# COMPULSIVE AND IMPULSIVE ASPECTS OF SELF-INJURIOUS BEHAVIOR

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Self-injurious behavior (SIB) is seen in a range of different psychiatric disorders, including stereotypic movement disorder, Tourette's disorder, borderline personality disorder, and psychotic disorders. An immediate question is to what extent similar psychobiological mechanisms mediate SIB across so diverse a spectrum of conditions. It has been argued that specific neurobiological mechanisms may be responsible for various symptoms across diagnostic categories; could the same hold true for self-injurious behaviors?

A closer exploration of the phenomenology of SIB suggests that there are a number of distinct types of self-mutilation (1). "Compulsive" self-injurious behavior is arguably exemplified by the stereotypic self-injurious behavior of stereotypic movement disorder (SMD). By definition, such behavior is composed of repetitive, seemingly driven, but nonfunctional motor behavior. Stereotypical SIB is also seen in a range of specific syndromes, including Lesch-Nyhan syndrome, Cornelia de Lange syndrome, and Prader-Willi syndrome. Although SMD is commonly encountered in patients with developmental disabilities, there is also evidence of it in intellectually normal adult samples (2), in the form of behaviors such as skin picking and nail biting.

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) specifically excludes from the diagnosis of SMD the repetitive self-injurious symptoms of a range of other disorders such as pervasive developmental disorder, Tourette's disorder, and trichotillomania. Some of these behaviors arguably have an "impulsive" component in that they are preceded by increasing tension, and followed by pleasure, gratification, or relief. Similarly, certain self-injurious behaviors, perhaps predominantly in personality-

disordered patients, can plausibly be described as "impulsive" in nature. This phenomenologic distinction between "compulsive" and "impulsive" is intended only to be heuristic; clinically, there may be significant overlap, with the impulsive wrist-cutter, for example, going on to develop apparently compulsive repetitive SIB.

This chapter briefly reviews work from animal studies of SIB, including animal stereotypies and veterinary behavioral disorders, before going on to consider the neuropsychopharmacology of a range of clinical disorders characterized by SIB. These include SMD in developmentally disabled patients, specific syndromes characterized by stereotypic SIB, SMD in intellectually normal patients (e.g., skin picking, nail biting, etc.), Tourette's disorder, autistic disorder, trichotillomania, and impulsive SIB in predominantly personality-disordered patients. Throughout the chapter we follow a schema of reviewing phenomenology, neurochemistry, and neuroanatomy in turn.

#### **ANIMAL STEREOTYPIES**

#### **Phenomenology**

Stereotypy may be defined as the excessive production of one type of motor act (3). Stereotypic behavior is species specific, with common behaviors including grooming, gnawing, and pacing. A subset of these stereotypies are self-injurious; these include excessive grooming and self-biting. Animal stereotypies can be induced by confinement (e.g., to a small enclosure) and by deprivation (e.g., being reared alone). Deprivation stereotypies are more likely to result in SIB (4), particularly in higher mammals (3).

#### **Neurochemistry**

Animal research on stereotypic self-injurious behavior has highlighted the role of the dopaminergic, serotoninergic,

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and opioid systems. These systems also have important interactions with one another. Nevertheless, for the sake of simplicity, we list studies on each system in turn.

Early work with rodents demonstrated that amphetamines act to produce an increase in stereotypic behavior (5), including automutilation (6), and such findings have been replicated with different dopamine agonists in different species. These responses are prevented by 6-hydroxy-dopamine–induced lesions or by dopamine antagonists (7, 8), perhaps particularly by D1 antagonists (9,10). Furthermore, early destruction of dopaminergic neurons may lead to hypersensitivity of D1 receptors, with increased self-biting behavior in response to later administration of dopamine agonists (11).

Traditional serotonin models include the administration of a monoamine oxidase inhibitor with L-tryptophan to induce a hyperactivity syndrome in rats, and the use of 5-hydroxytryptophan to induce the head-twitch syndrome in mice and the wet dog shake in rats. Reviewing this literature, Jacobs and Fornal (12) conclude that serotonin facilitates gross motor output and inhibits sensory information processing. Certainly, isolation may be associated with decreased serotonin turnover (13). Furthermore, in confining or depriving environments, the animal may activate dorsal raphe neurons by performance of stereotypies (12).

In animal work, opioid agonists may induce autoaggression, and opioid antagonists may be particularly effective in reducing self-injurious stereotypies in younger animals (14). Indeed, it has been suggested that excessive opioid activity is responsible for SIB (15). However, an alternative hypothesis emphasizes that pain associated with SIB results in the release of brain endorphins and draws a parallel between such endogenous release of endorphins and addiction to an exogenous substance (16).

From an integrated brain-mind perspective, interactions and overlaps between environmental and pharmacologic inducers of stereotypy would be predicted. Indeed, compared to normally reared rodents, isolation-reared subjects show increased stereotypic responses after administration of amphetamine (17) or tail-pinch (18).

#### **Neuroanatomy**

There is evidence that corticostriatal circuits are important in mediating stereotypic behavior (3). First, infusion of the dopamine into the caudate results in stereotyped orofacial behaviors (grooming, gnawing). Conversely, infusion of dopamine blockers into the same areas reduces amphetamine-induced stereotypy. Second, frontal lesions and dopamine agonists produce similar behavioral and cognitive effects, and frontal lesions exacerbate the effects of these agents. Furthermore, striatal lesions may also lead to stereotypic behavior. Reviewing this literature and his own work, Ridley (3) concludes that loss of inhibition induced by frontal lesions results in a release of previously stored response se-

quences. This view is consistent with a view of striatal function that emphasizes the development, maintenance, and selection of motoric and cognitive procedural strategies. Different terms given to allude to this group of functions have included habit system, response set, and procedural mobilization (19).

#### **VETERINARY BEHAVIORAL DISORDERS**

#### **Phenomenology**

In addition to animal laboratory studies, there is an interesting literature on veterinary behavioral disorders characterized by SIB (20). Acral lick dermatitis, for example, is a condition characterized by excessive paw licking and scratching in dogs. This results in the characteristic dermatitis; in severe cases sequelae include osteomyelitis. The disorder is seen in certain breeds of large dog, and within breeds may be more common in particular families.

Different species may manifest a range of different kinds of SIB (20). Psychogenic alopecia is found in cats, with excessive depilation leading to bare patches. Feather-picking in birds is seen in a range of avian species, and can be complicated by severe hemorrhage. Although stereotypies may appear to arise spontaneously in companion and domestic animals, as in laboratory animals, confinement and deprivation are robust elicitors of stereotypic and self-injurious behavior.

#### Neurochemistry

The pharmacotherapeutic profile of acral lick dermatitis overlaps remarkably neatly with that of obsessive-compulsive disorder (OCD) (21). Thus, the disorder responds to selective serotonin reuptake inhibitors (SSRIs), but fails to respond to desipramine or fenfluramine. However, the disorder may also respond to opioid agents. Although not well studied pharmacologically, there are a number of reports indicating that psychogenic alopecia responds to treatment with SSRIs. In addition, administration of a dopamine blocker has been noted to lead to a decrease in symptoms. Similarly, feather-picking in birds and SIB in horses may respond to treatment with SSRIs (20).

We noted earlier the cross-sensitization between pharmacologic and environmental inducers of stereotypies (22). Conversely, it can be emphasized that environmentally induced SIB may respond to psychopharmacologic intervention. For example, in a placebo-controlled study of fluoxetine in isolation-reared primates, this SSRI was effective in reducing such symptoms (23).

#### **Neuroanatomy**

In the previous section, the possible involvement of frontostriatal circuits in animal stereotypic behavior was noted. With regard to stereotypic SIB in higher mammals, a particularly interesting finding is that socially isolated primates develop striatal cellular disorganization together with stereotypic and self-injurious behaviors (24). The neuroanatomy of early social isolation and other developmental stressors would seem to be a promising area for further investigation, one that may have direct relevance to some of the clinical disorders considered in the next part of this chapter.

## SMD IN DEVELOPMENTAL DISABILITY Phenomenology

SIB in patients with developmental disabilities may fall within the diagnostic category of SMD. This disorder is characterized by repetitive, seemingly driven, but nonfunctional motor behavior. Examples include body rocking, hand waving, head banging, and skin picking. The DSM-IV provides a subtype "with self-injurious behavior," to be used when bodily damage requires medical treatment. We have reviewed this disorder elsewhere (25,26), and draw extensively on those reviews here.

A number of the DSM-IV criteria for SMD address the severity of the behavior. It must "markedly interfere with normal activities" or result in "bodily injury that requires medical treatment." In patients with developmental disability the behavior must be sufficiently severe to be a focus of treatment, and the behavior must persist for at least 4 weeks. The DSM-IV also states that stereotypic behaviors in SMD should not be better accounted for by the compulsions of obsessive-compulsive disorder, the stereotypies of pervasive developmental disorder, or the tics of Tourette's disorder.

SIB in patients with developmental disability may not always meet the rather strict DSM-IV criteria for SMD. Nevertheless, there is evidence that stereotyped, self-injurious, and compulsive behaviors appear to be correlated in such patients (27). Certainly, the relatively large body of work on the pathogenesis and treatment of stereotypic behaviors in this population may be useful in understanding and managing SIB.

Reports of the incidence of SIB in patients with developmental disability range from 3% to 46% (27,28). Head banging, head and body hitting, eye gouging, biting, and scratching are the most common of these behaviors (29). Behaviors may cause permanent and disabling tissue damage and may sometimes be life threatening. For example, severe head banging or hitting may lead to cuts, bleeding, infection, retinal detachment, and blindness. Incidence of SIB in patients with developmental disability is dependent on a number of factors that vary within this heterogeneous population, including extent of cognitive impairment (29) and institutionalization status (28).

#### **Neurochemistry**

It has been argued that there is phenomenologic evidence of similarities between SIB in patients with developmental disability and symptoms in patients with OCD (28). Furthermore, as noted earlier, in patients with developmental disability, there are significant positive associations between the occurrence of self-injury, stereotypy, and compulsions (27). Nevertheless, relatively few studies have directly explored the role of serotonin in mediating SIB in such patients.

There is, however, some evidence of the value of SSRIs in the treatment of SIB in developmental disabled patients. A retrospective review suggested that response of SIB in such patients was higher for SSRIs and was not predicted by comorbid depressive symptoms (30). Indeed, both open and controlled (31) studies have confirmed the efficacy of SSRIs in the treatment of SIB in developmental disabilities. Although this research is consistent with a role for serotonin in the mediation of SIB in mental retardation, questions remain about whether the effects of these agents are not "downstream" of their primary actions and about their specificity. Several methodologies are available for delineating different aspects of serotonin dysfunction in psychiatric patients, and the "pharmacologic dissection" strategy of comparing responses to clomipramine and desipramine has been useful in showing that serotonin plays a specific role in several disorders characterized by unwanted repetitive and/or self-injurious behaviors (32,33). A similarly designed study in mental retardation patients with SIB would be of interest.

It may be noted here that other agents with serotoniner-gic effects have also been studied for the treatment of SIB in developmental disability (28,34). 5-Hydroxytryptophan (5-HT) has been shown useful in only a minority of open studies. Buspirone (15 to 45 mg/day), a 5-HT<sub>1A</sub> agonist, has been somewhat effective in small groups of adults with developmental disability and SIB. Eltoprazine, a selective 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> agonist, has yielded conflicting evidence of efficacy.

A number of agents, such as lithium and beta-blockers, have multiple neurotransmitter effects including serotoninergic effects. Although early studies in this area suffered from methodologic flaws, lithium has long been used with some apparent success in the treatment of SIB and aggressive behaviors in patients with mental retardation (28,34). Propranolol (90 to 410 mg/day) was reported to reduce SIB and aggression in a small case series of patients with mental retardation. Also, in a controlled study, pindolol (40 mg/day) was significantly more effective than placebo in 14 patients with developmental disability and SIB (35).

There has been relatively little direct work on the dopamine system in patients with developmental disability and SIB. Dopamine blockers, however, are often successfully used to manage SIB in such patients (28,34). Preliminary evidence suggests that the atypical neuroleptics, which have both dopaminergic and serotoninergic effects, may also be useful in SIB and other target symptoms in this patient population (36,37). Given their apparently favorable side-

effect profile, controlled trials with such agents are warranted.

Increased plasma enkephalin levels in patients with developmental disability compared with normal controls have been reported (38). Although this may support the excessive opioid hypothesis, it is also possible that decreased endogenous brain opioid levels ultimately lead to compensatory overproduction (39). It has also been argued, however, that opioid effects on self-injury may be primarily mediated via the dopamine or serotonin system (28).

There is some evidence that the opiate antagonists naloxone and naltrexone lead to a reduction in frequency of self-injury in different patient populations, including those with developmental disability (28,34). However, the total number of patients in such studies is relatively small, and the study designs have been criticized (39,40). Indeed, in a placebo-controlled study of 32 subjects with mental retardation and SIB and/or autism, naltrexone (50 mg/day) failed to have an effect on SIB and increased the incidence of stereotypic behavior (40). Although this finding does not entirely rule out a role for the opioid system, it further emphasizes the need for caution in drawing conclusions from open trials of treatment for SIB.

SIB may vary in women with mental retardation according to the stage of menstrual cycle. In one study, fluctuations in SIB were associated with early and late follicular phases. Although there are currently insufficient data for a specific association between self-injurious behavior and hormonal factors, such an association warrants further attention.

Further attention should perhaps also be paid to the role of the  $\gamma$ -aminobutyric acid (GABA)ergic system in SIB in developmental disability. The use of benzodiazepines in this population has not been well studied. The anticonvulsant valproic acid, however, was effective in reducing SIB and aggression in 12 of 18 patients with mental retardation and affective symptoms in a 2-year open trial (41). Positive response to valproate was associated with a past history of seizure disorder.

## SYNDROMES WITH SELF-INJURIOUS BEHAVIOR

#### Phenomenology

Lesch-Nyhan syndrome (LNS) is an X-linked recessive disorder of purine synthesis. Patients present with hyperuricemia and neuropsychiatric symptoms including spasticity, choreoathetosis, dystonia, mental retardation, aggression, and self-injurious behavior. SIB in LNS is dramatic, and most commonly consists of biting of fingers and lips, although head banging, tongue biting, eye/nose poking, and self-scratching also occur (42).

Cornelia de Lange syndrome (CLS) is a rare congenital disorder characterized by a distinctive appearance and mental retardation. Patients with CLS manifest excessive grooming behavior (hand licking and hair stroking) and SIB including head slapping and self-scratching (43).

Prader-Willi syndrome (PWS) is a congenital disorder that affects approximately 1 in 10,000 newborns and is one of the five commonest abnormalities seen in birth defect clinics (53a,53b). PWS is associated with marked hyperphagia, and the disorder is the most common dysmorphic form of obesity. In addition, PWS is characterized by behavioral disturbances, mental retardation, sleep disturbances, neonatal hypotonia, and hypogonadism. Behavioral disturbances include compulsive self-mutilation, impulsive temper outbursts, and classic obsessive-compulsive behaviors (44,45). SIB is common and not necessarily associated with cognitive impairment (45). It includes skin and nose picking, nail biting, lip biting, and hair pulling (45). Patients frequently have chronic skin sores.

#### Neurochemistry

Both the biochemical abnormality [virtual absence of hypoxanthine-guanine phosphoribosyltransferase (HPRT)] and the underlying genetic defect (a mutation of the HPRT locus located at q26-28 of the X-chromosome) in LNS are well identified. However, the mechanisms underlying neuropsychiatric symptoms are less clear. Nevertheless, the biochemical systems implicated do include the dopaminergic and serotoninergic systems.

Early postmortem findings in three patients with LNS demonstrated dramatically reduced levels of dopamine, homovanillic acid, and dopa decarboxylase in the basal ganglia (46), placing particular emphasis on the dopamine system. Animal studies with HPRT-deficient models and clinical studies of neurotransmitters and metabolite levels in patients with the disorder support the importance of dopaminergic mediation of symptoms (47).

It is interesting to note that although patients with both LNS and Parkinson's disorder demonstrate decreased dopamine neurons and motoric symptoms, there are important differences. Parkinson's disorder, for example, is characterized by diminished motor output, whereas LNS is characterized by uncontrolled and exaggerated motor activity. These differences may reflect the importance of the developmental stage at which dopaminergic deficits occur (11). Although dopamine supersensitivity has also been hypothesized to play a role in SIB in LNS (9), and dopamine blockers have been used for their treatment, long-term treatment with these agents is not clearly of benefit in LNS. Further understanding of the developmental neurobiology underlying this syndrome is therefore needed.

Phenomenologic similarities have been noted between excessive grooming in CLS and animal dopamine agonist-induced stereotypies. Nevertheless, there is little direct research to support a dopamine hypothesis of CLS. Indeed, the underlying neurobiology of this interesting syndrome remains relatively poorly understood.

Research has also focused on the serotonin system in LNS. Studies of cerebrospinal fluid (CSF) 5-hydroxyindol-eacetic acid (5-HIAA) have been inconsistent in LNS, but there may be slightly increased putamen serotonin and 5-HIAA (46). In addition, early reports suggested 5-HT (1 to 8 mg/kg) was useful in the treatment of self-injurious behaviors in LNS. However, only a minority of subsequent studies have confirmed this finding (28).

In an early study, CLS patients were found to have reduced whole blood serotonin levels (48). Several possible mechanisms underlying this finding were considered, including a dysfunction in serotonin metabolism, failure to bind to platelets, and transporter abnormalities. Again, however, putative serotonin dysfunction may simply reflect dysfunction in other systems.

Serotoninergic mediation of PWS is raised by the role of serotonin and the efficacy of serotoninergic agents in appetite control and eating disorders, compulsive skin picking, impulsive aggression, and obsessive-compulsive-related disorders. A double-blind trial of fenfluramine found that this agent was useful for weight loss and other-directed aggressive behavior in PWS patients, but did not affect SIB (49). However, the SSRI fluoxetine has been described as useful for SIB in a number of cases of PWS. Similarly, a survey of caregivers suggested that SSRIs may be helpful for both impulsive-aggressive and compulsive symptoms in some PWS patients (45).

There is relatively little work on other systems in these disorders. GABAergic systems have been postulated to play a role in LNS, but again this hypothesis has not translated into successful pharmacotherapeutic strategies. Opioid antagonists have been reported to decrease appetite in some PWS patients, but controlled work has not supported their efficacy.

Abnormalities of chromosome 15 have been implicated in the etiology of PWS, and recent research using cytogenetic and molecular techniques suggests that identification of a specific genetic basis is possible in most patients. In about 70% of patients a cytogenetically visible deletion can be detected in the paternally derived chromosome 15 (15q11q13), whereas in about 20% of patients both copies of chromosome 15 are inherited from the mother (maternal uniparental disomy). Genotype-phenotype correlations in 167 patients with PWS found no significant difference in skin picking between patients with or without a chromosomal deletion (50). Nevertheless, the abnormal gene product in PWS may ultimately provide crucial information on the neurochemistry of the SIB characteristic of these patients.

#### **Neuroanatomy**

Most recently, volumetric magnetic resonance imaging (MRI) and positron-emission tomography (PET) techniques have documented reduced caudate volume and re-

duced dopamine transporters in caudate and putamen (51) as well as decreased dopa decarboxylase activity and dopamine storage throughout the dopaminergic system in LNS (52). It is possible that in LNS there is reorganization of the cortical-basal ganglia-thalamic pathways during development (52).

A number of authors have suggested hypothalamic-pituitary dysfunction in PWS. Again, however, further work is needed to extend these preliminary findings and to determine the relationship with behavioral symptoms. Indeed, at present little is ultimately understood about the underlying neurobiology of self-injury and other behavioral symptoms in this fascinating disorder.

### SMD IN INTELLECTUALLY NORMAL INDIVIDUALS

#### **Phenomenology**

Skin picking and scratching appear to be not uncommon symptoms (53). The incidence of so-called neurotic excoriations in dermatology clinics has been estimated to be around 2%. Medical complications of skin picking include infection and scarring. Furthermore, skin picking may be associated with significant distress and dysfunction. At times, patients with these behaviors may meet criteria for OCD. However, in many other patients, this is not the case. Skin picking may also be seen in patients with the putative OCD spectrum disorders trichotillomania and body dysmorphic disorder.

Nail biting (onychophagia) is a common behavior that is not, however, necessarily benign (33). Nail biting may be associated with serious infection, nail bed damage and scarring, craniomandibular dysfunction, and dental disorders. The apparent ubiquity of mild nail biting should not discourage clinical and research attention to patients with more severe forms of the behavior.

A range of other common self-injurious stereotypies may be seen in intellectually normal adults including lip biting and eye rubbing (1). Certain kinds of stereotypies, such as thumb sucking and head banging, appear more common in children, although on occasion these behaviors may also be seen in intellectually normal adults (2). In a college population, the total number of stereotypic behaviors was significantly associated with increased scores of obsessive-compulsive symptoms, of perfectionism, and of impulsive-aggressive traits (54). Importantly, stereotypic behaviors may be associated with significant medical complications, and they may also lead to distressing feelings of shame and lowered self-esteem, as well as to social avoidance and occupational impairment.

#### **Neurochemistry**

Case reports suggested that the SSRIs may have a role in the treatment of skin picking. Indeed, in a series of 30 patients with skin picking, an open trial of sertraline demonstrated efficacy (55). Similarly, a retrospective treatment review of body dysmorphic disorder patients with skin picking indicated that SSRIs were often effective, whereas other agents were not (56). Finally, in their controlled study Simeon and colleagues (53) found that fluoxetine was significantly superior to placebo in decreasing compulsive skin picking in intellectually normal patients.

In nail biting, clomipramine appeared more effective than desipramine, although results were not perhaps as robust as those seen in classic OCD (33). The authors emphasized that there was a high dropout rate at every stage of the study, which appeared in sharp contrast to that seen in other psychiatric populations. They did, however, suggest that their data were consistent with the hypothesis that similar biological systems mediate a spectrum of grooming disorders, including OCD and trichotillomania.

Castellanos and colleagues (2) compared clomipramine and desipramine in a crossover trial of SMD patients. Although clomipramine appeared promising in a number of cases, too few patients completed the trial to demonstrate a clear benefit of clomipramine over desipramine. Nevertheless, several case reports suggest that SSRIs may be useful in patients with skin picking, head banging, and other self-injurious stereotypic behaviors (26). Given that dopamine agonists may result in SIB (57), a possible role for dopamine blockers, and the new atypical neuroleptics in particular, also warrants further consideration. Ultimately, controlled and long-term studies are needed to formulate rational approaches to the pharmacotherapy of SMD.

#### Neuroanatomy

To our knowledge, there have been no studies on the neuroanatomy of stereotypic movement disorder in normal controls. Given the ubiquity of these behaviors, and the presumptive role of cortico-striatal-thalamic-cortical (CSTC) circuits, this seems an area that may be worth investigating in more detail.

#### **AUTISM**

#### **Phenomenology**

Autistic disorder (or classic autism) is a pervasive developmental disorder characterized by impairment in social interactions, communication deficits, and restrictive and stereotyped behaviors. Stereotyped SIBs are common in patients with this disorder and may also be seen in other pervasive developmental disorders that do not meet the narrower criteria for autistic disorder (58). Common forms of SIB in autism include hand/wrist biting, head banging, self-scratching, self-hitting, self-pinching, and hair pulling.

It has been argued that repetitive behaviors in autism cannot simply be subsumed under the banner of OCD. Indeed, compared to patients with OCD, adults with autism were found to have a different range of repetitive symptoms. They were more likely to demonstrate repetitive ordering, hoarding, touching, tapping, or rubbing, and self-injurious behaviors (59). Nevertheless, it may be postulated that there are at least some similarities in the underlying neurobiological mediation of autism and OCD.

#### Neurochemistry

There does seem to be evidence of serotoninergic dysfunction in autism (60). Several studies have found elevated platelet serotonin levels in autism. Neuroendocrine challenge studies with serotoninergic agents have indicated reduced serotoninergic responsivity in autism. Furthermore, in a tryptophan depletion study, autism resulted in increased SIB, motor stereotypies, and anxiety.

Despite early reports of the efficacy of fenfluramine in open trials in autism, subsequent controlled trials were disappointing. However, both open and placebo-controlled (61) trials with SSRIs have demonstrated efficacy in reducing symptoms such as SIB in autism. Furthermore, the SSRI clomipramine was more effective than the noradrenergic reuptake inhibitor desipramine in autism (62). Nevertheless, not all studies of these agents have been positive (63).

Other neurochemical systems may also play a role in the mediation of self-injurious behaviors in autism. A PET study demonstrated reduced dopaminergic activity in the anterior medial prefrontal cortex (64). Controlled trials have demonstrated that dopamine blockers (like SSRIs) are effective in about 50% of patients with autism for target symptoms including SIBs (65,66). Clinical experience indicates that where a medication is ineffective in autism, an agent from a different class of medication may be useful (60). The atypical neuroleptics, with their combined dopaminergic and serotoninergic effects, also warrant further study.

Various authors have suggested a role for the opioid system in autism (40). However, studies of opioid levels in autism have been inconsistent. Furthermore, despite promising open trials, in controlled studies the effect of opioid blockers on target symptoms including SIB in autism has been disappointing.

There is promise for delineating the specific albeit multiple genetic factors underlying autism (60). Interestingly, there is preliminary evidence of a familial link with Tourette's disorder. Most recently, a possible link to the serotonin-transporter gene has been suggested. Such work may ultimately lead to a clearer understanding of the neurochemistry of autism and self-injury and to specific therapeutic interventions.

#### **Neuroanatomy**

The neuroanatomy of autism has also received increasing attention in recent years (67). Preliminary postmortem studies have found abnormalities in the cerebellum and lim-

bic system, including the hippocampus and amygdala. Neurophysiologic research has demonstrated various abnormalities including aberrant processing in frontal association cortex. Early work with pneumoencephalography suggested left temporal horn dilatation, and an early MRI study found hypoplasia of the posterior cerebellar vermis, but later studies have been inconsistent. Functional brain imaging studies are also so far inconsistent, although perhaps suggestive of dysfunction in association cortex. Clearly, much remains to be done to understand the neuroanatomy of SIB, and indeed to integrate behavioral and biological findings in this disorder.

#### TOURETTE'S SYNDROME

#### **Phenomenology**

Compulsive self-injurious behavior is only rarely seen in OCD. In contrast, SIB is seen in 13% to 53% of Tourette's syndrome (TS) patients (68). A wide range of behaviors may be seen, particularly head banging and self-punching or slapping, but also including lip biting and tongue biting, eye poking, skin picking, and self-punching or -slapping. Medical complications have included subdural hematoma and vision impairment.

In a large study, SIB in TS was not correlated with intellectual function, but was significantly associated with severity of motor tics and with scores of hostility and obsessionality (68). Furthermore, SIB has been described as one of the compulsions that are more common in patients with TS than in OCD. Thus, although the neurobiology of SIB per se in TS has not been well studied, it is possible that this overlaps with that underlying tics and compulsions.

#### Neurochemistry

Several neurochemical systems have been implicated in TS, most notably the dopamine system, but including also the serotoninergic, noradrenergic, opiatergic, hormonal, and immunologic systems (see Chapter 117). However, to our knowledge little of this work has focused specifically on the neurochemistry of SIB in TS.

#### Neuroanatomy

From a neuroanatomic perspective, there is strong evidence that prefrontal—basal ganglia—thalamic circuits are involved in OCD. There is also increasing evidence that these circuits are among those that mediate TS (see Chapter 117). Of note, increased metabolism in the orbitofrontal cortex and putamen correlated with complex behavioral and cognitive features such as self-injurious behavior (69). As in OCD, further work is needed to determine whether this reflects a primary deficit or functional compensation.

#### **TRICHOTILLOMANIA**

#### **Phenomenology**

The term *trichotillomania* was coined over a century ago to describe patients with hair pulling. Hair pulling most frequently occurs from the scalp, although it can occur from a wide range of body areas, including the eyebrows, eyelashes, beard, axillae, and pubis (70). Plucking may be confined to a single patch, may involve different areas, or may cover the entire scalp. Some patients also report pulling hair from a child, significant other, or pet.

Patients with hair pulling may demonstrate a range of other stereotypic and self-injurious behaviors (70,71). Although hair pulling may lead to significant medical complications, including trichobezoar after ingestion of pulled hair, it is perhaps more commonly associated with significant feelings of shame and lowered self-esteem. Indeed, both the personal and the economic costs of this disorder may be significant.

#### **Neurochemistry**

Research on the neurobiology of hair pulling was boosted by a seminal trial comparing clomipramine and desipramine in trichotillomania (32). As in OCD, trichotillomania responded selectively to the SSRI. Nevertheless, although the SSRIs have seemed effective for trichotillomania in a number of open trials, these agents have proved disappointing in placebo-controlled trials (72).

Furthermore, although Swedo and colleagues found that trichotillomania response to clomipramine may be sustained over time, there are also reports that initial response to SSRIs in patients with hair pulling may be lost during continued treatment (72). Taken together, this work indicates that it may be premature to overly emphasize the specific role of serotonin in trichotillomania.

Indeed, few studies of trichotillomania patients have directly assessed monoamine concentrations. Ninan and colleagues (73) obtained CSF from a small group of patients with trichotillomania and found that CSF 5-HIAA levels did not differ from normal controls. However, baseline CSF 5-HIAA did correlate significantly with degree of response to SSRIs. This finding is redolent of some work on OCD and suggests that in both disorders response to SSRIs may be accompanied by a fall in CSF 5-HIAA levels.

There are also few studies of serotoninergic pharmacologic challenges in trichotillomania. Stein and colleagues (74) found that the 5-HT agonist m-chlorophenylpiperazine (mCPP), which has exacerbated OCD symptoms in some studies, did not lead to an increase in hair pulling in women with trichotillomania (74). The interpretation of these data is not straightforward; for example, whereas OCD symptoms may be present throughout the day, hair pulling is often triggered only in particular settings. Of in-

terest, however, trichotillomania subjects described an increase in feeling "high," a phenomenon previously documented in patients with borderline personality disorder. It might be speculated that hair pulling in trichotillomania and self-injurious stereotyped behaviors in impulsive personality patients have some overlapping characteristics (71).

There is increasing evidence that dopamine plays a role in OCD and related disorders, perhaps particularly in those with a marked motoric component. There is some preliminary data that dopamine also plays a role in hair pulling. One report noted exacerbation of hair pulling by methylphenidate in a series of children (75). A similar phenomenon can be seen in adults with trichotillomania. Furthermore, preliminary open data suggests that augmentation of SSRIs with dopamine blockers may be useful in the treatment of hair pulling (76,77). The atypical neuroleptics, which have dopamine and serotonin antagonist effects, may also be effective augmenting agents in OCD and trichotillo-

Christenson and colleagues found no significant differences in either pain detection or pain tolerance thresholds between trichotillomania patients and controls. On the other hand, this group have suggested that the opioid blocker naltrexone may be effective in the treatment of trichotillomania, indicating that further research on the opioid system in hair pulling may be useful (74).

Trichotillomania is predominantly a disorder of women in the clinical setting. It frequently begins around the time of the menarche, and in some women there is premenstrual exacerbation of symptoms (70). Nevertheless, to our knowledge there are no studies that directly explore hormonal mechanisms and hair pulling. Although there is therefore currently insufficient evidence to indicate a specific link between hair pulling and hormonal mechanisms, further work in this area seems warranted.

Genetic studies might shed light on the particular neurochemical mediators of trichotillomania. Nevertheless, there have been few such studies. Christenson et al. (79) reported that 8% of 161 trichotillomania patients had first-degree relatives with hair pulling. Another study failed to show elevated rates of trichotillomania in first-degree relatives of trichotillomania probands, but did find elevated rates of OCD (80). Furthermore, elevated rates of trichotillomania have been found in a cohort of patients with both OCD and TS as compared to those with TS or OCD alone (Miguel et al., unpublished data).

#### **Neuroanatomy**

The neuroanatomy of trichotillomania is comparatively poorly researched. There are only occasional reports of hair pulling in association with neurologic disorders, although once again basal ganglia lesions have been implicated (74). Neuropsychological and neurologic soft sign studies have

also been partly consistent with involvement of the CSTC system in trichotillomania (74). Furthermore, a few studies of brain imaging in trichotillomania have now been under-

Stein and colleagues (81) employed brain MRI and found no differences in caudate volume in female patients with trichotillomania and normal controls. O'Sullivan and colleagues (82) similarly found no difference in caudate volumes in trichotillomania and controls on MRI, but did find that patients with trichotillomania had reduced left putamen volumes. This finding is of particular interest given work demonstrating reduced left putamen volumes in Tourette's syndrome.

Swedo et al. (83) found increased right and left cerebellar and right superior parietal glucose metabolic rates in trichotillomania patients compared with normal controls. This finding does not seem to support the hypothesis that orbitofrontal-basal ganglia circuits are key to this disorder, and differs from findings obtained in OCD and Tourette's. However, patients were scanned at rest, rather than during hair pulling or during the performance of a neuropsychological test that might have activated these structures. Swedo and colleagues also found that anterior cingulate and orbital-frontal metabolism correlated negatively with clomipramine response, a result they had previously found in OCD. They concluded that increased orbital-frontal metabolism may comprise a compensatory response to basal ganglia pathology in both these disorders.

Stein et al. (74) studied single photon emission computed tomography (SPECT) scans in patients with trichotillomania before and after pharmacotherapy with the SSRI citalopram (74). During treatment there was a reduction in activity in left and right inferior-posterior and other frontal areas. In nonresponders there was an increase in baseline left and right superior-lateral frontal areas. These data are again to some extent consistent with work suggesting that trichotillomania, like OCD, is mediated by corticostriatal circuits.

The neuroimmunology of OCD and TS has recently been an important focus of study. Of particular interest to research on trichotillomania, Swedo et al. (84) reported that like OCD symptoms, hair pulling may relapse after streptococcal infections. In addition, a case report of a patient in whom hair-pulling symptoms appeared closely linked with Sydenham's chorea has been published (85). Both choreiform symptoms and hair pulling remitted in response to penicillin treatment.

Nevertheless, no data have yet been published that establish a causal connection between Streptococcus or Sydenham's chorea and hair pulling. Furthermore, Niehaus et al. (86) recently found that D8/17, a marker of susceptibility to developing sequelae after Streptococcus infection, was not more frequent in patients with trichotillomania than in controls. It remains possible, however, that particular subtypes of trichotillomania have a specific neuroimmunologic etiology. Further research in this area is warranted.

#### **IMPULSIVE SIB**

#### **Phenomenology**

Common behaviors in this category include skin cutting, skin burning, and self-hitting. These behaviors frequently permit those who engage in them to obtain rapid but short-lived relief from a variety of intolerable states, in this sense serving a morbid and pathologic but life-sustaining function. Descriptive and systematic data indicate that SIBs of this type are typically impulsive, and hence their proposed classification in our schema.

Bennum (87), for example, reported that 70% of self-mutilators feel they have no control over the act. Favazza and Conterio (88) found that 78% of individuals in their sample decided to self-mutilate on the spur of the moment, and another 15% made the decision within an hour of the act. The act was then always (30%) or almost always (51%) carried out. Other studies by this group have also emphasized an association between impulsivity and self-mutilation (89). In another sample, less than 15% of self-mutilators reported any inner struggle to resist the behavior (90). Simeon et al. (91) found a significant correlation between the degree of self-mutilation and an independent measure of impulsivity.

An aggressive component has also been descriptively identified in impulsive SIB. Studies of impulsive self-mutilators show that 18% to 45% of individuals report anger toward themselves and 10% to 32% report anger toward others leading up to the acts of self-injury (87,90). Bennum (87) found that self-mutilators had greater outwardly directed hostility than nonmutilating depressives, while not differing in inwardly directed hostility. Simeon et al. (91) reported that, compared to nonmutilating controls matched for personality disorder diagnoses, self-mutilators had lifetime histories of greater aggression and sociopathy, and the degree of self-mutilation correlated significantly with chronic anger.

Some individuals engage in these self-injurious behaviors only a limited number of times in their lifetimes, whereas others do so quite frequently and habitually (1). As with other conditions on the compulsive-impulsive spectrum, the distinction between compulsive and impulsive repetitive self-injury may not always be sharp and clear. Impulsive repetitive self-injury can at times become so habitual as to occur on a daily or weekly basis and without clearly identifiable precipitating external events or affective states, as if it were a compulsion. It could be speculated that individuals who have an obsessive-compulsive predisposition may be more prone to become fixated on SIBs that were initially more episodic and impulsive and over time become habitual and dystonic. Interestingly, the few studies that have exam-

ined obsessionality in impulsive self-injury may indeed support such a notion. In one study comparing 22 female inpatient nonpsychotic "repetitive self-cutters" with 22 demographically matched inpatient controls, the patients with self-injury were significantly more obsessional than the controls while not differing in depression, anxiety, phobia, or hysteria (90). In another study comparing mutilating and nonmutilating antisocial women confined to a criminal ward, the self-injurers were found to be significantly more obsessional (92). On another note, impulsive and compulsive self-injurious behaviors can be comorbidly encountered in a certain proportion of individuals.

Although epidemiologic studies are lacking, it has been indirectly estimated that the incidence of impulsive self-injury may be at least 1/1,000 people annually (1). It is more common in females, and typically begins in adolescence or early adulthood, although it has been described as early as in the latency or even the preschool years. It is more commonly associated with certain disorders such as borderline personality disorder, antisocial personality disorder, posttraumatic stress disorder, dissociative disorders, and eating disorders. Of all these diagnoses, the one that appears most commonly associated with SIB is borderline personality disorder, but this is neither a necessary nor a sufficient condition, and the assumption of such may lead to premature diagnostic formulation and closure.

The relationship between impulsive self-injurious behaviors and suicide attempts warrants brief mention here. The coexistence of both behaviors in individuals with severe personality disorders may be more the rule than the exception. In a large, thoroughly studied series of chronically hospitalized highly disturbed patients, of 141 borderline females ten had histories of self-injury alone, whereas 20 had histories of both self-injury and suicide attempts (93). However, a 15-year follow-up of these patients suggested that history of self-injury alone was not a predictor of future suicide whereas a history of suicide attempts was; this observation indeed supports the distinct conceptualization of the two behaviors.

Traumatic experiences commonly predate and appear to contribute to the development of impulsive self-injury, and these traumatic experiences are more typically childhood ones. Although speculative, comparisons can arguably be made between the stereotypic and aggressive behavior of isolation reared primates, and symptoms of impulsive aggression and autoaggression in patients with impulsive personality disorders. In one large study of habitual female self-mutilators, childhood abuse was noted in 62% of the subjects. Of these, 29% reported both sexual and physical abuse, 17% reported only sexual abuse, and 16% reported only physical abuse. The onset of the abuse was typically early, reported as early latency, and it often involved family members (88). Indeed, abused and neglected children can begin to exhibit SIB from a disturbingly early age.

One comprehensive study attempting to tease out the contribution of various factors to the genesis and perpetuation of self-destructive behaviors followed 74 personalitydisordered individuals over a 4-year period (94). A portion of this group had a history of self-mutilation, and within the self-mutilating group there was an 89% incidence of major disruptions in parental care and a 79% incidence of childhood trauma such as physical abuse, sexual abuse, or witnessing domestic violence. Sexual abuse most strongly predicted self-injury, which was also associated with younger age at the time of the abuse, as well as with childhood chaos, separations, and neglect. Dissociative experiences also correlated with self-mutilation. Interestingly, neglect and separation from caregivers predicted continuation of the self-injury in the face of treatment efforts, leading the authors to postulate that the latter traumas impaired the capacity to form trusting stable bonds with others that could then facilitate treatment change. Another study of borderline personality disorder inpatients compared to personality-disordered controls similarly found that both parental sexual abuse and emotional neglect were significantly related to self-mutilation (95).

#### **Neurochemistry**

Research over the last quarter century, has highlighted the role of the serotoninergic system in impulsive aggression. Initially focusing on serotoninergic dysregulation in attempted or completed suicide, studies later demonstrated similar neurochemical derangement in outwardly directed acts of impulsive aggression, as well as in inwardly directed aggression without suicidal intent.

As a background we briefly review the studies establishing a connection between serotoninergic dysregulation and impulsive aggression. An important series of studies by Brown et al. (96,97) demonstrated a decrease in CSF 5-HIAA in patients with personality disorder, and found that this decrease correlated with scores on a lifetime aggression scale. A series of subsequent studies have confirmed a relationship between CSF 5-HIAA and impulsive or aggressive behaviors. Linnoila et al.'s work (98) is of particular interest insofar as it specifically divided aggressive behaviors into impulsive and nonimpulsive forms, and CSF 5-HIAA correlated only with impulsive aggression.

A range of other static measures of serotonin function is consistent with serotonin hypofunction in impulsive aggression (99). In addition, neuroendocrine challenge studies, which provide a dynamic measure of serotoninergic function, confirm this relationship. Coccaro et al. (100), for example, administered fenfluramine to personality-disordered patients and found that prolactin response, a measure of net serotonin function, correlated inversely with impulsive aggression. Similarly, abnormal neuroendocrine responses after mCPP challenge have been observed in borderline personality disorder.

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 (hypothalamus) have been consistent postmortem changes in suicide completers (101). Recent genetic findings suggest that particular polymorphisms in the serotonin system may account for some of the variance in symptoms in impulsive personality disorders; such work may ultimately prove of significant value in understanding the neurobiology of SIB.

We previously presented descriptive data conceptualizing impulsive SIB as a form of impulsive aggression. Direct neurobiological data in impulsive SIB are very limited, yet consistent with serotoninergic dysregulation, and we summarize them below. Lopez-Ibor et al. (102) found that inpatient depressives with histories of self-injury without suicidal intent had lower CSF 5-HIAA than those without self-injury histories. Coccaro et al. (100) reported a significant correlation between self-damaging acts and a blunted prolactin response to the serotonin agonist fenfluramine in patients with personality disorders. Simeon et al. (91) reported a significant negative correlation between the frequency of self-mutilation and platelet imipramine binding, a peripheral serotoninergic index. In contrast to these studies, Gardner et al. (103) compared CSF 5-HIAA levels in borderline personality-disordered patients with and without self-mutilation, and found no difference. However, it cannot be ruled out that the different incidence of suicide attempt histories in the two groups may have concealed an association between CSF 5-HIAA and self-mutilation. In this regard, Simeon et al. (91) found a 44% reduction in CSF 5-HIAA in a small subsample of self-mutilators compared to nonmutilators who had never made suicide attempts. In a study by Siever and Trestman (104), self-directed aggression in personality-disordered subjects, as measured by a composite score of suicide attempts and SIB, was inversely correlated to the prolactin response to fenfluramine challenge. In a smaller sample of female personality-disordered patients, the relationship did not reach statistical significance (105).

More indirect evidence for underlying serotoninergic dysfunction in self-mutilation comes from open-treatment treatment studies utilizing SSRIs. Fluoxetine has been reported useful in decreasing SIB in a number of studies of borderline personality disorder. For example, in an open study of fluoxetine in 22 borderline and schizotypal patients, a 97% decrease in self-mutilating episodes was found (106). Clomipramine was apparently useful for SIB in OCD patients, many of whom had a history of sexual abuse (107). In an open trial of venlafaxine in subjects with borderline personality disorder (108), five out of seven subjects who engaged in self-injury ceased to do so after 12 weeks of treatment; of note, venlafaxine is both a serotonin and nor-

epinephrine reuptake inhibitor. Further pharmacologic trials, conducted in a double-blind fashion, and assessing larger numbers of patients, are needed to conclusively determine whether SSRIs are efficacious in treating self-injury, whether the response is selective in comparison to other pharmacologic agents, how the response compares to the change in other target symptoms, as well as to clarify the time course and maintenance of the therapeutic response.

Other neurotransmitter systems may also be involved in the neurobiology of impulsive SIB but have been even less studied. Siever and Trestman (104) have suggested that, in addition to serotoninergic dysfunction, noradrenergic dysregulation may be implicated in the expression of impulsive aggression. Specifically, noradrenergic hyperreactivity may mediate increased arousal and irritability and trigger acts of impulsive aggression, in conjunction with behavioral disinhibition mediated by serotoninergic dysfunction. A relationship between CSF MHPG and impulsive aggression has not been consistently replicated, but there is some evidence that personality-disordered patients may have increased growth hormone responses to clonidine challenge. We are not, however, aware of any studies of the noradrenergic system specifically in self-injuring individuals. A treatment study describing some success with venlafaxine in self-injury was mentioned above.

Another system implicated in impulsive SIB is the opioid system. Indeed, habitual self-mutilators commonly report the relief of depersonalization and other dissociative states as the motivation to injure themselves, and relative analgesia to the self-inflicted injury is often present in the emotional state surrounding such acts. The role of the endogenous opioid system in stress-induced analgesia seems established.

Actual data examining the opioid system in SIB or SIBprone groups are limited. Russ and colleagues (109) examined the pain response to a cold pressor test in individuals with borderline personality disorder. Compared to subjects who experienced pain during self-injury, those who experienced analgesia reported less pain during the experiment. However, naloxone pretreatment did not increase discomfort induced by the test (110), casting some doubt on an endogenous opioid hypothesis. In one study of the opioid system, Coid et al. (111) found that habitually self-mutilating individuals had higher plasma metenkephalin than normal comparison subjects, but the finding might have been secondary to recent self-injury itself. A recent open study of naltrexone in female patients with SIB accompanied by analgesia and dysphoria reduction, and typically accompanied by a history of abuse, found that SIB symptoms ceased in six of seven subjects (112). However, these results need to be replicated in controlled studies.

#### **Neuroanatomy**

There has been little study of the neuroanatomy of SIB per se in borderline personality disorder (BPD). However, it would again seem relevant to this chapter to emphasize the increasingly large literature correlating frontal hypofunction with impulsive aggression. The classic case of Phineas Gage is an excellent example of the marked dysfunction, with increased impulsivity and perseveration, that results from frontal lesions. Subsequent studies of head injury and of frontal lobe surgery have led to multiple descriptions of such dysfunction.

A body of neuropsychological literature, although open to different interpretations, also points to a relationship between frontal dysfunction and impulsive aggression. Some of the strongest evidence of involvement of frontal lobe dysfunction, however, in impulsive aggression emerges from recent brain imaging studies. Preliminary findings include the demonstration of a significant association between decreased metabolic rates in prefrontal cortex and aggression in personality-disordered and aggressive patients. Similarly, there is increasing imaging evidence for neuronal dysfunction in antisocial personality disorder (113). Also, BPD subjects had diminished response to fenfluramine challenge in a number of areas of prefrontal cortex (114).

It is perhaps important to emphasize the way in which neurobiological factors in BPD may intersect with psychosocial ones. An abusive background, for example, may result in neurobiological changes that then further promote risk-seeking behavior in adult life. Research on the neurobiology of posttraumatic stress disorder similarly may provide a useful framework for developing hypotheses about childhood abuse and subsequent changes in personality. Such work may also shed light on the multiple roots of "impulsive" SIB.

#### **CONCLUSION**

In the literature on the obsessive-compulsive spectrum, it has been suggested that compulsive and impulsive symptoms and disorders reflect different kinds of psychobiological mechanisms. Compulsive symptoms, for example, may be mediated by serotonin and frontal hyperfunction, whereas impulsive symptoms may be mediated by serotonin and frontal hypofunction. In reality the complex neurobiology of compulsivity and impulsivity cannot be captured by so simplistic a contrast. Nevertheless, such contrasts arguably have some heuristic value.

Does this contrast apply also to compulsive and impulsive SIB? Perhaps patients with SMD have frontal/serotoninergic hyperfunction, whereas patients with BPD have frontal/serotoninergic hypofunction? Currently, there are insufficient data to make so bold a claim. Furthermore, in clinical and biological reality, the situation may be much more complex than this, with patients demonstrating both compulsive and impulsive features, and with disorders such as OCD, SMD, and BPD exhibiting brain areas of both serotonin hyperfunction and serotonin hypofunction.

Indeed, an alternative hypothesis is that stereotypic SIB can be seen after a number of different situations. First, in patients with overactivation of the basal ganglia, there may be excessive release of various motoric sequences, including SIB. Second, in patients with hypofrontal function, there may be an inability to control such programmed sequences. Environmental conditions such as deprivation may also disrupt the balance in corticostriatal circuits (3), in such a way as to produce symptoms.

Fortunately there a now a range of different approaches to understanding the neurobiology of unwanted repetitive symptoms. These include brain imaging, genetics, neuroimmunology, and pharmacological dissection. Although such approaches have shed light on some relationships between the OCD spectrum disorders, much further work is required before it is possible to make phenomenologic distinctions (such as compulsive vs. impulsive SIB) on the basis of differential psychobiological mechanisms.

In tackling this area of research, it may also be possible to integrate neurobiological with psychosocial data; compulsive SIB, for example, may be seen not only in response to a pharmacologic challenge but also after isolation, whereas impulsive behavior that is induced by an environmental stressor may nevertheless be mediated by specific neurobiological mechanisms. Future research should see an expansion in our understanding of the neuropsychopharmacology of compulsive and impulsive SIB, and thus in our ability to intervene effectively with patients who demonstrate these distressing and disabling symptoms.

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