Neurobiology of Impulsivity and the Impulse Control Disorders

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Clinical impulsivity has been characterized in both dimensional and categorical terms. Whereas DSM-III-R classifies personality disorders characterized by impulsivity and impulse control disorders as discrete entities, impulsive symptoms and traits can also be conceived in terms of an underlying behavioral dimension. The authors review research on impulsivity and the impulse control disorders from a biological perspective. In particular, they critically review evidence that the serotonin neurotransmitter system mediates symptoms and traits of impulsive personality disorders and the impulse control disorders.

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Impulsivity has long been seen both as an important clinical problem[1,2] and a core dimension of human personality.[3,4] More recently, research on impulsivity has been encouraged by several factors. First, operational criteria have been provided by DSM-III and DSM-III-R[5] for Axis I disorders with impulse control symptoms (intermittent explosive disorder, kleptomania, pathological gambling, pyromania, trichotillomania) and for Axis II disorders with impulsive traits (borderline personality disorder, antisocial personality disorder). Second, there have been advances in the psychometrics of impulsivity.[6–8] Third, neurobiological work has suggested that impulsive symptoms and traits may have similar underlying mechanisms and pharmacotherapeutic responses.[9]

In this article we provide a critical review of the neurobiological research on impulsivity, focusing in particular on work on the serotonin neurotransmitter system. We discuss research that has focused on impulsivity as a dimension of personality or behavior, then describe research on the specific categories of impulse control disorders. Before considering these neurobiological studies, however, we briefly discuss the dimension of impulsivity and the categories of impulse dyscontrol.

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PHENOMENOLOGY

The well-known tension in psychiatric nosology between dimensional and categorical approaches is evident in work on impulsivity and the impulse control disorders. There is a long tradition of regarding impulsivity symptoms and traits as important in a number of different psychiatric disorders. Bleuler,[10] for example, described impulsive traits in various personality disorders. More recently, researchers have suggested that impulsivity is a core behavioral or personality dimension that plays an important role in a spectrum of different disorders.[3,4,9]

On the other hand, there is also an important body of work on disorders characterized specifically by impulsivity. DSM-III-R,[5] for example, lists the essential features of disorders of impulse control as:

1. Failure to resist an impulse, drive, or temptation to perform some act that is harmful to the person or others. There may or may not be conscious resistance to the impulse. The act may or may not be premeditated or planned.
2. An increasing sense of tension or arousal before committing the act.
3. An experience of either pleasure, gratification, or release at the time of committing the act. The act is ego-syntonic in that it is consonant with the immediate conscious wish of the individual. Immediately following the act there may or may not be genuine regret, self-reproach, or guilt.

DSM-III-R includes only five disorders in the section on disorders of impulse control not elsewhere classified. However, the residual category of impulse control disorders NOS (not otherwise specified) may include repetitive self-mutilation, compulsive shopping, and compulsive sexual behavior.

Dimensional and categorical nosological approaches are not necessarily contradictory. Frosch and Wortis,[1] for example, suggest that impulsivity is characterized by ego syntonicity, a pleasurable component, minimal distortion of the original impulse, and irresistibility. They then divide the impulse disorders into two groups. The first is characterized by discrete symptoms and includes the impulsion neuroses (kleptomania, pyromania, addiction); the perversions or impulsive sexual disorders; and catathymic crises (where an isolated and sudden act of violence takes place). The second is characterized by a diffuse impulse disturbance that permeates the personality without attaching itself to any one kind of impulse. Similarly, those who favor a dimensional view of impulsivity might note that the DSM-III-R criteria for disorders of impulse control also characterize other disorders, such as psychoactive substance abuse, paraphilias, and bulimia—disorders that are not specifically grouped together in DSM-III-R. Furthermore, these criteria may also characterize certain behaviors, such as aggressive and autoaggressive acts. Finally, the DSM-III-R criteria may apply to certain Axis II disorders and traits. The criteria for borderline personality disorder include impulsivity itself; inappropriate, intense anger or lack of control of anger; and recurrent suicidal threats, gestures, or self-mutilating behavior. The criteria for antisocial personality disorder include impulsivity itself; irritability and aggression; and reckless regard of personal safety.

It is tempting to suggest that the phenomenological similarity between a diffuse impulse disturbance and specific impulse control disorders is based on similar underlying mechanisms. However, the heterogeneity of these impulsive symptoms and traits suggests that this may be an overly simplistic model. Neurobiological studies, reviewed in the next sections, may prove helpful in determining the relationship between these disorders.

NEUROBIOLOGY OF IMPULSIVITY

In this section we review neurotransmitter research that has focused on impulsivity as an underlying personality or behavioral dimension. Much of this work has used aggressive and autoaggressive (suicidal) behaviors as an index 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).

Serotonin Studies

It has been suggested that all animals across phylogenetic levels share a basic behavioral feature: the presence of a behavioral facilitation system that mobilizes an animal's behavior toward active engagement with the environment and a behavioral inhibition system that arrests ongoing behavior.[11-13] The experimental anxiety paradigms of punishment, extinction, and novelty provide a method of studying the neurobiology of behavioral inhibition.[11-13]

Researchers have concluded, after manipulation of central neurotransmitters in these paradigms, that serotonergic neurons play a role in behavioral inhibition. Specifically, decrease in serotonergic transmission leads to an inability to adopt passive or waiting attitudes, or to accept situations that necessitate or create strong inhibitory tendencies.[12] For example, serotonin (5-hydroxytryptamine; 5-HT) synthesis inhibitors and serotonin receptor antagonists counteract the suppressive effects of punishment, and their effects are reversed by

injection of a serotonin precursor or by a serotonin reuptake inhibitor.[11] This preclinical work provides an impetus to explore the role of serotonin in human impulsivity.

An important series of studies by Brown et al.[14,15] demonstrated a decrease in 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) in patients with personality disorder and found that this decrease correlated with scores on a lifetime aggression scale. Subsequent studies[16-24] have confirmed a relationship between CSF 5-HIAA level and impulsive or aggressive behaviors (Table 1). The work of Linnoila et al.[18] is of particular interest insofar as it specifically divided aggressive behaviors into impulsive and nonimpulsive forms, and CSF 5-HIAA level was correlated with only impulsive aggression.

Other measures of serotonin confirm the involvement of the serotonin system in impulsive aggression. Lower serum ratios of tryptophan to other neutral amino acids, suggestive of serotonin deficiency, are found in alcoholics arrested for assaultive behavior compared with other alcoholics or nonalcoholic control subjects.[25] In children and adolescents with conduct disorder, there is a negative correlation between platelet imipramine binding and impulsive aggression.[26,27] Low monoamine oxidase activity has been found in a variety of disinhibitory syndromes and is correlated with impulsive aggression.[28] Platelet uptake of serotonin is inversely correlated with impulsivity in aggressive subjects.[29]

More recently, neuroendocrine challenge studies have confirmed a role for serotonin in impulsive aggression (Table 2). Coccaro et al.[30] administered fenfluramine to personality disorder patients and found that prolactin response (a measure of net serotonin function) correlated inversely with impulsive aggression. Personality disorder patients challenged with *m*-chlorophenylpiperazine (m-CPP), a putative postsynaptic serotonin agonist, also demonstrated a blunted prolactin response that correlated inversely with impulsive aggression.[31] Hollander et al.[32] demonstrated blunting of prolactin response to m-CPP in borderline patients. Finally, patients challenged with buspirone, a 5-HT_{1A} agonist, demonstrated a blunted prolactin response that correlated inversely with irritability.[33] Moss et al.[34] found that in antisocial personality disorder patients with substance abuse there was a blunted prolactin response to m-CPP that correlated with measures of assaultive aggression but not with other measures of impulsivity. Only one study has failed to replicate the finding of blunted prolactin response; Fishbein et al.[35] found an increased prolactin response to fenfluramine in impulsive substance abusers.

The literature on serotonin and suicide brings another dimension to the relationship between serotonin and impulsive aggression. Early postmortem studies found that brainstem levels of serotonin or 5-HIAA are decreased in suicide victims, and subsequent studies confirm that decreased serotonin and/or 5-HIAA in brainstem (raphe nuclei) and/or subcortical nuclei (hy-

TABLE 1. Studies of CSF 5-HIAA and impulsive aggression

Authors	Population/Diagnosis	Measure
Brown et al.[13,15]	Personality disorder (military)	↑ aggression
Bioulac et al.[16,17]	Personality disorder XYY (prisoners)	—
Linnoila et al.[18]	Personality disorder (prisoners)	↑ antisocial and explosive personality disorders
Lidberg et al.[19,20]	Murderers	↑ emotional and violent murders
Schalling et al.[21]	Patients, volunteers	↑ impulsivity
van Praag[22]	Depression	↑ aggression
Roy et al.[23]	Volunteers	↑ hostility
Kruesi et al.[24]	Disruptive behavior disorders	↑ aggression

Note: CSF = cerebrospinal fluid; 5-HIAA = 5-hydoxyindoleacetic acid; ↑ = increased.

TABLE 2. Pharmacological challenges in impulsive patients

Authors	Diagnosis	Measure	Response
Coccaro et al.[30]	Personality disorders	↑ impulsive aggression	↓ prolactin response to fenfluramine
Coccaro et al.[31]	Personality disorders	↑ impulsive aggression	↓ prolactin response to m-CPP
Hollander et al.[32]	Borderline personality disorder	—	↓ prolactin response to m-CPP
Coccaro et al.[33]	Personality disorders	↑ impulsive aggression	↓ prolactin response to buspirone
Moss et al.[34]	Antisocial personality and substance abuse	↑ assaultive aggression	↓ prolactin response to m-CPP

Note: ↑ = increased; ↓ = decreased; m-CPP = *m*-chlorophenylpiperazine.

pothalamus) are the most consistent postmortem changes in suicide completers.[36]

Stanley and Mann[37] found reduced imipramine binding in the brains of suicide completers, and this finding has been replicated in the majority of subsequent studies. Imipramine binding is thought to be associated with presynaptic binding sites, and reduced imipramine binding may indicate a decrease in functional serotonergic terminals, with consequent reduction in serotonin release. Further, Stanley et al.[38] found an increase in 5-HT_2 binding in suicide victims, a finding again replicated in the majority of subsequent studies. An increase in 5-HT_2 binding may reflect the brain's reaction to a decrease in functional serotonergic neurons, with consequent upregulation of postsynaptic serotonin binding sites.

Asberg et al.[39] found that in depressed subjects with low CSF 5-HIAA there was an increased incidence of committed or attempted suicide by violent means. Subsequent studies on populations from Scandinavia,[40,41] the United States,[42] Holland,[43,44] Britain,[45] India,[46] Hungary,[47,48] and Spain[49] have confirmed that suicidal depressed patients have lower CSF 5-HIAA than nonsuicidal depressed patients. Studies in which suicidal depressed patients do not have lower CSF 5-HIAA tend to have more bipolar patients.[50,51] Furthermore, studies by Oreland et al.,[52] Traskman et al.,[53] van Praag et al.,[43,44] and Banki et al.[47,48] on suicidal patients with a variety of diagnoses indicate that the association between CSF 5-HIAA level and suicidal behavior holds particularly in those with violent suicide attempts.

Suicide has also been measured in some of those studies of impulsive aggression mentioned earlier. The work of Brown et al.,[13,15] Linnoila et al.,[18] Lidberg et al.,[19,20] and van Praag[43,44] demonstrated lower CSF 5-HIAA in subjects with increased suicidal behavior. Although Gardner et al.[54] did not find increased violence in borderline patients with low CSF 5-HIAA, these patients did have increased suicide attempts. In the study by Coccaro et al.,[30] blunted neuroendocrine responses to fenfluramine were correlated with a history of suicide attempts in both depressed and personality disorder patients but were associated with impulsive aggression in personality disorder patients only.

Other Neurotransmitters

Although the studies reviewed above provide strong evidence for the involvement of serotonin in impulsivity, other neurotransmitter systems may also play a role. In animal models, for example, manipulation of the dopaminergic[55] and noradrenergic[56] systems directly affects aggression.

There is work that indicates the involvement of these neurotransmitters in human impulsivity as well. Cloninger[57] has emphasized the interaction of the different neurotransmitter systems in producing personality variation. He theorizes that impulsivity primarily involves serotonergically mediated behavioral disinhibition and dopaminergically mediated novelty seeking. Similarly, King[58] has suggested that mesolimbic dopamine determines response thresholds and is therefore responsible for variations in impulsivity versus inhibition. Indeed, Barratt[59] found that high-impulsive volunteers perform significantly more spontaneous eye-blinks than do low-impulsive ones, suggesting changes in the dopamine system. In preliminary work, King et al.[60] found that histrionic traits in DSM-III-R personality disorder patients tend to correlate with CSF dopamine.

Evidence also exists for the role of the noradrenergic system in impulsivity. Brown et al.[13] found that CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) correlated with a history of aggressive behavior in one sample of personality disorder subjects, but the researchers did not replicate this finding in a second study.[15] Coccarro et al.[61] found a correlation between irritability and growth hormone response to the $alpha_2$-noradrenergic agonist clonidine in personality disorder patients and volunteers.

Suicidal behavior may also involve a variety of neurochemical systems.[36] Most postmortem studies have shown increased beta-adrenergic receptor binding in the prefrontal/temporal cortex in many subjects, although this finding has not been consistent.[62] Conversely, there appears to be reduced $alpha_1$-noradrenergic receptor binding in the prefrontal/temporal cortex and caudate nucleus.[63]

Treatment

Controlled pharmacotherapy studies suggest that a number of medications may be useful in the treatment of impulsivity (Table 3). Notably, many of these medications act on the serotonin system. Lithium, for example, was one of the first psychotropics shown to be valuable in reducing impulsive aggressive behaviors in different psychiatric disorders.[64] Controlled trials include work with aggressive prisoners,[65] "emotionally unstable characters,"[66] and patients with borderline personality disorder.[67] The complex neurotransmitter effects of lithium include an effect on second messengers related to the serotonin system. Similarly, carbamazepine, another medication with complex effects, was found in a controlled study to reduce behavioral dyscontrol in borderline personality disorder.[68] Beta-blockers, which also bind to 5-HT_1–like receptors,[69] have been found in open trials to lead to improvements in aggressive patients with neuropsychiatric disorders[70,71] and in patients with impulsive aggression.[72]

More recently, several trials have focused on the use of specific serotonergic medication in the treatment of impulsivity. An open trial of fenfluramine led to decreased suicidal behavior in patients with different diagnoses.[73] Tryptophan was found useful by Bioulac et al.[16,17] in treating aggression in XYY prisoners, and a controlled trial of tryptophan led to a decrease in the need for antipsychotics and sedatives in aggressive inpatients with different diagnoses.[74] Several open studies of fluoxetine have indicated that it is effective in the treatment of patients with borderline personality disorder,[75–78] reducing impulsive aggression and self-injury. Buspirone, a 5-HT_{1A} agonist, may be effective in the treatment of aggression in neuropsychiatric conditions,[79] but there is preliminary work indicating that it is not effective in the treatment of borderline personality disorder.[80]

On the other hand, medications that do not act on the serotonin system may also be useful. Neuroleptics have been useful in decreasing a variety of symptoms in personality disorder, including hostility and suicidality.[45,70,81–83] There may also be a role for various antidepressants,[70] anxiolytics,[84–86] and anticonvulsants.[87,88] The reduction of dysphoria may lead to reduction of impulsivity secondary to dysphoria,[70,89] but antidepressants do not necessarily decrease impulsivity per se.[90,91]

Summary

The studies detailed above include a wide variety of disorders. The convergence of their findings on the possible importance of serotonin dysfunction in impulsivity is therefore particularly impressive. Taken together, the studies suggest the value of positing a dimension or spectrum of impulsivity that is neurobiologically based. Serotonin is, however, a complex neurotransmitter system with multiple receptor subtypes and complex interactions with other neurotransmitter systems, and the serotonin hypothesis of impulsivity is therefore perhaps best conceived of as an initial heuristic research model rather than a definitive model. Furthermore, the limited number of controlled studies of serotonergic medications limits conclusions about their efficacy in the treatment of impulsivity.

NEUROBIOLOGY OF IMPULSE CONTROL DISORDERS

Neurobiological research on the DSM-III-R impulse control disorders is in its infancy (Table 4). In this section we discuss the five categories specified in DSM-III-R. We also discuss self-mutilation, the best studied of the impulse control disorders NOS. As noted earlier, diagnoses such as substance use disorder and bulimia may also meet the DSM-III-R criteria for impulse control disorders. A review of the neurobiology of these disorders is, however, beyond the scope of this article.

Several of the studies discussed in the first part of this article used subjects who displayed no evidence of overt neurological dysfunction and who therefore may have met criteria for intermittent explosive disorder. Thus, there is perhaps tentative evidence of decreased CSF 5-HIAA and of response to serotonergic and other medications in this group of patients. Fava et al.[92] have described the use of serotonergic antidepressants for anger attacks in a few patients. A more comprehensive study by Mattes[93] found that carbamazepine was more effective than propranolol in reducing rage outbursts in patients with intermittent explosive disorder.

TABLE 3. Controlled pharmacotherapy studies relevant to impulsivity

Authors	Diagnosis	Medication	Outcome
Fink et al.[81] & Klein[82]	Emotionally unstable character	Chlorpromazine	↓ affective instability
		Imipramine	↑ anger
Stephens & Shaffer[87]	Anxiety neurosis	Phenytoin	↓ hostility
Rifkin et al.[66]	Emotionally unstable character	Lithium	↓ affective instability
Sheard et al.[65]	Personality disorders (prisoners)	Lithium	↓ aggression and anger
Montgomery & Montgomery[45]	Personality disorder and parasuicide	Flupenthixol	↓ suicide attempts
Montgomery et al.[90]	Personality disorder and parasuicide	Mianserin	no ↓ suicide attempts
Hirsch et al.[91]	Parasuicide	Nomifensine or mianserin	no ↓ suicide attempts
Soloff et al.[83]	Borderline personality disorder	Haloperidol	↓ hostility, impulsivity
Cowdry & Gardner[68]	Borderline personality disorder	Carbamazepine	↓ behavioral dyscontrol
		Tranylcypromine	trend to ↓ behavioral dyscontrol
		Trifluoperazine	↓ suicidality
		Alprazolam	↑ behavioral dyscontrol
Volavka et al.[74]	Aggressive inpatients	Tryptophan	↓ need for antipsychotics and sedatives
Links et al.[67]	Borderline personality disorder	Lithium	↓ global symptoms
Wolf et al.[80]	Borderline personality disorder	Buspirone	no ↓ global symptoms

Very little neurobiological research has been done on kleptomania,[94] and there are no controlled treatment studies of kleptomania. Nevertheless, there is some anecdotal evidence that this disorder does respond to various antidepressants, including those acting on the serotonin system.[95]

Pathological gamblers have greater CSF MHPG but similar CSF 5-HIAA levels compared with control subjects.[96] Nevertheless, pharmacological challenge with clomipramine revealed blunted prolactin response in pathological gamblers.[97] Furthermore, there are reports of the use of lithium in this disorder.[98] Our group has found that clomipramine may be useful in the treatment of pathological gambling.[99]

Virkkunen et al.[100] found lower CSF 5-HIAA and MHPG in fire setters compared with violent offenders and normal control subjects. All the arsonists in the study met DSM-III criteria for borderline personality disorder, and many exhibited occasional explosive behavior, usually after consuming alcohol.

Little work has been done on the neurochemistry of trichotillomania. One controlled trial showed preferential response to a predominantly serotonergic reuptake blocker compared with a predominantly noradrenergic reuptake blocker.[101] However, a later controlled study found that fluoxetine was not useful.[102] Anecdotal reports suggest that serotonin reuptake blockers may be effective only in the short term.[103,104] Our own experience is that low doses of pimozide, a dopamine antagonist, may be useful in augmenting the response to serotonin reuptake blockers.[104]

Of the disorders classified as impulse control disorders NOS, substantial research has been done only on self-mutilation. Lopez-Ibor et al.[49] found that in patients with major depression, those with "self-injuries that do not constitute a vital threat" had lower CSF 5-HIAA concentrations than other patients. Simeon et al.[105] found that in personality disorder patients, self-mutilation and impulsivity showed a significant negative correlation with the number of platelet imipramine binding receptor sites. However, self-mutilators did not differ from nonmutilators in CSF 5-HIAA level or in platelet imipramine binding. There have been case reports that serotonin reuptake blockers are useful in the treatment of self-mutilation,[106,107] but these patients had comorbid obsessive-compulsive disorder. Several medications, including lithium, have been used to treat self-injurious behavior in the mentally retarded.[54] In an open study of personality disorder, Markovitz et al.[78] found that fluoxetine led to decrease in self-mutilation. Indirect evidence for the role of the opiate and the dopamine systems in self-mutilation has recently been reviewed by Winchel and Stanley.[108]

In summary, studies of the neurobiology of the impulse control disorders show both similarities and differences among the disorders themselves and between these disorders and the dimension of impulsive behavior and personality. The serotonin hypothesis of impulsivity again appears to have heuristic value, but the relative lack of work on the neurobiology of the impulse control disorders makes any conclusions about their mechanisms tentative.

CONCLUSIONS

This article has not addressed the role of psychological mechanisms in impulsivity and the impulse control disorders.[6,109,110] It is not unlikely, however, that different kinds of psychological mechanism result in different forms of clinical impulsivity. Further work on this aspect of the pathogenesis of impulsivity is necessary to complement the neurobiological research on which this review has focused.

TABLE 4. Neurobiology of the impulsive disorders

Disorder	CSF Metabolite Status	Pharmacological Challenge Outcome	Controlled Trials Outcome
Intermittent explosive disorder	↓ 5-HIAA ↓ MHPG[100]	—	Carbamazepine response[92]
Kleptomania	—	—	—
Pathological gambling	no ↓ 5-HIAA ↓ MHPG[96]	Blunted serotonergic response[97]	—
Pyromania	↓ 5-HIAA ↓ MHPG[100]	—	—
Trichotillomania	—	—	Clomipramine response[101] Fluoxetine nonresponse[102]
Self-mutilation	↓ 5-HIAA[49] no ↓ 5-HIAA[105]	—	—

Note: CSF = cerebrospinal fluid; 5-HIAA = 5-hydroxyindoleacetic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol.

The concept that impulsivity is a failure in serotonergically mediated behavioral inhibition has proved remarkably fertile. Despite the disagreement on how best to classify and measure impulsive symptoms, there has been notable convergence on the conclusion that impulsive aggression and autoaggression correlate with serotonergic hypofunction and respond to treatment with serotonin reuptake blockers. Further controlled trials are, however, warranted. The development of more specific serotonin agonists and antagonists may lead to future treatment advances.

Neurobiological studies of the impulsive disorders have not progressed far. Early work indicates that serotonin dysfunction may be a component of many of them, but other neurotransmitters may also be involved. Further neurobiological research will be necessary to elucidate their relationship to one another and to the impulsivity dimension.

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