbances, compulsive symptoms, and ineffective coping mechanisms may dominate the pathological gambler's profile.

In support of this view, elevations on depression scales have been consistently found. Pathological gamblers' scores on the Beck Depression Inventory (Blaszczynski, McConaghy, & Frankova, 1990; Lyons, 1984) were elevated relative to controls. Additionally, elevated scores on depression subscale scores were found on the MMPI (Bolen et al., 1975; Graham & Lowenfeld, 1986; Moravec & Munley, 1983). Thus, it is possible that for a subgroup of gamblers, behavior which may appear to be sensation-seeking may more accurately be described as an attempt to alleviate depression. For

another subgroup, depression may occur as a result of gambling losses or termination of gambling activity.

Inconsistent scores on the Eysenck Personality Inventory Extroversion Scale have been found among pathological gamblers. Both average extroversion scale scores (Moran, 1970; Seager, 1970) and low extroversion scale scores (Koller, 1972) were found on this scale. These results may reflect sampling bias or heterogeneity in the types of gambling activities preferred. Of note, the gamblers scored high on the neuroticism scale (Carrasco et al., 1994; Moran, 1970; Seager, 1970).

Thus, the most consistent findings regarding dimensional variables in PG appear to be associated with impulsivity, compulsivity, and depression. Neurobiological correlates of these dimensions have been investigated, providing further insight into some of the underlying mechanisms that may be relevant to pathological gamblers.

#### NEUROBIOLOGICAL CORRELATES

Very few neurobiological investigations have been conducted to assess the relationship between pathological

gambling and constructs of impulsivity (Carrasco et al., 1994; Moreno, Saiz-Ruiz, & Lopez-Ibor, 1991; Roy, Adinoff, Roehrich, Lamparski, & Linnoila, 1988; Roy, DeJong, & Linnoila, 1989). However, numerous investigations of serotonergic function in other disorders associated with impulsive behavior have been conducted. These studies have provided theoretical and structural models for neurobiological studies in pathological gambling.

#### Serotonin and Impulsive/Aggressive Behavior

Pre-clinical studies have shown that a decrease in central nervous system (CNS) serotonin is associated with suppression of inhibitory responses (Sanger & Blackman, 1976; Tye, Everitt, & Iversen, 1977; Tye, Iversen, & Green, 1979). As such, predatory and affective aggressive behavior have been linked to decreased levels of CNS serotonin (Eichelman, 1987). Predatory aggressive behavior is an interspecies phenomenon (e.g., mouse-killing in rats), whereas affective aggressive behavior is an intraspecies behavior (e.g., behavior change following displacement from social hierarchy in dominant male vervant monkeys or from social isolation in rats). Moreover, increased sensitivity,

irritability and responsiveness have been associated with decreased levels of central serotonin (Valzelli, 1981). Thus, reduced central serotonin function in animals may reflect a reduced threshold to respond to a situation which may incite an impulsive or aggressive reaction.

These studies have relevance when placed in the context of behaviors seen in impulsive/aggressive individuals who have difficulty with delayed gratification and those who are minimally impacted by punishment and/or negative behavioral consequences (Brown & Linnoila, 1990). Moreover, it has been suggested that increased arousal and irritability may lead to decreased capacity to refrain from responding. This, in turn, may increase the likelihood of the manifestation of aggressive behavior toward self or others (Coccaro, 1992). Since pathological gambling is highly associated with impulsivity and self-directed aggressive behavior (i.e., suicidality), these studies have relevance for the neuro-biological study of pathological gambling.

In contrast to the association of decreased serotonergic activity and impulsivity/aggression, increased serotonergic activity has been associated with compulsive, ruminative,

behaviorally inhibited, harm avoidant conditions evident in obsessive-compulsive disorder (Hollander, DeCaria, et al., 1992; Zohar, Mueller, Insel, Zohar-Gadouch, & Murphy, 1987) and anorexia (Kaye, Ebert, Gwirtsman, & Weiss, 1984).

Peripheral and central serotonergic indices have been used to identify neurobiological substrates associated with measures of impulsive/aggressive behaviors.

#### Peripheral Serotonergic Indices

Platelet monoamine oxidase (MAO) activity is a peripheral index of serotonergic function (Levitt, Pintar, & Braekefield, 1982). Low platelet MAO activity has been linked to tendencies toward impulsivity and monotony avoidance (Perris et al, 1980; Schalling & Asberg, 1979; Schalling et al., 1980), risk-taking and sensation-seeking behavior (Murphy, Belmaker, & Buchsbaum, 1977; Von Knorring, Oreland, & Winbald, 1984; Ward, Catts, Norman, Burrows, & McConaghy, 1987), and suicidal tendencies (Buchsbaum, Haier, & Murphy, 1977; Gottfries, Von Knorring, & Oreland, 1980). Since pathological gambling has been associated with these variables, it is interesting to note that pathological gamblers have also been reported to have low platelet MAO

activity relative to normal controls (Carrasco et al., 1994). Platelet MAO activity, however, has been shown to be poorly correlated with brain MAO activity (Young, Laws, Sharbrough, Weinshilboum, & Laws, 1986), and as such, offers limited information regarding the underlying pathophysiology associated with impulsivity.

#### Central Serotonergic Indices

Studies of central serotonergic function in relationship to impulsive/aggressive disorders and behaviors have focused on indices such as cerebrospinal fluid (CSF) 5-hydroxy-indoleacetic acid (5-HIAA), a metabolite of serotonin; brain imipramine (IMI) binding and serotonin (5-HT) concentration; and peripheral hormonal responses, such as plasma prolactin, cortisol and growth hormone, to administration of 5-HT precursors, agonists, antagonists, and reuptake blockers.

#### CSF 5-HIAA Studies

Several investigations have suggested that reduced CSF 5-HIAA may be associated with impulsive/aggressive behaviors (Asberg et al., 1976; Bioulac, Benezech, & Renaud, 1980; Linnoila et al., 1983; Roy, Virkkunen, Guthrie, Poland, & Linnoila, 1986; Roy, Virkkunen, & Linnoila, 1987; Virkkunen,

Nuutila, Goodwin, & Linnoila, 1987). Low levels of CSF 5-HIAA were found in 1) male personality disorder patients with a history of aggressive behavior (Brown et al., 1982; Brown et al., 1979; Brown et al., 1985); 2) suicide attempters and suicide victims in various diagnostic groups (Asberg, Schalling, Traskman-Bendz, & Wagner, 1987; Mann et al., 1992; Traskman et al., 1981); 3) violent criminal offenders (Lidberg, Tuck, Asberg, Scalia-Tomba, & Bertilsson, 1985; Linnoila et al., 1983); 4) impulsive arsonists (Virkkunen et al., 1987); and 5) impulsive/aggressive healthy control subjects (Asberg et al., 1987; Roy, Adinoff, & Linnoila, 1988). Low CSF 5-HIAA has been interpreted as suggesting diminished pre-synaptic 5-HT function. Pre-synaptic function is implicated since the enzymatic breakdown and metabolism of serotonin by monoamine oxidase A (MAO-A) occurs in the storage vesicles of the presynaptic neuron following reuptake. The end product of this breakdown is 5-HIAA. CSF 5-HIAA levels are often referred to as an index of the rate of central serotonin turnover (Bradford, 1986). Thus, the association of impulsive/aggressive behavior and reduced CSF 5-HIAA may

reflect a relationship between impulsivity/aggression and diminished pre-synaptic function.

Interestingly, in pathological gamblers, levels of CSF-5HIAA were not significantly different from normal controls (Roy, Adinoff, Roehrich, Lamparski, & Linnoila, 1988). It was suggested that sampling bias may have occurred, since DSM-III criteria were used, requiring the exclusion of pathological gamblers who had comorbid antisocial personality disorder. Since antisocial personality disorder is associated with poor impulse control, exclusion of those with a comorbid diagnosis may have contributed to the negative findings.

In a study of borderline personality disorder patients, low levels of CSF 5-HIAA were linked to serious suicide attempts rather than impulsivity per se. This relationship was hypothesized since the low levels of CSF 5-HIAA were not associated with violence, self-mutilation or presence of major depression (Gardner, Lucas, & Cowdry, 1990). Another study implicated a specific gene predisposing individuals to behavior such as suicidality, not associated with impulsivity or a particular psychiatric disorder (Nielsen

et al., 1994). It was suggested that CSF 5-HIAA concentration may be influenced by a genetic variant of the tryptophan hydroxylase (TPH) gene, and as such, may influence the manifestation of suicidality. The hydroxylation of tryptophan may be rate-limiting in serotonin biosynthesis (Cooper & Melcer, 1961), and may account for this association.

#### 5-HT Concentration, Imipramine Binding, and Related Neuroanatomy

Other presynaptic indices of 5-HT function associated with impulsivity/aggression include reduced levels of brain serotonin (associated with brain stem terminal storage pools and cortical nerve terminal activity) (Beskow, Gottfries, Roos, & Winblad, 1976; Bourne et al., 1968; Cochran, Robins, & Grote, 1976; Korpi et al., 1986; Lloyd, Farley, Deck, & Hornykiewicz, 1974; Pare, Yeung, Price, & Stacey, 1969; Shaw, Camps, & Decleston, 1967) and tritiated imipramine binding (associated with serotonin nerve terminal transporters) in brainstem, frontal cortex, and select raphe nuclei in suicide victims (Asberg et al., 1987; Paul,

Rehavi, Skolnick, & Goodwin, 1984; Stanley, Viggilio, & Gershon, 1982).

Brain serotonin is most highly concentrated in the raphe nuclei. This group of nuclei runs through the brain stem from the medulla to the back of the midbrain, divided into the rostral and caudal group (Azmitia, 1987). Other parts of the brain stem (e.g., locus coeruleus) interconnect with these nuclei, and give rise to ascending and descending projections. Ascending fibers project from cell bodies of the raphe to the forebrain via the median forebrain bundle. Descending fibers project to the dorsal and lateral horns and to the intermediolateral column of the spinal cord to the spinal cord (Dahlstrom & Fuxe, 1964; De Simoni, Giglio, Dal Toso, Kostowski, & Algeri, 1985; Quirk & Azmitia, 1983; Slater & Patel, 1983). Serotonin neurons also innervate neuronal structures in the cortex, basal ganglia, substantia nigra, caudate, putamen, amygdala, hippocampus, septum, tegmentum, mammillary bodies, hypothalamus, thalamus, and spinal dorsal horns, with the greatest concentration of serotonin fibers in the limbic and sensory areas (Azmitia & Segal, 1978). The septo-hippocampal system has been

implicated in the inhibitory response to environmental cues (Depue & Spoont, 1986), suggesting that the inhibition or the facilitation of aggressive, sexual, and social behaviors may be influenced by serotonergic function .

In pre-clinical studies, decreased presynaptic 5-HT<sub>1a</sub> receptor densities in the brainstems of alcohol preferring (Wong & Murphy, 1989) and isolation-reared rats were found relative to controls (Wright, Crespi, Marsden, Jones, & Robbins, 1989; Wright, Ismail, Upton, & Marsden, 1991), while densities of cortical and hippocampal postsynaptic 5-HT<sub>1a</sub> receptors were increased. The respective decreases and increases in receptor density may reflect adaptation of a dysregulated 5-HT system.

#### Serotonergic Challenge Procedures

Pharmacological challenge procedures are regarded as a safe and reliable means of investigating the functional status of serotonin (Mueller et al., 1986; Mueller et al., 1985; Murphy, Mueller, Garrick, & Aulakh, 1986). Serotonergic challenge tests, provoking postsynaptic and/or overall (reflecting pre and postsynaptic) 5-HT receptor activity provide dynamic indices of serotonergic function.

The responsiveness of the serotonergic system in the hypothalamic-pituitary axis is associated with the level of hormonal release. Augmented neuroendocrine release suggests serotonergic postsynaptic receptor hypersensitivity, while a blunted response is indicative of hyposensitivity (Murphy et al., 1986; van Praag, Lemus, & Kahn, 1987). Peripheral hormonal responses, such as plasma prolactin, cortisol, and growth hormone, to administration of 5-HT precursors, agonists, antagonists and reuptake blockers, provide a means of assessing dynamic 5-HT function. Additionally, changes in behavioral measures, such as target symptoms and affective states, which occur during the challenges provide a means of identifying the impact of serotonergic probes.

Serotonergic agents have been used in pharmacological challenge tests to provoke neuroendocrine and behavioral responses in various psychiatric disorders, including those associated with measures of impulsivity and aggression. Challenge agents used in studies of disorders within the impulsive-compulsive spectrum have included serotonergic agents such as intravenous (IV) clomipramine (CMI), a serotonergic and noradrenergic reuptake blocker, meta-

chloro-phenylpiperazine (m-CPP), a partial postsynaptic 5-HT agonist, and fenfluramine, a 5-HT presynaptic releaser and reuptake inhibitor. These agents affect pre and postsynaptic 5-HT receptor function.

#### Intravenous Clomipramine Challenge in Pathological Gamblers

Intravenous clomipramine (12.5 mg), a serotonin and noradrenaline reuptake blocker (Bertilsson, Asberg, & Thoren, 1974), was used in a challenge procedure to assess neuroendocrine response in pathological gamblers and normal controls (Moreno et al., 1991). It was hypothesized that if IV administration of CMI was delivered in small doses and measured over a short period of time, the noradrenergic reuptake blocking effects of its metabolite, desmethyl-clomipramine would be minimized. The noradrenergic action would not occur since the drug would avoid the first-pass metabolic effect through the liver. As such, IV CMI was viewed as a useful serotonergic challenge agent. The sample included a total of eight male and female pathological gamblers and eight age and sex matched normal controls. The gender ratio was not specified. PG patients had lower baseline prolactin levels and a significantly blunted

prolactin response only at 60 minutes post clomipramine infusion, relative to controls. No significant differences in cortisol or growth hormone levels were found. Thus, the blunted prolactin response to IV CMI challenge was interpreted as reflecting hyposensitive serotonergic receptor function in pathological gamblers.

These results, however, are difficult to interpret for the following reasons. First, gender effects on prolactin release were not described in this study, and as such, the analyses (which combined male and female neuroendocrine data) may have been confounded. In addition, female prolactin release varies according to phase of menstrual cycle, and as such, variability in prolactin release during a serotonergic challenge may increase if phase of menstrual cycle is not controlled.

More specifically, during the course of the menstrual cycle, prolactin secretion appears to vacillate along with estrogen levels (Cooke, 1989; Goodman, 1988). As estrogen levels escalate abruptly during ovulation, a dramatic, transient increase in prolactin may also occur. Therefore, it is important to identify the time of occurrence of menses

and ovulation when determining and interpreting levels of prolactin secretion in response to IV CMI in female subjects (Backstrom, McNeilly, Lesak, & Baird, 1982; Djahnbakhch, McNeilly, Warner, Swanston, & Baird, 1984; Gonen & Casper, 1990; Inaudi, Reymond, Rey, Genazzani, & Lemarchand-Beraud, 1992; Tennekoon & Lenton, 1993).

The second methodological limitation is the lack of a placebo control, thus limiting the specificity of the active drug's action relative to an inactive agent as a control.

Albeit, this study represents the first pharmacological challenge test in pathological gamblers. The investigators suggest that the serotonergic dysregulation found in this study is similar to that which has been found in other impulsive style disorders.

#### M-Chlorophenylpiperazine Challenges

M-Chlorophenylpiperazine (m-CPP), a partial 5-HT receptor agonist (Hamik & Peroutka, 1989; Hoyer, 1988) has been used in challenge procedures to investigate serotonergic receptor function in a range of psychiatric disorders, especially those within the impulsive-compulsive behavior spectrum. Since m-CPP was used in this

dissertation as a challenge agent, a review of its use and effect on neuroendocrine function in impulsive and compulsive disorders has relevance.

#### M-CPP: Response in Healthy Control Subjects

In healthy control subjects, significant increases in prolactin, cortisol and ACTH levels were found with administration of 0.5 mg/kg (Hollander, DeCaria, et al., 1992; Kahn, Wetzler, Asnis, & van Praag et al, 1990; Moss, Yao, & Panzak, 1990; Mueller et al., 1985; Zohar et al., 1987) and 0.75 mg/kg of oral m-CPP (Mueller et al., 1986). Increased neuroendocrine levels were also demonstrated with IV administration of m-CPP (0.1 mg/kg) (Charney et al., 1988; Charney, Woods, Goodman, & Heninger, 1987).

#### M-CPP: Response in Patients with Impulsive Style Personality Disorders

Studies examining neuroendocrine response to oral m-CPP (0.5 mg/kg) challenge in patients with personality disorders associated with impulsivity have yielded fairly consistent results. Male patients with borderline personality disorder exhibited significantly increased cortisol levels in response to oral m-CPP, relative to male control patients

(Hollander et al., 1994). Similarly, significantly increased cortisol response was found in male antisocial personality disorder patients with substance abuse, relative to controls (Moss et al., 1990). By contrast, prolactin response to oral m-CPP was significantly decreased in the antisocial personality disorder patients with substance abuse relative to controls (Moss et al., 1990). Similarly, a trend toward a blunted prolactin response was found in the borderline patients, however statistical significance was not reached (Hollander et al., 1994). Importantly, neuroendocrine response to m-CPP may have been altered by the abuse of specific drugs in the antisocial personality disorder patient group. In that study, the sample size was too small to test for this potential confound. In addition, borderline personality disorder most likely reflects a heterogeneous group (e.g., depressed/nondepressed), and as such, may influence both neuroendocrine and behavioral findings unless certain variables (i.e., depression) are controlled either during sample selection or during statistical analyses.

Of note, in the same study, prolactin response was significantly, inversely correlated with three subscales of the Psychopathic States Inventory (Haertzen, Martin, Ross, & Neidert, 1980). Prolactin response was inversely correlated with the Assaultive, Negative Affects, and Increased Need subscales, but not with the Impulsivity index or psychometric measures of impulsivity. Cortisol response to m-CPP did not correlate with psychometric measures (Moss et al., 1990). Moreover, impulsivity was not found to discriminate antisocial personality disorder group classification. The authors speculated that in antisocial personality disorder patients with substance abuse, serotonergic dysfunction may be associated with assaultiveness and dysphoria rather than impulsivity (Moss et al., 1990).

#### M-CPP: Response in Patients with Trichotillomania

Similar to pathological gambling, trichotillomania (TTM) is characterized as an impulse control disorder (American Psychiatric Association, 1994). Symptoms include repetitive thoughts or acts of hair pulling, which are perceived by the individual as either irrational and undesirable and/or as

pleasurable. Symptom target areas include pulling hair from the head, eyelashes, eyebrows, body hair and pubic hair (Swedo, 1993).

Oral administration of m-CPP (0.5mg/kg), compared to placebo, to female patients with trichotillomania yielded no significant difference in peak change neuroendocrine response relative to healthy female controls (Stein, Hollander, Cohen, Simeon, & Aronowitz, 1995). However, m-CPP induced significant increases in feeling "high," relative to clonidine, an alpha-2 adrenergic receptor agonist (Reid, Da Wing, Mathias, Franke, & Neill, 1977; Van Zwieten, 1980), and placebo challenges (Stein et al., in press). This type of response (i.e., "high", euphoric, "spacy") has also been reported during m-CPP challenges in patients with other impulsive style disorders such as 1) impulsive (borderline) personality disorder patients (Hollander et al., 1994); 2) male alcoholics, some of whom had comorbid antisocial personality disorder (Benkelfat et al., 1991), and 3) cocaine addicts (Buydens-Branchey & Branchey, 1993). Thus, this type of behavioral response to

m-CPP may also be found in other impulsive style disorders such as pathological gambling.

M-CPP: Response in Patients with Obsessive-Compulsive Disorder

Disparate findings have emerged from various m-CPP challenge studies in patients with obsessive-compulsive disorder (OCD). Whereas one study found that oral administration of m-CPP (0.5 mg/kg) stimulated normal prolactin and blunted cortisol response in patients with OCD (Zohar et al., 1987), another study found a blunted prolactin response in male OCD patients and a normal cortisol response in both male and female OCD patients (Hollander, DeCaria, et al., 1992) relative to normal controls. In another investigation, IV m-CPP (0.1 mg/kg) administration yielded a blunted prolactin response in female OCD patients and normal cortisol release with no gender differences relative to normal controls (Charney et al., 1988).

Behavioral responses to m-CPP challenge in OCD patients were also variable. In some studies, oral administration of m-CPP (0.5 mg/kg), significantly exacerbated obsessive-

compulsive symptoms, as well as anxiety in a subgroup of OCD patients compared to placebo and healthy controls (Hollander, DeCaria, et al., 1992; Hollander et al., 1988; Zohar, Insel, Zohar-Kadouch, Hill, & Murphy, 1988; Zohar et al., 1987). In contrast, another study found no differences in OC symptoms between oral m-CPP (0.5 mg/kg) and placebo administration in patients with OCD (Pigott et al., 1993). IV administration of m-CPP (0.1 mg/kg) also resulted in mixed findings. In one study, marked increases were found in both OC symptoms as well as anxiety (Pigott et al., 1993), whereas in another IV m-CPP challenge, only increases in anxiety were found (Charney et al., 1988) relative to healthy controls. These contradictory results suggest that behavioral responses to m-CPP challenge may reflect 5-HT heterogeneity and various methodological factors such as dose and route of drug administration (Pigott et al., 1993). Additionally, behavioral responses to drug challenges may be associated with cognitive "set" or "expectations". However, since these studies are usually conducted in a double-blind and placebo-controlled fashion, the potential for this type of contamination is minimized, or at least

equally distributed across active drug and placebo challenges.

M-CPP: Response in Patients with Eating Disorders

Eating disorders fall within the spectrum of impulsive-compulsive disorders (Hollander, 1993). As such, m-CPP challenges have been conducted in patients with anorexia and bulimia nervosa (Brewerton, Brandt, Lesem, Murphy, & Jimerson, 1990). Administration of oral m-CPP (0.5 mg/kg) to female, low weight anorexics as well as weight recovered anorexics resulted in significantly blunted prolactin response compared to healthy control subjects (Brewerton et al., 1990). Similarly, following administration of oral m-CPP (0.5 mg/kg), female bulimic patients' prolactin response was significantly lower than healthy controls (Brewerton et al., 1990; Brewerton, Murphy, & Jimerson, 1991). Binge eating and vomiting may affect central 5-HT synthesis, downregulating postsynaptic 5-HT receptors which may result in decreased neuroendocrine response. Conversely, blunted neuroendocrine response may predispose patients toward bulimia nervosa (Kaye, Gwirtsman, Brewerton, George, & Wurtman, 1988).

Thus, mixed neuroendocrine and behavioral responses to m-CPP challenges were found among patients with disorders characterized by impulsive and compulsive behavior. However, blunted prolactin and enhanced cortisol response to m-CPP was most frequently associated with male impulse disorder patients, compared to controls, and increased feelings of "high" frequently occurred in impulsive disorder patients following m-CPP administration. In this dissertation, m-CPP challenges were conducted in male pathological gamblers and male controls.

#### Fenfluramine Challenges

Fenfluramine is a 5-HT releaser and reuptake blocker (Borroni, Ceci, Garattini, & Mennini, 1983; Costa, Groppetti, & Revuelta, 1971; Fuxe, Farnebo, Hamberger, & Orgen, 1975). The fenfluramine challenge procedure has been used as an index of "net" central serotonergic function (Coccaro, Siever, Klar, et al., 1989; Siever, Murphy, Slater, de la Vega, & Lipper, 1984). Neuroendocrine response to fenfluramine challenge in studies of patients with impulsive/aggressive behavior has varied. Both blunted and

enhanced prolactin levels have been reported following fenfluramine probe.

Similar to pharmacological challenges with other serotonergic agents, blunted prolactin response to fenfluramine stimulation has been found in some groups of patients associated with impulsivity and aggression. One study (Coccaro, Siever, Klar, et al., 1989) examined prolactin response to fenfluramine among groups of normal controls and patients with personality and major affective disorders, with and without a history of suicide attempts and alcohol abuse. Blunted prolactin response to fenfluramine most highly correlated with a subgroup of personality disorder patients who had a history of impulsivity and aggression. Those DSM-III defined borderline personality disorder patients with a history of at least one suicide attempt and episodic alcohol abuse accounted for the decreased prolactin responses revealed in the three group comparison. Only patients with personality disorders showed an inverse relationship between prolactin response to fenfluramine challenge and measures of irritable impulsive aggression when compared to patients with

affective disorders or normal controls. Noradrenergic dysregulation and resultant disruption of a behavioral activation system may have accounted for the lack of association between decreased prolactin response to fenfluramine challenge and impulsive aggression within the major affective disorder patients. Further, blunted prolactin response to fenfluramine challenge was found in: 1) borderline vs. non-borderline personality disorder patients; 2) patients with a history of suicide attempt(s) vs. nonsuicide attempters; and 3) patients with a history of alcohol abuse vs. non-alcohol abusers (Coccaro, Siever, Klar, et al., 1989). (Coccaro, Siever, Klar, et al., 1989; Siever, 1987).

In an investigation of sociopathy and serotonergic function, male offenders with the diagnosis of antisocial personality disorder and matched healthy controls underwent an oral administration (30mg) of fenfluramine during a challenge procedure. Significant blunted prolactin responses were found in the group of males with antisocial personality disorder relative to healthy controls (O'Keane et al., 1992). In another study, a trend toward blunted

prolactin response to fenfluramine challenge was found in an eating disorder group compared to normal controls (McBride, Anderson, Khait, Sunday, & Halmi, 1991).

Thus, these studies support the hypothesis that impulsive/aggressive style disorders are associated with hyposensitivity of particular serotonin systems.

In contrast to these studies, enhanced prolactin response to fenfluramine stimulation has also been found. Augmented prolactin response to fenfluramine was found in aggressive boys with attention-deficit hyperactivity disorder (ADHD), relative to non-aggressive boys with ADHD (Halperin et al., 1994). However, since a normal control group was not included in this study, the authors indicated that it was not possible to determine if the outcome actually represented an enhanced response in the aggressive group, or a blunted response in the non-aggressive group. As such, they suggested that the findings should be interpreted with caution. Upon replication, the enhanced prolactin response following fenfluramine stimulation found initially in aggressive boys with ADHD was lost. Subsequently, additional analyses using the entire sample

from both studies were performed, showed that the younger aggressive boys with ADHD had a significantly enhanced prolactin response, compared to younger non-aggressive boys with ADHD. No significant differences were found between the older-age groups, although prolactin response was somewhat blunted among the older-age aggressive boys with ADHD. Thus, these findings suggest that as a function of age, the association between level of aggression and 5-HT function in boys with ADHD may differ.

In another study, enhanced prolactin and cortisol responses to fenfluramine challenge were reported in polysubstance abusers who were most aggressive and impulsive (Fishbein et al., 1989). This study also found that peak cortisol levels following fenfluramine administration were more predictive of impulsivity measures than peak prolactin levels in this population. This may be related to the fact that prolactin release is regulated by serotonergic and dopaminergic neurons, whereas cortisol release is regulated primarily by serotonin via adrenocorticotropin hormone (ACTH) release (Tuomisto & Mannisto, 1985; van Praag et al., 1987).

Thus, although some of the fenfluramine challenge studies in patients with impulsive/aggressive behavior reflect hyposensitive postsynaptic 5-HT receptors, more recently, enhanced prolactin response to fenfluramine has been found. As such, this enhanced response may be related to decreased 5-HT availability or release, and subsequent development of upregulated or hypersensitive 5-HT postsynaptic receptors. It is also possible that methodological flaws have contributed to the discrepant findings.

#### Neurochemical Mechanisms and Serotonergic Challenge Agents

The following section of this dissertation describes neurochemical mechanisms which may underlie some of the processes involved in fenfluramine and m-CPP challenges. Since m-CPP challenges were conducted in this dissertation with male pathological gamblers, a more extensive description of m-CPP's relationship to serotonergic function is provided.

#### Excitatory Role of Serotonin

Evidence from rat studies suggest that prolactin and corticosterone secretion are derived from excitation of the

serotonergic neurotransmitter system. Peripheral administration of 5-HT precursors, agonists, or antagonists via intraventricular 5-HT injections, as well as electrical stimulation of the raphe, all provide evidence for the stimulatory role of 5-HT on hormonal secretion on prolactin and corticosterone release (Advis, Simpkins, Bennett, & Meites, 1979; Calogero et al., 1990; Calogero et al., 1989; Fuller, 1990; Krulich et al., 1979; Van de Kar, 1991). Increased serum prolactin concentration has been found in rats following administration of 5-HT precursors, agonists and uptake inhibitors (Clemens, Sawyer, & Cerimele, 1977; Kamberi, Mical, & Porter, 1971; Lawson & Gala, 1973; Morgan & Herbert, 1978), whereas decreased serum prolactin concentration has been associated with inhibition of serotonergic function (Chen and Meites, 1975; Gil-Ad, Zambotti, Carruba, Vicentini, & Muller, 1983; Kordon, Blake, & Sawyer, 1973).

M-CPP, a serotonin agonist, and fenfluramine, a serotonin releaser/reuptake blocker, are associated with serotonin's excitatory action on prolactin release.

#### Fenfluramine

D-fenfluramine is a 5-HT releaser and reuptake blocker (Borroni et al., 1983; Costa et al., 1971; Fuxe, et al., 1975). It simultaneously affects pre and postsynaptic activity by releasing endogenous pools of 5-HT in presynaptic neurons while blocking reuptake into the presynaptic terminals (Borroni et al., 1983; Rowland & Carlton, 1986). D-fenfluramine's active metabolite, d-norfenfluramine, may serve as a direct post-synaptic 5-HT receptor agonist. Consequently, postsynaptic 5-HT receptors are stimulated both directly and indirectly (Costa et al., 1971; Fuxe et al., 1975; Garattini et al., 1979; Invernizzi, Kmiecziak-Kolada, & Samanin, 1982; Kuhn et al., 1981; Quattrone, Schettini, DiRenzo, Amoroso, & Annunziato, 1982; Rowland & Carlton, 1986). Thus, the prolactin response to d-fenfluramine stimulation may be, in part, produced by direct stimulation of the postsynaptic 5-HT receptors via norfenfluramine. There does not appear to be a direct interaction between serotonin and the pituitary gland's prolactin-secreting cells (Kato et al., 1985; MacLeod & Login, 1977). Stimulation of prolactin response to fenfluramine depends on both the amount of available

serotonin for release as well as the responsivity of serotonin postsynaptic receptors. Fenfluramine stimulated prolactin response does not distinguish between pre and post synaptic processes which contribute to prolactin release. Since fenfluramine may stimulate several 5-HT receptor subtypes, specificity of its action toward prolactin release is difficult to assess. However, amesergide, a 5-HT<sub>2a</sub>/5-HT<sub>2c</sub> receptor antagonist, was recently found to block fenfluramine prolactin release (Coccaro, personal communication), thus suggesting specificity of its action at these 5-HT receptor sites.

Thus, although the locus of control of fenfluramine prolactin release is not yet clearly understood and is subject to the influence of numerous variables, the utility of prolactin stimulation via the fenfluramine challenge as an index of "net" central serotonergic function is indicated.

#### M-CPP

#### M-CPP and 5-HT Receptor Subtypes

M-CPP, a metabolite of the antidepressant trazodone (Caccia, Ballabio, Samanin, Zanini, & Garattini, 1981), is a

partial 5-HT receptor agonist (Hamik & Peroutka, 1989; Hoyer, 1988). M-CPP binds potently to 5-HT1a, 5-HT2c (formerly 5-HT1c), 5-HT1d (which is the human analogue of the rat 5-HT1b subtype), 5-HT2a (formerly 5-HT2), and 5-HT3 receptors (Hamik and Peroutka, 1989; Hoyer, 1988; Kilpatrick, Jones, & Tyers, 1987), although it seems to have the highest affinity for the 5-HT2c receptor subtype (Gothert & Schlicker, 1987; Hoyer, 1988; Peroutka, 1988).

5-HT1a receptor sites are highly concentrated in the limbic regions (Hamon, Cossery, Spampinato, & Gozlan, 1986) and the raphe nuclei, and less densely located in the cerebral cortex (Peroutka, 1988). 5-HT1b receptors are found only in rodent brain membranes, possibly serving as autoreceptors at the nerve terminals (Engel, Gothert, Hoyer, Schlicker, & Hillenbrand, 1986). These receptors are located primarily in the cerebral cortex, dorsal subiculum, globus pallidus, and substantia nigra (Gothert & Schlicker, 1987; Peroutka, 1988). 5-HT1d receptors are located in basal ganglia, cerebral cortex, and substantia nigra (Heuring & Peroutka, 1987). Autoreceptors from rabbit, guinea-pig, and humans may be of the 5-HT1d subtype (Galzin

et al., 1988; Schipper & Tulp, 1988; Schlicker et al., 1989). Although the 5-HT<sub>1b</sub> and 5-HT<sub>1d</sub> receptors have similar pharmacological, anatomical, and biochemical composition, they seem to mediate 5-HT autoreceptors in different species (Hoyer & Middlemiss, 1989). 5-HT<sub>3</sub> receptor sites are highly concentrated in nuclei of the lower brain stem, area postrema, and substantia gelatinosa of the spinal cord, whereas lower concentrations were found in certain regions of the limbic system (Waeber, Hoyer, & Palacios, 1989).

5-HT<sub>2a</sub> receptors have been localized in the cortex, striatum, hippocampus, dorsal raphe nucleus, diencephalon, facial nerve nucleus (Gothert & Schlicker, 1987; Peroutka, 1987, 1988), and smooth muscle cells and platelets (Leysen, 1985). In rodents, 5-HT<sub>2a</sub> agonists cause behavioral effects such as head twitching, and clonic seizures, while in humans, hallucinations, vasoconstriction and platelet aggregation occur.

5-HT<sub>2c</sub> receptors are located in membranes from choroid plexus, cortex (Pazos & Palacios, 1985) and caudate membranes (Hoyer, Waeber, Pazos, Probst, & Palacios, 1988).

Localization in membranes of choroid plexus suggests that CSF production may be associated with 5-HT<sub>2c</sub> receptors (Chaffoy de Courcelles, Leysen, & de Clerck, 1988). The 5-HT<sub>2c</sub> receptors in the limbic system are associated with mood, behavioral, and hallucinogenic effects, whereas in the hypothalamus, these receptors appear to affect appetite, thermoregulation, sleep, sexual behavior, and neuroendocrine function (Kennett & Curzon, 1988a, 1988b). Additionally, 5-HT<sub>2c</sub> receptor agonists may provoke anxiogenic reactions in rats (Kennett, Whitton, Shah, & Curzon, 1989).

M-CPP's agonist properties have been associated with stimulation of 5-HT<sub>2c</sub> and 5-HT<sub>2a</sub> receptors. 5-HT<sub>2c</sub>/5-HT<sub>2a</sub> agonist effects have been associated with prolactin release (Quattrone, Schettini, Annunziato, & Di Renzo, 1981), an effect which can be blocked or reversed by metergoline, a 5-HT<sub>1</sub>/5-HT<sub>2a</sub> antagonist (Aloi, Insel, Mueller, & Murphy, 1984; Aulakh, Cohen, Hill, Murphy, & Zohar, 1987; Heninger, Krystal, & Smith, 1988; Quattrone et al., 1981; Samanin, Mennini, Ferraris, Bendotti, & Borsini, 1980), ritanserin, a 5-HT<sub>2a</sub> antagonist, in rhesus monkeys (Heninger et al., 1988), and amesergide, a 5-HT<sub>2a</sub>/5-HT<sub>2c</sub> antagonist, in normal

controls (Hollander, unpublished observation). This antagonist effect has been associated with 5-HT receptor sensitivity change produced by these drugs or by lesions (Aloi et al., 1984; Maj & Lewandowska, 1980; Samamin et al., 1979).

#### M-CPP: Binding to Non-Serotonergic Receptors

In addition to binding to serotonin receptors, m-CPP potently binds to alpha2-adrenergic receptors (Hamik & Peroutka, 1989), but does not affect norepinephrine release in animals (Fuller, Snoody, Mason, Hemrick-Luecke, & Clemens, 1981). M-CPP binds weakly to other alpha and beta adrenergic receptors, and minimally to dopamine and muscarinic cholinergic receptors (Hamik and Paroutka, 1989). Further, increases in plasma growth hormone levels in humans have been observed, but only with intravenous administration of m-CPP (Charney et al., 1987).

#### M-CPP: Neuroendocrine Stimulation

M-CPP induces secretion of prolactin, cortisol/corticosterone and ACTH (Aloi et al., 1984; Aulakh et al., 1988; 1992; Fuller, 1981; Hollander, DeCaria, et al., 1992; Maj & Lewansdowska, 1980; Quattrone et al., 1981). Although

prolactin release is generally associated with m-CPP's effect on postsynaptic 5-HT receptors, it is also possible that presynaptic 5-HT mechanisms may, in part, underlie its effect on prolactin release (Baumann, Rutter, & Auerbach, 1993; Freo et al., 1990).

In one study, it was found that m-CPP produced enhanced extracellular 5-HT in ventromedial diencephalon in rats via presynaptic mechanisms associated with 5-HT transporters, resulting in subsequent prolactin release (Baumann et al., 1993). The investigators suggested that the enhanced 5-HT response was induced by m-CPP and mediated by the interaction of m-CPP with 5-HT transporters, and therefore, partially mediated by presynaptic mechanisms. In another study, it was found that dosage may play a role in m-CPP's effect on pre and postsynaptic serotonergic function. Lower doses of m-CPP were associated with presynaptic autoreceptor stimulation, decreasing 5-HT function, in contrast to higher doses reflecting postsynaptic stimulation, increasing 5-HT function (Freo et al., 1990). Supportive evidence was derived from m-CPP's effect on glucose metabolism in rats.

Thus, it may be difficult to precisely gauge the relative contribution of m-CPP's effect on pre and postsynaptic receptor-stimulated neuroendocrine release. Therefore, the effect of m-CPP on postsynaptic 5-HT receptor sensitivity needs to be interpreted with caution (Baumann et al., 1993).

M-CPP's direct postsynaptic agonist properties have been associated with stimulation of 5-HT<sub>2a</sub> and 5-HT<sub>2c</sub> receptors and subsequent prolactin release (Quattrone et al., 1981). 5-HT<sub>2a</sub> and 5-HT<sub>2c</sub> activity in the hypothalamic-pituitary-axis (HPA) provokes secretion of prolactin via anterior pituitary, a response which can also be antagonized by 5-HT<sub>2a</sub>/5-HT<sub>2c</sub> receptor blockers (Lewis & Sherman, 1985; Quattrone et al., 1983). Pretreatment with an oral dose of amesergide (LY237733) (50mg), a highly selective 5-HT<sub>2a</sub>/5-HT<sub>2c</sub> receptor antagonist, was found to block oral m-CPP's (0.5 mg/kg) effect on prolactin release during placebo-controlled, double-blind challenges in male normal controls (Hollander, unpublished observation). Thus, the prolactin response to m-CPP stimulation may also be produced by direct postsynaptic 5-HT receptor stimulation.

Physiological and Behavioral Response to M-CPP

In humans, oral administration of 0.5 mg/kg of m-CPP was found to provoke nausea (Kahn et al., 1990), hyperthermia (Kahn et al., 1990; Murphy, Mueller, Hill, Tolliver, & Jacobsen, 1989), sweating, light-headedness, palpitations, and chest pressure (Kahn et al., 1990).

In rats, behavioral response to m-CPP administration was found to provoke decreased food consumption (Aulakh et al., 1987; Aulakh, Zohar, Wozniak, Hill, & Murphy, 1989; Bagdy, Szemeredi, Kanyicska, & Murphy, 1989; Fuller, Snoody, Mason, & Owen, 1981; Kennett & Curzon, 1988b; Mennini et al., 1980; Samanin et al., 1979), decreased locomotion (Aulakh et al., 1987; Aulakh et al., 1989; Bagdy, Calogero, Aulakh, Szemeredi, & Murphy, 1989; Bagdy, Szemeredi, Kanyicska, & Murphy, 1989; Freo et al., 1990; Kennett & Curzon, 1988a; Lucki, Ward, & Frazer, 1989; Sills, Lucki, & Frazer, 1985; Vetulani, Sansone, Bednarczyk, & Hano, 1982), and increased anxiety (Aulakh et al., 1987; Kennett et al., 1989; Samanin et al., 1980), as defined by decreased social interaction (Kennett et al., 1989) that is unrelated to the decrease in locomotion (Whitton & Curzon, 1990).

In summary, m-CPP affects neuroendocrine release, physiological, and behavioral responses via its actions on central 5-HT. As such, m-CPP is a very useful tool in the study of serotonergic receptor function, especially in disorders associated with impulsivity and compulsivity.

#### Roles of Non-serotonergic Neurotransmitters in Studies of Impulsivity

Non-serotonergic neurotransmitter systems have also been implicated in the facilitation, inhibition, and modulation of impulsive behavior. For example, in addition to receiving serotonergic input from the median raphe nucleus, the septo-hippocampal system also receives noradrenergic fibers from the locus coeruleus and the frontal cortex. These systems have been linked to the existence of a behavioral inhibition system, suggesting increased sensitivity to stimuli associated with reward and decreased sensitivity to stimuli associated with non-reward (Gray, 1970; Gray, Feldon, Rawlins, Owen, & McNaughton, 1978).

Pathological gamblers have been characterized as behaviorally disinhibited. In one study, pathological gamblers were found to have significantly higher CSF

3-methoxy-4-hydroxy-phenylglycol (MHPG) levels, a metabolite of norepinephrine (i.e., noradrenaline), and significantly greater urinary output of norepinephrine than control subjects (Roy, Adinoff, & Linnoila, 1988). Since the noradrenergic system has been associated with arousal (Fuxe, Hokfelt, & Ungerstedt, 1970; Usdin & Snyder, 1973), and pathological gambling has been associated with increased arousal (Anderson & Brown, 1984; Boyd, 1976; Brown, 1986; Brown, 1987; Commission on the Review of the National Policy Toward Gambling, 1976; Dickerson, Hinchey, & Falve, 1987) as well as increased tonic activity of the central noradrenergic system (Roy, Adinoff, Roehrich et al., 1988), it is possible that the noradrenergic system may also play a role in the pathophysiology of pathological gambling, especially in relation to associated arousal and extroversion.

Dopamine may also play a significant role in impulsivity, gambling, or both. Differences between mesolimbic cell numbers and the dopaminergic release into the limbic striatum have been found. These differences suggest that the facilitation of a response may be

associated with mesolimbic dopaminergic pathways, which appear to decrease the response threshold to certain environmental cues (King, 1986).

Relative balances between various neurotransmitter systems may also contribute to the manifestation of impulsive behavior. An interaction between decreased serotonin metabolism (Soubrie, 1986) and increased norepinephrine (Eichelman, Thoa, & Ng, 1972; Thoa, Eichelman, Richardson, & Jacobowitz, 1972), dopamine (Eichelman, Thoa, & Perez-Cruzet, 1972; Geyer & Segal, 1974), or acetylcholine (Eichelman & Thoa, 1973) metabolism may influence the manifestation of impulsive behavior. This neurobiological framework may have implications for impulsive behavior observed in various psychiatric syndromes (Plutchik & van Praag, 1989).

Although involvement of the noradrenergic, dopaminergic and cholinergic neurotransmitter systems have been strongly implicated in studies of impulsivity, this study focused on the associated role of serotonergic receptor function and constructs of impulsivity in pathological gamblers.

Phenomenological and Neuropsychological Constructs of  
Impulsivity: Integration with Biological Measures

Although psychobiological approaches toward understanding the etiology of impulse control disorders have been attempted, integration has not occurred without problems. One of the primary obstacles in associating biological correlates with constructs of impulsivity relates to the paucity of research associating clusters of biological measures to clusters of personality measures, since there are complex interrelationships among them (Barratt & Pritchard, 1986). General personality models which would further clarify these interrelationships are needed. Further complicating psychobiological integration is the fact that impulsivity, as a dimensional construct, cuts across various psychiatric disorders (i.e., pathological gambling, eating disorders, explosive disorders, substance abuse, personality disorders) and as such, lacks universal operational criteria and a systematic means of assessment (Moss et al., 1990). Thus, it is not surprising that disparate findings manifest with regard to impulsivity measures and their theoretical constructs

(Gerbing, Ahadi, & Patton, 1987; Paulsen & Johnson, 1980) as well as neurobiological correlates associated with impulsive behavior (Carrasco et al., 1994; Coccaro et al., 1989; Fishbein et al., 1989; Haertzen, Martin, Ross, & Neidert, 1980; Moss et al., 1990; Roy et al., 1987). Nevertheless, continued attempts have been made to assess these relationships with a wide range of converging data since important contributions may be made toward further understanding the pathophysiology associated with impulsive disorders.

Impulsiveness has been viewed as a multi-dimensional variable (Barratt, 1965; Eysenck & Eysenck, 1977; Gerbing, Ahadi, & Patton, 1987; Schalling, Edmon, & Asberg, 1983; Twain, 1957) related to the control of thoughts and behavior (Barratt, 1972). As such, both multi-factored self-report inventories and information-processing assessments have been used to measure constructs of impulsivity.

One widely-used, multi-factored, self-report impulsiveness inventory is the Barratt Impulsiveness Scale-11. This scale is based on three empirically-derived factors: 1) Activity Level and Attention; 2) Careful Planning

and 3) Impulsivity (Patton and Barratt, 1992). These three constructs evolved from factor analyses based on three a priori substrates of impulsivity associated with earlier versions of the scale which included motor, cognitive, and non-planning impulsiveness.

Information processing measures associated with constructs of impulsivity have included assessments which evaluate cognitive tempo (reflectivity/impulsivity), time estimation, planning ability, and perceptual motor tasks. Highly impulsive individuals have been associated with fast cognitive tempo and time estimation, poor planning ability, and impaired performance on perceptual motor tasks (Barratt, 1967; Barratt, 1981; Barratt, 1985; Barratt, Pritchard, Faulk, & Brandt, 1987). The Matching Familiar Figures Test (Kagan, Rosman, Day, Albert, & Phillips, 1964) and the Porteus Maze Test (Porteus, 1965) have been widely used as measures of cognitive tempo and planning/perceptual motor ability, respectively.

In this dissertation, the relationship between the above-mentioned assessments associated with constructs of impulsivity and the neuroendocrine and behavioral measures

of the m-CPP challenges were examined in the pathological gamblers as a secondary analysis.

### Overall Summary

Pathological gambling (PG) is a disabling disorder which affects at least two-and-one-half million Americans and their families. PG has been characterized as an impulse control disorder. It is associated with constantly recurring gambling behavior that is maladaptive, in that personal, familial and/or vocational endeavors are disrupted.

Depression and substance abuse often co-occur with PG. The incidence of suicidality is extremely high. Despite the fact that this disorder is a widespread public health problem, few controlled studies of causes or treatment have been conducted. The primary purpose of this dissertation is to investigate serotonergic receptor function in male pathological gamblers. The secondary purpose is to examine the relationship between serotonergic receptor function and constructs of impulsivity in male pathological gamblers.

Numerous studies of neurobiological function in impulsive disorders have been reviewed. These studies provided a framework for conducting neurobiological studies

in pathological gambling. Overall, serotonergic dysfunction has been implicated in disorders of impulsivity and aggression. Since pathological gambling can be described as a disorder of impulsivity and has been highly associated with aggression toward self (i.e., suicidality), these theoretical and structural models have relevance.

Peripheral and central serotonergic indices have been used to identify neurobiological substrates associated with constructs of impulsive and aggressive behavior. Results of these studies suggest that impulsive/aggressive behavior may be associated with: 1) low platelet MAO activity; 2) reduced CSF 5-HIAA; 3) reduced levels of brain serotonin; 4) decreased brain imipramine binding; 5) dysregulated prolactin response to a variety of serotonergic probes via pharmacological challenge procedures; and 6) increased feelings of "high" in response to m-CPP challenge. These findings suggest that there is a relationship between dysregulated serotonergic receptor function and impulsive/aggressive behavior.

Therefore, it was hypothesized that in response to administration of a single dose of oral m-CPP (0.5 mg/kg),

compared to placebo, prolactin release would be blunted and a behavioral response, feeling "high", would be increased in the pathological gamblers relative to nonreferred controls. Further, it was hypothesized that phenomenological and neuropsychiatric assessments of the constructs of impulsivity would correlate with neuroendocrine and behavioral responses to the m-CPP challenge in pathological gamblers.

In this dissertation, serotonergic receptor function in pathological gamblers was assessed via m-CPP and placebo challenge procedures. Changes in neuroendocrine levels and behavioral ratings in response to 5-HT stimulation were used as measures of serotonergic activity. Ten male pathological gamblers and ten sex matched nonreferred controls participated in randomized, double-blind placebo-controlled m-CPP challenges. Additionally, neuropsychological and phenomenological measures of constructs of impulsivity were used to assess the relationship between PG and measures of impulsivity. These results were correlated with outcome measures of m-CPP and placebo challenges, assessing the

relationship between neurobiological substrates and measures of impulsivity in pathological gamblers.

### Hypotheses

#### Primary Hypotheses

- 1) A blunted prolactin response following m-CPP stimulation, compared to placebo, would be found in male pathological gamblers relative to male controls.
- 2) An elevated "high" response on the Analog Scale following m-CPP stimulation, compared to placebo, would be found in male pathological gamblers relative to male controls.

#### Secondary Hypothesis

- 3) Phenomenological (Barratt Impulsiveness Scale-11) and neuropsychological (Porteus Maze Q and Matching Familiar Figures Test I-R) scores would correlate with neuroendocrine (prolactin) and behavioral ("high") responses to m-CPP stimulation in male pathological gamblers.

## Method

### Subjects

Subjects included 10 medically healthy adult male pathological gamblers and 10 sex-matched nonreferred

controls. A total of 54 pathological gamblers were screened for eligibility and willingness to participate in this study. Ultimately, 10 pathological gamblers were consecutively recruited from advertisements in the media, from amongst mental health professionals, self-help groups, employee assistance programs, the Compulsive-Impulsive Disorders Outpatient Program at New York State Psychiatric Institute (NYSPI), and from an in-patient pathological gambling and substance abuse treatment unit at the Veterans Administration Medical Center in Lyons, New Jersey.

Diagnosis of PG was based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (APA, 1987). All PG patients underwent a clinical diagnostic interview by a psychiatrist and met DSM-III-R criteria for pathological gambling. The South Oaks Gambling Screen (SOGS) (Lesieur & Blume, 1987) was administered by a trained clinician as a supplement to the DSM-III-R diagnosis of PG. All patients met criteria on the South Oaks Gambling for probable pathological gambling [mean (SD)=13.56 (4.12); range = 6-20; scores greater than 5 suggest PG]. Duration of illness ranged from 6 to 20 years

[mean (SD)=21.87 (9.23)]. Largest amount of money lost in one day ranged from \$100.00 to \$>10,000.00, with an average of approximately \$6,000.00/day. Types of gambling included horse race/off-track betting, sports betting, numbers, card playing, bingo, and the stock market.

Although the patients' primary diagnosis was pathological gambling, one patient also met criteria for obsessive-compulsive disorder and another for generalized anxiety disorder. One patient had a history of alcohol abuse but was alcohol-free for at least two weeks prior to the challenges.

Exclusion criteria included DSM-III-R diagnosis of schizophrenia, other psychotic disorders, or an organic mental disorder. Subjects who were currently depressed and were taking antidepressant medication, or who had current, repetitive and frequent thoughts of suicide were excluded from this study. Further, subjects with a major medical illness, substance dependence, or a positive drug screen were also excluded.

The Hamilton Depression Scale (17 item) (HAM-D) was administered by a trained clinician to assess recent

patterns and severity of depression (Hamilton, 1960). A score of 20 strongly suggests depression. Although no patients had a primary depressive illness as assessed by DSM-III-R criteria, two patients scored greater than 20 on the Hamilton Depression Scale, suggesting depression [(group mean (SD)= 10.66 (8.42)]. However, no relationship was found between Hamilton Depression Scale scores and m-CPP peak change prolactin levels ( $r=.082$ ,  $p=.833$ ) in the pathological gamblers. Thus, depression severity, as assessed by the Hamilton Depression Scale, did not appear to compromise m-CPP prolactin response in the gamblers.

To determine comorbid Axis II diagnoses (i.e., personality disorders), the Structured Clinical Interview for DSM-III-R Axis II (SCID-II) (Spitzer, Williams, & Gibbon, 1987) was administered to all PG patients by a trained psychiatrist. SCID II Axis II personality disorder (PD) diagnoses were found in six pathological gamblers and included paranoid PD, schizotypal PD, schizoid PD, borderline PD, antisocial PD, avoidant PD, passive-aggressive PD, dependent PD and self-defeating PD.

The pathological gamblers [mean (SD)= 40.22 (10.06)] were older than the nonreferred control subjects [mean (SD)= 29.87 (7.62)] [ $t=-2.41(df=15), p=.03$ ]. Their overall level of cognitive functioning was in the average range (WAIS-R vocabulary subscale scores [mean(SD)=10.67 (2.0)]; WAIS-R block design subscale scores [mean (SD)=7.22 (2.22)]), with relative strength found in the verbal domain. Educational level ranged from 10 to 18 years [mean (SD)=14.22 (2.53)].

The nonreferred control subjects were consecutively recruited from a healthy control subject pool recruitment center at NYSPI and from responses to subject recruitment postings located at NYSPI. All nonreferred control subjects underwent a clinical diagnostic interview based on DSM-III-R criteria as assessed by a trained psychiatrist. All nonreferred control subjects met criteria for "having never been mentally ill".

### Procedure

This study was approved by the Institutional Review Boards (IRB) of New York State Psychiatric Institute, Queens

College, and the Lyons Veterans Administration Medical Center.

All PG out-patients and nonreferred control subjects underwent an initial telephone screening conducted by a psychologist or trained research assistant. PG inpatients were screened on their unit by a study psychiatrist. Following screening, PG outpatients and control subjects who appeared eligible for intake were asked to come to the Compulsive-Impulsive Disorders Program and the Anxiety Disorders Clinic at NYSPI to meet with a study psychiatrist for a diagnostic intake. PG inpatients were already available on their unit for a diagnostic intake by a study psychiatrist.

Once the research protocols were explained to the subjects, they were asked to sign IRB approved consent forms. They then underwent a clinical diagnostic evaluation (DSM-III-R) by a study psychiatrist. Although some control subjects were previously assessed by trained raters using DSM-III-R Axis I structured clinical interviews, all control subjects underwent a clinical diagnostic interview by a study psychiatrist.

All subjects who met eligibility criteria of the study underwent a medical evaluation, consisting of a medical history, a physical exam, urinalysis, blood chemistry and an electrocardiogram (EKG). Prior to the first pharmacological challenge, subjects were off all psychotropic medication for at least two weeks, although this duration varied depending on the type of medication (e.g., Prozac required a five week drug-free period). They also remained drug-free, except for administration of m-CPP, until completion of the study.

Once medically clear, pathological gamblers were administered the following diagnostic assessments: the Structured Clinical Interview for DSM-III-R (SCID-II) (to diagnose personality disorders), the South Oaks Gambling Screen (SOGS) (to assess severity of PG), and the Barratt Impulsiveness Scale-11 (BIS-11) (to assess type and severity of impulsivity). Pathological gamblers also underwent testing which was used to estimate IQ. This testing consisted of one verbal (Vocabulary) and one performance (Block Design) subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R). PG patients were additionally administered the Matching Familiar Figures Test (MFFT) and

the Porteus Maze Test (PMT) to assess constructs of impulsivity.

### Measures

#### I. Diagnostic Measures

- a. SCID-II
- b. SOGS
- c. BIS-11

#### II. Neuropsychological Measures

- a. WAIS-R subtests
  - 1. Vocabulary
  - 2. Block Design
- b. MFFT
- c. PMT

#### III. Behavioral Measure During m-CPP/Placebo Challenges

- a. Ratings on the Analog Scale - "High"  
Subscale

#### IV. Biological Measures During m-CPP /Placebo Challenges

- a. Prolactin and cortisol levels in response to m-CPP
- b. Prolactin and cortisol levels in response to  
placebo

c. M-CPP plasma levels

I. Diagnostic Measures

a. Structured Clinical Interview for DSM-III-R (SCID II)  
9/1/89)

The SCID-II (Spitzer & Williams, 1986) is a structured interview designed to evaluate the presence of DSM-III-R personality disorder diagnoses. Questions are clustered according to individual DSM-III-R personality disorders. Single questions are asked to elicit a response. If the response is ambiguous, the interviewer may probe to clarify the answer. A didactically trained psychiatrist, an experienced rater, administered the SCID-II to the pathological gamblers.

Interrater reliability of the SCID-II has been assessed, resulting in good overall findings (O'Boyle & Self, 1990). In a study of 20 depressed inpatients, diagnostic agreement between two raters who independently rated the same interview was measured by the kappa statistic (Fleiss, 1981). Good interrater reliability of the SCID-II was demonstrated, with a kappa = 0.74, indicating "substantial" agreement (Landis & Koch, 1977). Interrater reliability was

also assessed by interclass correlations (Ebel, 1951) between the raw dimensional scores for each disorder, where very good agreement was found (range = .95 - 1.0).

Validation of the SCID-II has been based on the "longitudinal expert evaluation using all data" (LEAD) (Spitzer, 1983). This method has been used as a standard for diagnostic comparisons with structured interviews since no distinct external validators exist. Personality disorders are a reflection of behaviors or traits of current or longterm functioning that are observed in many settings rather than a reflection of behaviors related to an episode of illness.

The LEAD was operationalized in an in-patient study, to examine the relationship between SCID-II diagnoses and longitudinal diagnoses (Skodal, Rosnick, Kellman, Oldham, & Hyler, 1988). Results showed overall predictive power ranging from 0.45 (narcissistic) to 0.95 (antisocial). Thus, this study demonstrated variability among the distinct SCID-II diagnostic categories validly identified, using the LEAD standard. Nevertheless, with one exception (narcissistic), SCID-II's overall diagnostic power to

predict longitudinal diagnoses of individual personality disorders ranges from moderate to high.

b. South Oaks Gambling Screen (SOGS)

The SOGS is a screening questionnaire based on DSM-III-R criteria for pathological gambling (Lesieur & Blume, 1987). This 20 question inventory was used as a structured interview by a trained clinician. Questions focus on types, frequency and amount of gambling, family history of gambling and questions which have psychosocial relevance.

In its development, the SOGS correctly diagnosed 95% of female and 98% of male Gamblers Anonymous (GA) members. Validity was also determined by a cross-check of SOGS and DSM-III-R. Ninety-seven percent of 213 GA members, 4% of 384 college students and 1% of hospital employees were classified as pathological gamblers when diagnostic criteria included total scores of five or more on the SOGS and at least four DSM-III-R PG criteria. The SOGS and the DSM-III-R criteria were highly correlated ( $r=.94$ ,  $df\ 747$ ,  $p<.001$ ). An internal consistency reliability check showed that the SOGS is highly reliable (Cronbach's alpha = .97,

$p < .001$ ). Test-retest correlations yielded  $r = .71$ ,  $df = 110$ ,  $p < .001$  (Lesieur & Blume, 1987).

c. Barratt Impulsivity Scale-11 (BIS-11)

The BIS is a self-rating scale which attempts to measure constructs of impulsivity. The BIS divides constructs of impulsivity into three dimensions: 1) motor impulsiveness, 2) cognitive impulsiveness, and 3) non-planning impulsiveness. The motor impulsiveness (Im) subscale uses items which assess impulsive behavior such, as "I do things without thinking." The cognitive impulsiveness (Ic) subscale uses items which assess impulsivity according to cognitive style related to thinking or decision-making, such as "I make up my mind quickly." The non-planning impulsiveness (Inp) subscale uses items which assess impulsivity related to a lifestyle represented by an orientation toward the present time rather than an orientation toward the future, such as "I save regularly" or "I plan tasks carefully" (Barratt, 1972). More recently, it was found that the items originally identified within each of these three a priori factors did not sort as precisely into the selected categories as was originally hypothesized

(Patton & Barratt, 1992). As a result, a new item analysis was performed and an empirically derived factor structure identified three new factors which included: 1)Factor 1-Activity Level and Attention; 2)Factor 2-Careful Planning; and 3)Factor 3-Impulsivity (Patton and Barrett, 1992). Norms are available for comparisons based on either a priori factors or the empirically derived factor structure.

The BIS is based on a four-point rating scale for each question with a response ranging from rarely to always. The subject must choose one response and the subscales are totaled. A sum of the original subscale scores can be compared to norms based on a group of 300 college students, plant workers and police officers (Barratt, 1985). Subjects scoring at or above two standard deviations above the mean are considered impulsive. The original BIS was found to be highly correlated with other questionnaire measures of impulsivity such as the Thorndike Impulsiveness Scale ( $r=.70$ ,  $N=114$ ), the Impulse Expression Subscale of the Omnibus Personality Inventory ( $r=.50$ ,  $N=156$ ), the Disinhibition Subscale of the Zuckerman Sensation Seeking

Scale ( $r=.47$ ,  $N=42$ ), and the Eysenck E Scale ( $r=.68$ ,  $N=212$ ) (Barratt, 1959, 1972; Barratt & Patton, 1983).

The Barratt Impulsiveness Scale was not found to correlate significantly with non-questionnaire measures of impulsivity such as the Porteus Maze Test and the MFFT. In one study, the BIS correlated with the Porteus Maze Q Score ( $r=.33$ ,  $N=120$ ), the MFFT Latency Score ( $r=-.26$ ,  $N=47$ ) and the MFFT Error Score ( $r=-.08$ ,  $N=47$ ) (Barratt & Patton, 1983). Barratt suggested that different constructs or variables were being assessed, and as such, viewed impulsivity as a multidimensional construct both inter and intra-instrumentally. Thus, BIS subscales were treated as separate constructs of impulsivity in the analyses.

## II. Neuropsychological Measures

### a. Wechsler Adult Intelligence Scale-Revised (WAIS-R)

The Vocabulary and Block Design subtests of the WAIS-R were used to estimate intelligence. The Vocabulary subtest ( $r=.81$ ) and the Block Design subtest ( $r=.68$ ) are the Verbal and Performance Scale subtests, respectively, most highly correlated with Full Scale IQ scores.

### b. Matching Familiar Figures Test (MFFT)

The MFFT is a widely used measure which is hypothesized to estimate impulsivity (Gerbing et al., 1987), although there is controversy regarding its validity. It was originally developed to assess dimensions of impulsivity in children (reviewed by Messer, 1976).

The MFFT has been used as a measure of impulsivity-reflectivity as an indication of cognitive style (Kagan, Rosman, Day, Albert, & Phillips, 1964). Cognitive tempo is hypothesized to be the factor that accounts for the contrasting conceptual styles of impulsivity and reflectivity as measured by the MFFT. Cognitive tempo is defined as the tendency to consistently respond either slowly or quickly to a set of stimuli in which one selection, among several other possible choices, must be made (Kagan et al., 1964).

This is a matching-to-sample test in which two practice and 12 test line drawings of familiar objects are presented. Each set contains one standard figure and eight variants of the figure, one of which is the exact duplicate of the standard figure. The subject's task is to select the drawing which exactly matches the standard figure.

Corrective feedback is used when an error occurs. Five errors are permitted per item. Latency scores (i.e. the time it takes for the subject to make the first response) and error scores (i.e. the number of incorrect responses made until the correct response is made) provide measures of impulsivity/reflectivity.

These two measures, latency and error scores, are based on the assumptions that: 1) this test contains some aspect of response uncertainty, and 2) a response is influenced by the desire to produce a fast and accurate response as opposed to the potential stress associated with the production of an inaccurate response (Kagan, 1966). The subject can be categorized as having one of four cognitive styles based on the median split for both average latency response and total number of errors. The four classifications include: 1) Fast/Inaccurate - scores below the median in response to time, and above the median in number of errors (Impulsive); 2) Slow/Accurate - scores above the median in response to time, and below the median in number of errors (Reflective); 3) Fast/Accurate - scores below median on both variables; 4) Slow/Inaccurate - scores

above the median on both variables (Schwartz, Friedman, Lindsay, & Narrol, 1982). Subjects scoring within the Fast/Inaccurate category are considered to have an impulsive cognitive style.

However, it has been suggested that the median split method is subject to methodological problems (Ault, Mitchell, & Hartmann, 1976; Bentler & McClain, 1976; Block, Block, & Harrington, 1974; Salkind, 1978). One of the basic problems is that subjects are categorized rather than scaled by being placed in one of four cells. Consequently, within cell discriminations are not made between subjects (Salkind, 1978). Further, statistical power may be lost when continuous measures are artificially dichotomized. This loss may occur when similar scores positioned around the median are classified arbitrarily into different categories (Block et al., 1974). Therefore, rather than the median split method, an impulsivity-reflectivity (I-R) index (Bentler & McClain, 1976; Loper & Hallahan, 1980) was used to score and analyze the MFFT data in this dissertation. Error and latency scores were transformed into T scores, and the distribution of the standard scores for latency were

inverted so that shorter latencies would be associated with higher scores. This method allowed all scores greater or less than 100 to reflect impulsivity and reflectivity, respectively.

Based on a series of 3 studies using the MFFT in adults, reliability coefficient alphas ranged from high (0.93 to 0.94) for latency to moderate (0.54 to 0.68) for errors (Davidson, 1984). Thus, although consistent levels of internal reliability across studies were demonstrated, latency was found to be a more reliable variable. In another study, good inter-item consistency between observed scale scores for latency ( $r=.75$ ) and errors ( $r=.89$ ) were found (Gerbing et al., 1987).

Correlation coefficients between latency and error scores ranged from low/moderate ( $r=-0.59$  to  $-0.51$ ) in one study (Davidson, 1984), to moderate ( $r=-0.66$ ) in another study (Gerbing et al., 1987). Thus, error scores and response time were negatively correlated, demonstrating moderate construct-related validity.

No relationship was found between the MFFT and phenomenological measures such as the Impulsivity Scale of

the Personality Research Form and the Self-Control Scale of the California Personality Inventory (Davidson, 1984). Moreover, multiple correlations from separate regressions of the MFFT on 12 self-report impulsivity components demonstrated a weak relationship between self-reports of impulsivity and the MFFT (Gerbing et al., 1987). Thus, it appears that different constructs related to "impulsivity" are being measured neuropsychologically relative to phenomenological measures.

c. Porteus Maze Test (PMT)

This test was originally designed to assess cognitive functions which are involved in foresight and planning. The Vineland Revision contains 12 mazes for years III through XII, XIV and Adult. The mazes become progressively more difficult as age level increases. The subject must find the way from the starting point to the end point without lifting the pencil and without entering into blind alleys. As soon as a mistake is made, the maze is immediately removed and the subject is handed another blank maze to trace. This procedure is done up to three times if the subject fails to

successfully work his way through the maze on the initial trial. The test is untimed.

Scores are recorded in terms of test age (TA) and qualitative errors (Q scores). The Test Quotient is calculated from a table which matches chronological age with test age. Test age is calculated by the cumulative number of credits given, based on the levels of test years completed and the corresponding number of trials needed to successfully complete each level. The qualitative score is said to be a measure of impulsivity (Docter & Winder, 1954; Eysenck, 1955; Porteus, 1942, 1955, 1959). It has also been suggested that the qualitative score assesses direct behaviors such as carelessness in the execution of the tasks and failure to follow instructions (Gow & Ward, 1982). The Q score, initially investigated to assess the relationship between antisocial behavior and impulsivity, has generally been found to correlate with variables defined as impulsivity, extroversion, carelessness and a tendency toward speed rather than accuracy (Payne, 1961).

The Porteus Maze Test has been cited as a reliable and valid measure of the constructs associated with impulsivity,

ability to delay gratification, planning ability, foresight, and judgment (Riddle & Roberts, 1977). However, studies examining reliability of the Q score are limited.

Nevertheless, one study demonstrated that the reliability of scoring qualitative errors is very high ( $r=.95$ ) (Docter, 1972). Test-retest reliability outcomes vary from moderate, following a 3 day interval between testing ( $r=.51$ ) (Docter, 1972) to high ( $r=.95$ ) (Morganthau, 1922), following a one month interval between test administrations ( $r=.87$ ) (Porteus, 1933).

In a study of high school students who had disciplinary problems, significantly higher Q scores were found on their Porteus Maze Test performance relative to non-behaviorally problematic students (Porteus, 1942). The inference made from this finding was that students with disciplinary problems are more impulsive. In other investigations, Q scores were significantly, negatively correlated with delayed gratification, determined by subjects choosing between an immediate or delayed reward (Erikson & Roberts, 1971; Roberts & Erikson, 1968; Weintraub, 1973).

Thus, the Porteus Maze Test may make a distinct contribution as an assessment of impulsiveness and related behaviors.

### III. Behavioral Measure During m-CPP/Placebo Challenges

#### Analog Scale - "High" subscale

The Analog Scale is a thirteen item, clinician-rated scale which was designed to measure changes in affective and behavioral states during a biological challenge (e.g., depression, anxiety, drowsiness, high, anger, etc). Each item is rated on a 5 point scale: 0 = "Not At All; 1 = Between Not At All and Moderately; 2 = Moderately; 3 = Between Moderately and Extremely; 4 = Extremely (Most Ever). Increased scores on the "high" subscale and subject reports of feeling "high," "spacy," "derealized" and "depersonalized" during m-CPP challenges have been particularly associated with disorders of impulsivity, as indicated previously in this text. Therefore, since PG is associated with impulsivity, and since pathological gamblers frequently report feeling "high" when gambling, clinician ratings on the Analog Scale were conducted throughout the

m-CPP and placebo challenges to primarily assess changes on the "high" subscale between groups and across drug and time.

#### IV. Biological Measures During m-CPP/Placebo Challenges

Changes in prolactin and cortisol levels, in response to administration of a single oral dose of m-CPP (0.5 mg/kg) and placebo, were used as measures of serotonergic receptor function. M-CPP plasma levels were used to assess rates of m-CPP absorption and metabolism. If m-CPP was not adequately absorbed and metabolized, then the prolactin and cortisol levels, in response to m-CPP stimulation, would not be valid.

#### M-CPP and Placebo Challenge Procedures

The rationale for conducting a m-CPP challenge procedure as a means of assessing serotonergic receptor function has been discussed previously in this dissertation. A description of the challenge procedures follows.

Subjects were medication-free for a minimum of two to five weeks prior to the pharmacological challenges, depending on the type of medication they were taking. Most patients had never taken a psychotropic medication. All subjects remained on a low monoamine diet for 72 hours prior

to each pharmacological challenge. The purpose of maintaining this diet was to control for effects of tyramine, found in the prohibited foods, on prolactin levels. Challenges were separated by at least 48 hours to avoid carry-over effects. The order of m-CPP and placebo was randomized. The m-CPP and placebo challenge procedures were identical in terms of medicine administration, rating scale administration, blood-drawings and vital sign monitoring. Both subjects and clinical raters were blind to the agent used in each procedure.

Following an overnight fast, subjects either arrived at the Biological Studies Unit of NYSPI at 8:00 AM or were available at 8:00 AM on the in-patient addictions unit at the Lyons Veterans Administration Medical Center. Each study site provided a controlled environment and safe setting. Once the study began, all subjects remained in bed throughout the 6-hour procedure. Subjects were not allowed to sleep or eat during the challenge. At 8:30 AM, an indwelling intravenous catheter was inserted into the subjects' forearm vein by a technician, a nurse, or a study doctor. At 9:30 AM, a study psychiatrist administered

either oral m-CPP (0.5 mg/kg) or an identical capsule of placebo.

Blood pressure and pulse were measured at 30 minute intervals. Blood drawings (12cc) for prolactin, cortisol and plasma m-CPP levels were obtained at -30, 0, 90, 180, and 210 minutes during each challenge by a technician, nurse or study psychiatrist. Selection of the timing of blood drawing was based on previous and current m-CPP challenges conducted at NYSPI with patients who have compulsive and impulsive disorders. Sixty minutes after the IV catheter is inserted (time=0, medication administration time) has been previously determined as a stable baseline from which neuroendocrine and behavioral changes can be measured over time (Hollander, DeCaria, Nitsescu et al., 1992). Additionally, the selected blood draw intervals have been shown to be sensitive to neuroendocrine and behavioral changes in response to m-CPP stimulation in healthy controls and patients with obsessive-compulsive disorder (Hollander, DeCaria, Nitsescu, et al., 1992).

Clinician ratings of mood and affect were obtained at baseline and at hourly intervals throughout each challenge.

Thoroughly trained and reliable raters administered clinical rating scales. Narrative reports of side effects (elicited by a general inquiry by the rater about how the subject was feeling) were also obtained at baseline and at hourly intervals throughout the study. Generally, the most frequently occurring side effects associated with m-CPP included headache, nausea, and bodily coolness. Nausea and bodily coolness were transient side effects that diminished over the course of the challenge procedure. Occasionally, headache carried over into the evening or to the next morning, and ranged from mild to moderate. These same side effects were experienced transiently by some of the patients and controls, with no serious adverse events. Placebo is an inert substance which has no side effect profile. As such, the only side effect from this cluster that was reported with placebo administration was mild headache, which may have been associated with fasting.

At the completion of the procedure, patients were provided with a late lunch. Prior to terminating the procedure for the day, subjects were reassessed by the study doctor for persistent side effects. If any residual side

effects remained that may have potentially put the subject at risk, the subject did not leave the unit and was monitored to ensure safety. Once the risk potential diminished, the subject could then leave the unit. All patients were offered participation in a double-blind placebo-controlled treatment study, with clomipramine (Anafranil), a serotonin reuptake blocker, for three months following the challenges. If the patient was randomized into a placebo condition, he was offered three months of free treatment with Anafranil following the placebo phase, unless he was a responder to placebo. If a patient was unable to tolerate study medication, the patient would be offered free, open treatment with another standard antidepressant.

#### Assays

To determine prolactin and cortisol levels found in the plasma of these subjects from the m-CPP and placebo challenges, radioimmunoassay procedures were performed. Radioimmunoassays are typically performed by taking a plasma sample containing an unknown amount of hormone (e.g., prolactin; cortisol) mixed in a test tube with a known

amount of antibody and a known amount of radioactive iodinated hormone. The unlabeled hormone competes with the iodine-labeled hormone for antibody binding. The greater the amount of hormone available in the plasma sample, the less the amount of iodinated hormone available for binding to the antibody. Radioactive iodine that is bound to the antibody is separated from the unbound iodinated hormone by a physiochemical process. The amount of hormone present in the plasma can then be indirectly determined by comparison with a standard curve (Goodman, 1994).

In this study, plasma prolactin levels were assayed by a radioimmunoassay kit with a select antibody obtained at the National Pituitary Agency. Intra-assay and inter-assay coefficients of variance for this kit were in the acceptable range of 3.8% and 5.7%, respectively. Plasma cortisol was assayed by radioimmunoassay (Micromedic Cortisol RIA Kit), with intra-assay and inter-assay coefficients of variance of 3.1% and 4.6%, respectively, also in the acceptable range. In order to maintain consistency and to decrease inter and intra-assay variance, all of the subject's neuroendocrine samples were assayed in a single run and in duplicate. The

neuroendocrine values that are reported are the means of the duplicate values. If the duplicate values differed beyond the acceptable levels of variance, the samples were reanalyzed. This situation seldomly occurred.

All subjects plasma m-CPP levels were assayed by the high-performance liquid chromatographic method. A high-performance liquid chromatographic method was developed as a specific assay for plasma m-CPP (Suckow, Cooper, Kahn, 1990). This assay method was developed to decrease the time and increase the sensitivity of the chromatographic analysis, relative to a more complex gas chromatography with electron capture detection (GC-ECD) method (Caccia, Ballabio, Fanelli, Guiso, & Zanini, 1981), or other high-performance liquid chromatographic methods using UV detection (Miller & DeVane, 1986; Wong & Marzouk, 1985) and electrochemical detection (Suckow et al., 1990). As a result, this method can determine the plasma pharmacokinetic profile of the m-CPP challenge (Suckow et al., 1990).

In this study, verification of the identity and the purity of the m-CPP (Aldrich Chemical Company, Milwaukee, WI) was conducted with a high performance liquid

chromatography using "Model 510 solvent delivery pump, an Untra WISP Model 715 autosampler and a Model 440 UV detector with an extended-wavelength module operating at 214 nm" (Waters Assoc., Milford MA, USA) (Suckow et al., 1990, p. 229). This system has provided a stable, reliable, and sensitive method of analysis over a three-year period, with plasma m-CPP intra-and inter-assay coefficients of variance of 3.5-6.8% and 6.8%, respectively (Suckow et al., 1990).

#### Data Analysis

##### Primary Hypotheses

##### Hypothesis 1:

1) A blunted prolactin response following m-CPP stimulation, compared to placebo, would be found in male pathological gamblers relative to male controls.

##### To test hypothesis 1:

1) A three-way mixed analysis of covariance (ANCOVA) with two within-in group variables (drug and time) and one between-group variable (group), covarying for age and plasma m-CPP levels, was performed to assess differences between groups in prolactin response following m-CPP and placebo

stimulation over time. Significant main effects or interactions would be further analyzed by post hoc t-tests.

Hypothesis 2:

2) An elevated "high" response on the Analog Scale following m-CPP stimulation, compared to placebo, was be found in male pathological gamblers relative to male controls.

To test hypothesis 2:

2) A two-way (group x drug) ANCOVA, covarying for age and plasma m-CPP levels, would be performed to assess differences between groups in mean peak change scores on the "high" subscale of the Analog Scale following m-CPP and placebo stimulation. Significant main effects or interactions would be further analyzed by post hoc t-tests.

Secondary Hypothesis

Hypothesis 3:

3) Phenomenological (Barratt Impulsiveness Scale-11) scores and neuropsychological (Porteus Maze Q and Matching Familiar Figures Test IR) scores would correlate with neuroendocrine (prolactin) and behavioral ("high") responses to m-CPP stimulation in male pathological gamblers.

3) To test hypothesis 3:

The relationships between phenomenological/neuropsychological measures and peak change (peak-baseline) neuroendocrine/behavioral measures were be calculated by Pearson Product Moment Correlation Coefficients.

All statistical analyses were based on two-tailed tests, with alpha levels  $\leq 0.05$ .

## Results

### Description of the Sample

#### Sample Size

Inspection of neuroendocrine data distribution revealed two outliers (i.e., values greater than two standard deviations above the group mean) with regard to m-CPP stimulated prolactin release. Mean m-CPP peak change prolactin scores of one pathological gambler (36 ng/mL) and one control subject (30 ng/mL) were more than two standard deviations above their respective group means (SD) of 11.3(9.16) and 8.6(8.67) (see Figures 1-3). Since enhanced prolactin response may be associated with a number of non-specific stressful events that can occur during the course of the challenge, these subjects were eliminated from the

subsequent data analyses. Plasma m-CPP levels were also inspected to ensure m-CPP absorption and metabolism. One additional control subject's peak plasma m-CPP level was extremely low (4ng/mL), with plasma m-CPP levels unchanged across time, without subsequent m-CPP prolactin response (see Table 1). Consequently, this patient was not included in the analyses as it appeared that the medication was not adequately absorbed.

Thus, based on preliminary data inspection, the original sample consisting of 10 pathological gamblers and 10 nonreferred controls was reduced to nine pathological gamblers and eight controls. The statistical analyses that follow were based on this revised sample.

#### M-CPP and Neuroendocrine Release

#### Effects of Age and Plasma m-CPP Absorption/Metabolism on m-CPP Prolactin Release

Effects of age and plasma m-CPP metabolism were controlled for in analyses of m-CPP prolactin response. There were significant between-group differences in age and great within-group variability in plasma m-CPP levels,

although mean peak plasma m-CPP levels did not significantly differ between pathological gamblers [mean (SD)=37.55 (29.7)] and controls [mean (SD)=25.54 (13.68)] [ $t=1.09$  ( $df=12$ ),  $p=.298$ ]. However, neither age nor peak plasma m-CPP levels correlated with peak change in prolactin levels in either pathological gamblers (age:  $r=.135$ ,  $p=.730$ ; plasma m-CPP:  $r=-.011$ ,  $p=.977$ ) or controls (age:  $r=.108$ ,  $p=.799$ ; plasma m-CPP:  $r=-.053$ ,  $p=.900$ ). Thus, no relationship was found between age, plasma m-CPP, and prolactin response to the m-CPP challenge.

#### Effects of m-CPP and Placebo on Neuroendocrine Release:

##### Changes in Prolactin Release (see Table 2)

Changes in plasma prolactin release following m-CPP and placebo administration were assessed across the two groups over time using a three-way (Group x Drug x Time) mixed analysis of covariance (ANCOVA), controlling for age and peak plasma m-CPP levels. There were significant main effects for Drug [ $F=70.45(1,15)$ ,  $p=.000$ ] and Time [ $F=14.29(3,45)$ ,  $p=.000$ ], as well as a significant Drug x Time interaction [ $F=14.85(3,45)$ ,  $p=.000$ ]. Although no Group effect was found [ $F=1.38(1,13)$ ,  $p=.261$ ], there was a

significant Group x Drug interaction [ $F=8.19(1,15)$ ,  $p=.012$ ], a trend toward a Group x Time interaction [ $F=2.40(3,45)$ ,  $p=.08$ ], and a trend toward a Group x Drug x Time interaction [ $F=2.56(3,45)$ ,  $p=.067$ ] such that there was a greater rise in m-CPP-induced prolactin in pathological gamblers relative to controls, independent of placebo effects (see Figure 4).

Post hoc t-tests revealed that pathological gamblers' prolactin levels [+180 minutes: mean(SD)=14.77 (2.06); +210 minutes: mean(SD)=15.34(4.40)] were significantly increased relative to controls [+180 minutes: mean(SD)= 10.56 (3.24); +210 minutes: mean(SD)=10.09(3.33)] at 180 minutes ( $t=3.15(12)$ ,  $p=.009$ ) and 210 minutes ( $t=2.80(15)$ ,  $p=.014$ ) post-m-CPP administration, but not following placebo administration.

Group differences in m-CPP and placebo peak change prolactin levels were assessed using a two-way analysis of covariance, controlling for age and peak plasma levels. Findings revealed a significant Drug effect [ $F=79.11(1,15)$ ,  $p=.000$ ] and a trend toward a Group x Drug interaction [ $F=4.03(1,15)$ ,  $p=.063$ ] (see Figure 5), falling just short of the statistical significance that was revealed in the three-

way mixed analysis of m-CPP prolactin response across time. These results suggest that m-CPP, as compared to placebo, significantly raised prolactin levels in both pathological gamblers ( $t=8.10(8)$ ,  $p=.000$ ) and controls ( $t=4.64(7)$ ,  $p=.002$ ), with a trend toward m-CPP, compared to placebo, increasing prolactin levels more in pathological gamblers relative to controls.

#### M-CPP and Behavioral Response

##### Effects of Age and Plasma m-CPP Levels on "High" Response:

Neither age nor peak plasma m-CPP levels were correlated with changes in "high" subscale ratings on the Analogue Scale. There were no correlations between age and m-CPP-induced peak change "high" ratings (i.e., peak - baseline) in either gamblers ( $r=-.409$ ,  $p=.274$ ) or controls ( $r=-.311$ ,  $p=.453$ ). Further, peak plasma m-CPP levels did not correlate with m-CPP-induced peak change "high" ratings in either gamblers ( $r=-2.931$ ,  $p=.444$ ) or controls ( $r=-.311$ ,  $p=.453$ ). Thus, as was found between age/peak plasma m-CPP levels and m-CPP peak change prolactin levels, no relationship was found between age/peak plasma m-CPP levels

and m-CPP peak change "high" scores in either gamblers or controls.

#### Effects of M-CPP and Placebo on Analog Subscales

##### Changes in "High" Subscale Ratings (see Table 3)

Differences in peak "high" ratings following administration of m-CPP and placebo were assessed between the two groups using a two-way (Group x Drug) analysis of covariance, controlling for age and plasma m-CPP levels. There was a significant main effect for Drug [ $F=9.25(1,15), p=.008$ ], a trend toward a Group effect [ $F=4.43(1,13), p=.055$ ], and a significant Group x Drug interaction [ $F=4.60(1,15), p=.049$ ]. Post hoc t-tests revealed that m-CPP, compared to placebo, significantly affected "high" ratings in gamblers ( $t=3.04(8), p=.016$ ) but not in controls ( $t=1.00(7), p=.35$ ) (see Figure 6). Thus, similar to the enhanced m-CPP prolactin response found in gamblers, an increased m-CPP, compared to placebo, peak change "high" response was also found in gamblers relative to controls. However, m-CPP peak change prolactin levels did not correlate with m-CPP peak change "high" ratings in either gamblers ( $r=.360, p=.341$ ) or controls ( $r=-.454$ ,

$p=.258$ ). These findings suggest that although m-CPP affected changes in prolactin levels and "high" ratings in the same direction in gamblers, the underlying mechanisms associated with these changes may not be the same.

Relationships Among Neuroendocrine, Behavioral, Phenomenological and Neuropsychological Measures in Pathological Gamblers

No significant relationships were found between changes in m-CPP prolactin levels and 1) Barratt Impulsiveness Scale factors, 2) MFFT Impulsive-Reflective Index scores, or 3) Porteus Maze Q scores in pathological gamblers. Using Pearson Product Moment Correlation Coefficients to assess these relationships, no significant correlations were found between m-CPP peak change prolactin levels and BIS Factor 1: Activity Level and Attention ( $r=-.022$ ,  $p=.956$ ), BIS Factor 2: Careful Planning ( $r=.308$ ,  $p=.419$ ), BIS Factor 3: Impulsivity ( $r=.077$ ,  $p=.842$ ), MFFT Impulsive-Reflective Index scores ( $r=-.132$ ,  $p=.735$ ) or Maze Q scores ( $r=-.004$ ,  $p=.992$ ). However, BIS total scores significantly correlated with m-CPP peak change cortisol levels ( $r=.718$ ,  $p=.045$ ).

Moreover, no relationships were found between m-CPP peak change "high" ratings and neuropsychological and phenomenological measures. As assessed by Pearson Product Moment Correlation Coefficients, no correlations were found between m-CPP peak change "high" ratings and BIS Factor 1: Activity Level and Attention: ( $r=.085, p=.827$ ), Factor 2: Careful Planning: ( $r=-.162, p=.697$ ), and Factor 3: Impulsivity: ( $r=.011, p=.978$ ) scores. Further, neither MFFT Index scores ( $r=.297, p=.437$ ) nor Maze Q scores ( $r=.264, p=.492$ ) correlated with m-CPP peak change "high" ratings.

Post-hoc analyses included data reduction to derive a single composite factor associated with impulsivity (based on the three BIS factor scores, MFFT I/R index, and the Porteus Maze Q score). As assessed by Pearson Product Moment Correlation Coefficients, Bonferroni-corrected, significant correlations were neither found between the composite impulsivity factor and peak change m-CPP prolactin levels nor peak change m-CPP "high" ratings in pathological gamblers.

Thus, the neuropsychological and phenomenological measures associated with constructs of impulsivity were not

found to have a relationship with either of the primary m-CPP measures (i.e., prolactin; "high").

#### Exploratory Analyses: Neuroendocrine and Behavioral Measures

##### Changes in Cortisol Release:

Changes in plasma cortisol release following m-CPP and placebo administration were assessed across the two groups over time using a three-way (Group x Drug x Time) mixed analysis of covariance (ANCOVA), covarying for age and peak plasma m-CPP levels. There were significant main effects for Drug [ $F=19.22(1,1), p=.001$ ] and Time [ $F=5.3(3,42), p=.003$ ], as well as a significant Drug x Time interaction [ $F=16.25(3,42), p=.000$ ]. There were no significant Group x Drug [ $F=.01(1,14), p=.931$ ], Group x Time [ $F=0.11(3,42), p=.954$ ], or Group x Drug x Time [ $F=.97(3,42), p=.415$ ] interactions (see Figure 7). Thus, although cortisol levels were significantly increased by m-CPP compared to placebo over time, the magnitude of the change did not differ between groups.

Peak plasma m-CPP levels significantly correlated with m-CPP peak change cortisol levels ( $r=.770, p=.025$ ) in

gamblers but not in controls ( $r=.351$ ,  $p=.395$ ). This finding suggests that there is a relationship between rate of m-CPP absorption/metabolism and rate of m-CPP cortisol release in pathological gamblers.

#### Changes in Anxiety Ratings

Results revealed that m-CPP did not significantly affect ratings of anxiety and no differences were found between groups. Peak change anxiety ratings following administration of m-CPP and placebo were assessed between the two groups using a two-way (Group x Drug) analysis of covariance, controlling for age and plasma m-CPP levels. There were no significant main effects for Drug [ $F=1.60(1,15)$ ,  $p=.225$ ] or Group [ $F=.28(1,13)$ ,  $p=.606$ ]. Further, there was no significant Group x Drug interaction [ $F=.75(1,15)$ ,  $p=.400$ ] (see Figure 8). Thus, whereas m-CPP affected changes in "high" ratings in gamblers, there was no impact on ratings of anxiety.

### Discussion

#### Overview

The primary focus of this dissertation was to assess differences in neuroendocrine and behavioral responses to m-

CPP and placebo challenge procedures in male pathological gamblers and sex matched controls as a means of assessing central serotonergic postsynaptic receptor function in pathological gamblers. The secondary focus was to assess the relationship between serotonergic postsynaptic receptor function, via the challenge measures, and constructs of impulsivity, via select neuropsychological/ phenomenological measures, in male pathological gamblers.

The results of this dissertation associated with the proposed hypotheses are summarized as follows: 1) male pathological gamblers had a significant increase in prolactin release at +180 and +210 minutes following oral m-CPP (0.5 mg/kg), but not after placebo administration, relative to controls; 2) pathological gamblers had significantly increased m-CPP "high" response compared to placebo "high" response, relative to controls; 3) no relationships were found between the challenge measures (i.e., m-CPP prolactin levels and "high" ratings) and the neuropsychological/phenomenological measures (i.e., Matching Familiar Figures Test - Impulsivity-Reflectivity Index

scores, Porteus Maze Test Q scores, or Barratt Impulsiveness Scale factor scores).

#### Neuroendocrine Response to M-CPP

##### Prolactin Response to M-CPP

Male pathological gamblers were found to have a significantly increased prolactin response to m-CPP, compared to placebo, at 180 and 210 minutes following m-CPP administration, relative to controls. The direction of this finding is opposite to that which was hypothesized. Both blunted (Brewerton et al., 1990; Brewerton, et al., 1991; Coccaro, Siever, Klar, et al., 1989; Handlesman, Holloway, Shiekh, Sturiano, & Bernstein, 1993; Hollander et al., 1994; O'Keane, 1992; Moreno et al., 1991; Moss et al., 1990) and more recently, enhanced (Fishbein et al., 1989; Halperin et al., 1994; Halperin, Newcorn, Schwartz et al., 1994; Handlesman et al., 1993) prolactin response to a variety of serotonergic challenge probes in subjects with impulsive and aggressive disorders have been found. Therefore, the observed increased may be related to a number of factors as indicated below.

There are several factors relevant to this dissertation which may account for differences in the magnitude and direction of prolactin response in relation to a serotonergic probe among individuals with impulsive disorders. These factors include: 1) substance abuse (Coccaro, Siever, Klar et al., 1989; Handlesman et al., 1993; Moss et al., 1990) and depression (Coccaro, Siever, Klar et al., 1989; Hollander et al., 1994) comorbidity; 2) comorbid Axis II personality disorders; 3) age (Halperin, Newcorn, Schwartz et al., 1994); 4) m-CPP absorption and metabolism; and 5) the overlapping boundaries between impulsive and compulsive disorders (i.e., pathological gambling, trichotillomania, pyromania, substance abusers, antisocial personality disorder, borderline personality disorder, eating disorders, obsessive-compulsive disorder, depression, and attention-deficit hyperactivity disorder). The effects of these potential confounds associated with the direction or magnitude of the effect of m-CPP on prolactin release in this sample of pathological gamblers are addressed as follows.

Factor one refers to the effect of comorbid substance abuse/dependence and/or depression on the prolactin response to a serotonergic agent. Alcohol abuse/dependence has been associated with a blunted prolactin response to serotonergic agents such as fenfluramine in alcohol-abusing male borderline personality and affective disorder patients relative to non-alcohol abusing patients (Coccaro, Siever, Klar et al., 1989) and in male alcoholics (Handlesman et al., 1993). In this dissertation, one of the nine pathological gamblers had a history of alcohol abuse/dependence. His m-CPP peak change prolactin level (5ng/mL) was the lowest level among the gamblers, and the only level which was one standard deviation (3.07) below the group mean (8.52). His prolactin level was similar to the mean of the control group ( $5.91 \pm 3.57$ ), but still higher than 38% of the controls. Thus, his history of alcohol abuse/dependence may have had a blunting effect on his prolactin response to m-CPP, (as reflected in his prolactin level relative to his group mean and standard deviation), however, this response was still not blunted, as might be expected, relative to the controls. One may speculate that

despite the potential blunting effects of a history of alcohol abuse/dependence on his prolactin responsivity, there may be underlying mechanisms associated with pathological gambling that have sustained 5-HT postsynaptic receptor hypersensitivity in this gambler, or at the very least, no significant blunting relative to the controls. Certainly, effects of comorbid substance abuse/dependence in pathological gambling is one area that needs to be investigated with large, discrete samples of male and female pathological gamblers with and without a history of substance abuse/dependence (alcohol-like vs cocaine-like substances) since it is estimated that approximately 50% of pathological gamblers are also substance abusers.

Depression and suicidality have been associated with blunted prolactin response to fenfluramine (Coccaro, Siever, Klar et al., 1989). In this sample, although no one was diagnosed with depression, two patients had Hamilton Depression Scale scores above 20, suggesting moderate to severe depressive symptomatology. However, when Hamilton Depression Scale scores were correlated with m-CPP peak change prolactin levels, no relationship was found ( $r = -.082$ ,

$p=.833$ ). In addition, all patients were carefully screened for history/current suicidality. No patients were found to have attempted suicide, and no patients were at risk for suicide throughout participation in this study. Thus, there was no potential for neuroendocrine effects associated with suicidality to bias m-CPP prolactin response in this group of pathological gamblers.

The second factor, comorbidity of Axis II personality disorders, may also play a role in level of prolactin release in response to serotonergic agents in an impulse disorder. Siever & Davis (1991) proposed a psychobiological model of the dimensions that cut across Axis I disorders and Axis II personality disorders including: (1)cognitive/perceptual organization; (2)impulsivity/aggression; (3)affective instability; and (4)anxiety/inhibition, and have described neurobiological correlates that have been hypothesized to be associated with each of these dimensions. Specifically, they report that the impulsive/aggressive dimension has been generally linked to a reduction in serotonergic activity, as has been previously discussed in this dissertation. Discrete studies in Axis II disorders

most frequently associated with disorders of impulsivity/aggression have included borderline and antisocial personality disorders. These personality disorders have been associated with blunted prolactin response to serotonergic agents as have been found in male borderline personality disorder patients relative to non-borderline personality disorder patients (Coccaro, Siever, Klar et al., 1989) and normal controls (Coccaro, Siever, Klar et al., 1989; Hollander et al., 1994), as well as male antisocial personality disorder patients (O'Keane et al., 1992). Thus, one might expect that comorbidity of an impulsive personality disorder in male patients may have a blunting effect on prolactin release in response to serotonergic receptor stimulation. Further, it might be expected that comorbidity of an impulsive personality disorder with an Axis I disorder of impulse control, such as pathological gambling, may further potentiate an already hyposensitive serotonergic receptor response. However, as has been described, results of this dissertation revealed that pathological gamblers were found to have serotonergic

receptor hypersensitivity, as evidenced by an enhanced m-CPP prolactin response relative to controls.

Effect of Axis II disorders on serotonergic receptor function was not systematically assessed in this study since the sample size of affected individuals was so small. However, upon gross inspection of the data, there did not appear to be a pattern between level of prolactin response and diagnosis of borderline or antisocial personality disorder in the pathological gamblers. There was no pattern of blunting, relative to the control group mean, as one might have expected. Although the controls were not assessed for Axis II disorders via the SCID-II as were the pathological gamblers, on clinical interview, they presented with no evidence of psychopathology or history of psychopathology. However, it cannot be said with certainty that no control subject would have met criteria for an Axis II disorder. Albeit, in this small sample, there did not appear to be a relationship between comorbidity of borderline and/or antisocial personality disorders in the pathological gamblers and prolactin response.

The third factor refers to the effects of age on serotonin receptor function (i.e., prolactin release in response to a serotonergic agent) as has been found among aggressive and non-aggressive children with ADHD (Halperin, Newcorn, Schwartz et al., 1994).

In this dissertation, results showed no apparent relationship between age and m-CPP-induced peak change in prolactin in either pathological gamblers or controls. However, since pathological gamblers were older than the controls, age was controlled for in all relevant analyses to eliminate any possible confounding effects on prolactin release that may have existed as a function of age.

Factor four refers to the effect of plasma m-CPP absorption and metabolism on subsequent prolactin release. Certainly, if m-CPP was not properly absorbed and metabolized (as was evident in one control from the original sample), prolactin response would have been compromised. In this study, there were no significant between-group differences in the levels of plasma m-CPP absorption and metabolism, although there was great within-group

variability. Consequently, plasma m-CPP level was used as a covariate in the analyses.

The final factor focuses on the boundary between impulsivity and compulsivity, and is the one factor that is difficult to reconcile. There is a great deal of overlap with regard to phenomenology, neurobiology and pharmacology within the spectrum of compulsive and impulsive style disorders, making the dissection of this spectrum difficult. Many impulsive and compulsive disorders have overlapping characteristics in this regard. For example, in pathological gambling, although considered a disorder of impulse control, there are factors which are associated more with compulsive style rather than impulsive style disorders. For example, phenomenologically, although pathological gamblers have been described as sensation-seeking (Custer, 1982), some studies show that they score significantly lower on the Zuckerman Sensation-Seeking Scale Thrill and Adventure-Seeking Scale (Blaszczynski, Wilson, & McConaghy, 1986) as well as the sensation-seeking scale total score (Blaszczynski et al., 1976; Carrasco et al., 1994) relative to normal controls. Further, on the Tri-Dimensional

Personality Questionnaire (Cloninger, 1987), Harm Avoidance Scale scores were significantly higher among pathological gamblers compared to normal controls (Carrasco et al., 1994). These types of characteristics, risk and harm avoidance, are often associated with compulsive style disorders such as obsessive-compulsive disorder.

Behavioral factors also overlap between impulsive and compulsive disorders. For example, in pathological gambling, there is the build-up and release of tension prior to and following the act of gambling, similar to that which is seen along this spectrum of disorders such as compulsive handwashing in obsessive-compulsive disorder, hair-pulling in trichotillomania, purging in bulimia, expression of tics in Tourette's Syndrome, and substance use in substance abuse disorders.

Inconsistencies in neurobiological measures, such as CSF 5-HIAA levels, have also been shown, such that pathological gamblers were not found to have the predicted blunting of CSF 5-HIAA levels (Roy, Adinoff, Roehrich et al., 1988) as has been shown in disorders of impulsivity and aggression.

Finally, neuropharmacological treatment with serotonin reuptake inhibitors have been used to successfully treat compulsive style disorders such as obsessive-compulsive disorder and anorexia nervosa, and have also shown some short-term effectiveness in treating impulse control disorders which have both impulsive and compulsive features such as trichotillomania (Leonard et al., 1989) and pathological gambling (Hollander, Frenkel, DeCaria, Truongold, & Stein, 1992). Thus, the lack of discrete phenomenological, behavioral, and neurobiological boundaries between impulsive and compulsive style disorders makes it difficult to categorically define and interpret similarities and differences along that spectrum on select measures, such as prolactin response to a serotonergic agent, as it may relate to the pathophysiology of a specific disorder such as pathological gambling.

In sum, although serotonergic dysfunction in male pathological gamblers was predicted, the direction of the finding was opposite to that which was hypothesized. Instead of a hyposensitive prolactin response to m-CPP stimulation, as had been found in several studies of other

impulsive disorders, an enhanced m-CPP prolactin response was found, compared to placebo, relative to controls, suggesting serotonergic postsynaptic receptor hypersensitivity. This effect appeared to be independent of age and plasma m-CPP absorption and metabolism. Further, comorbid depression, substance abuse/dependence, borderline and antisocial personality disorder did not appear to have a direct bearing on the magnitude or direction of the m-CPP prolactin response in pathological gamblers. Thus, independent of these factors, oral m-CPP (0.5 mg/kg) appeared to stimulate an enhanced prolactin response in this sample of male pathological gamblers relative to controls.

#### M-CPP's Effect on Prolactin Release

Although m-CPP has been found to affect prolactin release via pre-synaptic mechanisms (Baumann et al., 1993; Freo et al., 1990), prolactin release has been generally associated with m-CPP's effect on postsynaptic 5-HT receptors. M-CPP's agonist properties have been associated with stimulation of 5-HT<sub>2a</sub> and 5-HT<sub>2c</sub> receptors in the HPA which provokes secretion of prolactin via the anterior pituitary (Citron, et al., 1981). Enhanced prolactin

release may be related to decreased presynaptic availability or release, and subsequent development of upregulated or hypersensitive serotonergic postsynaptic response. Although this idea of a compensatory mechanism offers an interesting and viable explanation, it is not yet clear how the end result of this mechanism relates to overall serotonergic function (Coccaro et al., 1989).

A final note regarding the implications of serotonergic postsynaptic receptor hypersensitivity in pathological gambling refers to treatment. As seen in the treatment of panic disorder with 5-HT agonists, 5-HTP, and clomipramine, 30-50% of patients report an initial increase in anxiety (two week period), and subsequent therapeutic effects following eight weeks of treatment (Kahn and Westenberg, 1985; Den Boer et al., 1987; Kahn et al., 1987). This pattern may initially occur in response to stimulation of hypersensitive 5-HT postsynaptic receptors and increased anxiety, with a gradual down-regulation of the receptors which simultaneously occur with therapeutic effects (Kahn and van Praag, 1988). Thus, since serotonergic postsynaptic receptor hypersensitivity has been found in pathological

gamblers, the results of these treatment studies offer important implications for the neural mechanisms of pathological gambling.

#### Cortisol Response to M-CPP

M-CPP significantly increased cortisol levels compared to placebo over time, however, the magnitude of the increase did not differ between groups. This finding is in contrast to the increased cortisol response that was found in other impulsive patients such as male borderline (Hollander et al., 1994) and male antisocial personality disorder patients with substance abuse (Moss et al., 1990). Differences in the prolactin and cortisol response to m-CPP may relate to differences in the hypothalamic pathways that mediate serotonergic stimulation (Van de Kar, Karteszi, Bethea, & Ganoong, 1985). Additionally, cortisol release may also be directly stimulated by brain neuronal serotonin agonists at adrenal cortical levels (Bagdy, Calogero, Murphy, & Szemeredi, 1989; Gibbs & Vale, 1983) and at anterior pituitary levels (Fuller & Snoddy, 1980; Fuller, 1981).

One might have expected to see a rise in cortisol levels in the pathological gamblers, as compared to controls,

reflecting level of arousal, but did not. Since the noradrenergic system has been associated with arousal (Fuxe et al., 1970; Usdin & Snyder, 1973), and since pathological gamblers have been associated with both increased arousal (Anderson & Brown, 1984; Boyd, 1976; Brown, 1986; Brown, 1987; Dickerson et al, 1987) and increased tonic activity of the central noradrenergic system (Roy, Adinoff, Roehrich et al., 1988), hormonal response to noradrenergic measures may best assess arousal in pathological gamblers. As such, it is possible that the noradrenergic system also plays an important role in the pathophysiology of PG.

Finally, it is likely that other systems such as the dopaminergic and opiate systems play an important role in the pathophysiology of pathological gambling since these systems have an important role in addiction and central nervous system reward mechanisms. Further, other non-serotonergic neurotransmitter systems may play a role in the facilitation, inhibition, or modulation that is associated with impulsive behavior in pathological gambling. Interactions among these systems may also contribute to the manifestation and modulation of these related behaviors.

### Behavioral Response to M-CPP

#### "High" Response to M-CPP

Pathological gamblers had a significantly increased mean "high" response to m-CPP stimulation compared to placebo. Although there was also an increase in mean m-CPP "high" ratings among the controls, the magnitude of this response was small, and between-group differences were just short of reaching significance ( $p=.055$ ). These findings are consistent with an ever-growing body of literature which suggests that m-CPP elicits an increased euphoric effect in patients with various types of impulsive behaviors/ disorders relative to healthy controls or placebo. For example, oral m-CPP (0.5mg/kg), compared to clonidine, an alpha 2 adrenergic agent, and placebo, induced significant increases in feeling "high" in a group of patients with trichotillomania (Stein et al., 1995). Similar results were found among patients with borderline personality disorder (Hollander et al., 1994) in response to m-CPP compared to placebo. In disorders of substance abuse, male alcoholics, some of whom had comorbid antisocial personality disorder (Benkelfat et al., 1991), cocaine addicts (Buydens-Branchey

& Branchey, 1993), and alcoholics (Krystal et al., 1994) also experienced increased "high" feelings in response to m-CPP stimulation. Thus, pathological gamblers appear to have increased sensitivity to the euphorogenic properties of m-CPP, similar to that which has been elicited in others with impulsive disorders.

#### M-CPP's Agonist Properties

M-CPP's agonist properties are associated with stimulation of 5-HT<sub>2a</sub> and 5-HT<sub>2c</sub> receptors. Although stimulation of these receptors is associated with hypothalamic prolactin release (Citron et al, 1981), it is also associated with behavioral responses via brain structures and systems that have been linked to hallucinogenic effects. For example, 5-HT<sub>2a</sub> receptors localized in the cortex (Gothert & Schlicker, 1987; Peroutka, 1987, 1988) and 5-HT<sub>2c</sub> receptors located in the cortex (Pazos & Palacios, 1985) and limbic system (Kennett & Curzon 1988a, 1988b) have been associated with hallucinogenic effects upon stimulation. Depending on the particular group of impulsive patients, the subjective "high" experienced appears to be linked to familiarity with

a particular 'substance' in relation to the specific psychopathology of that individual. For example, borderline patients who experienced an increased m-CPP "high" described feeling "spacy," "derealized," "depersonalized," as felt at the end of an LSD trip (Hollander et al., 1994). Alcoholic patients have described the m-CPP "high" experienced as an ethanol-like "high" in response to m-CPP (Krystal et al., 1994; Benkelfat et al., 1991). Among the pathological gamblers, the m-CPP "high" experienced was described as similar to the disinhibited feelings and state that they've experienced while gambling. Interestingly, results from an adapted dissociative symptom scale (Jacobs, 1988) that had been given to a subgroup of the pathological gamblers (n=6) at baseline revealed, to varying degrees of intensity that, "during or shortly after gambling": (1) five of six (83%) have felt as though they were in a trance; (2) two of six (33%) have experienced depersonalization symptoms; (3) two of six (33%) have experienced an altered identity; and (4) three of six (50%) have experienced memory blackouts. These dissociative symptoms did not occur outside of a gambling setting and were also independent of concurrent substance

use. These dissociative symptoms are also often experienced by patients with substance abuse (e.g., alcohol, marijuana, LSD) and depersonalization disorder, which have been associated with the serotonin system.

Thus, in pathological gamblers, there appears to be an increased vulnerability or sensitivity toward a cluster of euphorogenic-like variables which appear to have an association with other disorders likewise linked to impulsivity, euphorogenesis, and serotonergic dysfunction.

Of note, although the behavioral response to m-CPP in pathological gamblers was similar to that of other impulsive disorders, the prolactin response to m-CPP veered in the opposite direction. Perhaps the non-serotonergic neurotransmitter systems (e.g., norepinephrine, dopamine) which have been implicated in the facilitation, modulation and inhibition of impulsive behavior and reward systems may also exert influence on the unique neuroendocrine effects in pathological gamblers.

Relationships Between Neuropsychological/Phenomenological  
and Primary Neuroendocrine and Behavioral Outcome Measures

It was predicted that neuropsychological and phenomenological measures associated with constructs of impulsivity would correlate with neurobiological and neurobehavioral measures associated with m-CPP stimulation in pathological gamblers. Results revealed that no relationships were found between m-CPP-stimulated prolactin levels/ "high" ratings and (1) Matching Familiar Figures Test - Impulsivity-Reflectivity Index scores, (2) Porteus Maze Test Q scores, or (3) Barratt Impulsiveness Scale factor scores. The primary factors which may account for these negative findings involve (1) the lack of universal operational criteria of constructs of impulsivity; (2) an inherent difficulty in generalizing factors associated with constructs of impulsivity as defined by psychometric instruments (i.e., tendency to exercise insufficient control, rapid responding, and increase in rate of errors) to functional and structural correlates associated with impulsivity, since it is often defined as a global behavior rather than a construct with multifaceted elements; and/or a small sample size.

The Barratt Impulsiveness Scale and the Matching Familiar Figures Test were selected for use in this dissertation since the instruments themselves and the methods of assessing the results of these instruments have been examined and modified numerous times to address the issues of the multidimensional aspects associated with constructs of impulsivity. Nevertheless, the neuropsychological and phenomenological instruments used in this study to assess impulsivity showed no relationship to measures of serotonergic sensitivity in pathological gamblers. Importantly, the outcome of these secondary analyses may be affected by the small sample size and reduced power. This can be assessed via power analysis. Thus, the relationship between serotonergic receptor function in male pathological gamblers and psychometric constructs of impulsivity requires further investigation.

Of note, an interesting finding emerged upon inspection of the norms that were presented by Patton and Barratt (1992) of the three factor scores of impulsivity among various groups of impulsive patients. Inspection revealed that as a group, the pathological gamblers' mean overall

Factor 3 Impulsivity scale (see appendix) score was two standard deviations greater than the overall mean score of patients who were depressed, cocaine abusers, polydrug abusers, and alcohol abusers, suggesting that pathological gamblers are even more impulsive (as defined by this factor) than other groups considered to have problems of impulse control.

### Conclusions

The results of this dissertation suggest that serotonergic abnormalities may be present in male pathological gamblers, as evidenced by enhanced neuroendocrine and behavioral responses to m-CPP stimulation. In addition, there does not appear to be a relationship between 5-HT postsynaptic receptor hypersensitivity and selected neuropsychological and phenomenological constructs of impulsivity in male pathological gamblers. It is possible that impulsivity associated with male pathological gamblers may be related to the initial arousal associated with novelty-seeking behavior, behavioral activation, and sensitivity to reward

systems which may be mediated by noradrenergic and dopaminergic function. In support of this idea, one study found increased levels of CSF 3-methoxy-4-hydroxy-phenylglycol (MHPG), a metabolite of norepinephrine, and greater urinary norepinephrine output in male pathological gamblers (Roy et al., 1988). Further, dopaminergic facilitation may be associated with decreased response threshold to certain environmental cues, such as may be seen in decreased sensitivity to a non-reward situation.

In contrast, 5-HT postsynaptic receptor hypersensitivity may be associated with a disruption in the behavioral inhibition system, reflecting impairment in the ability to inhibit behavior once it is initiated. Perhaps the serotonergic postsynaptic receptor dysfunction observed in these male pathological gamblers may be associated with the harm avoidant, compulsive aspects of pathological gambling behavior. The 'behavior completion model' previously described theoretically represents this view.

In conclusion, there appears to be serotonergic postsynaptic receptor dysfunction in male pathological gamblers that does not seem to be associated with constructs

of impulsivity, and instead, may be more related to constructs of compulsivity. This statement should be regarded as speculative given the limitations of this study which follow.

#### Limitations of the Dissertation

There are a number of limitations in this study which highlight the need for caution when interpreting the observed results in this dissertation. First, the sample size used in this study was small. Thus, generalization of these findings are speculative. Findings may represent outcome unique to this particular sample. Larger samples are needed in future investigations.

Diagnostic psychiatric assessments were based on clinical psychiatric interviews by study psychiatrists. Semi-structured interviews (i.e., SCID I, SCID II) were not systematically used to evaluate all subjects for Axis I and Axis II disorders. Consequently, diagnostic criteria, especially Axis II diagnostic criteria, were not available for use in assessing relationships between personality

disorders and measures of serotonergic sensitivity dimensionally.

Another limitation is that one of the gamblers included in this study had a history of alcohol abuse/dependence, even though he was alcohol-free for at least two weeks prior to the challenges. Although it is not clear what impact a history of alcohol abuse may have had on the neuroendocrine and behavioral results of the challenge, this subject's m-CPP prolactin response was lower than most others in the PG group. Since decreased prolactin response to serotonergic stimulation has been found in alcohol abusers, it is not surprising to find a decreased prolactin response relative to others in his group. Thus, although it is possible that the inclusion of this particular subject may have biased the neuroendocrine findings, this subject's prolactin response possibly further implicates the difference between the patient and control group prolactin response. It would be interesting to examine whether dually-diagnosed pathological gamblers (i.e., substance abusing pathological gamblers) have a different neuroendocrine profile in response to a

serotonergic challenge relative to non-substance abusing pathological gamblers.

Further, in this dissertation, serotonin was the only neurotransmitter under direct investigation. However, as a result of this study, new hypotheses regarding the relative roles that other neurotransmitters may play (e.g., norepinephrine and dopamine) have been generated. Future investigations with the additional use of noradrenergic and dopaminergic agents may help further elucidate the interaction and the relationship between neurotransmitter receptor function and constructs of impulsivity and compulsivity in pathological gamblers.

Additionally, constructs of impulsivity were not measured in the controls, and thus, the dimensional view of the range of responses to the m-CPP challenges could not be assessed.

Finally, this PG sample was limited to males only. As increasing numbers of females are diagnosed with pathological gambling, the need to include females in subsequent studies becomes obvious. In future studies with female pathological gamblers, phase of menstrual cycle must

be taken into consideration during pharmacological challenges.

Future studies should address each of these issues in an attempt to provide a more methodologically and conceptually-sound investigation.

#### Final Summation

New groups of pathological gamblers and controls need to be studied to validate that the observed differences between the groups found in this dissertation were not unique to these particular samples. The need for further research to elucidate the pathophysiology of pathological gambling, where very little is known, is obvious. Further, the application of this knowledge toward the development of methods for identifying and treating pathological gamblers during adolescence as well as adulthood is essential. If the development of neurobiological markers become more apparent, then prevention or lessening of the disabling conditions associated with pathological gambling may be possible.

The process involved in the development of this dissertation was an attempt to (1) review and present an overview of the literature associated with gambling and pathological gambling; (2) to begin promoting public awareness on pathological gambling; (3) to initiate neuropsychobiological research toward understanding the pathophysiology of pathological gambling; (4) to provide the author with an opportunity to develop proposals and grants for future research, toward the end goal of developing effective methods for the treatment of pathological gambling.

### **Tables**

Table 1. Plasma m-CPP Absorption/Metabolism and  
m-CPP Prolactin Response

Table 2. Mean (SD) Prolactin Levels

Table 3. Mean (SD) "High" Peak Change Ratings

Table 1  
Plasma M-CPP Absorption/Metabolism and M-CPP Prolactin Response

Pathological Gamblers

| Peak Plasma m-CPP Levels | M-CPP Peak Change Prolactin Levels |
|--------------------------|------------------------------------|
| 1. 68.00                 | 5.90                               |
| 2. 11.00                 | 7.60                               |
| 3. 13.00                 | 7.00                               |
| 4. 53.00                 | 14.60                              |
| 5. 97.00                 | 8.10                               |
| 6. 27.00                 | 10.10                              |
| 7. 19.00                 | 6.70                               |
| 8. 37.00                 | 5.00                               |
| 9. 13.00                 | 11.70                              |
| 10. 61.00                | 35.00*                             |

Controls

| Peak Plasma n-CPP Levels | n-CPP Peak Change Prolactin Levels |
|--------------------------|------------------------------------|
| 1. 28.60                 | 5.70                               |
| 2. 15.00                 | 1.90                               |
| 3. 14.80                 | 12.10                              |
| 4. 35.40                 | 2.10                               |
| 5. 34.80                 | 9.00                               |
| 6. 49.60                 | 5.80                               |
| 7. 12.10                 | 3.10                               |
| 8. 14.00                 | 7.60                               |
| 9. 44.60                 | 29.90*                             |
| 10. 4.00                 | 00.00*                             |

\* Subjects eliminated from the study

**Table 2. Mean (SD) Prolactin Levels**

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| <b>Across Time</b><br>(minutes following drug administration) |             |                          |                          |          |
|---------------------------------------------------------------|-------------|--------------------------|--------------------------|----------|
| <b>Time</b>                                                   | <b>Drug</b> | <b>Gamblers</b><br>(n=9) | <b>Controls</b><br>(n=8) | <b>p</b> |
| 0                                                             | m-CPP       | 8.07 (2.20)              | 7.25 (1.91)              |          |
| 90                                                            | m-CPP       | 13.74 (3.26)             | 12.06 (5.79)             |          |
| 180                                                           | m-CPP       | 14.78 (2.07)             | 10.56 (3.24)             | *.009    |
| 210                                                           | m-CPP       | 15.34 (4.40)             | 10.09 (3.33)             | *.014    |
| 0                                                             | Placebo     | 7.60 (2.45)              | 7.65 (2.63)              |          |
| 90                                                            | Placebo     | 7.22 (2.14)              | 6.54 (2.00)              |          |
| 180                                                           | Placebo     | 7.07 (2.83)              | 6.93 (2.36)              |          |
| 210                                                           | Placebo     | 7.33 (2.63)              | 7.69 (3.08)              |          |

\*(Statistical significance  
Student t-test, 2-tailed)

| <b>Peak Change Scores (Peak-Base)</b> |             |                          |                          |          |
|---------------------------------------|-------------|--------------------------|--------------------------|----------|
| <b>Time</b>                           | <b>Drug</b> | <b>Gamblers</b><br>(n=9) | <b>Controls</b><br>(n=8) | <b>p</b> |
| Peak<br>Change                        | m-CPP       | 8.52 (3.07)              | 5.91 (3.57)              |          |
| Peak<br>Change                        | Placebo     | 0.06 (2.13)              | 0.56 (0.69)              | .063     |

Two-way ANCOVA  
Group x Drug interaction  
[F=4.03(1,15),p=0.063]

**Table 3. Mean (SD) "High" Peak Change Ratings**

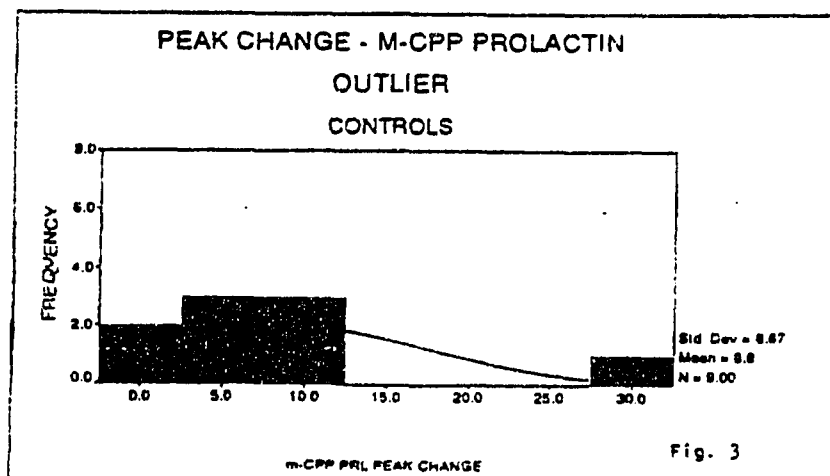
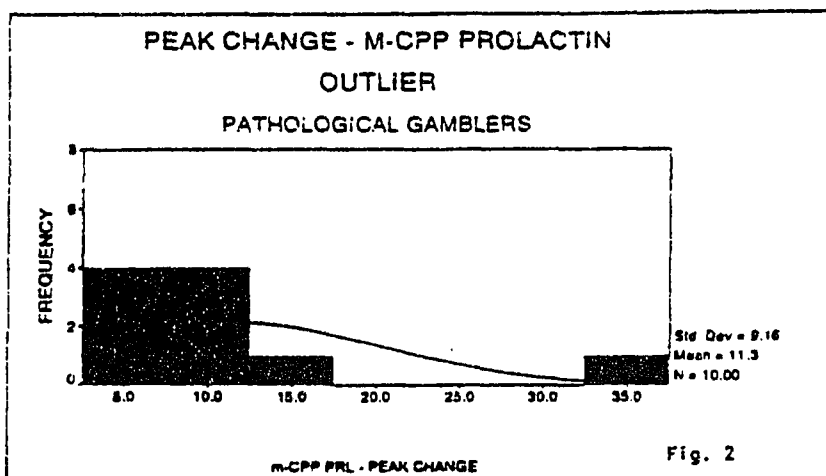
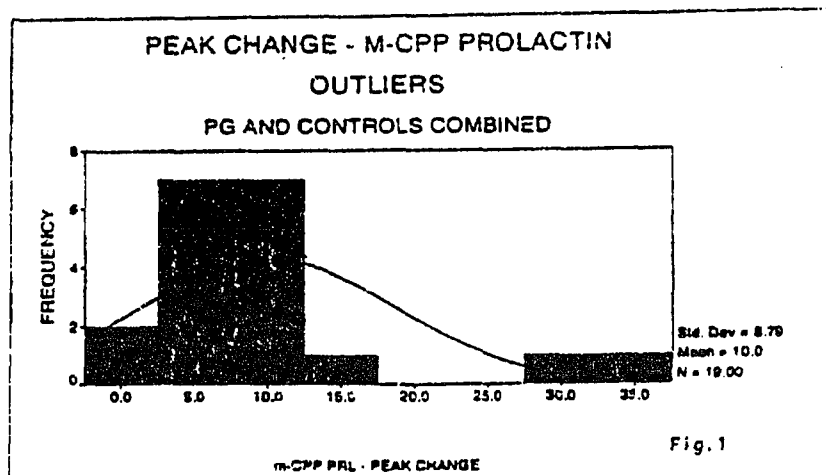
| <b>Time</b>    | <b>Drug</b> | <b>Gamblers</b><br>(n=9) | <b>Controls</b><br>(n=8) | <b>p</b> |
|----------------|-------------|--------------------------|--------------------------|----------|
| Peak<br>Change | m-CPP       | 1.44 (1.42)              | 0.38 (1.06)              |          |
|                |             | *p=.016                  |                          | #p=.049  |
| Peak<br>Change | Placebo     | 0.00 (0.00)              | 0.13 (0.35)              |          |

\*,# (Statistical significance)  
#Two-Way ANCOVA Group x Drug Interaction, F=4.6(1,15),p=.049  
\*Paired t-tests, 2-tailed

**Figure Captions**

- Figure 1: Mean m-chlorophenylpiperazine (m-CPP) peak change (peak-base) prolactin levels in 10 male pathological gamblers and 10 male nonreferred controls. Outliers ( $>2SD$  above the group mean): 1 control (mean=30 ng/mL) and 1 pathological gambler (mean=36 ng/mL).
- Figure 2: Mean m-chlorophenylpiperazine (m-CPP) peak change (peak-base) prolactin levels of 10 male pathological gamblers. Outlier ( $>2SD$  above the group mean of 11.3: 1 pathological gambler (mean=36 ng/mL).
- Figure 3: Mean m-chlorophenylpiperazine (m-CPP) peak change (peak-base) prolactin levels of 10 male nonreferred controls. Outliers ( $>2SD$  above the group mean of 8.6: 1 control (mean=36 ng/mL).
- Figure 4: Mean plasma prolactin levels across time in 9 male pathological gamblers and 8 male nonreferred controls following oral m-chlorophenylpiperazine (m-CPP) (0.5 mg/kg) and placebo administration. Post hoc t-tests  $*p<.01$ ;  $**p<.05$ .
- Figure 5: Mean m-chlorophenylpiperazine (m-CPP) and placebo peak change (peak-base) prolactin levels in 9 male pathological gamblers and 8 male nonreferred controls.
- Figure 6: Mean m-chlorophenylpiperazine (m-CPP) and placebo peak change (peak-base) "high" ratings in 9 male pathological gamblers and 8 male nonreferred controls. Post hoc t-tests  $*p<.05$ .

- Figure 7: Mean plasma cortisol levels across time in 8 male pathological gamblers and 8 male nonreferred controls following administration of oral m-chlorophenylpiperazine (m-CPP) (0.5 mg/kg) and placebo administration.
- Figure 8: Mean m-chlorophenylpiperazine (m-CPP) and placebo peak change (peak-base) anxiety ratings in 9 male pathological gamblers and 8 male nonreferred controls.



# Mean m-CPP/Placebo Prolactin

PG vs. Controls

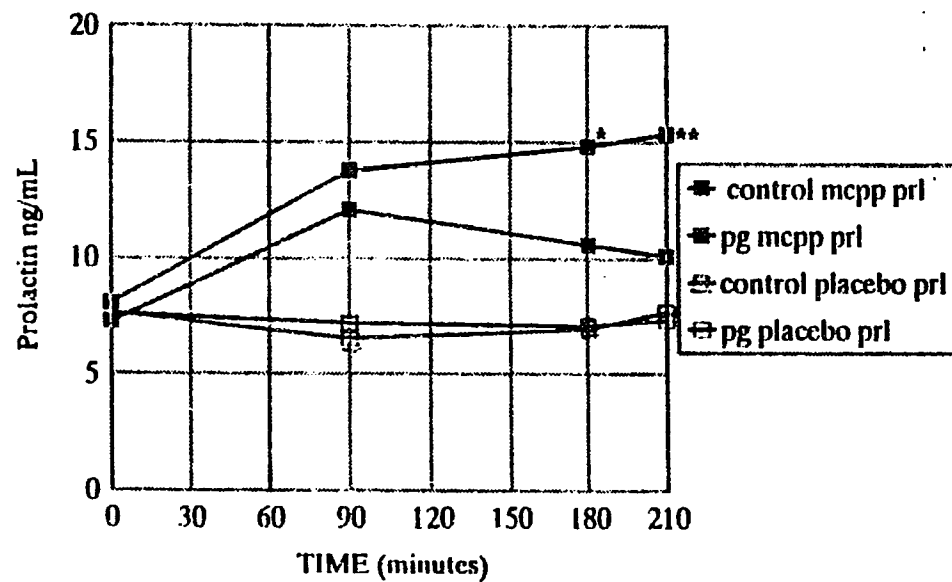


Fig. 4

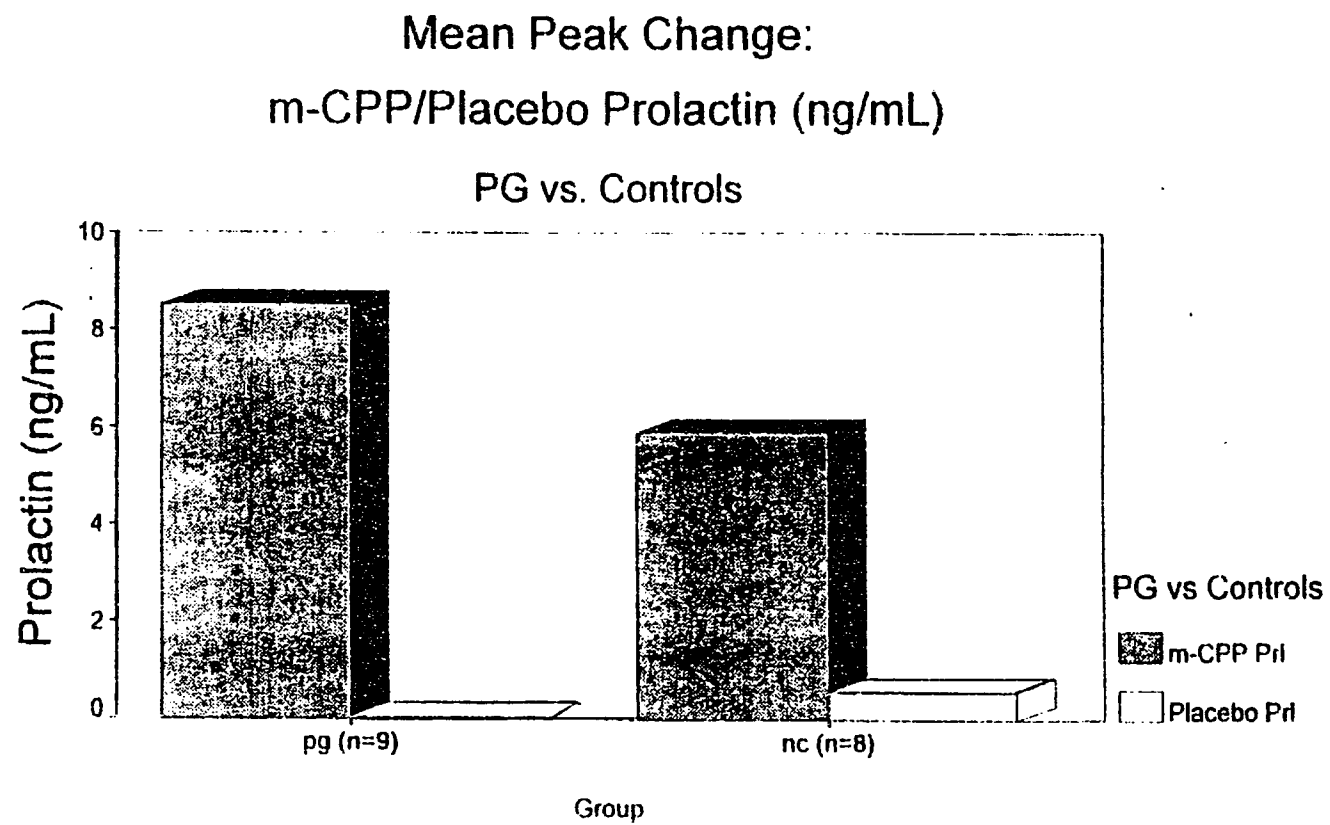


Fig. 5

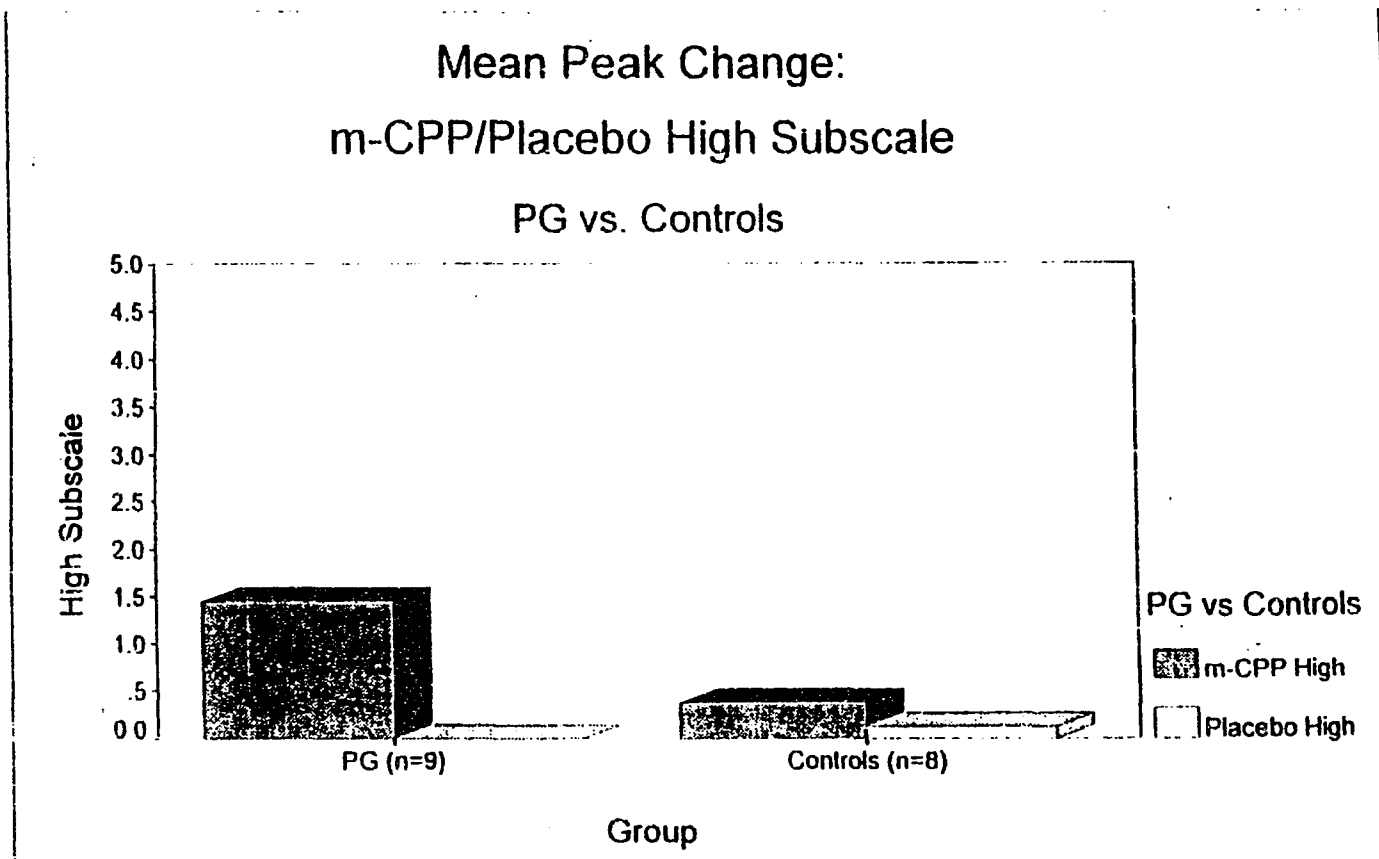


Fig. 6

# Mean m-CPP/Placebo Cortisol

PG vs. Controls

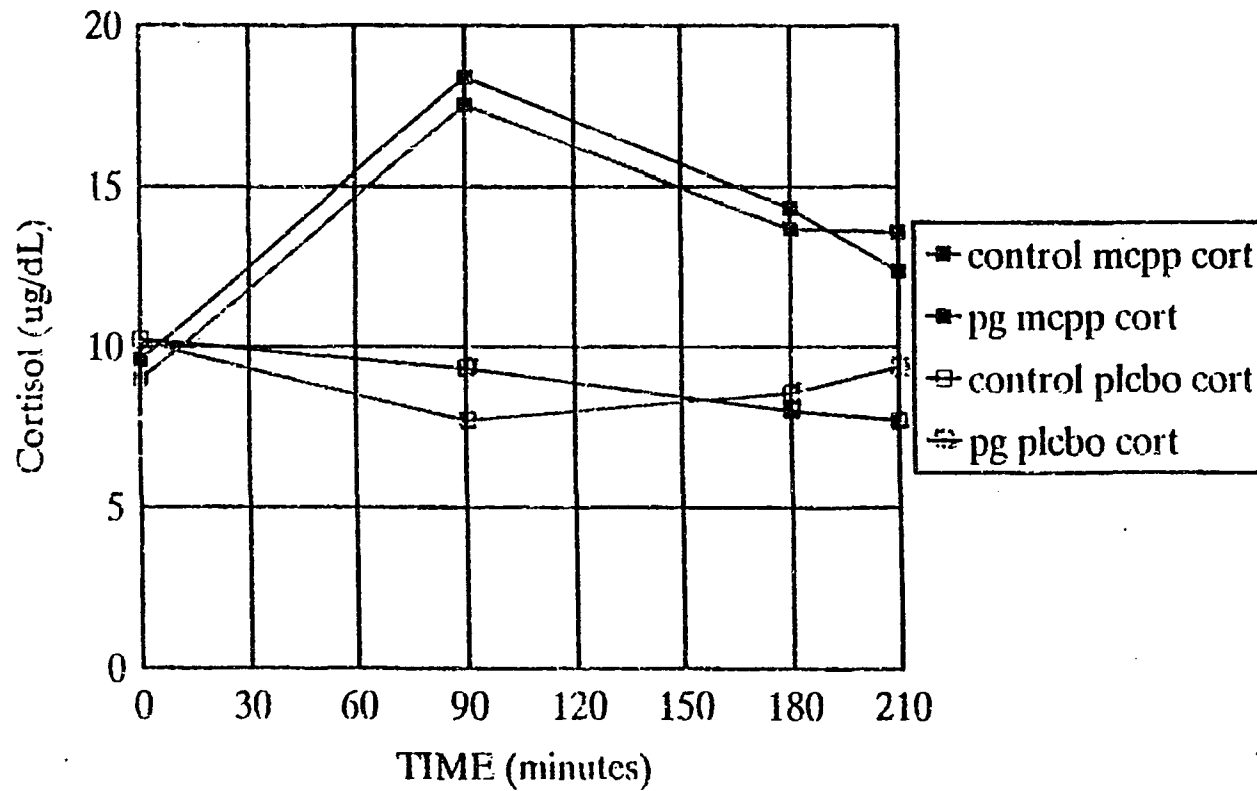


Fig. 7

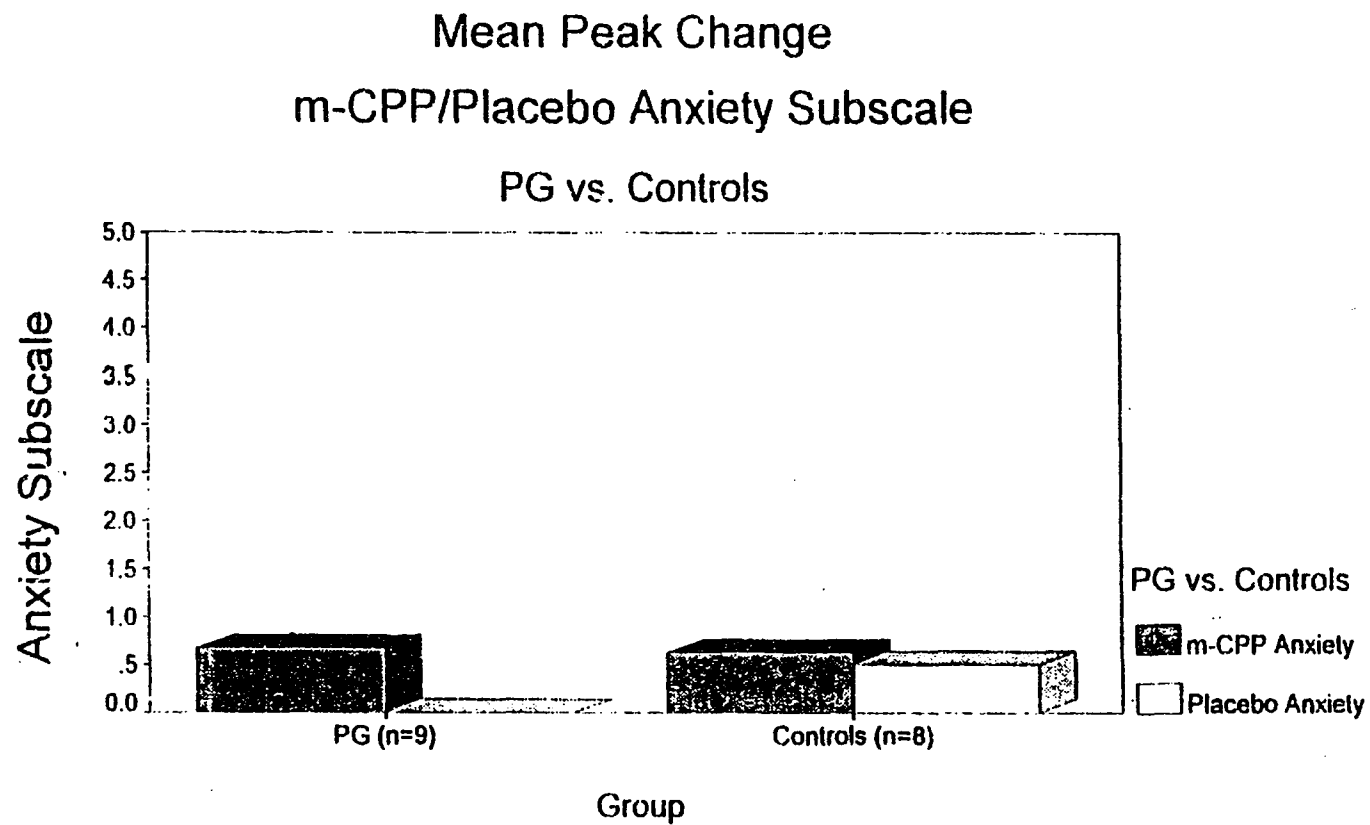


Fig. 8

Appendices

Analog Scale

South Oaks Gambling Screen

Barratt Impulsiveness Scale

Consent Form

### Analog Scale

Name: \_\_\_\_\_

Date: \_\_\_\_\_

Time: \_\_\_\_\_

---

|             | Not At<br>All |   | Moderately |   | Extremely |
|-------------|---------------|---|------------|---|-----------|
| 1.Talkative | 0             | 1 | 2          | 3 | 4         |
| 2.Happy     | 0             | 1 | 2          | 3 | 4         |
| 3.Drowsy    | 0             | 1 | 2          | 3 | 4         |
| 4.Nervous   | 0             | 1 | 2          | 3 | 4         |
| 5.Sad       | 0             | 1 | 2          | 3 | 4         |
| 6.Calm      | 0             | 1 | 2          | 3 | 4         |
| 7.Depressed | 0             | 1 | 2          | 3 | 4         |
| 8.Anxious   | 0             | 1 | 2          | 3 | 4         |
| 9.Energetic | 0             | 1 | 2          | 3 | 4         |
| 10.Fearful  | 0             | 1 | 2          | 3 | 4         |
| 11.Mellow   | 0             | 1 | 2          | 3 | 4         |
| 12.High     | 0             | 1 | 2          | 3 | 4         |
| 13.Angry    | 0             | 1 | 2          | 3 | 4         |

## SOUTH OAKS GAMBLING SCREEN

Name \_\_\_\_\_ Date \_\_\_\_\_

1. Please indicate which of the following types of gambling you have done in your lifetime. For each type, mark one answer: "not at all," "less than once a week," or "once a week or more."

- |    | not<br>at<br>all | less<br>than<br>once<br>a<br>week | once<br>a<br>week<br>or<br>more |                                                                                  |
|----|------------------|-----------------------------------|---------------------------------|----------------------------------------------------------------------------------|
| a. | _____            | _____                             | _____                           | play cards for money                                                             |
| b. | _____            | _____                             | _____                           | bet on horses, dogs or other animals (at OTB, the track or with a bookie)        |
| c. | _____            | _____                             | _____                           | bet on sports (parlay cards, with bookie, or at Jai Alai)                        |
| d. | _____            | _____                             | _____                           | played dice games (including craps, over and under or other dice games) or money |
| e. | _____            | _____                             | _____                           | went to casino (legal or otherwise)                                              |
| f. | _____            | _____                             | _____                           | played the numbers or bet on lotteries                                           |
| g. | _____            | _____                             | _____                           | played bingo                                                                     |
| h. | _____            | _____                             | _____                           | played the stock and/or commodities market                                       |
| i. | _____            | _____                             | _____                           | played slot machines, poker machines or other gambling machines                  |
| j. | _____            | _____                             | _____                           | bowled, shot pool, played golf or some other game of skill for money             |

2. What is the largest amount of money you have ever gambled with on any one day?

- |                                  |                                       |
|----------------------------------|---------------------------------------|
| _____ never have gambled         | _____ more than \$100 up to \$1000    |
| _____ \$1 or less                | _____ more than \$1000 up to \$10,000 |
| _____ more than \$1 up to \$10   | _____ more than \$10,000              |
| _____ more than \$10 up to \$100 |                                       |

3. Do (did) your parents have a gambling problem?

- \_\_\_\_\_ both my father and mother gamble(d) too much
- \_\_\_\_\_ my father gambles (or gambled) too much
- \_\_\_\_\_ my mother gambles (or gambled) too much
- \_\_\_\_\_ neither one gambles too much

4. When you gamble, how often do you go back another day to win back money you lost?

- \_\_\_\_\_ never
- \_\_\_\_\_ some of the time (less than half the time I lose)
- \_\_\_\_\_ most of the time I lose
- \_\_\_\_\_ every time I lose

5. Have you ever claimed to be winning money gambling but weren't really? In fact, you lost?

- \_\_\_\_\_ never (or never gamble)  
 \_\_\_\_\_ yes, less than half the time I lost  
 \_\_\_\_\_ yes, most of the time

6. Do you feel you have ever had a problem with gambling?

- \_\_\_\_\_ no  
 \_\_\_\_\_ yes, in the past but not now  
 \_\_\_\_\_ yes

7. Did you ever gamble more than you intended to? .....

Yes No

8. Have people criticized your gambling? .....

Yes No

9. Have you ever felt guilty about the way you gamble or what happens when you gamble? .....

Yes No

10. Have you ever felt like you would like to stop gambling but didn't think you could? .....

Yes No

11. Have you ever hidden betting slips, lottery tickets, gambling money, or other signs of gambling from your spouse, children or other important people in your life? .....

Yes No

12. Have you every argued with people you live with over how you handle money? .....

Yes No

13. (If you answered yes to question 12): Have money arguments ever centered on your gambling? .....

Yes No

14. Have you ever borrowed from someone and not paid them back as a result of your gambling? .....

Yes No

15. Have you ever lost time from work (or school) due to gambling? .....

Yes No

16. If you borrowed money to gamble or to pay gambling debts, who or where did you borrow from? (check "yes" or "no" for each)

|                                                                    | Yes | No  |
|--------------------------------------------------------------------|-----|-----|
| a. from household money .....                                      | ( ) | ( ) |
| b. from your spouse .....                                          | ( ) | ( ) |
| c. from other relatives or in-laws .....                           | ( ) | ( ) |
| d. from banks, loan companies or credit unions .....               | ( ) | ( ) |
| e. from credit cards .....                                         | ( ) | ( ) |
| f. from loan sharks ("Shylocks") .....                             | ( ) | ( ) |
| g. you cashed in stocks, bonds or other securities .....           | ( ) | ( ) |
| h. you sold personal or family property .....                      | ( ) | ( ) |
| i. you borrowed on your checking account (passed bad checks) ..... | ( ) | ( ) |
| j. you have (had) a credit line with a bookie .....                | ( ) | ( ) |
| k. you have (had) a credit line with a casino .....                | ( ) | ( ) |

**Scoring**

Scores on the South Oaks Gambling Screen itself are determined by adding up the number of questions that show an "at risk" response:

Questions 1, 2, and 3 are not counted.

\_\_\_\_\_ Question 4: most of the time I lost, or every time I lost

\_\_\_\_\_ Question 5: yes, less than half the time I lost, or yes, most of the time

\_\_\_\_\_ Question 6: yes, in the past, but not now, or yes

\_\_\_\_\_ Question 7: yes

\_\_\_\_\_ Question 8: yes

\_\_\_\_\_ Question 9: yes

\_\_\_\_\_ Question 10: yes

\_\_\_\_\_ Question 11: yes

\_\_\_\_\_ Question 12 not counted

\_\_\_\_\_ Question 13: yes

\_\_\_\_\_ Question 14: yes

\_\_\_\_\_ Question 15: yes

\_\_\_\_\_ Question 16a: yes

\_\_\_\_\_ Question 16b: yes

\_\_\_\_\_ Question 16c: yes

\_\_\_\_\_ Question 16d: yes

\_\_\_\_\_ Question 16e: yes

\_\_\_\_\_ Question 16f: yes

\_\_\_\_\_ Question 16g: yes

\_\_\_\_\_ Question 16h: yes

\_\_\_\_\_ Question 16i: yes

Questions 16j and 16k not counted

Total = \_\_\_\_\_ (20 questions are counted)

5 or more = probable pathological gambler

# Barrett Impulsiveness Scale

Rate each of the following items according to the following key:

- 1 = always or almost always false
- 2 = mostly false
- 3 = mostly true
- 4 = always or almost always true

Work quickly without stopping to think too long about any one item.

1. I plan tasks carefully. \_\_\_\_\_
2. I do things without thinking. \_\_\_\_\_
3. I am happy go lucky. \_\_\_\_\_
4. I have racing thoughts. \_\_\_\_\_
5. I plan trips well ahead of time. \_\_\_\_\_
6. I am self-controlled. \_\_\_\_\_
7. I concentrate easily. \_\_\_\_\_
8. I save regularly. \_\_\_\_\_
9. I find it hard to sit still for long periods of time. \_\_\_\_\_
10. I am a careful thinker. \_\_\_\_\_
11. I plan for job security. \_\_\_\_\_
12. I say things without thinking. \_\_\_\_\_
13. I like to think about complex problems. \_\_\_\_\_
14. I change jobs. \_\_\_\_\_
15. I act "on impulse". \_\_\_\_\_
16. I get easily bored when solving thought problems. \_\_\_\_\_
17. I have regular medical/dental check ups. \_\_\_\_\_
18. I act on the spur of the moment. \_\_\_\_\_
19. I am a steady thinker. \_\_\_\_\_
20. I change where I live. \_\_\_\_\_
21. I buy things on impulse. \_\_\_\_\_
22. I finish what I start. \_\_\_\_\_
23. I walk and move fast. \_\_\_\_\_
24. I solve problems by trial-and-error. \_\_\_\_\_

(OVER)

## Barratt Impulsiveness Scale (page 2)

Rate each of the following items according to the following key:

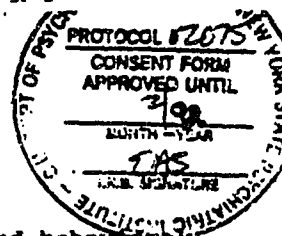
- 1 = always or almost always false
- 2 = mostly false
- 3 = mostly true
- 4 = always or almost always true

Work quickly without stopping to think too long about any one item.

- 25. I spend or charge more than I earn. \_\_\_\_\_
- 26. I talk fast. \_\_\_\_\_
- 27. I have outside thoughts when thinking. \_\_\_\_\_
- 28. I am more interested in the present than the future. \_\_\_\_\_
- 29. I am restless at lectures or talks. \_\_\_\_\_
- 30. I plan for the future. \_\_\_\_\_

IRB #2075

CONSENT FORM  
M-CPP AND CLONIDINE CHALLENGE  
(G)

**Purpose**

The purpose of this study is to examine biological and behavioral factors which may be related to people with gambling problems. In order to do this, the investigators will give me m-CPP and clonidine. M-CPP is a component of a marketed antidepressant drug, trazodone. While m-CPP itself is not yet an approved compound, the FDA has approved its investigational use for research purposes. Clonidine is a medication frequently used to treat hypertension, although its use in this study is only for research purposes, and is not being used for treatment. I understand that the results of the m-CPP and clonidine tests will be compared to a placebo procedure in order to evaluate the responsiveness of certain brain chemicals.

**Study Procedures**

This study will involve my coming into the laboratory on three separate occasions to receive m-CPP, clonidine or placebo (sugar pill). I understand that I will not know which medication I will be receiving on the days of the test.

I must be off all psychotropic medication for four weeks prior to the study. I may be off any active medication for as long as 5 months if I agree to enter the placebo-controlled treatment study.

I will receive a psychiatric and medical evaluation to exclude the presence of any medical problem which would interfere with my ability to participate in this study. The medical evaluation will include a physical exam, an EKG, a urinalysis and blood tests. I will be also be asked to maintain a special diet, of which I have been give a copy, for 72 hours prior to each procedure. I will be asked to have nothing to eat or drink except water from midnight prior to each of the 3 days of testing.

Each procedure will be done in the Biological Studies Unit at the New York State Psychiatric Institute and will last approximately 6 hours. I will be asked to be here at 8 a.m. I will be asked to give a urine sample to screen for drug or alcohol use each morning of the biological tests. The results will be kept confidential. A needle will then be placed in my arm for drawing blood samples. To avoid repeatedly sticking me to obtain blood samples, a small plastic tube will be left in my vein so that samples can be drawn without discomfort. The total amount of blood to be drawn is less than 6 tablespoons each day (3 days x 6 tbs. each day = approximately 18 tablespoons for the entire study).

I will receive oral m-CPP, clonidine or placebo. During the procedure, I will be given various behavioral rating scales to assess my symptoms. My blood pressure and heart rate will be monitored.

I understand that I may also be given the option of participating in a 10 week treatment study with Anafranil and placebo. This will be explained in a separate consent form. I understand that I will be asked to repeat the m-CPP, clonidine and placebo tests after I have been on medication for 10 weeks in the treatment study. A separate consent form will be given at that time.

In addition to the m-CPP and clonidine tests, I will also be asked to participate in neuropsychiatric testing. This will be explained in a separate consent form.

CF-F mcpp/clonpgcf

IRB #2075

Risks and Benefits

Possible risks from M-CPP are nausea, stomachaches, headaches, vomiting, anxiety, and a feeling of bodily coolness and mood change. It is possible that dizziness, low blood pressure, palpitations, and rapid heartbeat may occur with this drug, but are uncommon. These side effects may last up to 2 hours. I may also get a headache or feel dizzy from not eating. If I am sufficiently uncomfortable, I may ask the doctor to stop the procedure at any time and it will be stopped.

Clonidine may cause sedation, dry mouth, dizziness and a mild drop of blood pressure. Because of the sedation and dizziness associated with clonidine, due caution should be exercised when considering driving home or doing exercise for 24 hours following the clonidine dose, and should be avoided. A medical doctor will be present throughout the procedure. In the unlikely event of blood pressure becoming too low, medical doctors present at the study will provide immediate treatment. I will be monitored for 4 hours in the Biological Studies Unit after the clonidine is given to me.

Occasionally, redness and tenderness (a hematoma) may develop at the site where blood was taken or where an intravenous line was located. If this occurs, it will usually disappear in a few days.

If I am currently taking medication it is also possible that I may not be able to tolerate the taper (having medications decreased in dose or duration). In the event of relapse, I will be put back on effective medication and will be monitored weekly by the study psychiatrist until my condition has stabilized. If I relapse after I enter the study, I will be offered free treatment for 6 months.

There are no direct benefits to me for my participation in this study. However, I will be offered treatment in another research study which is an Anafranil/placebo treatment study, or appropriate open treatment free of charge for six months at the Anxiety Disorders Clinic. I may also be referred to Gamblers Anonymous or to individual/group psychotherapy or back to my treating doctor/clinic.

Research Standards and Participants' Rights

I may refuse to participate or withdraw from this study at any time without loss of benefits to which I am otherwise entitled.

I understand that my identity and participation in this study will be kept confidential except that my records can be reviewed by State and Federal regulatory agencies. My records will be kept in locked files and access to them will be restricted to the research staff.

Should any information gathered be used for scientific publications or presentations, my anonymity will be strictly preserved.

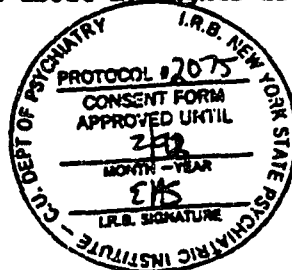
The investigators are available to answer questions at any time. Their telephone number is 212-960-2367. The Investigators are Eric Hollander, M.D. and Michael Liebowitz, M.D.

The New York State Psychiatric Institute-Columbia University, Department of Psychiatry Institutional Review Board has approved recruitment of subjects for this study.

I understand that I can contact the Institutional Review Board at 212-960-5758, if I have any complaints or questions about my rights as a research subject.

CF-F mcpp/clonpgcf

-2-



IRB #2075

Medical Compensation for Research-Related Injuries

Federal regulation require that we inform you about our institution's policy with regard to compensation and payment for treatment of research-related injuries. Short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute will be provided. In addition, we will provide assistance in arranging follow up care in such instances.

New York State Psychiatric Institute does not provide compensation or payment for treatment of research related injuries. However, you should be aware that participation in this research does not waive any of your legal rights to seek such compensation through the courts.

I have been given a copy of this consent form to keep.

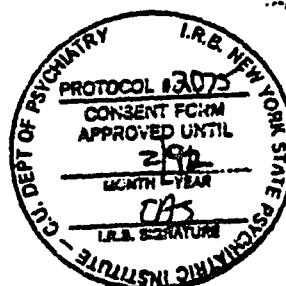
NAME: \_\_\_\_\_

SIGNATURE: \_\_\_\_\_

DATE: \_\_\_\_\_

I have discussed the proposed research with this patient and, in my opinion, this patient understands the benefits and risks and is capable of freely consenting to participate in this research.

Date \_\_\_\_\_ Signature \_\_\_\_\_  
Study Doctor



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