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Part II
Aggression in Other Psychiatric Disorders

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Phenomenology and Psychobiology of Aggression and Intermittent Explosive Disorder

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Human aggression occurs when an individual assaults or attacks another in the context of defense or in the context of securing access to resources needed for survival. As such, aggression represents a fundamental aspect of human behavior. Over the course of civilization, however, human aggression has become less advantageous, with the use of aggression for reasons other than self-defense generally viewed as unacceptable. In this chapter, we examine the biology of primary aggression both as a continuum and as a clinical diagnosis.

Aggression as a Continuum

Phenomenology

Aggressive behavior can vary in both form and type. With respect to form, aggression can be verbal (e.g., snapping, name-calling, arguments, threats) and/or physical (e.g., throwing things, breaking things, pushing or hitting someone, physically injuring someone). The aggression can also be direct (yelling at or hitting someone) or indirect (gossiping about someone, damaging an object). Indirect aggression aimed at damaging a person's interpersonal relationships is called *relational aggression* (Murray-Close et al. 2010). What all forms of aggression have in common is intent to harm, though the function or "type" of aggression may differ.

Aggression can be *socially sanctioned* (as in, e.g., soldiers and law enforcement) or *medically related*. Neither type of aggression is typically the focus of aggression interventions, because in the former the aggression is not seen as problematic and in the latter there is a clear medical cause for the behavior. Other, more "primary" types of aggression are *premeditated* (i.e., instrumental) aggression and *impulsive* (i.e., affective or reactive) aggression (Barratt et al. 1997; Dodge 1991). The critical difference between these types of aggression is that in premeditated aggression, the harm caused by the aggressive behavior is merely a means to an end (e.g., punching someone to steal his or her wallet), whereas in the case of impulsive aggression the desire to harm another is a primary goal of the aggressive act (e.g., to take revenge). Though aggressive acts can include both instrumental and impulsive facets, most aggression is predominantly impulsive. Furthermore, primary aggression can be viewed both along a continuum (i.e., dimensionally) and as a dichotomy between normative and pathological aggression (i.e., diagnostically).

Psychobiology

Psychobiological studies involving human aggression as a dimension are numerous and involve those related to behavioral genetics and neurobiology (i.e., central and peripheral neurochemistry and dynamic responsiveness to neurotransmitter challenge) and neuroimaging. Impulsive aggressive behavior, in particular, appears to be associated with significant genetic influence and with reduced function in in-

hibitory neural pathways and/or an imbalance in inhibitory and excitatory influences on behavioral responses to social threat and/or frustration.

Behavioral Genetics

Aggression is under both genetic and environmental influence, with up to 50% of the variability in measures of aggression accounted for by genetic factors (Miles and Carey 1997). Our own twin studies using aggression support these findings, showing that the genetic influence of the aggression increases with the severity of the aggressive acts. Specifically, genetic influence is 28% for verbal aggression, 35% for aggression against objects, and 45% for aggression against others (Coccaro et al. 1997a). In addition, impulsivity is under similar genetic influence in these types of studies, and the genetic correlation of impulsivity and aggression is correspondingly substantial, supporting the conceptualization of aggression as a form of dysregulation (Seroczynski et al. 1999).

Neurobiology

The neurobiological study of human aggression began in the 1970s when Brown and colleagues (1979, 1982) reported a strong inverse relationship between cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) levels, an index of serotonin (5-HT) function, and a lifetime measure of aggressive behavior—a finding consistent with previous animal studies reporting inverse relationships between 5-HT and aggressive responding (Valzelli and Garattini 1968). This relationship has also been reported in other studies of severely aggressive individuals (Linnoila et al. 1983, Virkkunen et al. 1987, 1989) but not in those involving individuals with less intense aggressive behavior (Coccaro et al. 1997b, 1997c; Møller et al. 1996). In addition to this inverse correlation between CSF 5-HIAA and aggression, inverse correlations with aggression have also been reported with the hormonal responsiveness to 5-HT selective agents (Duke et al. 2013), including fenfluramine (an indirect 5-HT agonist: Coccaro et al. 1989, 2010a), ipsapirone (a 5-HT_{1A} agonist: Almeida et al. 2010), and *m*-chlorophenylpiperazine (m-CPP) (a 5-HT_{2C} receptor agonist: Coccaro et al. 1997b; Moss et al. 1990). These latter studies suggest that 5-HT receptors are sub-sensitive to 5-HT activation so that there is a reduction in 5-HT activity and, thus, in 5-HT-mediated behavioral inhibition.

Other neurochemical systems may also be relevant in human aggression. At this time, there are preliminary data supporting positive relationships between aggression and catecholamines (norepinephrine: Coccaro et al. 2003; dopamine: Coccaro and Lee 2010; Limson et al. 1991), other amines (glutamate: Coccaro et al. 2013), peptides (vasopressin: Coccaro et al. 1998; substance P: Coccaro et al. 2012b; neuropeptide Y: Coccaro et al. 2012a), and circulating cytokines (e.g., interleukin-6 [IL-6]: Coccaro et al. 2014; Marsland et al. 2008; Suarez 2003). There are similar data supporting an inverse relationship between aggression and oxytocin (Lee et al. 2009). However, with the exception of studies manipulating 5-HT as a strategy to reduce (Dougherty et al. 1999) or increase (Berman et al. 2009) impulsive aggression, few studies have been conducted to explore how manipulating non-5-HT systems reduces, or has no effect on, impulsive aggressive behavior in humans.

Molecular Genetics

Molecular genetic studies of aggression are far fewer than those for other psychiatric disorders, such as schizophrenia and depressive and bipolar disorders. The first candidate gene study of relevance reported that five individuals, in a Dutch kindred with X-linked borderline intellectual ability, had recurrent impulsive aggressive behavior, low activity for the enzyme monoamine oxidase A (MAO-A), elevated urinary levels of noradrenergic metabolites, and reduced urinary levels of both serotonergic and dopaminergic metabolites (Brunner et al. 1993). Although subsequent studies did not replicate these findings in unaffected males (Rosenberg et al. 2006), a stepwise relationship between low MAO-A activity, early life trauma, and aggression and criminality in young adult males (Caspi et al. 2002), as well as increased aggression in MAO-A knockout mice compared with wild-type mice (Scott et al. 2008), has been reported. A more recent study, involving healthy volunteers, reported an inverse relationship between brain MAO-A activity, assessed with positron emission tomography (PET), and aggression across several cortical and subcortical areas (Alia-Klein et al. 2008).

The next candidate gene study involved polymorphisms of the gene for tryptophan hydroxylase (TPH), an enzyme catalyzing the reaction that serves as the rate-limiting step in the synthesis of 5-HT, with stud-

ies involving healthy volunteers reporting a relationship between aggression and the U allele of the TPH polymorphism (Manuck et al. 1999). Another important candidate gene study in this area involves the relationship between polymorphisms of the 5-HT transporter (5-HTT) and antisocial behavior and aggression. Meta-analysis of these studies reveals a moderately strong association between presence of the s allele (with reduced synthesis of the 5-HTT) and aggression across many studies (Ficks and Waldman 2014). A number of other studies report a relationship between polymorphisms for the gene related to catechol O-methyltransferase (COMT), an enzyme that metabolizes norepinephrine and dopamine, and aggression. In one study of patients with schizophrenia, the presence of the Met/Met (low COMT activity) versus the Val/Val (high COMT activity) genotype was associated with aggression (Tosato et al. 2011), a finding confirmed in two meta-analytic studies (Bhakta et al. 2012; Singh et al. 2012). Selected haplotypes of the COMT gene were also associated with aggression in a separate study of schizophrenia patients (Gu et al. 2009), whereas no association between COMT polymorphisms and aggression was reported in a more recent study involving patients with schizophrenia (Mohamed Saini et al. 2015). Another, modestly sized study of individuals with personality disorders reported that individuals with the G allele for COMT had higher aggression scores compared with individuals with other genotypes (Flory et al. 2007), Lastly, individuals with schizophrenia who have the Val/Met genotype for the gene associated with brain-derived neurotrophic factor (BDNF) were reported to have higher aggression scores compared with those with the Val/Val genotype in one study (Spalletta et al. 2010) but not two other studies (Chung et al. 2010; Guan et al. 2014) involving patients with schizophrenia.

Molecular Epigenetics

Beyond strict genetic influence, environmental factors are critical, and these factors account for more of the variance in measures of aggression than do genetic factors (Coccaro et al. 1997a). Environmental factors in aggression include, among others, history of childhood trauma, witnessing of aggression, modeling of aggressive behavior observed in parents and caretakers, history of head trauma, and aversive social interaction in the "here and now" (Crick and Dodge 1996). These fac-

tors operate, at least partially, through epigenetic mechanisms that work to turn genes on and off. For example, greater methylation of the 5-HTT promoter has been reported in young adults with prominent histories of physical aggression in whom PET studies also show reduced synthesis of 5-HT, bilaterally, in the orbitofrontal cortex (OFC) (Wang et al. 2012).

Structural Neuroimaging

Neuroimaging studies have begun to identify sites of neurotransmitter action in the brain, mostly in regard to 5-HT. The first published study in this area reported reduced glucose metabolism on PET in the left OFC and anterior cingulate cortex (ACC) in six impulsively aggressive individuals, compared with five healthy control subjects, after *d,l*-fenfluramine challenge (Siever et al. 1999). A similar finding was reported in a larger subject group using m-CPP challenge (New et al. 2002). In addition, a 12-week course of treatment with fluoxetine normalized OFC function in a similar group of impulsively aggressive subjects, supporting the idea that deficits in OFC function are at least partially accounted for by abnormalities in 5-HT function (New et al. 2004a). Other neuroimaging studies suggest that impulsively aggressive individuals have abnormal 5-HT synthesis and reuptake in medial frontal gyrus, anterior cingulate gyrus, superior temporal gyrus, and corpus striatum compared with healthy control subjects (Leyton et al. 2001).

Functional Neuroimaging

In addition to neuroimaging studies relating to neurochemistry, other studies have reported on structural and functional aspects of the brain as they relate to aggression. The first published studies in this area reported reduced glucose utilization in prefrontal and temporal cortices in individuals with a history of violence (Volkow et al. 1995) and an inverse correlation between glucose utilization in the prefrontal cortex with life history of aggression in subjects with personality disorders (Goyer et al. 1994). Later studies suggested metabolic hypoactivity in frontal brain regions, and hyperactivity in subcortical regions, in impulsive aggressive murderers compared with healthy control subjects (Raine et al. 1998). Subsequent structural magnetic resonance imaging (MRI) studies have reported a significant reduction of prefrontal volume in individuals with antisocial personality disor-

der compared with a control group (Raine et al. 2000). Functional MRI (fMRI) studies of healthy subjects show that anger-inducing paradigms activate the prefrontal cortex (Blair et al. 1999; Damasio et al. 2000; Dougherty et al. 1999; Kimbrell et al. 1999), while similar studies report reduced activity in this area in typically aggressive individuals with borderline personality disorder (Soloff et al. 2000).

In addition to the prefrontal cortex, the amygdala is also involved in the regulation of aggression, as demonstrated by the fact that electrical stimulation of the amygdala increases aggression and amygdalectomy reduces aggression (see Eichelman 1983). Despite this observation, both epileptic patients with episodic aggressive outbursts (van Elst et al. 2000) and individuals with antisocial personality disorder (Veit et al. 2002) have been shown to have reduced amygdalar volume, a finding that might suggest reduced activation of the amygdala when stimulated.

Summary

Studies of aggression as a continuum suggest significant genetic, epigenetic, and biological influences, most notably 5-HT deficits and dysregulation of the frontolimbic brain circuits. Though it is likely that the biobehavioral relationship between aggression and its neurobiological substrate is primarily dimensional in nature, there is also some support for the possibility that pathological aggression is qualitatively distinct from aggression of lesser severity (Ahmed et al. 2010). Furthermore, interventions designed to reduce impulsive aggression require diagnostic criteria for the identification of who could, or should, be treated for problematic impulsive aggressive behavior. To date, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnosis that best represents pathological primary aggression is intermittent explosive disorder (IED) (American Psychiatric Association 2013).

Impulsive Aggression as Clinical Diagnosis: Intermittent Explosive Disorder

When sufficiently frequent and severe, impulsive aggression may meet the DSM-5 diagnosis of intermittent explosive disorder (American Psychiatric Association 2013; see also Coccaro 2012). Impulsive aggression is also observed in other diagnostic conditions, but when aggression is not directly due to another psychiatric disorder, a diag-

nosis of IED may be made. In this way, IED represents a disorder of primary impulsive aggression, while other behavioral disorders in which aggression may occur (e.g., psychosis, mania) can be referred to as disorders of secondary aggression.

Phenomenology

Diagnostic Criteria

The essence of recurrent problematic impulsive aggression has been in the DSM since its first edition. However, criteria for IED did not unequivocally require impulsive aggression as its hallmark characteristic until the fifth edition. IED in DSM-5 is characterized by at least one of the following types of impulsive aggressive outbursts (Coccaro 2011): frequent but low-intensity verbal or physical outbursts occurring twice weekly, on average, for at least 3 months or infrequent but high-intensity behavioral outbursts occurring three times per year. The outbursts are out of proportion to stressors (i.e., provocation), impulsive and anger based (i.e., not premeditated), associated with marked distress and impairment, and not better accounted for by another mental disorder or medical condition (i.e., outbursts do not only occur during the presence of another disorder). Generally, IED has its onset in childhood and peaks in adolescence: Studies of adults report the mean age at onset as the midteens (Coccaro et al. 2005; Kessler et al. 2006); studies of adolescents report the mean age at onset as about 12 years (McLaughlin et al. 2012). The mean duration of IED ranges from more than 10 years to nearly the whole lifetime, which suggests a persistent and chronic course without treatment. A large (2:1) preponderance of males over females has been suggested by small clinical reports, though community survey data suggest this ratio is closer to 1.5:1.0 (Kessler et al. 2006). Other sociodemographic variables (e.g., age, race, education, marital status, occupational status, family income) show only modest correlations with IED, suggesting that the disorder cuts cross racial and sociocultural groups (Kessler et al. 2006).

Epidemiology

Though early versions of DSM characterized IED as a "rare" disorder, subsequent studies suggest that IED may be among the more common psychiatric (DSM-IV; American Psychiatric Association 1994) disorders in the United States (Kessler et al. 2006). The National Comor-

bidity Survey Replication (NCS-R) reported a lifetime prevalence of DSM-IV IED in the United States of 7.3% by "broad criteria" and 5.4% by "narrow criteria," and a past-year prevalence of 3.9%, and 2.7%, respectively (Kessler et al. 2006). Inspection of the data reveals meaningful differences between the two IED types, with "narrow" IED being far more severe than "broad" IED (Coccaro 2012). "Broad" IED stipulates only three aggressive outbursts during a lifetime, whereas "narrow" IED required at least three aggressive outbursts in a single year.

The prevalence of IED may not be as high in non-U.S. countries, however, where the lifetime estimate of DSM-IV IED may range from only 0.1% (i.e., Nigeria) to 1.2% (i.e., Colombia, South Africa), with an average of 0.6%, compared with 2.7% for the United States (Scott et al. 2016). Reasons for this cross-national difference are not known with any certainty but are likely related to variation in general risk factors, cultural factors that have an impact on willingness to disclose information about one's own psychopathology, and other methodological factors.

The lower rate for the United States in the cross-national study is attributable to the fact that the algorithm used to make the DSM-IV diagnosis of IED required the presence of impairment, on the Sheehan Disability Scale, in addition to three anger attacks in the same year. A separate analysis of the U.S. data using different impairment criteria suggests that the lifetime rate of DSM-IV IED in the United States is 3.6% (Coccaro et al. 2017b), down from the 5.4% in the original report (Kessler et al. 2006). In addition, a survey study of more than 5,300 nondeployed army service members (Army STARRS) reported lifetime pre- and postenlistment rates of DSM-IV IED of 15.5% and 4.8%, respectively (Nock et al. 2014). Despite these data, the community rate of DSM-5 IED is not known, because DSM-5 criteria for IED require either low-intensity but high-frequency impulsive aggressive outbursts (Criterion A1) or high-intensity but low-frequency outbursts (Criterion A2).

Since the data instrument used in the NCS-R (Kessler et al. 2006) and the cross-national study (Scott et al. 2016) only sought information about Criterion A2, not A1 (i.e., type of impulsive aggressive outbursts), the prevalence of IED diagnosed on the basis of only Criterion A1 in the NCS-R sample is unknown. New data from our own studies suggest that more than one-fifth of those with current IED meet Cri-