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Neuropsychiatric Aspects of Aggression and Impulse-Control Disorders

Eric Hollander, M.D.
Heather A. Berlin, Ph.D., M.P.H.

The concepts of impulsivity and aggression play important roles not only in clinical psychiatry but also in everyday life. *Impulsivity* is defined as the failure to resist an impulse, drive, or temptation that is harmful to oneself or others. Impulsive behavior is impetuous and lacks deliberation. An impulse may be sudden in onset and transitory, or a gradual increase in tension may reach a crescendo in an explosive expression of the impulse, resulting in violence without regard for self or others. What makes an impulse pathological is an inability to resist it and its expression in an inappropriate environment.

Aggression is any form of behavior directed toward harm or injury of another person. It constitutes a multidetermined act that often results in physical (or verbal) injury to others, self, or objects. The behavioral manifestations of aggression are characterized by heightened vigilance and enhanced readiness to attack. Aggressive acts may be classified as defensive, premeditated, or impulsive. *Impulsive aggression* refers to impulsive and aggressive behavior occurring simultaneously. Sometimes impulsivity has been confused with aggression. Pathological gambling, for example, is impulsive but does not necessarily involve aggression. Likewise, a premeditated, well-planned assassination attempt is aggressive but not necessarily impulsive. Impulsive aggression correlates more clearly with biological indices of neurotransmitter function than does premeditated aggression. Often impulsivity and aggression are expressed together, as in antisocial personality disorder (ASPD).

Impulsivity and aggression may be part of the defining characteristics of many psychiatric illnesses, including personality disorders such as borderline personality disorder (BPD) and ASPD; neurological disorders characterized by disinhibited behavior; attention-deficit/hyperactivity disorder; substance and alcohol abuse; bulimia; and impulse-control disorders such as intermittent explosive disorder. Impulsivity is also a significant correlate of suicide and violent behavior.

The concepts of impulsivity and aggression are diagnostically nonspecific but may be viewed as dimensional constructs. A closer look at clinical syndromes characterized by these behaviors may also help elucidate the biological underpinnings of impulsivity and aggression.

Impulsive aggressive behaviors are severe behavioral disturbances with substantial associated morbidity and mortality. These behaviors may also lead to prolonged social, vocational, and family dysfunction; violent crimes (including murder, rape, robbery, and assault); accidents

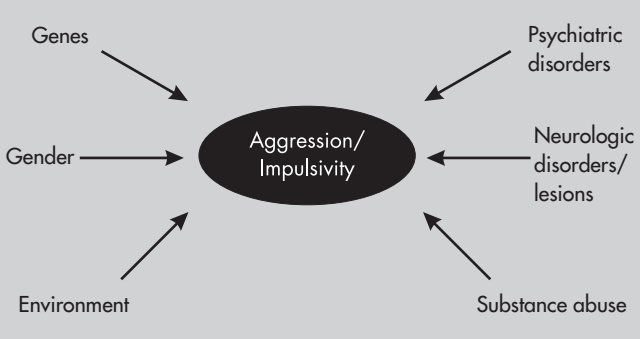

FIGURE 13–1. Factors contributing to aggression and impulsivity.

(including reckless driving); and injuries. Individuals who manifest impulsivity and aggression often become involved with the legal system and need repeated psychiatric evaluation and treatment and government financial assistance.

Clearly, the causes of impulsivity and aggression are complex and involve a combination of biological, developmental, psychosocial, and cultural factors (Figure 13–1). In this chapter, we focus on the neuropsychiatry and neurobiology of impulsivity and aggression, discuss specific disorders of impulse control, and highlight treatment strategies for managing impulsive and aggressive behavior.

EPIDEMIOLOGY

We live in a violent society. In the United States, homicide is the second leading cause of death among those 15–24 years of age. The four crimes classified as violent by the Federal Bureau of Investigation (FBI) are homicide, armed robbery, rape, and assault. Impulsivity and aggression are often the causes of crime, violence, homicide, suicide, substance abuse, and accidents and injuries. A greater percentage of the aggression in our society is associated with the young, and half of all homicides are committed by those younger than age 25. A 2000 report by the Bureau of Alcohol, Tobacco and Firearms revealed that 40.9% of crime gun possessors were 25 years of age or younger (U.S. Department of the Treasury 2002).

The highest rates of death and homicide are among young, poor, urban men. Overall, rates of death by homicide are about three times greater for men than for women. Homicide remains the leading cause of death of black men and women between ages 15 and 34. The fact that homicide is the leading cause of death for young blacks is explained partly by the low rate of natural deaths in the young in general and partly by high rates of poverty and concentration in large central cities, protecting them from the leading cause of death for young whites—motor vehicle accidents. Much lower rates of homicide have been reported in countries such as England, Sweden, and Japan, which all have strict gun control laws.

There are more than 20,000 homicides in the United States each year, and men are three times more likely than women to be killed. In 90% of homicides, the perpetrator and victim involved are the same race, and a handgun is used in more than 50% of the murders. Alcohol use is associated with 25%–75% of homicides. Homicide often occurs in families in the context of domestic quarrels and when members have access to firearms. In domestic violence, women are more likely to attack their husbands than vice versa. The Epidemiologic Catchment Area (ECA) project suggested that the rate of family violence was increasing among both blacks and whites, particularly in the younger populations (Federal Bureau of Investigation 1991).

Aggression and impulsivity are clearly linked to violence in our society. The etiology of violence, impulsivity, and aggression is multifactorial and not fully understood. A better understanding of the biological underpinnings of violence and aggression is only a part of the remedy, and these statistics help convey the depth of the problem and the degree to which it affects our culture.

MEASUREMENTS OF IMPULSIVITY AND AGGRESSION

Direct in vitro laboratory tests of impulsivity and aggression are currently unavailable. This discussion focuses on instruments that have been specifically designed to quantify aggressive and impulsive behavior. Most studies examining the biological basis of impulsivity and aggression in humans have used either interview or self-reported assessments. Rating scales measuring aggressive or impulsive behavior have been developed, covering both personality dimensions and clinical syndromes. These rating scales have been used as tools for measuring prognosis and outcome. The scales, which can be specific or comprehensive, measure both internally experienced variables (e.g., mood) and externally observable variables (e.g., behavior).

One of the problems in measuring aggression is the potential for discrepancies between self-rating scales and observer scales. Verbal aggression is difficult to assess because it may be a function of social class and clinical status. Some patients threaten others but are not aggressive in person, whereas others store their rage and ultimately explode in anger. How a patient handles aggressive urges requires evaluation not only of what he or she says but also of past behavior. On the other hand, measurement of

severe aggressive behavior (i.e., physical aggression) is often limited to observer scales because data based on the patients' own reports are likely to be biased on the basis of social desirability. Because there is social stigma attached to violent, aggressive behavior, few patients will honestly report their true behavior. In addition, patients with reduced verbal capacity or cognitive impairments (i.e., dementia) are often limited in their self-reporting. Observer scales are mainly used with moderately to severely aggressive hospitalized or institutionalized patients and are limited in distinguishing between chronic baseline aggression and exacerbations or heightened states of sporadic verbal or physical aggression.

Traditionally, before more valid and reliable instruments were developed, projective tests such as the Rorschach test or Thematic Apperception Test (TAT) were used to quantify aggression. Currently the most commonly used aggression questionnaire is the Buss-Durkee Hostility Inventory. In the subsections that follow, we summarize briefly the various strategies used to assess aggression and impulsivity in humans.

Self-Report Assessments

Buss-Durkee Hostility Inventory

The Buss-Durkee Hostility Inventory (BDHI; Buss and Durkee 1957) is the most widely used self-report assessment of aggression. It is a 75-item true/false questionnaire that measures different aspects of hostility, aggression, and danger (e.g., "I seldom strike back, even if someone hits me first: true or false"). There are eight subscales: assault, indirect hostility, irritability, negativism, resentment, suspicion, verbal hostility, and guilt. The BDHI has good test-retest reliability and good reports of positive concurrent validity.

Hostility and Direction of Hostility Questionnaire

The Hostility and Direction of Hostility Questionnaire (HDHQ; Philip 1969) is a true/false questionnaire containing 51 items derived from the Minnesota Multiphasic Personality Inventory (Hathaway and McKinley 1989). It contains five subscales, of which only one, "acting out hostility," is relevant to aggressive behavior. The HDHQ has modest to good test-retest reliability for its subscales.

Spielberger State-Trait Anger Expression Inventory

The Spielberger State-Trait Anger Expression Inventory (STAEI; Spielberger 1988) is a 44-item scale that divides behavior into state anger (i.e., current feelings) and trait anger (i.e., disposition toward angry reactions). (Sample items: "How I feel right now: I feel irritated"; "How I generally feel: I fly off the handle.") The STAEI takes about 15 minutes to complete.

Barratt Impulsiveness Scale, Version 11

The Barratt Impulsiveness Scale, version 11 (BIS-11; Patton et al. 1995) is a self-administered questionnaire of trait impulsivity with 30 items scored on a 4-point scale. The BIS-11 assesses long-term patterns of behavior; subjects are asked questions about the way they think and act without relation to any specific time period. The BIS-11 is made up of three subscales: nonplanning impulsivity (attention to details), motor impulsivity (acting without thinking), and cognitive impulsivity (future-oriented thinking and coping stability). This and previous versions of the BIS were designed primarily as research instruments to aid in the description of impulsivity in healthy individuals and to explore the role of impulsivity in psychopathology. Barratt (Barratt et al. 2005) has suggested that a Total score at or higher than 75 could indicate an impulse-control disorder, whereas a Total score in the range of 70–75 could indicate pathological impulsivity.

Massachusetts General Hospital Hairpulling Scale

The Massachusetts General Hospital (MGH) Hairpulling Scale (Keuthen et al. 1995) is a seven-item self-report questionnaire, scored on a 5-point Likert scale, that was developed to evaluate the severity of trichotillomania. This measure was modeled after the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) but differs from the Y-BOCS in that it does not include questions on obsessional ideation. The MGH Hairpulling Scale assesses the urge to pull hair, the actual amount of pulling, perceived control over hair pulling, and associated distress. The scale was designed to evaluate the baseline severity of trichotillomania and to assess change in symptom severity over time. It is intended for both clinical and research settings. Because the MGH Hairpulling Scale was developed relatively recently, there are no standardized scores.

Gambling Symptom Assessment Scale

The Gambling Symptom Assessment Scale (G-SAS; Kim et al. 2001) is a 12-item self-rated scale designed to assess gambling symptom severity and change during a treatment (an outcome measure). It measures gambling urges, thoughts, and behavior. The scale was designed primarily for gamblers who have prominent gambling urges. Since almost all gamblers have urges to gamble, the scale can be applied to pathological gamblers in general, but it was not

designed for those who do not have urges to gamble. Each item is scored on a 5-point scale. All items ask for an average symptom based on the past 7 days.

Kleptomania Symptom Assessment Scale

The Kleptomania Symptom Assessment Scale (K-SAS; Grant and Kim 2002) is an 11-item self-rated scale designed to measure the thoughts, urges, and behaviors associated with compulsive stealing. The scale was constructed on the basis of the observation that the thought patterns and behaviors of patients with kleptomania are similar to those of patients with substance addiction or behaviors such as compulsive gambling. The K-SAS is a modification of the G-SAS (Kim et al. 2001) and is designed to measure the change in kleptomania symptoms during treatment. Each item is scored from 0 to 4. Higher total scores reflect greater symptom severity. In two treatment samples, the mean scores ranged from 22 to 37 (Grant and Kim 2002; Grant et al. 2003).

Interview Assessments

Life History Assessments: The Brown-Goodwin Assessment for Life History of Aggression

The Brown-Goodwin Assessment (BGA; G. Brown et al. 1979) is one of the most commonly used assessments of aggressive behavior. It is rated by a clinician on the basis of direct interview with the patient and/or review of medical records and other information about the patient (including information from informants). The BGA has 11 assessments of aggression: temper, fighting, assault, school discipline, civilian discipline, antisocial behavior not involving police, antisocial behavior involving police, military discipline, military judicial discipline, property damage, and verbal aggression.

Pathological Gambling Modification of the Yale-Brown Obsessive Compulsive Scale

The Pathological Gambling Modification of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS; DeCaria et al. 1998) was modified from the original reliable and valid Y-BOCS (Goodman et al. 1989a, 1989b). Although a relatively new measure, PG-YBOCS is one of the most widely used clinician-rated measures of PG. It consists of 10 clinician-administered questions that measure the severity of pathological gambling over a recent time interval (usually within the past 1–2 weeks). The first five questions assess urges and thoughts associated with pathological gambling, whereas the last five questions assess the behavioral component of the disorder. Both sets of questions focus on time occupied by gambling, interference due to gambling, distress associated with gambling, resistance against gambling, and degree of control over gambling, which corresponds to DSM-IV criteria for pathological gambling (American Psychiatric Association 1994). Scores of 0 through 4 are assigned according to the severity of the response. Each set of questions is totaled separately as well as together for a total score.

South Oaks Gambling Screen—Interview or Self-Report

The South Oaks Gambling Screen (SOGS; Lesieur and Blume 1987, 1993), developed as a quantifiable structured instrument to assess pathological gambling, is a 20-item questionnaire that can be administered in either interview (by professionals and nonprofessionals) or self-report format. The SOGS may also be completed by an informant to provide a cross-check of an individual's responses. Although the SOGS questions do not correspond exactly with either DSM-III-R (American Psychiatric Association 1987) or DSM-IV criteria for pathological gambling, they assess the essential features of the disorder as defined in both DSM editions. Specifically, the SOGS assesses recurrent and maladaptive gambling behavior that disrupts personal, family, and vocational pursuits. Whereas DSM-III-R and DSM-IV also address the emotional components of gambling, the SOGS does not; rather, it focuses primarily on associated maladaptive social and financial behavior. The SOGS addresses gambling behavior across the lifetime. Past-year (Abbott and Volberg 1991) and past 6-month (Ladouceur and Sylvain 2000) versions have been developed for research. Scores are obtained by summing all positive responses. The authors identify 5 as a cutoff score for indicating probable pathological gambling, a score of 3–4 as signifying some problem, and a score of 0–2 as suggesting no problem.

Psychiatric Institute Trichotillomania Scale

The Psychiatric Institute Trichotillomania Scale (PITS; Winchel et al. 1992), developed to assess trichotillomania, is a six-item semistructured interview designed to be administered by a clinician. This measure assesses the number of hair-pulling sites, quantity of hair loss, time spent pulling and thinking about pulling, resistance to hair-pulling urges, distress regarding hair-pulling behavior and its consequences, and interference with daily activities. The PITS is designed to evaluate current symptom severity (i.e., during the past week) as well as change in symptom profile and severity over time. The measure includes a seven-item hair-pulling history interview, in which the interviewer asks questions about age at onset, course of illness, sites of hair pulling, and associated maladaptive

behavior. The responses from this section are not included in the final score but are used to aid scoring of the six items that form the heart of the interview. Items are rated on an 8-point scale. Higher total scores reflect greater severity. Neither normative data nor cutoff scores are provided.

Direct Laboratory Assessments of Aggression

Direct laboratory assessments of aggression assess the extent to which a subject responds aggressively to an opponent in a simulated "game" involving the subject giving an electric shock to his or her "opponent" or another measure of aggression. The three major direct laboratory assessments are discussed below.

Buss "Aggression Machine" Paradigm

In the Buss "Aggression Machine" (BAM; Buss 1961), the experimental subject's task is to teach his or her opponent a concept by showing an example of the concept. If the opponent is correct, a feedback button notifies the experimental subject, who is instructed beforehand not to deliver a shock in this circumstance. If the opponent is incorrect, the experimental subject has to press one of 10 buttons that deliver increasing intensities of electric shock.

Taylor Competitive Reaction Time-Task

The Taylor Competitive Reaction Time-Task (TCRTT; Taylor 1987) is a modification of the BAM. In the TCRTT, the experimental subject is engaged in a reaction time-task with an opponent.

Cherek Point Subtraction Aggression Paradigm

The Cherek Point Subtraction Aggression Paradigm (PSAP; Kelly and Cherek 1993) is a modification of the TCRTT, whereby the investigator is able to set the level of preoccupation for each session.

Although these rating measurements are useful, it is helpful to consider their limitations in the evaluation of dangerousness. Assessment of release from prison or hospital depends more on subjective parameters, such as the patient's alliance or compliance with medication, than on several tests, and the patient's history is still the most important determinant in the process of risk assessment.

Direct Laboratory Assessments of Impulsivity

The advantages of laboratory measures of impulsivity include their suitability for repeated use and thus for treatment studies, and their potential for use in both animals and humans, allowing for comparative studies of the basic biochemistry of these behaviors. For example, animal studies using paradigms that are based on reward-choice models and response disinhibition/attentional models have found evidence for a negative correlation between impulsivity and serotonin function (Evenden 1999; Puumala and Sirviö 1998). The primary disadvantages of these measures are that they do not incorporate the social aspects of impulsivity and do not measure long-term patterns of behavior.

Three broad categories of behavioral laboratory paradigms have been used to measure impulsivity: 1) punishment and/or extinction paradigms (Matthys et al. 1998), 2) reward-choice paradigms (Ainslie 1975), and 3) response disinhibition/attentional paradigms (Dougherty et al. 1999; Halperin et al. 1991). However, the construct of impulsivity is multifaceted and can be described in a variety of different ways.

Some tests measure impulsivity in terms of behavioral inhibition or the ability to suppress behavior when faced with punishment, novelty, or nonreward. This inhibition or suppression is typically measured by a go/no-go task in which behavioral inhibition is needed or an overt conflict emerges between making ("go") and refraining from ("no-go") a response based on reward, punishment, or nonreward. Another behavioral measure of impulsivity is delay of reinforcement. This approach, taken by Logue (1995) and others such as Trevor Robbins and his colleagues (e.g., Cardinal et al. 2001), considers self-control (the inverse of impulsivity) as a function of factors controlling the choice of delayed reinforcers (Logue 1988; Rachlin 1995). In other words, impulsivity is considered a problem with the ability to delay gratification. In this approach, impulsivity is usually measured as preference for a small immediate reward over a delayed larger reward.

Dickman (1993) identified two aspects of impulsivity: disinhibition and reflection-impulsivity. Syndromes of disinhibition are evidenced by, for example, an increased number of correct "go" responses in a "go/no-go" discrimination test (Newman et al. 1985). Reflection-impulsivity has been conceptualized as the cognitive processes involved in reflecting on the accuracy of available hypotheses (Kagan and Messer 1975). Operationally, the variable has been defined as a composite of two dimensions: latency to first response and accuracy of choice or total errors, which are combined in the Matching Familiar Figures Test (MFFT; Kagan et al. 1964; see also Kagan 1966), regarded as the primary (and often the only used) index of reflection-impulsivity. The MFFT is a standard, internally consistent, stable, reliable, and well-validated (Glow et al. 1981) measure of impulsivity in which participants select, from the set of highly similar pictures, the one that is exactly the same as the standard picture.

Participants were given 12 trials with 8 variants each to choose from, with a different target object for each trial. Mean time latency of the participants' first response across all trials and number of errors made before choosing the correct item were recorded. Dickman (1993) suggested reflection-impulsivity is a separate dimension, since results on the MFFT do not correlate with either self-report or other behavioral measures of impulsivity.

NEUROBIOLOGY AND NEUROPSYCHIATRY

In this section, we review neuroanatomical and neurotransmitter research that has focused on aggression and impulsivity as underlying personality or behavioral traits. Much of this work has used aggression and suicidality as indices of impulsivity. Although not all aggressive and suicidal behaviors are impulsive, these behaviors can arguably be seen as constituting a measure of the tendency to be impulsive (i.e., impulsive aggression). In addition, we discuss neuroendocrine and genetic correlates of impulsivity and aggression. Impulsivity and aggression are likely to be the result of several different independent factors interacting to modulate an individual's behavior.

Neurological Structures Involved in Aggression

A vast body of literature exists linking specific brain structures to aggressive behavior in mammals and nonhuman primates. Clinicians have also commonly observed that patients with neurological lesions may present with symptoms of aggression (Weiger and Bear 1988). A number of investigators hypothesize that for a subgroup of chronically aggressive persons, the root of the aggressive behavior is brain damage. D.O. Lewis et al. (1982) reported that every death row inmate studied by her team had a history of head injury, often inflicted by abusive parents. Her study concluded that death row inmates constitute an especially neuropsychiatrically impaired prison population. Although the connection between physical abuse, head injury, and aggression is uncertain, many studies do show an association between physical abuse and later aggressive behavior. Clinical reports of aggressive patients with specific neurological lesions may help delineate the structures that mediate these symptoms. In patients who present with aggressive symptoms, researchers have demonstrated neurological "soft signs"—a marker of subtle neurological dysfunction (Shaffer et al. 1985). Research on the major brain structures involved in mediating aggression has focused on the hypothalamus, amygdala, and prefrontal cortex. We briefly review the relationships between impulsive aggressive behavior, and these three structures.

Hypothalamus

The hypothalamus monitors internal status and orchestrates neuroendocrine responses via sympathetic arousal. It is involved in the regulation of the sleep-wake cycle, appetite, body temperature, and sexual activity. In combination with the pituitary, it is the major regulator of the autonomic nervous system. The mesolimbic dopaminergic pathway and the ascending serotonergic, noradrenergic, and cholinergic pathways from the brain stem have terminations in the hypothalamus.

The hypothalamus plays a major role in the expression of aggression in animals (Adams 2006; Eichelman 1971; Hassanain et al. 2005; Wasman and Flynn 1962). Stimulation of the anterior hypothalamus causes predatory attacks in cats, whereas activation of the dorsomedial aspect produces aggression in which the animal ignores the presence of a rat and attacks the experimenter. Destruction of aggression-inhibitory areas, such as the ventromedial nucleus of the hypothalamus, produces permanently aggressive cats and rats (Bard 1928; Reeves and Plum 1969). After cortical ablation, stimulation of the posterior lateral hypothalamus of the cat elicits sham-rage, a posture of preparation for attack. Stimulation of the posterior lateral portion of the hypothalamus shortens the latency of the attack, whereas stimulation of the medial ventral area prolongs the latency of attack (Eichelman 1971; Wasman and Flynn 1962). Hamsters tested for offensive aggression after microinjections of arginine vasopressin (AVP) directly within the anterior hypothalamus in combination with a 5-hydroxytryptamine (5-HT; serotonin) type 1B (5-HT_{1B}) receptor agonist have increased aggression, whereas those injected with AVP and a serotonin type 1A (5-HT_{1A}) receptor agonist have a dose-dependent inhibition of AVP-affiliated offensive aggression (Ferris et al. 1999). Structural lesions of the hypothalamus in humans may be associated with unplanned and undirected aggressive symptoms that often appear unprovoked but may be in response to physical discomfort (Haugh and Markesbery 1983; Ovsiew and Yudofsky 1983; Reeves and Plum 1969).

Amygdala

The limbic system encompasses the amygdala and temporal cortex. The amygdala activates and/or suppresses the hypothalamus and modulates input from the neocortex. It also has efferents to the extrapyramidal system. The amygdala may have a role in associating sensory experience with (hypothalamically directed) affects and

behaviors, including anger (Bear 1991). In a study using positron emission tomography (PET), the amygdala was shown to be more activated during the processing of visually presented linguistic threats than during the processing of neutral words (Isenberg et al. 1999).

Bilateral lesions of the amygdala tame a variety of hostile and vicious animals (Klüver and Bucy 1939), whereas irritative lesions or electrical stimulation can lead to rage outbursts. Removal of the amygdala from monkeys has been shown to result in decreased or no change in aggression (Downer 1961; Izquierdo et al. 2005). However, amygdalectomy in submissive monkeys may result in increased aggression (Dicks et al. 1969). Aggressive behavior following stimulation of the amygdala in cats varies according to their preexisting temperament (Adamac 1990). These findings suggest that the amygdala may not simply function to increase regulatory affects and behaviors, but rather it may mediate and balance their control. In monkeys, bilateral temporal lobectomy leads to hyperorality, hypersexuality, absence of fear response, increased touching, and visual agnosia (Klüver-Bucy syndrome). Bilateral temporal lobe damage in humans leads to similar symptoms, including hypersexuality and visual and auditory agnosias (Lilly et al. 1983; Trimble et al. 1997). In addition, humans exhibit placidity, apathy, bulimia, and aphasia (Isern 1987; Marlowe et al. 1975). This syndrome appears to be a disconnection between sensory information about the environment and the regulation of affects and behaviors (e.g., aggression, sex, food) that usually help the person or animal negotiate that environment.

Seizure studies of the limbic area in humans give insight into the possible neuroanatomical underpinnings of aggression. Whereas bilateral temporal lobe damage in humans may lead to Klüver-Bucy syndrome with a decrease in regulatory affects and behaviors, disorders of temporal lobe excitation may result in increased affect and aggression (Nachson 1988; Trimble and Van Elst 1999). Researchers have noted associations between aggression and temporal lobe epilepsy (TLE). Elliot (1992) found that 30% of 286 patients with intermittent violent outbursts had TLE. D.O. Lewis (1982) found psychomotor epilepsy in 18 of 97 (19%) incarcerated delinquent boys with a history of violence. Patients with TLE may demonstrate hyperemotionality and increased aggression. Interictal aggression is much more common than ictal or postictal aggression in TLE. Interictal aggression is often characterized by intense affect in response to environmental stimuli, whereas ictal and postictal aggression are spontaneous and unfocused.

In humans, reports of surgical intervention for the relief of mental or structural brain disease or epilepsy have shown that both the amygdala and other temporal lobe and limbic system structures contribute to aggression modulation. Two patients who underwent bilateral amygdalotomy for intractable aggression showed a reduction in autonomic arousal in response to stressful stimuli and a decrease in aggressive outbursts (Lee et al. 1998). Limbic system tumors, infections, and blood vessel abnormalities have also been associated with violence. Although it is clear that various limbic system structures have an inhibitory or excitatory effect on aggression, the precise mechanism of the aggression pathway is still far from established.

Prefrontal Cortex

The prefrontal cortex (PFC) modulates limbic and hypothalamic activity and is associated with the social and judgment aspects of aggression. The frontal cortex coordinates timing of social cues, often before the expression of associated emotions. Lesions in this area give rise to disinhibited anger after minimal provocation, characterized by an individual showing little regard for the consequences of affect and behavior. Weiger and Bear (1988) suggest that whereas TLE patients may express deep remorse over an aggressive act, patients with prefrontal lesions often indicate indifference. Patients with violent behavior have been found to have a high frequency of prefrontal lobe lesions, and orbitofrontal cortex lesions, in particular, tend to result in antisocial behaviors (Blair 2004; Seguin 2004). In a study of Vietnam veterans with a history of penetrating head injuries, patients with ventromedial lesions had higher verbal aggression scores than control subjects and patients with lesions in other brain areas (Grafman et al. 1996). Frontal lesions may result in the sudden discharge of limbic- and/or amygdala-generated affects that are no longer modulated, processed, or inhibited by the frontal lobe. Individuals consequently respond with rage or aggression when acting on feelings that would have ordinarily been modulated. Prefrontal damage may cause aggression by a secondary process involving lack of inhibition of the limbic area. Dorsal lesions of the PFC are associated with impairment in long-term planning and increased apathy. Orbital lesion s of the PFC are associated with increases in reflexive emotional responses to environmental stimuli (Luria 1980).

The PFC is involved in the executive functions that guide behavior like planning, response modulation, and inhibition, and plays an important role in self-regulation (Ernst et al. 2003; Goudriaan et al. 2004; Jentsch and Taylor 1999; Lyvers 2000; Rogers and Robbins 2001). Numerous studies report that patients with impulsivity have neurobiological and neurocognitive deficits in executive functions related to the PFC (Berlin et al. 2004, 2005; Cheung et al. 2004; Goudriaan et al. 2004, 2005; Spinella 2004). Findings indicate that pathological gamblers have impairments in several

aspects of executive functioning, including response inhibition, planning, and decision making (Cavedini et al. 2002; Goudriaan et al. 2004, 2005; Petry 2001a, 2001b; Petry and Casarella 1999; Regard et al. 2003).

PFC damage can cause disinhibition, such that behavior becomes largely guided by previously conditioned or prepotent responses that are inappropriate in the current situation (Berlin et al. 2004; Milner 1982; Robbins 1996). Specifically, damage within the orbitofrontal cortex (OFC) or prelimbic cortex of humans leads to a tendency to preferentially respond for immediate small rewards over delayed, more efficient rewards (Bechara et al. 2000; Damasio 1996). Further, studies of OFC lesions in humans have revealed an autonomic pattern of deficits (Damasio et al. 1990) and subtle executive deficits in real-world social contexts (Eslinger and Damasio 1985; Grattan et al. 1994). In accord, damage to the OFC has been associated with disinhibited or socially inappropriate behavior, misinterpretation of moods, and impulsivity (Damasio 1994; Levin et al. 1991; Rolls et al. 1994). In one study (Berlin et al. 2004), OFC lesion patients performed more impulsively on both self-report and cognitive-behavioral tests of impulsivity, reported more inappropriate behaviors, and performed worse on a stimulus-reinforcement association reversal task than patients with non-OFC prefrontal cortex lesions and neuropsychiatrically healthy control participants. Further, in another study (Berlin et al. 2005), OFC lesion patients and BPD patients performed similarly in that they were more impulsive and reported more inappropriate behaviors, BPD characteristics, anger, and less happiness than patients with non-OFC prefrontal cortex lesions and neuropsychiatrically healthy control groups. They were also less open to experience and had a faster perception of time (underproduced time) than the neuropsychiatrically healthy control participants. This implies that OFC dysfunction may contribute to some of the core characteristics of BPD, in particular impulsivity.

Orbitofrontal and ventrolateral PFC activation is thought to exhibit top-down control over limbic pathways (Drevets 1999; Herpertz et al. 2001; Morgan et al. 1993; Rauch et al. 1998) via extensive reciprocal connections with the amygdala and other limbic structures, thus playing a role in correcting and regulating emotional and behavioral responses (Drevets 1998; Hornak et al. 2003, 2004; Rolls et al. 1994). Therefore, limbic-orbitofrontal circuit dysfunction may be involved in impulsivity in at least in a subgroup of patients (Van Reekum 1993), via underactivation of prefrontal areas involved in inhibiting behavior, overstimulation of the limbic regions involved in drive, or a combination of both.

Positron emission tomography has allowed researchers to explore whether reduced serotonergic functioning occurs in specific brain regions in individuals with increased aggression and impulsivity. One imaging study showed that in contrast to control subjects, BPD patients have diminished response to serotonergic stimulation (*d,l*-fenfluramine) in areas of PFC associated with regulation of impulsive behavior, specifically the medial and orbital regions of the right prefrontal cortex, left middle and superior temporal gyri, left parietal lobe, and left caudate body (Soloff et al. 2000). Siever et al. (1999) found that impulsive aggressive patients had significantly blunted metabolic responses in orbital frontal, adjacent ventral medial, and cingulate cortex compared with control subjects. Finally, impulsive murderers have been shown to have lower left and right prefrontal functioning and higher right subcortical functioning in comparison to predatory murderers (Raine et al. 1998).

Other areas implicated in impulsivity and aggression include the midline thalamus, lateral preoptic region, mamillary bodies, hippocampus, and basal ganglia.

Neuropharmacology of Impulsivity and Aggression

Decreased Serotonin Function

There is significant evidence for the role of serotonergic dysregulation in impulsive aggression in both animals and humans (Table 13–1) (Åsberg et al. 1976; G. Brown et al. 1979, 1982; Ferrari et al. 2005; Sabrie 1986). This association has been shown with a variety of measures of serotonergic function. A decrease in brain serotonin is found in the brain stems of muricidal rats (i.e., aggressive rats that spontaneously kill mice introduced into their cages) and other animals made aggressive by isolation. The administration of tryptophan, a serotonin precursor, reduces or abolishes the violence (Depue and Spoont 1986). In primate studies, researchers have noted higher blood levels of serotonin and higher cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA) in monkeys that tend to be dominant and high-ranking in their colonies (Higley et al. 1992) and lower CSF concentration of 5-HIAA as an antecedent to greater alcohol consumption (Higley et al. 1996b).

In humans, Åsberg et al. (1976) initially noted an inverse relationship between violent/lethal suicidal behavior and CSF concentration of the serotonin metabolite 5-HIAA in depressed patients. Subsequent studies on populations in eight different countries confirmed that suicidal depressed patients have lower CSF concentration of 5-HIAA than nonsuicidal depressed patients. For example, Lidberg et al. (2000) found that homicide offenders with a history of suicide attempts had a lower CSF concentration of 5-HIAA than the remaining homicide offenders. This correlation is particularly strong in those

TABLE 13–1. Studies of serotonin with aggression and impulsivity

Study type	Study	Findings
Animal studies	Higley et al. 1996b	Lower CSF concentration of 5-HIAA in primates correlated with greater alcohol consumption
	Depue and Spoont 1986	Decreased brain 5-HT in the brain stems of aggressive rats
CSF 5-HIAA	Lidberg et al. 2000	Low 5-HIAA concentration in CSF in homicide offenders with history of suicide attempts
	Stanley et al. 2000	Low 5-HIAA concentration in CSF in aggressive population independent of suicidal behavior
	G. Brown et al. 1982	Low 5-HIAA concentration in CSF of patients with personality disorders: decrease correlated with scores on lifetime aggression scale
	G. Brown et al. 1982; Bioulac 1980; Lidberg et al. 1984; Linnoila et al. 1983	Inverse relationship between CSF levels of 5-HIAA and impulsive/violent behaviors
5-HT platelet studies	Coccaro et al. 1996	Reduced numbers of platelet 5-HT transporter sites associated with history of aggressive behavior in patients with personality disorders
	Mann et al. 1992	Increased platelet 5-HT content correlated with lifetime aggression in BPD patients
	Biegon et al. 1990; Marazziti and Conti 1991	Abnormal 5-HT levels in platelets correlated with impassivity and aggression
	Stoff et al. 1987	Decreased numbers of platelet 5-HTT sites in aggressive institutionalized subjects
	C. S. Brown et al. 1989	Platelet 5-HT uptake inversely correlated with Barratt Impulsivity Scale score in aggressive males
Serum tryptophan	C. E. Lewis 1991	Low serum ratio of tryptophan to other neutral amino acids in alcoholic persons arrested for assaultive behaviors compared with other alcoholic persons
5-HT PET studies	Siever et al. 1999	No significant increases in glucose metabolism in cingulate, orbital frontal, ventral medial frontal, and inferior parietal cortices in impulsive aggressive patients after administration of serotonergic releasing agent *d,l*-fenfluramine (significant increases were seen in healthy control subjects)
	New et al. 2002	No activation in the left anteromedial orbital cortex of patients with impulsive aggression in response to the serotonergic agonist m-CPP (such activation was seen in control subjects). The anterior cingulate, normally activated by m-CPP, was deactivated in patients, while the posterior cingulate gyrus was activated in patients and deactivated in controls.
	New et al. 2004b	Blunted prolactin response in impulsive aggressive men with personality disorders after administration of *d,l*-fenfluramine compared with healthy controls

TABLE 13–1. Studies of serotonin with aggression and impulsivity *(continued)*

Study type	Study	Findings
	New et al. 2004a	Increases in relative metabolic rate in the orbitofrontal cortex and significant clinical improvement in impulsive aggressive BPD patients after receiving the SSRI fluoxetine
	Frankle et al. 2005	Significant reduction in 5-HTT availability in the anterior cingulate cortex of individuals with impulsive aggression compared with healthy subjects

Note. BPD = borderline personality disorder; CSF = cerebrospinal fluid; 5-HIAA = 5-hydroxyindoleacetic acid; 5-HT = serotonin; 5-HTT = serotonin transporter; m-CPP = *m*-chlorophenylpiperazine; PET = positron emission tomography; SSRI = selective serotonin reuptake inhibitor.

with violent suicide attempts. Low CSF concentration of 5-HIAA has also been shown to be related to aggressive behavior independent of suicidal behavior in patients with Axis I disorders (Stanley et al. 2000). In addition, G. Brown et al. (1982) demonstrated a decrease in CSF concentration of 5-HIAA in patients with personality disorders and found that this decrease correlated with scores on a lifetime aggression scale. Many studies have confirmed an inverse relationship between CSF 5-HIAA level and impulsive and violent behaviors (Bioulac 1980; G. Brown et al. 1982; Lidberg et al. 1984; Linnoila et al. 1983). The individual case subjects and small populations studied include psychopathic military personnel, arsonists, murderers, violent suicidal patients, and behaviorally disrupted children and adolescents. Linnoila et al. (1983) reported reduced CSF 5-HIAA concentration in both impulsive violent offenders and impulsive arsonists compared with persons who commit premeditated violence, suggesting that it is nonpremeditated ("impulsive") aggression, specifically, that correlates with reduced central serotonin function in these individuals.

Suicidal behavior can be conceptualized as aggressive behavior directed toward the self, and studies have found that decreased brain stem levels of serotonin and 5-HIAA are consistent postmortem findings in suicide victims. Investigators have also correlated abnormal serotonin platelet studies with impulsivity and aggression (Biegon et al. 1990; Marazziti and Conti 1991). Platelets bind and transport serotonin. Decreased numbers of platelet serotonin transporter (5-HTT) sites are found in aggressive subjects with conduct disorder and in "aggressive" institutionalized psychiatric subjects (Stoff et al. 1987). In addition, an inverse correlation between platelet serotonin uptake and Barratt "Impulsivity" score has been reported in aggressive adult males (C.S. Brown et al. 1989). In children and adolescents with conduct disorder, there is a negative correlation between platelet imipramine binding and impulsive aggression (Stoff et al. 1987). In individuals with personality disorders, platelet-titrated paroxetine binding has been shown to be inversely correlated with Life History of Aggression total score and aggression score and with the BDHI Assault score (Coccaro et al. 1996).

Researchers have noted consistently reduced imipramine binding (C.S. Brown et al. 1989) and increased platelet serotonin type 2 (5-HT_2) binding in suicide victims (Biegon et al. 1990). Reduced numbers of platelet 5-HTT sites are associated with life history of aggressive behavior in patients with personality disorder (Coccaro et al. 1996). The reduced imipramine binding may reflect decreased serotonin release. Increased 5-HT_2 binding may reflect the brain's compensatory response to a decrease in functional serotonergic neurons, with consequent upregulation of postsynaptic 5-HT_2 binding sites. Additional findings that suggest the role of serotonin in impulsivity and aggression include reports of low serum ratios of tryptophan to other neutral amino acids in alcoholic subjects arrested for assaultive behaviors compared with other alcoholic subjects or nonalcoholic control subjects (C.E. Lewis 1991). Type 2 alcoholism is associated with both violent behavior and serotonergic deficit (LeMarquand et al. 1994; Virkkunen and Linnoila 1990). Individuals with a family history of alcoholism may be more sensitive to impulsivity in response to low serotonin levels, because tryptophan-depleted individuals with a family history of alcoholism made more errors in a modified Taylor task than did those with no family history of alcoholism (LeMarquand et al. 1999).

Several PET studies also suggest decreased serotonin function in brain areas involved in inhibition in impulsive and aggressive patients (Frankle et al. 2005; New et al. 2002, 2004a, 2004b; Siever et al. 1999). In one study, 5-HTT (PET radiotracer ^{11}C-labeled McN 5652) availability was significantly reduced in the anterior cingulate cortex of individuals with impulsive aggression compared

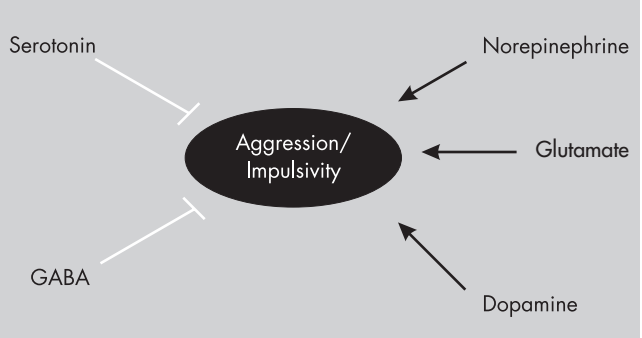

FIGURE 13–2. Neurochemistry of aggression and impulsivity. *White T-shaped lines* indicate that relative decrease in these neurotransmitters is related to increased impulsivity and aggression. *Black arrows* indicate that relative excess of these neurotransmitters is related to increased impulsivity and aggression. GABA = γ-aminobutyric acid.

with healthy controls (Frankle et al. 2005). Thus, pathological impulsive aggression may be associated with lower serotonergic innervation in the anterior cingulate cortex, an area involved in affective regulation.

Neurotransmitters other than serotonin likely influence aggressive and impulsive behavior—for example, γ-aminobutyric acid (GABA), norepinephrine, and dopamine (Oquendo and Mann 2000) (Figure 13–2). An α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor antagonist, NBQX, was found to increase impulsivity in rats. Normal behavior was restored by injection of a positive allosteric modulator of AMPA receptors, which indicated that the AMPA receptor, a type of glutamate receptor, is involved in the regulation of impulsivity (Nakamura et al. 2000).

One way to study the biology of impulsivity and aggression is to study the traits that cut across personality disorder diagnoses. For example, BPD and ASPD are characterized by impulsivity and aggression, behavioral dimensions that are hypothesized to have specific neurobiological correlates. Studies of patients with BPD have found increased platelet serotonin content that correlated with hostility and lifetime aggression, whereas platelet serotonin content was decreased in depressed patients (Mann et al. 1992). Platelet monoamine oxidase (MAO) has been described as a peripheral marker of cerebral MAO activity and has been found to occur at lower levels in individuals with a high level of impulsiveness—for example, in bullfighters (Carrasco et al. 1999) and bulimic patients (Carrasco et al. 2000). One study found platelet MAO levels significantly decreased in BPD patients compared with control subjects (Yehuda et al. 1989). However, another study (Soloff et al. 1991) did not find this association. These contradictory results suggest the complexity of neuronal mechanisms in producing behavior. One point to consider is that MAO is relatively nonspecific—it is involved in the breakdown of a number of monoamines—and the activity of MAO in platelets may not reflect MAO activity in the central nervous system (CNS).

Pharmacological Challenge Studies

Pharmacological challenges have confirmed a role for serotonin in impulsivity and aggression. The hypothalamic-pituitary-adrenal axis is involved in regulating the interaction between various neurotransmitters that appear, in part, to be stimulated by serotonin. Serotonin stimulation of the hypothalamus causes release of an unidentified prolactin-releasing factor (Ben-Jonathan et al. 1989) that acts on the pituitary, resulting in increased prolactin release. One way that impulsive, aggressive behavior has been linked to serotonergic abnormalities is via measurement of prolactin response to serotonin agonists. Serotonin agonists such as *m*-chlorophenylpiperazine (m-CPP) and fenfluramine stimulate serotonin release through the limbic-hypothalamic-pituitary axis and thereby increase plasma prolactin levels. This action is blocked by serotonin antagonists.

Pharmacological studies provide insight into the possible mechanisms of impulsivity and aggression. In animal studies, monkeys that have a low prolactin response to fenfluramine display more aggressive gestures when shown a slide of a threatening human being than do those with a high prolactin response (Kyes et al. 1995). Researchers have administered m-CPP and fenfluramine to impulsive and aggressive subjects, assaultive BPD and ASPD patients, and patients who attempted suicide, and found a blunted prolactin response that correlated inversely with impulsive aggression (Coccaro et al. 1997; Lopez-Ibor et al. 1990; Moss et al. 1990; New et al. 1997; O'Keane et al. 1992; Siever et al. 1999; 2002, 2004b). In patients with personality disorders, the prolactin response to these agents was inversely correlated with self-reported irritability and aggression, possibly reflecting decreased receptor sensitivity (Coccaro and Murphy 1990; Coccaro et al. 1989). This blunted prolactin response to selective and nonselective serotonergic agents may reflect multiple abnormalities at different functional levels of the serotonergic system. More recently, Siever et al. (1999) found that after receiving the serotonergic releasing agent *d,l*-fenfluramine, impulsive aggressive patients showed significantly blunted metabolic responses in orbital frontal, ventral medial, and cingulate cortex when compared with healthy controls, suggesting reduced serotonergic modulation of these regions in patients with impulsive aggression. In another study (New et al. 1997), patients with a personality disorder and history of self-mutilation

or suicide had blunted prolactin and cortisol responses to *d,l*-fenfluramine compared with those with neither, and those with both had the most blunted responses to fenfluramine. Thus, a central serotonin abnormality may be associated with both self-directed violence and suicidal behavior. In a later study using PET, New et al. (2004b) also found that the prolactin response to *d,l*-fenfluramine was blunted in impulsive aggressive men with personality disorders, both with and without suicidal histories, compared with controls. This response was not seen in impulsive aggressive women with personality disorders. This study replicates previous studies in which male patients with a personality disorder and related impulsive aggression and suicide attempts showed a blunted prolactin response to fenfluramine (see New et al. 2004b).

Rinne et al. (2000) found that the cortisol and prolactin responses to an m-CPP challenge in BPD patients were significantly lower than in control subjects and were inversely correlated with frequency of physical and sexual abuse. These data suggest that severe and traumatic stress during childhood affects the serotonergic system. In another study (New et al. 2002), patients with impulsive aggression did not show activation in the left anteromedial orbital cortex in response to the serotonergic agonist m-CPP, whereas control subjects did. The anterior cingulate, normally activated by m-CPP, was deactivated in patients, while the posterior cingulate gyrus was activated in patients and deactivated in controls. The decreased activation of inhibitory regions in patients with impulsive aggression in response to a serotonergic stimulus may contribute to their difficulty in modulating aggressive impulses.

Another line of evidence for serotonergic dysregulation in impulsive aggressive BPD patients stems from the fact that serotonergic drugs have been shown to improve these symptoms. Lithium, for example, has been reported to enhance presynaptic transmission of serotonin via second messenger systems (Coccaro et al. 1991) and has been shown to produce global improvement in BPD patients (Links et al. 1990). Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been reported to decrease impulsivity and aggression in BPD patients (Coccaro and Murphy 1990; Cornelius et al. 1989; Norden 1989). New et al. (2004a) found that impulsive aggressive patients with BPD had increases in relative metabolic rate in the orbitofrontal cortex and significant clinical improvement after receiving the SSRI fluoxetine. Thus, fluoxetine appears to have a normalizing effect on prefrontal cortex metabolism in impulsive aggressive patients. On the other hand, MAO inhibitors (MAOIs) have been shown to increase agitation and irritability in some BPD patients (Cowdry and Gardner 1988; Soloff et al. 1986). These studies support the hypothesis that increases in noradrenergic function, which in part are influenced by serotonergic mechanisms, may be associated with the tendency to act aggressively. Although studies are limited, the association between pharmacological enhancement of serotonin neurotransmission and reduced impulsivity in BPD patients supports the hypothesis that a decrease in serotonin transmission may underlie impulsivity in BPD patients.

However, a few studies failed to replicate the finding of blunted prolactin response in selected disorders of impulsivity and found augmented neuroendocrine response to serotonin agonists in impulsive substance abusers (Moss et al. 1990), patients with BPD (Hollander et al. 1994), and pathological gamblers. Patients with alcohol abuse (Moss et al. 1990), trichotillomania (Stein et al. 1993a, 1993b), and pathological gambling (DeCaria 1996) experienced a "high" compared with control subjects after receiving m-CPP. This high was characterized by feelings of "spaciness" and feelings of mild derealization or depersonalization and was described as similar to the highs reported when these patients were actually pulling hair (Stein 1995) or gambling (DeCaria 1996). In addition, male patients with BPD had greater increases in cortisol levels and marginally blunted prolactin responses compared with control subjects after receiving m-CPP (Hollander et al. 1994). The blunted prolactin response to serotonin agonists and the reported feeling of being high in impulsive and aggressive patients suggest aberrant serotonergic functioning in this population.

Although most of the research in impulsivity and aggression has focused on serotonergic function, there is also limited evidence for the role of norepinephrine. In fact, the serotonergic, noradrenergic, and dopaminergic systems are highly connected, and it is difficult to stimulate one without affecting the others. Animal studies support the hypothesis that the norepinephrine system has a direct effect on aggression. For example, MAOIs and tricyclic antidepressants, which increase the amount of central norepinephrine in the synaptic cleft, increase shock-induced fighting in rodents (Kantak et al. 1981). One study involving humans found that CSF concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG) correlated with aggressive behavior in a sample of subjects with personality disorders (G. Brown et al. 1979). Another study found a correlation between irritability and growth hormone response to the α-noradrenergic agonist clonidine in patients with personality disorders (Coccaro et al. 1991). Norepinephrine may modulate serotonergically mediated impulsive aggression. Decreases in norepinephrine, for example, may mediate depression, suicide, and inwardly directed aggression, whereas increases in norepinephrine may mediate outwardly directed aggression and irritability (Siever and Davis 1991). Overall, however, the role of

norepinephrine is less studied and is not as clear as the role of serotonin in impulsivity and aggression. Nonserotonergic medications have been useful in treating impulsivity and aggression in BPD patients. These include neuroleptics (Soloff et al. 1986), carbamazepine (Cowdry and Gardner 1988), and valproic acid (Hollander et al. 2001a; Stein et al. 1995). The reason for the effectiveness of these agents has not been established and lends support to the role of multiple neurotransmitters in the mediation of aggression and impulsivity.

Genetic Studies

Genetic studies in humans and animals have not yet supported a definitive association among impulsivity, aggression, and reduced serotonergic activity, but there is evidence to suggest they are related (Meyer-Lindenberg et al. 2006; Popova 2006). The Maudsley rat study, however, was an example of genetic breeding for aggressive behavior. Two groups of rats were bred. The first group (MNR) included rats that had low measures of impulsivity and high measures of inhibition. The second group (MR) had the opposite features. The MR strains bred from the second group were significantly more impulsive and demonstrated increased aggressive behavior compared with the MNR rats (Eichelman 1971). Neurochemically, the MNR strain showed lower limbic brain serotonin levels than the MR strain (Sudak and Maas 1964).

At the synaptic level, reuptake of serotonin is accomplished by a plasma membrane carrier called *serotonin transporter*, or 5-HTT. The gene for 5-HTT has been mapped to chromosome 17 (Collier et al. 1996). Preliminary evidence for a genetic disturbance in serotonergic function that might predispose individuals to impulsive aggressive behavior includes a study of the gene for the rate-limiting enzyme for serotonin synthesis, tryptophan hydroxylase (TPH). The gene for TPH has been mapped to the short arm of chromosome 11 and is one of the major candidate genes for psychiatric and behavioral disorders. Part of the gene for TPH has been discovered to exist as two alleles, U and L, with certain genotypes (UL and LL) being associated with impulsive aggressive behavior and suicidal behavior and low CSF levels of 5-HIAA in violent offenders (Nielson et al. 1994). Persons having the TPH U allele scored significantly higher on measures of aggression than did individuals homozygous for the L allele. Also, peak prolactin response was attenuated among male subjects, but not female subjects, having any U allele relative to LL homozygotes (Manuck et al. 1999). In another study, TPH genotype was found to be associated with impulsive aggressive behaviors in male patients with personality disorders, but not in female patients with the same disorders (New et al. 1998). Further studies are needed to clarify the role of TPH alleles in aggression and the differences between genders. The gene for the serotonin type 1B receptor (*HTR1B*) is located on chromosome 6 (Hamblin et al. 1992). A common polymorphism in the coding region of this gene is caused by a silent G to C substitution (Lappalainen et al. 1995). Some postmortem studies have reported decreased numbers of 5-HT_{1B} receptors in the frontal cortex of nondepressed suicide victims (Arranz et al. 1994). The allelic variability at the *HTR1B* locus may be associated with the susceptibility to suicide attempts in patients with personality disorders. New et al. (2001) found that the G allele at the *HTR1B* locus was associated with a history of suicide attempts in white patients with personality disorders. No relationship was found between *HTR1B* genotype and self-reported impulsive aggression, but self-report measures of aggression may not accurately reflect impulsive aggressive behavior. In summary, serotonin synthesis and regulation are at least partially controlled by genetic factors that likely contribute to an individual's propensity for impulsive and aggressive behaviors.

Currently, there are no controlled family history studies of individuals with impulse-control disorders (i.e., intermittent explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania). There are studies supporting associations between major mood disorder and alcohol and substance abuse in first-degree relatives of individuals with kleptomania and in first-degree relatives of pathological gamblers (Linden et al. 1986; Ramirez et al. 1983; Saiz et al. 1992). Other findings include associations between anxiety disorders in the families of individuals with kleptomania and violent behavior and attention-deficit/hyperactivity disorder in families of individuals with intermittent explosive disorder (McElroy et al. 1991).

Research involving monozygotic twins supports a hereditary aspect to aggressive behavior, with concordance rates for monozygotic twins being greater than those for dizygotic twins. Twin studies suggest that antisocial behavior in adult life is related more to genetic factors than to environmental factors (Cadoret et al. 1995).

Chromosomal studies have looked at the influence of chromosomal abnormalities in aggression, particularly the XYY syndrome (Bioulac et al. 1980). However, the link between XYY syndrome and violence has not been confirmed. Inborn metabolic disorders that affect the nervous system can be associated with aggressive personalities. These disorders, which diffusely affect the CNS and are inherited, include phenylketonuria, Lesch-Nyhan syndrome, Prader-Willi syndrome, Vogt's syndrome (a neuronal storage disorder), and Sanfilippo's syndrome (increased mucopolysaccharide storage).

Evidence for the Role of the Serotonin$_{1B}$ Receptor in Aggression

Animal models have been used to define more clearly the role of specific serotonin receptors in impulsivity and aggression. To define the contribution of serotonin receptor subtypes to behavior, mutant mice lacking the 5-HT$_{1B}$ receptor were generated by homologous recombination. These mice did not exhibit any obvious developmental or cognitive defects. However, they were noted to be extremely aggressive and attacked intruders faster and more intensely than did wild-type mice (Hen 1994). They also had increased impulsive aggression, more rapidly acquired cocaine self-administration, and increased alcohol consumption (Brunner and Hen 1997). These findings suggest a role for the 5-HT$_{1B}$ receptors in modulating aggressive, impulsive, and addiction behavior (Hen 1994).

Findings from genetic studies involving the 5-HT$_{1B}$ receptor gene in human subjects have been equivocal. In one study, a polymorphism of the 5-HT$_{1B}$ receptor gene was linked to aggressive and impulsive behavior in alcoholic individuals (Lappalainen et al. 1998). However, Huang et al. (1999), using two common polymorphisms, found no relationship between suicide, alcoholism, or pathological aggression and 5-HT$_{1B}$ receptor–binding indices or genotype.

Hollander et al. (1992) observed that a subgroup of patients with obsessive-compulsive disorder (OCD) experienced exacerbation of obsessive symptoms following m-CPP challenge studies. m-CPP has affinity for the 5-HT$_{1A}$, 5-HT$_{2C}$, and 5-HT$_{1D}$ receptor subtypes. Patients who underwent challenge studies with MK212, a serotonin agonist with affinity for the 5-HT$_{1A}$ and 5-HT$_{2C}$ receptor subtypes but not for the 5-HT$_{1D}$ subtype, did not manifest exacerbation of obsessions and compulsions. Because there are behavioral changes in a subgroup of OCD patients after administration of m-CPP but not of MK212, and because the activity of these two agonists differs with regard to only one receptor subtype, the 5-HT$_{1D}$ receptor, there is a suggestion that this receptor may modulate obsessions, of which sexual and aggressive symptoms may be prominent.

Endocrine Studies

Animal studies show that testosterone levels of male rhesus monkeys correlate positively with behavioral dominance and aggression. If a single male monkey is placed with other aggressive males, he becomes submissive and shows a decrease in plasma testosterone, revealing that endogenous hormone production can be affected by behavioral variables. The connection between the endocrine system and aggression and impulsivity is not clear. Some researchers have hypothesized that androgens may play a role in aggression. They suggest that the androgen insensitivity syndrome and the androgenital syndrome are examples of androgen excesses and deficiencies associated with aggressive and inhibited behavior, respectively. In one study, inmates who had committed personal crimes of sex and violence had higher testosterone levels than inmates who had committed property crimes of burglary, theft, and drugs. Inmates with higher testosterone levels also violated more rules in prison, especially rules involving overt confrontation (Dabbs et al. 1995). CSF free testosterone has been shown to be correlated with overall aggressiveness but not with measures of impulsivity (Higley et al. 1996a). Estrogens and antiandrogens have been used to reduce aggressiveness effectively in some violent sex offenders, although these agents clearly need to be better studied. Low salivary cortisol levels have been associated with persistence and early onset of aggression in school-age boys, suggesting that low hypothalamic-pituitary-adrenal axis activity correlates with aggressive activity (McBurnett et al. 2000).

Neuropsychiatric/ Neuropsychological Studies of Impulsivity and Aggression

Because aggression and impulsivity appear to be core features of both BPD and ASPD, much of the neuropsychiatric research in this area has focused on patients who meet criteria for these disorders. Researchers have suggested that impaired neuropsychiatric development could lead to personality pathology and that individuals with aggressive symptoms manifest subtle neuropsychiatric impairment. In this section, we review the neuropsychiatric and neuropsychological aspects of BPD and ASPD that give greater insight into the biological basis of impulsivity and aggression in these disorders.

Borderline Personality Disorder

BPD patients are often in a state of crisis. Their behavior is unpredictable and sometimes dangerous to self or others, and they rarely are able to achieve up to the level of their abilities. The painful nature of their lives is reflected in repetitive self-destructive acts that may include impulsive wrist slashing, self-mutilation, or suicide. There are fewer neuropsychological studies of BPD patients than of ASPD patients. BPD patients have commonly been thought, however, to have cognitive impairment on the basis of clinical observation of "ego deficits" (Kernberg 1975). BPD patients show no impairments in performance on structured psychological tests, such as the Wechsler Adult Intelligence Scale, but they have disturbed performance on

unstructured projective tests such as the Rorschach (Singer 1977). Although there is limited support for cognitive impairment in BPD, these studies support the idea that cognitive capacities in BPD are vulnerable to affective disruption and that patients lack stable self-organizing strategies. Neuropsychological studies of BPD patients support the association with impairment in complex information processing. Researchers have shown that, compared with control subjects, BPD patients had deficits on tests requiring the ability to plan multiple operations, to maintain a prolonged response over time, and to perform complex auditory and visual memory tasks (Burgess 1991). In addition, BPD patients also had significant impairment on tests of visual filtering and discrimination. These neuropsychological disturbances, particularly defects of memory, have been linked to the unstable, chaotic interactions characterized by impulsivity that are often seen in BPD patients. Neuropsychological studies have shown a variety of disturbances in BPD, including deficits in recall of learned material and completion of complex cognitive tasks (Burgess 1990; O'Leary et al. 1991).

In a time production task, where BPD patients were asked to read random numbers off of a computer screen (distracter task) and to stop at variable set time intervals, patients produced less time compared with healthy controls, indicative of a faster subjective sense of time (Berlin and Rolls 2004). Further, BPD patients' faster subjective sense of time correlated with both self-report and behavioral impulsivity. BPD patients also were less conscientious, extraverted, and open to experience, as well as more impulsive (by self-report and behaviorally), emotional, and neurotic, and they reported more BPD characteristics than did controls. The results suggest that some of these core characteristics of BPD may be on a continuum with impulsivity seen in the general population and that impulsivity, in particular, may be related to time perception deficits (i.e., a faster subjective sense of time). While impulsivity was correlated with time perception across all participants, emotionality, introversion, and lack of openness to experience were not. This suggests that different symptoms of the borderline personality syndrome may be separable and, therefore, may be related to different cognitive deficits and potentially to different brain systems.

Researchers have also studied neurological soft signs in BPD patients. The term *neurological soft signs* refers to nonlocalizing abnormalities not indicative of gross neurological disease. Soft signs are associated with a wide variety of developmental disabilities and include involuntary movements, a variety of apraxias, difficulties in performing rapid alternate movements, difficulties in discerning double simultaneous stimulation, and dysgraphesthesia. The assessment of neurological soft signs appears reliable and stable.

Work on patients with personality disorders characterized by impulsivity supports an association between these disorders and increased soft signs. Gardner et al. (1987) found significantly more soft sign neurological abnormalities in BPD patients compared with control subjects. Vitiello et al. (1990) found that increased soft signs were associated with impulsive responding on cognitive tests but not with global cognitive functioning.

Our group (Stein et al. 1993a) found that patients with DSM-III-R–diagnosed BPD had significantly more left-sided soft signs than did control subjects. These left-sided soft signs correlated with lowered neuropsychological test performance of visuospatial tasks and are thus consistent with right hemisphere dysfunction. However, there was also a significant association between history of aggression and right-sided soft signs. These findings are consistent with an association between impulsive aggression and left hemisphere dysfunction.

Evidence of neuropsychiatric abnormalities in personality disorders characterized by impulsivity has a number of clinical implications. Impairment in tasks of complex information processing, which appears to be associated with increased neurological soft signs, may contribute to difficulties in building and maintaining a coherent and stable sense of self and in using past experiences to organize present behavior and to predict future consequences. Impairment on verbal functions mediated by the left hemisphere may also contribute to impaired regulation of impulsivity and aggression insofar as verbal processing facilitates mental exploration before motor enactment, allowing greater appreciation of consequences and alternatives. In view of their nonspecificity and unclear etiology, however, neurological soft signs provide only a limited view of the neuropsychiatry of impulsivity and aggression.

In the only study to date comparing precise lesion patients with BPD patients on neuropsychological tests, Berlin et al. (2005) found that OFC and BPD patients performed similarly in that they were more impulsive and reported more inappropriate behaviors, BPD characteristics, anger, and less happiness than non-OFC prefrontal cortex lesion and neurologically and psychiatrically healthy control groups. They were also less open to experience and had a faster perception of time (underproduced time) than the neurologically and psychiatrically healthy controls. This implies that OFC dysfunction may contribute to some of the core characteristics of BPD, in particular impulsivity. In fact, neuroimaging studies show differences in the prefrontal cortex in people with BPD compared with normal subjects at baseline (De la Fuente et al. 1997; Goyer et al. 1994; Lyoo et al. 1998) and in response to aversive stimuli (Herpertz et al. 2001) and neuropharmacological probes associated with impulsivity (Leyton et al.

2001; Soloff et al. 2000). More specifically, there is some evidence from brain imaging studies for OFC dysfunction in BPD (Driessen et al. 2004; Schmahl et al. 2004; Van Elst et al. 2003; Vollm et al. 2004) and specifically for hypometabolism (De la Fuente et al. 1997; Goyer et al. 1994; Soloff et al. 2000) and reduced brain volume (Lyoo et al. 1998; Van Elst et al. 2003) of the OFC.

Electroencephalographic abnormalities have been associated with impulsive aggression, although definitive results have been inconclusive. While some have found no significant differences between these groups (Archer et al. 1988; Cornelius et al. 1986), electroencephalogram (EEG) abnormalities have been reported to be more prevalent in BPD patients than in control patients with other psychiatric disorders (Andrulonis et al. 1981; Cowdry et al. 1985; Snyder and Pitts 1984).The site of the reported abnormalities varies in that slow, fast, and mixed waves have been reported in frontal, frontotemporal, and occipital brain regions (Snyder and Pitts 1984). Increased risk for head injury might exist in patients with BPD because of their impulsivity and may account for the findings of different locations of EEG abnormalities in the brain (New et al. 1995).

PET studies in subjects with BPD have repeatedly reported functional abnormalities in the frontal lobe of the brain. One PET study showed an inverse correlation of global cerebral glucose metabolic rate and aggression; this finding was specific to the BPD group compared with patients with other personality disorders. Regional metabolic glucose rates in the frontal and parietal lobes were also depressed in BPD patients (Goyer et al. 1994). Similarly, in a PET study, De la Fuente et al. (1997) reported that patients with BPD had bilateral hypometabolism in premotor and prefrontal cortical areas compared with control subjects. Further, using PET neuroimaging during a pharmacological challenge with *d,l*-fenfluramine, Soloff et al. (2000) found that impulsive aggression in BPD patients was associated with diminished serotonergic regulation in the PFC, including medial and orbital regions. BPD patients had reduced activity in areas of the PFC associated with regulation of impulsive behavior following serotonergic stimulation. The diminished frontal metabolism in BPD patients could cause, act in parallel with, or exacerbate impaired serotonergic function and therefore be related to their impulsivity (De la Fuente et al. 1997).

Using magnetic resonance spectroscopy, Van Elst et al. (2001) examined the brains of patients with BPD and found a significant reduction of absolute *N*-acetylaspartate (NAA) concentrations in the dorsolateral frontal cortex of BPD patients compared with control subjects. In the first functional magnetic resonance imaging (fMRI) study with BPD patients, Herpertz et al. (2001) found that BPD patients, but not control subjects, had an elevated blood oxygen level–dependent fMRI signal bilaterally in the amygdala and fusiform gyrus and in the left medial and right ventrolateral PFC in response to aversive emotional stimuli. They suggested that BPD subjects' perceptual cortex may be modulated through the amygdala, leading to increased attention to emotionally relevant environmental stimuli, and that the medial/ventrolateral PFC may be a gateway for distinctive sensorial information and may modulate or inhibit amygdala-driven emotional responses and thus provide top-down control of the amygdala (see also Drevets 1999; Morgan et al. 1993; Rauch et al. 1998). More fMRI studies are needed to help clarify the previous, less differentiated, PET findings of hypofrontality in patients with BPD.

The functional abnormalities reported in studies of BPD patients suggest that structural brain abnormalities might exist in BPD as well. However, neither gross inspection nor quantitative measures have revealed brain computed tomography (CT) abnormalities in BPD patients more frequently than in psychiatrically healthy controls (Lucas et al. 1989; Schulz et al. 1983; Snyder et al. 1983). However, CT technology may not be sensitive enough to detect subtle variations in structural neuroanatomy. More advanced MRI studies have found structural abnormalities in BPD patients compared with healthy controls. The first MRI study that evaluated the structural abnormalities of the brain in subjects with the sole diagnosis of BPD found that BPD patients had a smaller frontal lobe volume compared with healthy subjects (Lyoo et al. 1998). Since impulsivity, a defining feature of BPD, has been reported to be closely related to frontal lobe dysfunction in people with impulsive personality disorders (Goyer et al. 1994; Stein et al. 1993a), and people with frontal lobe structural damage have shown problems with impulse control (Damasio et al. 1990), the finding of a smaller frontal lobe in BPD patients (Lyoo et al. 1998) may provide a structural basis for understanding this psychopathology in the context of BPD. While a number of lines of research are suggestive of biological disturbances associated, in particular, with the impulsive aspect of BPD, a neuroanatomical/physiological explanation of the etiology of BPD remains to be clarified.

Antisocial Personality Disorder

ASPD is characterized by continued antisocial or criminal acts but is not synonymous with criminality. Rather, it is an inability to conform to social norms and a pervasive pattern of disregard for and violation of the rights of others. A notable finding is patients' lack of remorse for their behavior. Persons with ASPD repeatedly get into fights or

are assaultive. Impulsivity in ASPD may manifest itself in a failure to show normal cautions and in increased recklessness. Impulsive behaviors may be driven by a need for excitement that expresses a disregard for the person's own safety and an intolerance for the feelings that he or she would otherwise experience. Conduct disorder is associated with ASPD later in life. Both ASPD and conduct disorder are associated with an increased use of illicit substances. Substance use and abuse is often impulsive, is frequently characterized by behavioral disinhibition, and commonly results in harm to oneself or others. The neurobiological association between certain behavioral characteristics of substance abuse, ASPD, and impulsive aggressive behavior in other contexts is beyond the scope of this chapter.

Neuropsychological testing of patients with ASPD has yielded mixed results. Using the Halstead-Reitan battery, Yeudall and Fromm-Auch (1979) studied laterality of cerebral dysfunction in various subject groups. They found impairments on variables sensitive primarily to left hemisphere dysfunction in violent criminals, alcoholic individuals with personality disorders, and adolescents with conduct disorders, but predominantly right hemisphere dysfunction in nonviolent criminals, alcoholic individuals with affective disorders, and individuals with affective personality disorders. Fedora and Fedora (1983) also found that prisoners with impulsive behaviors had evidence of left hemisphere impairment, particularly of the anterior regions.

EEGs and brain stem auditory evoked potentials of ASPD patients are not significantly different from those of control subjects (Fishbein et al. 1989). Conduct disorder in some children appears to be associated with later ASPD. Both disorders are characterized by impulsivity, aggression toward others, and violation of the rights of others. Our group has shown that patients with conduct disorder have greater neuropsychological impairment compared with control subjects (Aronowitz 1994). Conduct disorder patients have greater visuospatial, visuoperceptual, and visuoconstructional impairments compared with non–conduct-disordered patients (Aronowitz 1994). Socially appropriate behavior requires modulation of activity, self-restraint, flexibility, adaptation, and planning and anticipation of consequences. These abilities may be difficult for individuals with ASPD and conduct disorder, perhaps because of their neuropsychological deficits.

Using PET, Goyer et al. (1994) found that OFC, anterior medial frontal, and anterior temporal glucose metabolic rates were inversely associated with aggressive history in 17 patients with personality disorders (6 antisocial, 6 borderline, 2 dependent, and 3 narcissistic) compared with 43 healthy controls. In addition, using PET and replicating their earlier pilot study (Volkow and Tancredi 1987), Volkow et al. (1995) found that, compared with healthy controls ($N = 8$), 7 of 8 psychiatric patients with a history of repetitive violent behavior had significantly lower resting cerebral glucose metabolism values in the medial temporal and prefrontal cortices—regions that have been implicated in aggression and impulsivity.

Using PET during the continuous performance task, Raine et al. (1994) found that accused murderers ($n = 22$) had significantly lower glucose metabolism in both lateral and medial prefrontal cortices relative to age- and gender-matched controls ($n = 22$). On the same task, compared with age- and gender-matched controls ($n = 41$), murderers pleading not guilty by reason of insanity ($n = 41$) had reduced glucose metabolism in the prefrontal cortex, superior parietal gyrus, left angular gyrus, and corpus callosum, while abnormal metabolic asymmetries (left < right) were also found in the amygdala, thalamus, and medial temporal lobe (Raine et al. 1997). Thus, a network of abnormal cortical and subcortical brain processes may predispose people to violence. In a reanalysis of these data, Raine et al. (1998) found that the reduction in frontal activation was much more pronounced in murderers whose crimes had an affective rather than predatory basis. Affectively motivated crimes generally are considered to be more impulsive in nature than predatory murders that are, by definition, planned (Hoptman 2003). Davidson et al. (2000) suggest that impulsive violence results from a breakdown in the brain's ability to regulate negative affect. Thus, affective crimes may provide a window into the brain mechanisms underlying impulsive aggression. Finally, in a structural MRI study, ASPD ($n = 21$) patients, compared with healthy ($n = 34$), substance-dependent ($n = 26$), and psychiatric ($n = 21$) controls, showed an 11% reduction in prefrontal gray matter volume in the absence of brain lesions and a reduction in autonomic activity (skin conductance and heart rate) during a social stressor in which participants gave a videotaped speech on their faults (Raine et al. 2000). These deficits predicted group membership independent of psychosocial risk factors. This structural prefrontal deficit may underlie the lack of conscience, poor fear conditioning, low arousal, and decision-making deficits that often characterize antisocial psychopathic behavior.

Impulse-Control Disorders

The five impulse-control disorders listed in DSM-IV-TR are intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania (American Psychiatric Association 2000). Self-mutilation and sexual impulsivity are considered impulse-control disor-

ders not otherwise specified and include behavioral characteristics that overlap with those of a number of other DSM-IV-TR disorders.

There have been few studies examining the neurobiological underpinnings of DSM-IV-TR impulse-control disorders. Most of the studies have involved controlled pharmacotherapy studies for the treatment of impulsivity, which is discussed in the treatment section of this chapter. Pathological gamblers have higher CSF MHPG levels but similar CSF 5-HIAA levels compared with control subjects (Bergh et al. 1997). Pathological gamblers demonstrated dysregulated plasma prolactin response to intravenous clomipramine challenges (Moreno et al. 1991; Vazquez Rodriguez et al. 1991) relative to normal control subjects, indicative of serotonergic dysregulation. Our group demonstrated augmented neuroendocrine and behavioral response to m-CPP in pathological gamblers (DeCaria 1996). Some investigators have found clomipramine (Hollander et al. 1992) and fluvoxamine (Hollander et al. 1998, 2000) useful in the treatment of pathological gambling. There are also reports of the successful use of lithium in treating this disorder (Hollander et al. 2005a; Pallanti et al. 2002), as well as for kleptomania (Rocha and Rocha 1992), trichotillomania (Christenson et al. 1991), and sexual compulsions (Nishimura et al. 1997). Other mood stabilizers have been shown to be effective for impulse-control disorders—for example, divalproex sodium and topiramate for pathological gambling (Dannon et al. 2005; Pallanti et al. 2002) and tiagabine for impulse-control disorders with aggression (Kaufman et al. 2002).

Virkkunen et al. (1987) found lower CSF 5-HIAA and MHPG concentrations in persons who set fires compared with control subjects. All of the arsonists in the study met DSM-III criteria for BPD, and many demonstrated explosive behavior.

Very little neurobiological research has been done on kleptomania and trichotillomania. There is some anecdotal evidence that patients with kleptomania respond to various antidepressants, including SSRIs. Self-mutilation has been studied in patients with personality disorders, and one study showed a negative correlation between impulsive self-mutilation and the number of platelet imipramine-binding receptor sites (Stoff et al. 1987). Patients with personality disorders who exhibited self-mutilative behavior did not differ from patients with personality disorders without self-mutilative behavior in CSF 5-HIAA level or in platelet imipramine binding (Simeon et al. 1992). Case reports have noted the usefulness of lithium, SSRIs, and opiate antagonists in ameliorating self-mutilative behavior, again suggesting the heterogeneous nature of self-mutilation and the complexity of its underlying neurobiology.

TREATMENT OF IMPULSIVITY AND AGGRESSION

Pharmacotherapeutic Interventions

Impulsivity and aggression are behavioral characteristics that encompass a broad range of clinical problems. Studies on impulsivity and aggression have focused on a heterogeneous group of disorders with varied responses to pharmacotherapeutic interventions. In this section, we do not focus on the treatment of patients with epilepsy and patients with drug-induced aggression. These areas are reviewed elsewhere (see Chapter 16, Chapter 23, and Chapter 31).

Controlled studies suggest that a number of medications may be useful in the treatment of impulsivity and aggression. Given the evidence for decreased serotonergic function in impulsive and aggressive behaviors, many, but not all, of these medications involve direct serotonergic mechanisms. SSRIs have been shown to reduce impulsive aggressive behaviors in different psychiatric disorders. For example, fluvoxamine resulted in improvement in gambling severity in patients with pathological gambling compared with placebo in one double-blind study (Hollander et al. 2000). However, in some disorders characterized by impulsivity, SSRIs have a quick onset, but these effects may be transient and some patients may require additional augmentation with compounds such as lithium, buspirone, and anticonvulsants (Hollander and Wong 1995). The neurotransmitter effects of lithium are complex and include an effect on second-messenger systems related to the serotonergic system. Lithium has been found effective for impulsivity and aggression across different population such as prison inmates (Sheard 1971, 1975; Sheard et al. 1976, 1977; Tupin 1978; Tupin et al. 1973), children and adolescents with conduct disorders (Campbell et al. 1984, 1995; Fava 1997; Malone et al. 2000; Moll and Rothenberger 1998), deaf patients with impulsive aggression (Altshuler et al. 1977), and aggressive children (Siassi 1982).

Medications that are not serotonergically mediated, such as anticonvulsants, have also been useful in treating impulsivity and aggression across disorders (Berlin HA, Hollander E: "Mood Stabilizers for Personality Disorders and Impulsive Aggression," unpublished). Although evidence suggests that impulsivity and aggression are serotonergically mediated, a serotonergic hypothesis of impulsivity is not a definitive model. The complete role of serotonin activity and its complex interactions with other neurotransmitters and receptors in impulsivity and aggression have not yet been fully delineated.

BPD is a common clinical problem whereby researchers have used pharmacological interventions to target the char-

acteristic symptoms of impulsivity, aggression, lability, and hostility. Fluoxetine is the best-studied SSRI for the treatment of impulsivity and aggression. A number of open trials of fluoxetine in BPD suggest its efficacy in the treatment of impulsivity and aggression in BPD. Markowitz (1990) reported that BPD patients showed significant decreases in self-injurious behavior after treatment with fluoxetine 80 mg/day for 12 weeks. Three subsequent double-blind, placebo-controlled trials of fluoxetine confirmed the findings of the open trials (Markowitz 1992). Overall, controlled studies of fluoxetine, sertraline, and fluvoxamine suggest that these medications are of benefit to patients with impulsivity and aggression in the context of BPD. More studies are needed to assess further which behaviors are associated with responsivity to an SSRI, appropriate dosage, and longitudinal efficacy of those agents.

Researchers and clinicians have used lithium, carbamazepine, valproic acid, and, more recently, gabapentin, lamotrigine, and topiramate to treat the impulsivity, aggression, and mood instability seen in patients with bipolar disorder, and they subsequently reasoned that it might stabilize these same symptoms in BPD. In a double-blind, placebo-controlled trial (Cowdry and Gardner 1988), carbamazepine decreased impulsivity in a group of BPD patients. MAOIs have not been shown to decrease the behavioral dyscontrol or impulsivity seen in BPD. Furthermore, in BPD patients, overdosing on psychotropic agents is a common form of suicide, and MAOIs are clearly dangerous in these situations.

The tricyclic antidepressants have been extensively studied for their effects on depression in BPD patients. Although they are clearly effective for depressive symptoms, tricyclic antidepressants have not been shown to be particularly helpful in decreasing aggression and impulsivity in BPD (Soloff et al. 1986). Some BPD patients actually experienced increased anger, hostility, and aggression while taking imipramine (Klein 1968) and amitriptyline (Soloff et al. 1986). There are case reports of using desipramine or clomipramine effectively to treat violent outbursts in some patients and of using amitriptyline, trazodone, or fluoxetine for aggression associated with brain injury and anoxic encephalopathy. The potential for worsening impulsive aggressive symptoms and the danger of overdose in patients who have impaired self-control may limit the use of tricyclic antidepressants.

Neuroleptics are among the most studied medications for treatment of BPD, and they have been effective in treating violence associated with psychosis. Although they are the most commonly used medications for violence and aggression related to psychosis, neuroleptics are often chronically misused as sedatives. Further, some studies with BPD patients have shown that neuroleptics were not well tolerated and were statistically no better than placebo in the reduction of hostility, anger, and aggression (Goldberg et al. 1986; Soloff et al. 1986). However, in contrast, many studies demonstrate the efficacy of neuroleptics for the treatment of impulsivity and aggression in BPD patients (Nickel et al. 2006; Soler et al. 2005; Villeneuve and Lemelin 2005). In one 8-week open-label pilot study, BPD patients treated with olanzapine had decreased BIS-11 and BDHI scores compared with those treated with placebo (Schultz et al. 1999). Clinicians should keep in mind that neuroleptics, despite their efficacy, may result in a number of adverse side effects. They may cause tolerance to sedation and lead to increased doses and thereby increased side effects such as akathisia, extrapyramidal side effects, and anticholinergic toxicity. These specific side effects can worsen aggression in predisposed patients, particularly those with organic brain injury.

Mood stabilizers and anticonvulsants have been effective in treating impulsivity and aggression in patient populations. Our group (Stein et al. 1995) found that valproate led to significant overall improvement in 50% of a small sample of BPD patients who completed an 8-week open-label trial. Also, in a 10-week double-blind study, we found that valproate may be more effective than placebo (Hollander et al. 1998, 2001a). The medication was helpful for impulsivity, anger, and irritability, as well as for mood instability and anxiety. More recently, Hollander et al. (2003) conducted a large placebo-controlled, multicenter trial of divalproex for the treatment of impulsive aggression in Cluster B personality disorder, intermittent explosive disorder, or posttraumatic stress disorder. Entry criteria required evidence of current impulsive aggressive behavior (e.g., two or more impulsive aggressive outbursts per week on average for the previous month) and an Overt Aggression Scale—Modified (OAS-M) score of 15 or greater. Divalproex was superior to placebo in the treatment of impulsive aggression, irritability, and global severity in a large subgroup of patients with Cluster B disorders in terms of OAS-M Aggression scores. These results support previous findings of decreased impulsive aggressive behavior and irritability in BPD patients treated with divalproex (Hollander et al. 2001a), including those who failed to respond to other antiaggressive agents (i.e., SSRIs) (Kavoussi and Coccaro 1998). In the Hollander et al. (2003) study, unlike a previous pilot study in which divalproex was superior to placebo for the treatment of irritability and hostility in women with bipolar II and BPD (Frankenburg and Zanarini 2002), patients were excluded if they had bipolar I or bipolar II disorder with recent hypomania (during the past year). This suggests that the effect of divalproex in impulsive aggression may be unrelated to its effect in mania. However, the possibility

that the impulsive aggression of Cluster B personality disorders has an affective component, or that there is a subclinical mood disorder in Cluster B personality disorders, cannot be excluded.

Hollander et al. (2005b) examined clinical characteristics of BPD outpatients that might predict treatment response to divalproex for impulsive aggression. In this 12-week randomized, double-blind study, divalproex was superior to placebo in reducing impulsive aggression in BPD patients. Both pretreatment trait impulsivity and state aggression symptoms, independently of one another, predicted a favorable response to divalproex relative to placebo. However, baseline affective instability did not affect differential treatment response. These data may be helpful in identifying patient subgroups (e.g., those with high levels of trait impulsivity or state aggression) or baseline characteristics of BPD that could guide future trials of mood stabilizers. These data also suggest that BPD may be characterized by independent symptom domains that are amenable to treatment (Berlin and Rolls 1994; Berlin et al. 2004, 2005).

The potential efficacy of valproate in the treatment of BPD raises the question of the neurobiological underpinnings of the core features of BPD, namely, impulsivity and aggression. A number of points are relevant. First, a link between impulsive aggression and limbic abnormality has long been postulated. Although only a small percentage of BPD patients have seizure activity, more subtle neuropsychiatric abnormalities, including increased neurological soft signs, have been found in this population. The hypothesis that valproate alters limbic dysfunction by interrupting neuronal kindling is therefore of interest. Second, there is increasing evidence that serotonergic hypofunction may play a role in the mediation of BPD symptoms. Although valproate has multiple effects on neurotransmission, it is notable that valproate increases 5-HIAA levels. Further studies and larger sample sizes for the use of valproate in the treatment of BPD are warranted. Other anticonvulsants have all been shown to be effective in treating BPD—for example, carbamazepine (Cowdry and Gardner 1988; Gardner and Cowdry 1986; De la Fuente and Lotstra 1994; Denicoff et al. 1994), topiramate (Nickel et al. 2004, 2005), gabapentin (Biancosino et al. 2002), and lamotrigine (Pinto and Akiskal 1998; Preston et al. 2004).

Treatment in Developmentally Disabled Persons

Autistic disorder and mental retardation are often associated with impulsive outbursts, emotional lability, rage episodes, and aggression toward self and others. Treatment with fluoxetine has been found to decrease aggression, self-injury, and agitation in profoundly mentally retarded patients (Markowitz 1992). Lithium has been shown to be beneficial in a subset of children with rage, aggression, and irritability (DeLong 1978) and in mentally retarded patients with repeated, uncontrolled aggression and self-injury (Craft et al. 1987). Beta-blockers, which also bind to 5-HT_1-like receptors, have been found in open trials to lead to improvements in aggressive patients with neuropsychological disorders and in patients with impulsive aggression (Silver and Yudofsky 1995). Williams et al. (1982) documented the efficacy of propranolol in a diagnostically diverse population sharing the problem of rage outbursts. A series of case reports has indicated that carbamazepine treatment decreased rage outbursts and aggression in a group of patients demonstrating heterogeneous behaviors associated with aggression. In an open trial, our group reported that divalproex sodium (valproate) resulted in improvement in impulsive aggressive symptoms and affective instability in autism spectrum disorders (Hollander et al. 2001b). Further, in a double-blind, placebo-controlled trial of divalproex sodium, we (Hollander et al. 2006) found significant improvement in repetitive behaviors of autism spectrum disorders with divalproex sodium. In a multisite randomized, double-blind, placebo-controlled trial, McCracken et al. (2002) found that the atypical antipsychotic risperidone was well tolerated and efficacious for the treatment of aggression, self-injurious behavior, and tantrums in children with autistic disorder. Buspirone, a nonbenzodiazepine, nonsedating 5-HT_{1A} agonist, may be effective in the treatment of patients with developmental disabilities and head injury. These findings need further controlled trials. Eltoprazine, a phenylpiperazine derivative and mixed 5-HT_1 agonist, has shown antiaggressive properties in animal models. Eltoprazine-like compounds may be used in future treatment strategies and as a probe to further study the basis of impulsivity and aggression (Mak et al. 1995).

Highlights for the Clinician

Measurements of impulsivity and aggression

Self-report assessments

- Buss-Durkee Hostility Inventory
- Hostility and Direction of Hostility Questionnaire
- Spielberger State-Trait Anger Expression Inventory
- Barratt Impulsiveness Scale, Version 11
- Massachusetts General Hospital Hairpulling Scale
- Gambling Symptom Assessment Scale
- Kleptomania Symptom Assessment Scale

Interview assessments

- Brown-Goodwin Assessment for Life History of Aggression
- Pathological Gambling Modification of the Yale-Brown Obsessive Compulsive Scale
- South Oaks Gambling Screen
- Psychiatric Institute Trichotillomania Scale

Direct laboratory assessments of aggression

- Buss "Aggression Machine" Paradigm
- Taylor Competitive Reaction Time-Task
- Cherek Point Subtraction Aggression Paradigm

Direct laboratory assessments of impulsivity

Advantages: Suitable for repeated use and thus for treatment studies, have potential for use in both animals and humans, and allow for comparative studies of the basic biochemistry of these impulsive behaviors

Disadvantages: Do not incorporate the social aspects of impulsivity and do not measure long-term patterns of behavior

- Three broad categories of behavioral laboratory paradigms have been used to measure impulsivity:
  1. Punishment and/or extinction paradigms (Matthys et al. 1998)
  2. Reward-choice paradigms (Ainslie 1975)
  3. Response disinhibition/attentional paradigms (Dougherty et al. 1999; Halperin et al. 1991).
- Commonly used laboratory tests: go/no-go task, Matching Familiar Figures Test

Neurobiology and neuropsychiatry

Neurological structures involved in aggression

- Hypothalamus
- Amygdala
- Prefrontal cortex

Neuropharmacology of impulsivity and aggression

- Decreased serotonin function (see Table 13–1)

(continued)

Highlights for the Clinician *(continued)*

Pharmacological challenge studies

- Studies confirm a role for serotonin in impulsivity and aggression.
- In general, studies show that a blunted prolactin response to serotonin agonists is related to aggressive/impulsive behavior.

Genetic studies

- Genetic studies in humans and animals have not yet supported a definitive association among impulsivity, aggression, and reduced serotonin activity, but there is evidence to suggest they are related.

Evidence for the role of the 5-HT$_{1B}$ receptor in aggression

- Animal studies suggest a role for the 5-HT$_{1B}$ receptors in modulating aggressive, impulsive, and addiction behavior.
- Genetic studies involving the 5-HT$_{1B}$ receptor gene in human subjects have been equivocal.

Endocrine studies

- Animal studies show that testosterone levels of male rhesus monkeys correlate positively with behavioral dominance and aggression.
- Some researchers suggest that the androgen insensitivity syndrome and the androgenital syndrome are examples of androgen excesses and deficiencies associated with aggressive and inhibited behavior, respectively.

Neuropsychiatric/neuropsychological studies of impulsivity and aggression

- Because aggression and impulsivity appear to be core features of both borderline personality disorder (BPD) and antisocial personality disorder (ASPD), much of the neuropsychiatric research in this area has focused on patients who meet criteria for these disorders.
- Researchers have suggested that impaired neuropsychiatric development could lead to personality pathology and that individuals with aggressive symptoms manifest subtle neuropsychiatric impairment.
- A number of lines of research (e.g., imaging, neuropsychological testing, neurological soft signs) are suggestive of biological disturbances, in particular those related to prefrontal cortex, that are associated with the impulsive and aggressive aspects of BPD and ASPD.
- Few studies have examined the neurobiological underpinnings of DSM-IV-TR impulse-control disorders (i.e., intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania).
- Most of the studies of impulse-control disorders involve controlled pharmacotherapy studies for the treatment of impulsivity, which is discussed in the treatment section of this chapter.

Treatment of impulsivity and aggression

- Controlled studies suggest that a number of medications may be useful in the treatment of impulsivity and aggression.
- Given the evidence for decreased serotonergic function in impulsive and aggressive behaviors, many (but not all) of these medications involve direct serotonergic mechanisms. Selective serotonin reuptake inhibitors have been shown to reduce impulsive aggressive behaviors in impulsive or aggressive psychiatric disorders.
- Lithium has been found effective for impulsivity and aggression across different patient populations.

Highlights for the Clinician *(continued)*

- ✦ Researchers and clinicians have used lithium, carbamazepine, valproic acid, and, more recently, gabapentin, lamotrigine, and topiramate to treat the impulsivity, aggression, and mood instability in patient populations.
- ✦ Monoamine oxidase inhibitors (MAOIs) have not been shown to decrease the behavioral dyscontrol or impulsivity seen in BPD. Further, in BPD patients, overdosing on psychotropic agents is a common form of suicide, and MAOIs are clearly dangerous in these situations.
- ✦ Although they are clearly effective for depressive symptoms, tricyclic antidepressants have not been shown to be particularly helpful in decreasing aggression and impulsivity in BPD. Further, the potential for worsening impulsive, aggressive symptoms and the danger of overdose in patients who have impaired self-control may limit the use of tricyclic antidepressants.
- ✦ Neuroleptics are among the most studied medications for treatment of BPD, and they have been effective in treating violence associated with psychosis. However, neuroleptics are often chronically misused as sedatives and may not be well tolerated. Despite the efficacy of these agents, clinicians should keep in mind that neuroleptics may result in a number of adverse side effects.
- ✦ Mood stabilizers/anticonvulsants such as valproate (divalproex), carbamazepine, topiramate, gabapentin, and lamotrigine have been effective in treating impulsivity and aggression in patient populations, in particular BPD patients.

Treatment in the developmentally disabled

- ✦ Autistic disorder and mental retardation are often associated with impulsive outbursts, emotional lability, rage episodes, and aggression toward self and others.
- ✦ Various treatments have been shown to be effective in treating aggressive and impulsive symptoms (included self-harm) in these populations. These treatments include fluoxetine, lithium, β-blockers (which also bind to 5-HT_1–like receptors, such as propranolol), carbamazepine, divalproex sodium (valproate), risperidone, and buspirone (a 5-HT_{1A} agonist).
- ✦ Eltoprazine, a phenylpiperazine derivative and mixed 5-HT_1 agonist, has shown antiaggressive properties in animal models.
- ✦ Eltoprazine-like compounds may be used in future treatment strategies and as a probe to further study the basis of impulsivity and aggression.

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