Published in final edited form as:
Aggress Violent Behav. 2008 October ; 13(5): 383–395. doi:10.1016/j.avb.2008.06.003.

Role of Serotonin and Dopamine System Interactions in the Neurobiology of Impulsive Aggression and its Comorbidity with other Clinical Disorders

Dongju Seo and **Christopher J. Patrick**
Department of Psychology, University of Minnesota, Twin Cities

Patrick J. Kennealy
Department of Psychology and Social Behavior, University of California, Irvine

Abstract

Impulsive aggression is characterized by an inability to regulate affect as well as aggressive impulses, and is highly comorbid with other mental disorders including depression, suicidal behavior, and substance abuse. In an effort to elucidate the neurobiological underpinnings of impulsive aggression and to help account for its connections with these other disorders, this paper reviews relevant biochemical, brain imaging, and genetic studies. The review suggests that dysfunctional interactions between serotonin and dopamine systems in the prefrontal cortex may be an important mechanism underlying the link between impulsive aggression and its comorbid disorders. Specifically, serotonin hypofunction may represent a biochemical trait that predisposes individuals to impulsive aggression, with dopamine hyperfunction contributing in an additive fashion to the serotonergic deficit. The current paper proposes a modified diathesis-stress model of impulsive aggression in which the underlying biological diathesis may be deficient serotonergic function in the ventral prefrontal cortex. This underlying disposition can be manifested behaviorally as impulsive aggression towards oneself and others, and as depression under precipitating life stressors. Substance abuse associated with impulsive aggression is understood in the context of dopamine dysregulation resulting from serotonergic deficiency. Also discussed are future research directions in the neurobiology of impulsive aggression and its comorbid disorders.

Impulsive aggression plays a critical role in the manifestation of violent and criminal behavior and is considered an important psychopathological symptom of several mental disorders including borderline and antisocial personality disorders (Coccaro & Siever, 2000; Linnoila & Virkkunen, 1992). Previous research has reported associations among impulsive aggression, mood disorders, substance abuse, and suicidality, which suggest that these comorbid disorders have a common biological substrate (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Koller, Preuß, Bottlender, Wenzel, & Soyka, 2002; Placidi, Oquendo, Malone, Huang, Ellis, & Mann, 2001). Previous studies utilizing biochemical, anatomical, and brain imaging techniques have provided insight into the neurobiology of impulsive aggression; yet, the relationship between impulsive aggression and other comorbid conditions remains unclear. One of the problems in the neurobiology of impulsive aggression is the identification of common biological correlates

Address correspondence to Dongju Seo, Psychology Department, N218 Elliot Hall, University of Minnesota, 75 East River Road, Minneapolis, MN 55455, Email: seod@umn.edu Telephone: 612-360-9707 Fax: 612-625-6668.

for these comorbid disorders as well as differentiation among these varying comorbid conditions.

Impulsive aggression is a complex behavioral phenotype and multiple brain systems may contribute to its etiology and its high comorbidity with other disorders. The association between impulsive aggression and its comorbid disorders may result from biological predisposing factors, such as an imbalance among the functions of different neurochemical systems, or dysfunction in activities of executive brain regions. Specifically, low levels of the neurotransmitter serotonin (5-HT) have been associated with impulsive aggression in both human and animal studies (Asberg, Scalling, Trakeman-Bendz, & Wagner, 1987; Linnoila & Virkkunen, 1992). A number of studies indicate that serotonin and dopamine (DA) systems interact closely at a basic neurophysiological level (Daw, Kakade, & Dayan, 2002; Kapur & Remington, 1996; Wong, Feng, & Teo, 1995), and that impairment of the serotonin system function can lead to dysregulation of the dopamine system (De Simoni, Dal Toso, Fodritto, Sokola, & Algeri, 1987). Additionally, activation of the prefrontal cortex (PFC), specifically the orbital and ventromedial PFC, has been implicated in the behavioral control of aggression, and impairments in these areas are related to an increase in impulsive aggression (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Davidson, Putnam, & Larson, 2000). These lines of evidence suggest that aggression and its comorbid disorders may come from an underlying neurobiology, specifically serotonin and dopamine interaction in the prefrontal cortex. Other biological factors, such as norepineprine (Barrett, Edinger, & Siegel, 1990) and testosterone (Giammanco, Tabacchi, Giammanco, Di Majo, & La Guardia, 2005) may also contribute to aggression. However, the focus will be on the interaction between serotonin and dopamine, because of their well-established relations with impulsive aggression and their significance in explaining comorbid disorders.

This review is divided into three sections. First, the paper reviews the neurochemical bases of impulsive aggression, with a particular focus on interactions between the serotonin and dopamine systems. Second, the paper reviews the neuroanatomical bases of impulsive aggression with an emphasis on structural and functional abnormalities in the prefrontal cortex. Finally, the paper considers the role of the serotonin and dopamine systems in brain regions associated with emotion regulation. In addition, these neurobiological characteristics will be discussed as the primary predisposing factor in impulsive aggression and its comorbid disorders. Understanding the neurochemical mechanisms of impulsive aggression in the context of dysfunctional brain regions can help to elucidate the etiology of this complex behavioral phenotype and guide the development of effective treatments for aggression and the various disorders with which it is associated.

I. Neurochemical Mechanisms of Impulsive Aggression

Serotonin and Aggression

Research indicates that, in general, the neurotransmitter serotonin has an inhibitory action in the brain (Daw et al., 2002; Yan, 2002) and that it is deeply involved in the regulation of emotion and behavior, including the inhibition of aggression (Davidson et al., 2000; Volavka, 1999). Serotonergic dysfunction has been reliably associated with aggressive behaviors in animals and humans (Coccaro, 1989; Miczek, DeBold, & Van Erp, 1994; Raleigh, McGuire, Brammer, Pollack, & Yuwiler, 1991).

In animals, deficient serotonergic function has been associated with mice killing in rodents (Gibbons, Barr, Bridger, & Leibowitz, 1979). In non-human primates, low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been linked to heightened incidence of impulsive and aggressive behaviors (Fairbanks, Melega, Jorgensen, Kaplan, & McGuire, 2001; Higley & Bennett 1999). Low CSF 5-HIAA concentrations have also been

associated with poor impulse control and aggressive behaviors in adolescent monkeys (Mehlman, Higley, Faucher, Lilly, Taub, Vickers, Suomi, & Linnoila, 1994). In addition, associations between impulsivity, dangerous acts, and low CSF 5-HIAA concentrations were found in female primates (Westergaard, Suomi, Chavanne, Houser, Hurley, Cleveland, Snoy, & Higley, 2003).

In humans, a low concentration of 5-HIAA has been associated with lifetime aggression (Brown, Goodwin, Ballenger, & Gover, 1979), aggression in patients with mental disorders (Coccaro, 1989; Virkkunen, Rawlings, Tokola, Poland, Guidotti, Nemeroff, Bissette, Kalogeras, Karonen, & Linnoila, 1994), violent suicide attempts (Traskman-Bendz, Asberg, & Schalling, 1986), impulsive murder (Lidberg, Tuck, Asberg, Scalia-Tomba, & Bertilsson, 1985), and recidivism of murderers (Virkkunen, De Jong, Bartko, Goodwin, & Linnoila, 1989). A meta-analytic study (Moore, Scarpa, & Raine, 2002) that examined findings from 20 separate studies found that low levels of serotonin significantly contribute to aggressive behaviors, regardless of type of crime and mental health problems.

There is a consistent link between serotonin hypofunction and aggression, with serotonin hypofunction specifically associated with impulsive forms of aggression (Coccaro 1989; Virkkunen & Linnoila 1993). For example, an association has been demonstrated between impulsive aggression and a blunted prolactin response to fenfluramine, a pharmacological agent that increases the level of serotonin (Coccaro, Kavoussi, Cooper, & Hauger, 1997). Other research has reported lower CSF 5-HIAA levels in impulsive arsonists compared with habitually violent offenders, as well as healthy controls (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). In another study, impulsive violent offenders were found to have lower CSF 5-HIAA concentrations than non-impulsive violent offenders (Linnoila, Virkkunen, Scheinin, Nuutila, Rimon, & Goodwin, 1983). Additionally, impulsive alcoholic offenders show lower CSF 5-HIAA than non-impulsive alcoholic offenders and healthy controls (Virkkunen et al, 1994). These various lines of evidence support the hypothesis that it is the impulsive type of aggression in particular that is associated with serotonin hypofunction.

Impulsive aggression has shown to be influenced by genetic predispositions (Coccaro, Bergeman, McClearn, 1993; Deater-Deckard & Plomin, 1999). For example, behavioral genetic research has demonstrated that the impulsive-aggressive symptoms of borderline personality disorder have a stronger genetic basis than the full diagnostic criteria (Siever, Torgersen, Gunderson, Livesley, & Kendler, 2002). Genetic influences of serotonin on impulsive aggression have been observed in a number of studies. Research has found associations between serotonergic dysfunction, specifically low levels of the serotonin genotype 5-HT2A-1438 GG, and criminal behavior (Berggard, Damberg, Longato-Stadler, Hallman, Oreland, & Garpenstrand, 2003). Additionally, in individuals with anger-related traits, an association between a tryptophan hydroxlase gene polymorphism and 5-HIAA levels in CSF has been found (Rujescu, Giegling, Bondy, Gietl, Zill, & Moller, 2002). A polymorphism in the serotonin transporter gene (5-HTTLPR) has been associated with violent suicidal behavior (Courtet, Baud, Abbar, Boulenger, Castelnau, Mouthon, Malafosse, & Buresi, 2001). Further, individual differences in CSF 5-HIAA concentrations, specifically the association between CSF 5-HIAA and impulsive aggression, tend to remain consistent throughout different environments across time (Higley, King, Hasert, Champoux, Suomi, & Linnoila, 1996; Higley & Linnoila, 1997).

These results suggest that genetic influences on serotonergic systems contribute to individual differences in impulsive and aggressive behaviors. Given that the association between serotonin and impulsive aggression has been strongly demonstrated in the literature and is considered to have a heritable foundation, serotonergic hypofunction could represent a neurochemical trait that predisposes individuals to impulsivity and aggressive behaviors.

Dopamine and Aggression

The dopaminergic system is involved in behavioral activation, motivated behavior, and reward processing (Everitt & Robbins, 2000; Ikemoto & Panksepp, 1999). It also plays an active role in the modulation of aggressive behaviors. In animal studies, hyperactivity in the dopamine system is associated with increases in impulsive aggression (Harrison, Everitt, & Robbins, 1997; for a review, see Netter & Rammsayer, 1991). Studies on aggressive behaviors in rodents showed that elevated dopamine levels have been continuously observed before, during, and following aggressive fights (Hadfield, 1983; Miczek, DeBold, & Van Erp, 1994; Tidey & Miczek, 1996). In humans, the dopaminergic system has been linked to the recognition and experience of aggression. After administering a dopamine D_2 receptor antagonist, sulpiride, subjects showed an impaired ability to recognize angry facial expressions (Lawrence, Calder, McGowan, & Grasby, 2002). There is also evidence that impulsive behavior may be enhanced by elevated dopaminergic function (Bergh, Eklund, Sodersten, & Nordin, 1993; Brunner & Hen, 1997). Stimulants increase impulsivity in humans without the presence of an ADHD disorder (Sostek, Buchsbaum, & Rapoport, 1980). In addition, dopaminergic hyperfunction is associated with impulsivity and emotional dysregulation in patients with borderline personality disorders (Chotai, Kullgren, & Asberg, 1998; for a review, see Friedel, 2004).

Dopamine levels manipulated pharmacologically have been shown to increase or decrease aggressive behavior. The level of amphetamine has been linked to the level of aggressive social behavior (Hodge & Butcher 1975; Miczek & Yoshimura 1982; Miczek & Haney 1994). Administration of apomorphine to rats precipitates increases in shock-induced fighting (Ossowska, Kenk-Majewska, & Zebrawska-Lupina, 1996). In addition, antipsychotic agents targeting the D_2 dopamine receptors lowered the levels of anger in aggressive patients (Brizer, 1988). Atypical antipsychotic agents, such as risperidone (Rocca, Marchiaro, Cocuzza, & Bogetto, 2002), clozapine (Chengappa, Ebeling, Kang, Levine, & Parepally, 1999), and olanzapine (Schulz, Camlin, Berry, & Jesberger, 1999) have also been found to be effective in treating impulsive aggression. Overall, evidence from these studies suggests that there is substantial involvement of the dopamine system in aggressive behavior.

Serotonin and Dopamine Interaction

The serotonergic system has strong anatomical and functional interactions with the dopaminergic system (Kapur & Remington, 1996). More specifically, a reciprocal interaction between these two systems has been proposed (Daw et al., 2002; Wong et al, 1995). Approach and withdrawal related behaviors are thought to be determined by the balance between dopamine and serotonin activity (Deakin & Graeff, 1991)**,** with dopamine thought to encourage appetitive behaviors (Ikemoto & Panksepp, 1999) and serotonin thought to discourage appetitive behaviors and provoke withdrawal behaviors triggered by aversive stimuli (Daw et al, 2002).

Interactions between serotonergic and dopaminergic systems have been reported in anatomical and pharmacological studies. Dopamine neuronal cell bodies and terminal sites are modulated by serotonin and receive rich projections from serotonin neurons (e.g., Kapur & Remington, 1996). These strong neuronal connections promote the functional modulation of 5-HT over DA activities in the neural network (Kelland & Chiodo, 1996). For example, research has demonstrated that the 5 HT2 receptors inhibit DA activity, whereas the 5 HT2 receptor antagonists counteract the inhibition of the DA activity (Shi, Nathaniel, & Bunney, 1995; Sorensen, Kehne, Fadayel, Humphreys, Ketteler, Sullivan, Taylor, & Schmidt, 1993). Further, adminstration the 5-HT2c antagonist SB242, 084 results in increased dopamine levels in the frontal cortex of rats, indicating an inhibitory effect of the serotonergic system on frontal dopamine activity (Millan, Dekeyne, & Gobert, 1998).

Interactions of this kind between the serotonin and dopamine systems provide a framework for understanding mechanisms underlying impulsive aggression. Considering the functional regulation of serotonin over the dopamine system, deficient serotonergic function may result in hyperactivity of the dopamine system, promoting impulsive behavior. This relationship may account for co-occurring serotonin and dopamine dysfunctions in individuals with impulsive aggression. In support of this, prefrontal serotonin levels in rats decreased to 80% of baseline level during and after fights, whereas prefrontal dopamine levels increased to 120% after fights (Van Erp & Miczek, 2000). This inverse association between serotonin and dopamine levels during aggression was replicated in a subsequent study (Ferrari, vanErp, Tornatzky, & Miczek, 2003). These results suggest that decreased serotonergic activity in the context of aggressive behavior is closely associated with increased dopamine activity. Consistent with this research, dopamine triggered impulsivity in rats was increased by serotonin depletion or removal of the serotonin-1B receptor gene (Harrison et al 1997; Swann, 2003). In humans, low levels of 5-HIAA and high levels of the dopamine metabolite homovenillic acid (HVA) in CSF have been associated with high scores in the interpersonal and behavioral items of the Psychopathy Checklist-Revised (PCL-R) (Soderstrom, Blennow, Manhem, & Forsman, 2001). This result was independently replicated in a sample of violent and sexual offenders exhibiting psychopathic traits (Soderstrom, Blennow, Sjodin, & Forsman, 2003).

Although the relationship between serotonin hypofunction and impulsive aggression is a consistent finding in clinical neuroscience, only a few studies have examined the interaction between serotonergic and dopaminergic systems in individuals with impulsive aggression. Based on this strong association between serotonergic hypofunction and impulsive aggression that has a genetic basis, deficient serotonin function may be a neurochemical trait marker of impulsive aggression. In relation to this, dopaminergic hyperactivity may exert an additive effect on proneness to aggressive behavior, that is, secondary to serotonergic dysfunction. Given that the serotonergic system modulates dopaminergic activity, hyperactivity in the dopamine system in aggressive individuals may be attributed to disinhibition of the dopamine activity from deficient serotonergic function. To further understand the neurobiological bases of impulsive aggression, future research should investigate the nature of interactions between serotonin and dopamine system in individuals exhibiting impulsive aggression.

II. The Neuroanatomical Mechanism of Impulsive Aggression

Impulsive aggression has been linked to uncontrollable negative emotion, and an inability to regulate aggressive impulses, which can often lead to violent behaviors (Davidson et al, 2000; Heinrichs, 1989). Neuropsychological literature suggests that individuals with impulsive aggression may have abnormalities in brain regions involved in the control of emotion such as the prefrontal cortex, anterior cingulate cortex, amygdala, and nucleus accumbens (see reviews by Davidson et al, 2000; Friedel, 2004). In order to better understand the etiology of impulsive aggression, this section will review the roles of structural and functional abnormalities, as well as serotonin and dopamine in brain regions involved in emotion regulation.

Brain Abnormalities

Previous research has consistently demonstrated that the prefrontal cortex is crucially involved in the regulation of social and aggressive behavior (Davidson et al., 2000; Dolan, 1999; Grafman & Litvan, 1999). Individuals with antisocial personality showed an 11% reduction of PFC gray matter volume in comparison with controls (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000). The orbitomedial region of the PFC has been shown to exert control over anger and impulsive aggression (Davidson et al., 2000; Lapierre, Braun, & Hodgings, 1995). Further, deficits in the ventromedial PFC have been associated with the dysregulation of negative emotion (Quirk, Russo, Barron, & Lebron, 2000) and the abnormal processing of somatic or emotional signals (Bechara, Tranel, Damasio, & Damasio, 1996). Researchers have

hypothesized that impairment in the orbitomedial PFC may result in an inability to show emotion appropriate to the consequences of behaviors, which may lead to inadequate decision-making and affiliated behavior problems (Bechara, Tranel, & Damasio, 2000). Overall, the findings from structural imaging studies suggest that the inability of the PFC to regulate emotion and impulses may contribute to impulsive aggression and socially inappropriate behavior, causing damage to oneself and others.

Functional neuroimaging studies have also reported associations between hypofunction in the PFC and aggressive behaviors. A positron emission tomography (PET) study showed that the activity of the orbitofrontal PFC is generally reduced during the expression of aggressive behaviors in healthy individuals (Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000). Additionally, lower glucose utilization in the orbitofrontal PFC has been reported in aggressive patients with personality disorders (Goyer, Andreason, Semple, Clayton, King, Compton-Toth, Schulz, & Cohe, 1994). Further, single photon emission computed tomography (SPECT) brain scanning showed that patients with a history of violent behaviors displayed significantly decreased prefrontal activity compared to non-aggressive patient controls (Amen, Stubblefield, & Carmichael, 1996). Other researchers have reported that murderers, who display an extreme manifestation of aggression, have reduced prefrontal functioning (Raine, Meloy, Bihrle, Stoddard, LaCasse, & Buchsbaum, 1998a). Alcoholics with antisocial personality disorder also showed greater hypo-perfusion in frontal brain regions than other alcoholics (Hirono, Mega, Dinov, Mishkin, & Cummings, 2000), providing further evidence that there is a close association between deficient PFC function and aggressive behaviors.

Aggressive individuals appear to have an inability to regulate negative emotion in situations where they or others are vulnerable (Davidson et al., 2000). The inability to regulate negative emotion may result from impairment in the capacity of the PFC to inhibit emotional activation arising from subcortical structures, which are typically controlled by the prefrontal cortex (Davidson et al., 2000; Raine et al, 1998). Impaired regulatory control of the PFC may lead to excessive negative emotional reactivity and consequent violent behaviors. Relevant to this, fMRI studies of emotion regulation have revealed that activity in the PFC is reciprocally related to activation of subcortical emotion systems (i.e., amygdala and nucleus accumbens)—with activity in the PFC increasing, and activity in these subcortical regions decreasing, during directed efforts to suppress emotion (Ochsner, Ray, Cooper, Robertson, Chopra, Gabrieli, & Gross, 2004; Phan, Fitzgerald, Nathan, Moore, Uhde, & Tancer, 2005). The implication is that these subcortical structures are under direct regulatory control of the PFC. From this perspective, impairments in prefrontal brain regions may contribute a biological vulnerability to impulsive aggression by limiting the capacity to inhibit subcortical emotional centers. In support of this, aggressive individuals—specifically, murderers whose crimes were considered to be affective in nature (i.e., prompted by situation rage)—exhibited reduced activity in the PFC and increased activity in the basal ganglia and limbic system (Amen et al., 1996). Other data indicate that affective murderers display decreased prefrontal activity and increased subcortical (amygdala, midbrain, hippocampus, and thalamus) activity in comparison with premeditated murderers, who exhibited typical prefrontal activity (Raine et al., 1998a).

To summarize, results from structural and functional brain imaging studies indicate that hypofunctioning of the PFC, particularly the orbitomedial area, is related to impaired regulation of emotion and aggressive behaviors. Abnormal emotional behaviors are associated with increased subcortical activity, specifically in the amygdala, resulting from deficient prefrontal control of negative emotion. This abnormality may predispose individuals to emotional dysregulation and aggressive behaviors.

Neural Transmission in Emotion Regulation Circuitry

The PFC receives abundant monoamine neurotransmitter projections, including serotonin and dopamine projections, from other brain regions (Biver, Lotstra, Monclus, Wikler, Damhaut, Mendlewicz, & Goldman, 1996; Williams & Goldman-Rakic, 1998). As reviewed in the first section, the serotonin system interacts with the dopamine system functionally and anatomically (Kapur & Remington, 1996) and greatly influences emotion and behavior (Daw et al., 2002). In order to better understand the neurobiology of impulsive aggression, this section discusses serotonergic and dopaminergic abnormalities in the neural circuitry of emotion regulation, specifically in the prefrontal cortex.

Serotonergic neurotransmission contributes to prefrontal regulation of emotional responses by influencing inhibitory synaptic transmission (Yan, 2002). The role of serotonergic neurotransmission in the PFC has been examined using fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging following administration of d-fenfluramine. Healthy subjects displayed increases in glucose metabolism in the left PFC, ventromedial PFC, and anterior cingulate cortex following d-fenfluramine administration (Mann, Malone, Diehl, Perel, Nichols, & Mintun, 1996). In contrast, individuals with impulsive aggression showed decreased activation in the left anteromedial orbital cortex and anterior cingulate cortex in response to a serotonergic stimulant, meta-chlorophenylpiperazine (New, Hazlett, Buchsbaum, Goodman, Reynolds, Mitropoulou, Sprung, Shaw, Koenigsberg, Platholi, Silverman, & Siever, 2002). In another study, impulsive and aggressive individuals demonstrated a decreased metabolic response to serotonergic stimulation in the anterior cingulate cortex (Frankle, Lombardo, New, Goodman, Talbot, Huang, Hwang, Slifstein, Curry, Abi-Dargham, Laruelle, & Siever, 2005). These results indicate that decreased serotonergic neurotransmission in brain regulatory systems such as the PFC and the anterior cingulate cortex may be a major neurobiological deficit that leads to inhibitory dysfunction and aggressive behaviors. These findings were replicated in several studies. For example, patients with impulsive aggression demonstrated deficient serotonergic function in the orbitofrontal and ventromedial PFC as well as cingulate cortex (Siever, Buchsbaum, New, Spiegel-Cohen, Wei, Hazlett, Sevin, Nunn, & Mitropoulou, 1999). Additionally, patients with borderline personality disorder (BPD) showed decreased responses to serotonergic stimulation in the prefrontal cortex, in particular the medial and orbitofrontal PFC (Soloff, Meltzer, Greer, Constantine, & Kelly, 2000). These findings further support the association between deficient serotonergic neurotransmission and impulsive aggression.

Dopamine hyperactivity in brain regions linked to reward-related motivation, such as the nucleus accumbens (NCC) and prefrontal cortex, also leads to increases in impulsive and aggressive behavior (see reviews by Everitt & Robbins, 2000; Friedel, 2004). Striatal dopamine transporter (DAT) density measured by [123I] beta-CIT SPECT exhibits enhanced distributional heterogeneity in the right striatum of violent offenders compared with healthy controls, suggesting disrupted dopaminergic transmission in aggressive individuals (Kuikka, Tiihonen, Bergstrom, Karhu, Rasanen, & Eronen, 1998). Further, an animal study showed that dopamine levels increased and serotonin levels decreased in the prefrontal cortex during and after aggression (van Erp & Miczek, 2000). Considering the close interaction between the serotonin and dopamine systems, impaired regulation of serotonin over dopamine in the PFC may result in the disruption of the dopamine system and aggressive behaviors. However, there have been few studies examining dopamine deficits in these brain regions, even though serotonin hypofunctioning in the PFC has been strongly found in studies on aggression. Future research utilizing brain-imaging techniques should examine the relations between serotonin and dopamine, particularly in the PFC, anterior cingulated cortex, amygdala, and striatum.

III. Impulsive aggression and its comorbid disorders

Impulsive aggression has been associated with various pathological conditions including depression, suicidal behavior, and substance abuse (Fava, Bless, Otto, Pava, & Rosenbaum, 1994; Koller et al, 2002). Studying impulsive aggression from the perspective of its relationship with comorbid disorders may provide insight into the etiology of impulsive aggression and the mechanism that predisposes individuals to develop this cluster of comorbid symptoms. This section discusses the biochemical and anatomical abnormalities of impulsive aggression and its interrelated disorders.

Depression and Impulsive Aggression

Impulsive aggression has been linked with depression as well as violent acts (Mammen, Kolko, & Pilkonis, 2002; Newman, Shapira, & Lerer 1998). Forty-four percent of individuals diagnosed with major depressive disorder have physically or verbally attacked another individual (Fava et al., 1994). Further, the severity of major depressive disorder has been associated with anger attacks (Tedlow, Fava, Uebelacker, Nierenberg, Alpert, & Rosenbaum, 1998).

Serotonergic hypofunction has been implicated as a possible source of comorbidity in individuals with depression and accompanying impulsive aggression. For example, research findings indicate that the prolactin response to fenfluramine, an indicator of serotonergic activity, is blunted in depressed patients (Mulder, Porter, & Joyce, 2003) and as well as in impulsive aggressive individuals (Newman et al., 1998). Pharmacological research has demonstrated that symptoms of impulsive aggression and depression were reduced by administration of fluoxetine, a selective serotonin-uptake inhibitor (Zanarini, Frankenburg, & Prachini, 2004). These results indicate that deficient serotonergic functioning underlies the link between impulsive aggression and depression, and may in part account for the comorbidity of these disorders.

Suicide and Impulsive Aggression

Impulsive aggression has been shown to be a robust predictor of suicidal behavior (Dumais, Lesage, Alda, Rouleau, Dumont, Chawky, Roy, Mann, Benkelfat, & Turecki, 2005a), which can be regarded as a form of self-directed aggression. Further, individuals who have exhibited suicidal behavior in the past demonstrate more impulsive and aggressive traits (Carballo, Oquendo, Giner, Zalsman, Roche, & Sher, 2006; Turecki, 2005). Suicidal ideation has been linked with impulsivity and irritability in a sample of 625 individuals (Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004). In addition, in a study of individuals with a diagnosis of mood disorder, those with a history of suicidal behaviors had higher levels of impulsivity and hostility than those without a history of suicidal behaviors, after controlling for severity of depression and length of lifetime illness (Michaelis, Goldberg, Davis, Singer, Garno, & Wenze, 2004). More specifically, violent suicidal behavior has been linked to elevated levels of impulsivity and lifetime aggression (Dumais, Lesage, Lalovic, Seguin, Tousignant, Chawky, & Turecki, 2005b).

Deficient serotonergic function is known to play an important role in the high comorbidity between impulsive aggression and suicide (Kamali, Oquendo, & Mann 2001). Low serotonin activity is associated with high-lethality suicide attempts (Mann & Malone, 1997), as well as impulsive and aggressive behaviors (Coccaro, Siever, Klar, Maurer, Cochrane, Cooper, Mohs, & Davis, 1989). Specifically, diminished serotonin activity is linked with the most violent type of suicidal behavior. For example, lower prolactin response to fenfluramine was seen in individuals with high lethality suicide attempts (Malone, Corbitt, Li, & Mann, 1996). In addition, several studies report strong associations between deficient serotonin system function

and violent suicide attempts (Asberg, Traskman, & Thoren, 1976; Mann et al., 1996; Mann & Malone, 1997).

Brain imaging studies suggest that individuals who display suicidal behavior may have shared brain dysfunction with individuals showing impulsive aggression. Vivo and postmortem studies report an association between suicidality and deficient serotonergic function in the ventral prefrontal cortex (see review by Kamali et al., 2001). A postmortem autoradiography study found that serotonergic abnormalities were localized in the ventral and ventro-lateral prefrontal cortex of those who committed suicide (Arango, Underwood, & Mann, 1997). Additionally, high lethality suicide attempters exhibit dysfunctional serotonergic activity in the ventromedial PFC and increased suicidal intent, when compared with low lethality suicide attempters (Oquendo, Placidi, Malone, Campbell, Keilp, Brodsky, Kegeles, Cooper, Parsey, Van Heertum, & Mann, 2003). Subsequently, Kamali and associates (2001) have theorized that the source of impulsive and aggressive behaviors may be the deficient inhibitory capabilities of the ventral PFC due to serotonergic hypofunction, which can result in self-directed impulsive aggression or suicide in the context of significant life stressors. The comorbidity of impulsive aggression and suicidal behavior suggests a common neurological mechanism, resulting in a predisposition to these behaviors that may be traced to deficient serotonergic function in the ventral PFC.

Substance Abuse and Impulsive Aggression

Substance abuse is closely associated with impulsive aggression and increased levels of impulsive behavior in general (Brady, Myrick, & McElroy, 1998; Cascella, Nagoshi, Muntanar, Walter, Haertzen, & Kumor, 1994). Research on substance abuse indicates that impulsive aggression may be related to personal characteristics that are evident before the onset of substance use (Cloninger, 1987; Higley & Bennett, 1999). This implies the possibility of a predisposition to substance abuse in individuals with impulsive aggression. To better understand the underlying basis for this comorbidity, research in the area of prefrontal dysfunction and neurochemical abnormalities will be considered.

Prefrontal dysfunction, particularly in the orbitomedial area, has been demonstrated as a common pathology for both impulsive aggression and substance abuse. As reviewed above, research studies in humans and primates have indicated that the prefrontal cortex plays an important role in the regulation of aggressive behavior (see review by Davidson et al., 2000). The prefrontal cortex also plays a critical role in the regulation of drug seeking behaviors (Volkow, Fowler, Wang, Hitzemann, Logan, Schyler, Dewey, & Wolf, 1993) and is susceptible to damage by continuous substance abuse (Nader, Morgan, Gage, Nader, Calhoun, Buchheimer, Ehrenkaufer, & Mach, 2006; Robinson, Galetta, McCluskey, Forman, & Balcer, 2001). Brain imaging research has characterized substance abusers with poor impulse control and orbitofrontal cortex dysfunction (Goldstein, Alia-Klein, Leskovjan, Fowler, Wang, Gur, Hitzemann, & Volkow, 2005; Volkow et. al, 1993). In addition, cocaine use has been found to produce morphological changes in the PFC and the nucleus accumbens (Robinson et al., 2001). Dysfunction in the orbitofrontal PFC is associated with an inability to inhibit aggressive behaviors and poor inhibitory control (Davidson, 2002; Friedel, 2004), as well as compulsive drug intake (Volkow et al, 1993). This suggests the possibility of a common biological factor between impulsive aggression and substance abuse.

Strengthening the association between impulsive aggression and substance abuse, similar neurochemical abnormalities, specifically in the dopaminergic system, have been observed in individuals at risk for aggressive behavior as well as substance abuse (Blum, Braverman, Holder, Lubar, Monastra, Miller, Lubar, Chen, & Comings, 2000; Soderstrom et al, 2001; Soderstrom, et al, 2003). The dopaminergic system plays a critical role in the processing of addictive qualities of drugs (Hyman, Malenka, & Nestler, 2006; Volkow, Wang, Telang,

Fowler, Logan, Childress, Jayne, Ma, & Wong, 2006). Research examining the relationship between dopamine and addiction indicates that low dopamine levels contribute to drug- and alcohol-seeking behavior (see review by Volkow, Fowler, Wang, & Swanson, 2004; Nader et al., 2006). However, high dopamine levels have also been observed in some populations of substance users such as type II alcoholics. For example, elevated dopamine activity in limbic brain regions, specifically the nucleus accumbens, have been associated with substance use (Hurd & Ungerstedt, 1989), type II alcoholism (Tiihonen Kuikka, Bergstrom, Hakola, Karhu, Ryynanen, & Fohr, 1995) and aggression (Miczek, Fish, DeBold, & de Almeida, 2002). This result suggests that the dysregulation of the dopamine system, both hypo- and hyper-activity, may contribute to the etiology of substance abuse.

To explain these discrepant results, the contribution of different subtypes of substance abuse has been suggested. Furthermore, the differences in behavioral manifestation associated with substance abuse may be caused by variations in dopaminergic neurotransmission. Specifically, two alcoholic subtypes with differential biological predispositions have been proposed (Cloninger 1987; Cloninger, Bohman, & Sigvardsson, 1981; Sigvardsson, Bohman, & Cloninger, 1996). Type I alcoholism is characterized by a later age of onset and the presence of anxiety symptoms. Type II alcoholism is characterized by an early age of onset, impulsivity, and antisocial behavior. In support of this, a SPECT study examining striatal DA transporter density levels found that violent alcoholics showed elevated density levels compared with control subjects, whereas non-violent alcoholics showed diminished levels suggesting differential dopamine abnormalities in non-violent versus violent alcoholics (Tiihonen et al., 1995). Similarly, using human postmortem brain autoradiography, dopamine D_2 receptor density in dorsal striatal structures was observed to be lower in type I alcoholics than in controls, whereas no difference was found between type II alcoholics and controls (Tupala, Hall, Mantere, Rasanen, Sarkioja, & Tiihonen, 2003). Additionally, type I and type II alcoholics exhibit differentiated dopamine receptor densities in cortical regions. Type I alcoholics exhibited lower levels, whereas type II alcoholics showed higher cortical dopamine D_2 receptor density in comparison to controls. In this study, the cortical dopamine D_2 receptors observed in type II alcoholics significantly reduced with age, perhaps resulting from decreased aggressive behaviors with age (Tupala, Hall, Halonen, & Tiihonen, 2004). Recent research has also demonstrated significantly higher cortical dopamine transporter (DAT) levels in type II alcoholics (Tupala, Halonen, & Tiihonen, 2006).

Given that the serotonergic system modulates the dopamine system, the high dopaminergic activity seen in type 2 alcoholics may be attributed to deficient serotonergic regulation of the dopamine system. In Cloninger's model, type 2 alcoholics have a serotonergic hypofunction (Cloninger, 1987). Further, serotonin deficits were found in early onset alcoholism in animal and human studies. Rhesus monkeys that exposed to stressors during early developmental stages showed low serotonin levels, which were linked to aggression and high tolerance to alcohol (Heinz, Higley, Gorey, Saunders, Jones, Hommer, Zajicek, Suomi, Lesch, Weinberger, & Linnoila 1998). These findings are consistent with low precursor serotonin availability in anxiety-prone, early-onset alcoholics (Buydens-Branchey, Branchey, Noumair, & Lieber, 1989). In addition, primates with low CSF-5-HIAA concentration show behaviors similar to Type II alcohol abuse: poor impulse control, risky behavior, and huge amounts of alcohol consumption (see review by Higley & Bennett, 1999). When comparing early versus late onset alcoholics, early-onset alcoholics show reduced 5-HIAA levels than late-onset alcoholics, indicating differential serotonergic function in subgroups of alcoholism (Fils-Aime, Eckardt, George, Brown, Mefford, & Linnoila, 1996).

The involvement of deficient serotonin function in reward-seeking behaviors has been demonstrated in animal studies with rats. Manipulations that increased serotonin activity decreased the effects of d-amphetamine and reactivity for conditioned reward (Fletcher,

1996). Further, a 5-HT receptor antagonist, metergoline, counteracted the regulatory effects of serotonin on d-amphetamine and reward-related behavior (Fletcher, Korth, & Chambers, 1999). These results suggest that 5-HT plays an important role in substance use and may serve as a predisposing factor by increasing the vulnerability to drug-seeking behaviors. More specifically, the serotonergic deficiency appears to contribute to substance abuse and aggression by facilitating greater impulsivity. In a sample of alcoholics, lower levels of 5-HIAA have been observed in impulsive offenders than in non-impulsive offenders (Virkkunen et al., 1994). Furthermore, serotonin hypofunction has been associated with impulse control problems in type II early-onset alcoholism (Cloninger, 1987; Higley & Bennett 1999).

In summary, the comorbidity observed between impulsive aggression and substance abuse suggests that a common biological mechanism, perhaps involving a hypofunction in orbitomedial cortex and neurochemical abnormalities in serotonin and dopamine systems, may underlie these impulsive behaviors. Specifically, studies on alcoholism suggest that impulsive aggression is associated with a certain subtype of substance abuse (i.e., type 2 alcoholism). A possible explanation for these relations may be deficient serotonergic regulation of dopaminergic activity, which results in poor behavioral inhibition characterized by acts of impulsive aggression and substance abuse.

Diathesis-Stress Model

Impulsive aggression is strongly associated with depression, suicidal behaviors, and substance abuse (Dumais et al., 2005a; Koller et al., 2002; Placidi et al., 2001; Sher, Oquendo, Galfalvy, Grunebaum, Burke, Zalsman, & Mann, 2005). Heightened susceptibility to psychological dysfunction and suicidal behavior has been attributed to these high comorbidities (Hawton, Houston, Haw, Townsend, & Harris, 2003). To more fully explicate mechanisms underlying impulsive aggression, it will be important to understand the common predisposing factor that links impulsive aggression with these other comorbid conditions.

In this regard, research on the relations that depression and impulsive aggression show with suicidal behavior is of interest. Major depression has been strongly linked to suicidal behaviors (Henriksson, Aro, Marttunen, Heikkinen, Isometsa, Kuoppasalmi, & Lonnqvist, 1993). However, studies report that lifetime suicide risk associated with depression is quite low, being 3.4 % for depressed individuals (Blair-West, Cantor, Mellsop, & Eyeson-Annan, 1999) and 2.2% for mixed inpatient/outpatient with affective disorders (Bostwick & Pankratz, 2000). This raises the question of what the specific factor underlying vulnerability to suicidal behavior might be. Impulsive aggression has been suggested as a risk factor for this vulnerability, and evidence of a shared neural substrate for impulsive aggression and suicidal behavior has been reported (Kamali et al., 2001; Oquendo et al, 2003). Further, aggression and impulsivity has been closely linked to a history of suicidal behavior (Mann et al., 1999). More specifically, impulsive aggression appears to be an underlying risk factor for lethal suicidal attempts in depressed individuals. In a study comparing two groups of males suffering major depression, one composed of those still living and the other of individuals who committed suicide, cluster B personality disorders and substance abuse/dependence were associated with a higher suicide risk. Further, suicide completers were found to be more impulsive and aggressive (Dumais et al., 2005b).

In order to better explain the roles of impulsive aggression and depression in suicidal behaviors, a diathesis-stress model has been developed, in which impulsive aggression and low serotonergic activity are considered the diathesis factor, and depression is considered the precipitating stressor (Placidi et al., 2001). Supporting this model, both the severity of lifetime aggression and higher lethality of suicide attempt were linked to lower CSF 5-HIAA concentrations in individuals suffering a major depressive episode (Placidi et al., 2001). This result suggests a biological association between impulsive aggression and severity of suicidal

behavior in depressed individuals. Placidi et al.'s model presents a viable explanation for comorbidities associated with impulsive aggression. It explains the biological relationship between impulsive aggression and suicide while differentiating their roots from depression. However, a weakness of the model is that depression is viewed not only as a precipitant for suicide, but also as an outcome that arises from some underlying vulnerability in combination with depressogenic life events. That is, depression may reflect a concomitant disturbance triggered by low serotonin activity in individuals with impulsive aggression, rather than a precipitating stressor. Additionally, this model does not specify the anatomic basis of the proposed neurological deficit and fails to consider the role of substance use, another condition that is frequently comorbid with impulsive aggression.

Nevertheless, in support of this model, brain-imaging studies provided evidence of differences between patients with depression and suicidal victims. Serotonergic abnormalities in widespread brain regions were found for depression, whereas localized serotonergic deficits in ventral PFC were found for suicide and impulsive aggression. For example, postmortem brain investigation revealed that an extensive lack of serotonergic transporter (5-HTT) binding in the PFC was found in individuals with major depression, while deficient 5-HTT binding in only the ventral part of the PFC were associated with suicidal behaviors (Mann, Huang, Underwood, Kassir, Oppenheim, Kelly, Dwork, & Arango, 2000). It is also consistent with the results of brain imaging studies demonstrating associations between depression and widespread serotonergic abnormalities (Anderson, Oquendo, Parsey, Milak, Campbell, & Mann, 2004). Further, deficient serotonergic function in the ventromedial PFC was associated with high lethality suicide attempts (Oquendo et al., 2003) and impulsive aggression (Siever et al., 1999). These results suggest that suicide and impulsive aggression are associated with deficient serotonin function in the localized PFC, specifically in the ventral PFC. Therefore, low serotonergic activity in the ventral PFC may be the underlying biological diathesis that predisposes individuals to both impulsive aggression and suicide. Although the serotonin hypofunction is localized, it may potentially lead to depression as well. A key precipitating stressor that actuates this constitutional predisposition to impulsive aggression and other comorbid conditions may be psycho-pathogenic life events such as failure, loss of employment or relationship partner, and severe family discord, etc. As a function of such life stressors, underlying pathological processes may be exacerbated and possibly give rise to extreme manifestations of self-destructive behavior.

It is unclear whether the comorbid pathology of substance abuse might also arise from deficient serotonin function in the ventral PFC, as there has been no brain imaging research in this area. However, substance abuse may result from a concomitant biological vulnerability such as dopamine dysregulation, resulting from serotonergic deficiency and leading to disrupted reward-seeking behavior. The close relation between these disorders in previous research points to the possibility of a similar biological vulnerability. For example, alcoholics who exhibit suicidal behavior tend to have strong impulsive and aggressive features (Koller et al., 2002). Additionally, the severity of alcoholism and impulsivity/aggression increases the risk for suicide (Sher et al, 2005; Sher, 2006). Also consistent with this possibility are findings from a recent study of depressed individuals with comorbid alcoholism. In comparison to depressed individuals without alcoholism, depressed subjects with alcoholism in this study showed higher impulsivity, aggression, and suicidal behaviors. Further, alcoholism was significantly associated with aggression in these subjects (Sher et al., 2005). The implication is that substance abuse and impulsive aggression may result from a common biological predisposing factor. Research demonstrating strong family transmission of substance use in conjunction with impulsive–aggressive tendencies (Hicks et al., 2004) also strengthens the possibility that substance use in impulsive-aggressive individuals may result from a common biological predisposition, such as dopamine disinhibition due to deficient serotonergic inhibitory function.

To summarize, a modified diathesis-stress model should include the role of a possible serotonin deficiency in the ventral PFC as a biological diathesis. The behavioral manifestation associated with this diathesis would be an inability to regulate negative emotion and aggressive impulses, which are directed both toward oneself and others. Individuals with this underlying diathesis may be easily drawn into violent fights and impulsive behaviors due to a deficient regulatory influence of the PFC over subcortical structures such as the amygdala. Additionally, such individuals--because they lack the normal regulatory control over the dopamine system that is provided by efficient serotonergic system function--may be prone to artificially regulating their negative emotions through the use of chemical substances. As a function of this, they may become even more impulsive and aggressive, creating a continuing vicious cycle of aggressive and addictive behavior. Ultimately, this predisposition may result in self-directed aggression or suicide during severe depressive episodes or under significant life stressors.

Conclusions and Research Directions

Impulsive aggression is a behavioral disposition characterized by the inability to regulate negative affect and impulses to harm oneself or others. It is highly comorbid with depression, substance use, and suicidal behaviors (Hicks et al., 2004; Horesh, Gothelf, Ofek, Weizman, & Apter, 1999; Koller et al., 2002). The available literature suggests that deficient serotonergic activity in emotion regulation circuitry, such as the prefrontal cortex and the anterior cingulate cortex, may be an important predisposing factor to impulsive aggression (New et al., 2002; Parsey, Oquendo, Simpson, Ogden, Van Heertum, Arango, & Mann, 2002; Siever et al., 1999). Additionally, serotonergic hypofunction may contribute to the hyperactivity of the dopaminergic system, which further promotes impulsive and aggressive behaviors. Considering that serotonin hypofunction in impulsive aggression has been reported frequently across the literature and has a heritable foundation, serotonin hypofunction may be a neurochemical vulnerability marker of impulsive aggression. Dopamine hyperactivity may secondarily contribute to impulsive aggression, given the modulation of serotonin system over dopaminergic activity.

Serotonergic dysfunction in the PFC also appears to underlie the comorbidity of impulsive aggression with depression, substance abuse, and suicidal behaviors. A modified diathesis-stress model has been proposed, in which a biological diathesis is regarded as a serotonergic deficiency in the ventral PFC. This deficiency can lead to dopamine hyperactivity as a result of reduced serotonergic control over the dopamine system. These pathological processes may result in a failure to regulate emotion, leading to impulsive and aggressive behavior towards the self and others. Additionally, dopamine hyperactivity resulting from deficient serotonergic regulation can promote substance abuse and other addictive behaviors. Further, individuals with impulsive aggression are vulnerable to depression as a function of low serotonergic activity. The presence of depression may contribute further to self-directed aggression or suicide during severe depressive episodes or under significant life stressors.

Understanding brain mechanisms underlying impulsive aggression and identification of risk factors is important to the prevention and treatment of impulsive aggression. Research has shown that pharmacological interventions such as serotonin reuptake inhibitors or antipsychotics can reduce impulsive aggression by increasing serotonergic activity or decreasing dopaminergic activity (Miczek et al., 2002; Swann, 2003). In addition, aggressive behaviors have been moderated by environmental enrichment, parental treatment, social skills training, and nutritional supplements (August, Hektner, Egan, Realmuto, & Bloomquist, 2002; Caspi, Moffitt, Morgan, Rutter, Taylor, Arseneault, Tully, Jacobs, Kim-Cohen, & Polo-Tomas, 2004; Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Raine, Mellingen, Liu, Venables, & Mednick, 2003). These results emphasize the importance of the identification of risk factors by demonstrating that good environment or proper treatment can have a beneficial

impact on individuals with impulsive aggression. Successful treatment of impulsive aggression should also consider the vulnerability to comorbid conditions. For example, early education of substance abuse prevention as well as training of emotion regulation techniques may be important to vulnerable individuals in order to prevent substance abuse.

Future studies should continue to invest effort toward identifying the biological and genetic risk factors underlying impulsive aggression. Specifically, future research efforts should be directed toward identifying the common and differential neurobiological characteristics of impulsive aggression and its comorbid disorders. In particular, brain imaging studies are needed to investigate the exact relations between serotonin and dopamine in the PFC. Different types of neurotransmitter receptors may contribute differently to the pathological conditions of impulsive aggression and its comorbid disorders. Selective radioligands labeled for SPECT and PET may assist in identifying structural distribution and density of serotonin and dopamine receptors. The combination of PET and fMRI imaging will also allow us to locate neurochemical abnormalities by providing high-resolution brain images. Further, the identification of genetic risk factors through the development of neurobiological endophenotype measures could facilitate proper intervention or treatment in the early stages of these disorders.

Understanding the neural mechanisms of impulsive aggression and the identification of risk factors will advance our understanding of complex brain-behavior relations and will provide insight into the etiology of impulsive aggression. This will help develop effective treatment strategies across impulsive aggression and its comorbid disorders.

Acknowledgments

This research was supported by grants MH65137 and MH072850 from the National Institutes of Health.

References

Amen DG, Stubblefield M, Carmichael B. Brain SPECT findings and aggressiveness. Annals of Clinical Psychiatry 1996;8:129–137. [PubMed: 8899131]

Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nature Neuroscience 1999;2:1032–1037.

Anderson AD, Oquendo MA, Parsey RV, Milak MS, Campbell C, Mann JJ. Regional brain responses to serotonin in major depressive disorder. Journal of Affective Disorders 2004;82:411–417. [PubMed: 15555692]

August GJ, Hektner JM, Egan EA, Realmuto GM, Bloomquist ML. The early risers longitudinal prevention trial: examination of 3-year outcomes in aggressive children with intent-to-treat and as-intended analyses. Psychology of Addictive Behaviors 2002;16:27–39.

Arango V, Underwood MD, Mann JJ. Postmortem findings in suicide victims. Implications for in vivo imaging studies. Aspects of the History of Psychology in American: 1892–1992 1997;836:269–287.

Asberg M, Traskman L, Thoren P. 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? Archives of General Psychiatry 1976;33:1193–1197. [PubMed: 971028]

Barrett JA, Edinger H, Siegel A. Intrahypothalamic injections of norepinephrine facilitate feline affective aggression via alpha 2-adrenocpetors. Brain Research 1990;525:285–293. [PubMed: 2174712]

Bechara A, Tranel D, Damasio H, Damasio AR. Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. Cerebral Cortex 1996;6:215–225. [PubMed: 8670652]

Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain 2000;123:2189–2202. [PubMed: 11050020]

Berggard C, Damberg M, Longato-Stadler E, Hallman J, Oreland L, Garpenstrand H. The serotonin 2A-1438 G/A receptor polymorphism in a group of Swedish male criminals. Neuroscience Letters 2003;347:196–198. [PubMed: 12875919]

Bergh C, Eklund T, Sodersten P, Nordin C. Altered dopamine function in pathological gambling. Neuropsychobiology 1993;28:30–6. [PubMed: 8255407]

Biver F, Lotstra F, Monclus M, Wikler D, Damhaut P, Mendlewicz J, Goldman S. Sex Difference in 5ht2 Receptor in the Living Human Brain. Neuroscience Letters 1996;204:25–28. [PubMed: 8929969]

Blair-West GW, Cantor CH, Mellsop GW, Eyeson-Annan ML. Lifetime suicide risk in major depression: sex and age determinants. Journal of Affective Disorders 1999;55:171–8. [PubMed: 10628886]

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, Lubar JO, Chen TJ, Comings DE. Reward deficiency syndrome: a biogentic model for the diagnosis and treatment of implusive, addictive, and compulsive behaviors. Journal of Psychoactive Drugs 2000;32:1–112.

Bostwick JM, Pankratz SV. Affective Disorders and Suicide Risk: A Reexamination. American Journal of Psychiatry 2000;157:1925–1932. [PubMed: 11097952]

Brady KT, Myrick H, McElroy S. The relationship between substance use disorders, impulse control disorders, and pathological aggression. American Journal Addictions 1998;6:355–366.

Brizer DA. Psychopharmacology and the management of violent patients. Psychiatric Clinics of North America 1988;11:551–568. [PubMed: 2905453]

Brown GL, Goodwin FK, Ballenger JC, Gover PF. Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Research 1979;1:131–139. [PubMed: 95232]

Brunner D, Hen R. Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. Abdominal Aortic Aneurysm: Genetics, Pathophysiology, and Molecular 1997;836:81–105.

Buydens-Branchey L, Branchey MH, Noumair D, Lieber CS. Age of alcoholism onset. II. Relationship to susceptibility to serotonin precursor availability. Archives of General Psychiatry 1989;46:231–6. [PubMed: 2919952]

Carballo JJ, Oquendo MA, Giner L, Zalsman G, Roche AM, Sher L. Impulsive-aggressive traits and suicidal adolescents and young adults with alcoholism. Internation Journal of Adolescent Medicine and Health 2006;18:15–9.

Caspi A, Moffitt TE, Morgan J, Rutter M, Taylor A, Arseneault L, Tully L, Jacobs C, Kim-Cohen J, Polo-Tomas M. Maternal expressed emotion predicts children's antisocial behavior problems: using monozygotic-twin differences to identify environmental effects on behavioral development. Developmental Psychology 2004;40:149–61. [PubMed: 14979757]

Cascella NG, Nagoshi CT, Muntaner C, Walter D, Haertzen CA, Kumor KM. Impulsiveness and subjective effects of intravenous cocaine administration in the laboratory. Journal of Substance Abuse 1994;6:355–366. [PubMed: 7780294]

Chengappa KN, Ebeling T, Kang JS, Levine J, Parepally H. Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder. Journal of Clinical Psychiatry 1999;60:477–484. [PubMed: 10453803]

Chotai J, Kullgren G, Asberg M. CSF monoamine metabolites in relation to the diagnostic interview for borderline patients (DIB). Neuropsychobiology 1998;38:207–212. [PubMed: 9813458]

Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Archives of General Psychiatry 1981;8:861–868. [PubMed: 7259422]

Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 1987;236:410–6. [PubMed: 2882604]

Coccaro EF. Central serotonin and impulsive aggression. British Journal of Psychiatry Supplements 1989;8:52–62.

Coccaro EF, Bergeman CS, McClearn GE. Heritability of irritable impulsiveness: a study of twins reared together and apart. Psychiatry Research 1993;48:229–42. [PubMed: 8272445]

Coccaro EF, Kavoussi RJ, Cooper TB, Hauger RL. Central serotonin activity and aggression: inverse relationship with prolactin response to *d*-fenfluramine, but not CSF 5-HIAA concentration, in human subjects. American Journal of Psychiatry 1997;154:1430–1435. [PubMed: 9326827]

Coccaro EF, Kavoussi RJ, Trestman RL, Gabriel SM, Cooper TB, Siever LJ. Serotonin function in human subjects: intercorrelations among central 5-HT indices and aggressiveness. Psychiatry Research 1997;73:1–14. [PubMed: 9463834]

Coccaro, EF.; Siever, LJ. The neuropsychopharmacology of personality disorders. In: Davis, K.; Charney, D.; Coyle, J.; Nemeroff, C., editors. Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia: Lippincott Williams & Wilkins; 2000.

Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL. Serotonergic studies in patients with affective and personality disorders: correlates with suicidal and impulsive aggressive behavior. Archives of General Psychiatry 1989;46:587–599. [PubMed: 2735812]

Comings DE, Blum K. Reward deficiency syndrome:genetic aspects of behavioral disorders. Progress In Brain Research 2000;126:325–341. [PubMed: 11105655]

Conner KR, Meldrum S, Wieczorek WF, Duberstein PR, Welte JW. The association of irritability and impulsivity with suicidal ideation among 15- to 20-year-old males. Suicide and Life-Threatening Behavoir 2004;34:363–73.

Courtet P, Baud P, Abbar M, Boulenger JP, Castelnau D, Mouthon D, Malafosse A, Buresi C. Association between violent suicidal behavior and the low activity allele of the serotonin transporter gene. Molecular Psychiatry 2001;6:338–41. [PubMed: 11326306]

Davidson RJ. Anxiety and affective style: role of prefrontal cortex and amygdale. Biological Psychiatry 2002;51:68–80. [PubMed: 11801232]

Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation-a possible prelude to violence. Science 2000;289:591–594. [PubMed: 10915615]

Daw ND, Kakade S, Dayan P. Opponent interactions between serotonin and dopamine. Neural Network 2002;15:603–16.

De Simoni MG, Dal Toso G, Fodritto F, Sokola A, Algeri S. Modulation of striatal dopamine metabolism by the activity of dorsal raphe serotonergic afferences. Brain Research 1987;411:81–88. [PubMed: 2440514]

Deakin JFW, Graeff FG. 5-HT and mechanisms of defence. Journal of Psyhopharmacology 1991;5:305–354.

Deater-Deckard K, Plomin R. An adoption study of the etiology of teacher and parent reports of externalizing behavior problems in middle childhood. Child Development 1999;70:144–54. [PubMed: 10191519]

Dolan RJ. On the neurology of morals. Nature Neuroscience 1999;11:927–929.

Dumais A, Lesage AD, Alda M, Rouleau G, Dumont M, Chawky N, Roy M, Mann JJ, Benkelfat C, Turecki G. Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. American Journal of Psychiatry 2005a;162:2116–2124. [PubMed: 16263852]

Dumais A, Lesage AD, Lalovic A, Seguin M, Tousignant M, Chawky N, Turecki G. Is violent method of suicide a behavioral marker of lifetime aggression? American Journal of Psychiatry 2005b;167 (7):1375–1378.

Everitt BJ, Robbins TW. Second-order schedules of drug reinforcement in rats and monkeys: measurement of reinforcing efficacy and drug-seeking behavior. Psychopharmacology (Berl) 2000;153:12–30.

Fairbanks LA, Melega WP, Jorgensen MJ, Kaplan JR, McGuire MT. Social impulsivity inversely associated with CSF 5-HIAA and fluoxetine exposure in vervet monkeys. Neuropsychopharmacology 2001;24:370–378. [PubMed: 11182532]

Fava M, Bless E, Otto MW, Pava JA, Rosenbaum JF. Dysfunctional a attitudes in major depression. Changes with pharmacotherapy. Journal of Nervous and Mental Disease 1994;182:45–9. [PubMed: 8277301]

Ferrari PF, vanErp AM, Tornatzky W, Miczek KA. Accumbal dopamine and serotonin in anticipation of the next aggressive episode in rats. European Journal of Neuroscience 2003;17:371–378. [PubMed: 12542674]

Fils-Aime ML, Eckardt MJ, George DT, Brown GL, Mefford I, Linnoila M. Early-onset alcoholics have lower cerebrospinal fluid 5-hydroxyindoleacetic acid levels than late-onset alcoholics. Archives of General Psychiatry 1996;53:211–6. [PubMed: 8611057]

Fletcher PJ. Injection of 5-HT into the nucleus accumbens reduces the effects of d-amphetamine on responding for conditioned reward. Psychopharmacology (Berl) 1996;126:62–9. [PubMed: 8853218]

Fletcher PJ, Korth KM, Chambers JW. Depletion of brain serotonin following intra-raphe injections of 5,7-dihydroxytryptamine does not alter d-amphetamine self-administration across different schedule and access conditions. Psychopharmacology (Berl) 1999;146:185–93. [PubMed: 10525754]

Friedel RO. Dopamine dysfunction in borderline personality disorder: a hypothesis. Neuropsychopharmacology 2004;29:1029–1039. [PubMed: 15039763]

Frankle W, Lombardo I, New A, Goodman M, Talbot P, Huang Y, Hwang D, Slifstein M, Curry S, Abi-Dargham A, Laruelle M, Siever L. Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [11C]McN 55652. American journal of psychiatry 2005;161(5):915–23. [PubMed: 15863793]

Gesch CB, Hammond SM, Hampson SE, Eves A, Crowder MJ. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. British Journal of Psychiatry 2002;181:22–28. [PubMed: 12091259]

Giammanco M, Tabacchi G, Giammanco S, Di Majo D, La Guardina M. Testosterone and aggressiveness. Medical Science Monitor 2005;11:136–145.

Gibbons JL, Barr GA, Bridger WH, Leibowitz SF. Manipulations of dietary tryptophan: effects on mouse killing and brain serotonin in the rat. Brain Research 1979;169(1):139–153. [PubMed: 572256]

Goldstein RZ, Alia-Klein N, Leskovjan AC, Fowler JS, Wang GJ, Gur RC, Hitzemann R, Volkow ND. Anger and depression in cocaine addiction: association with the orbitofrontal cortex. Psychiatry Research 2005;138:13–22. [PubMed: 15708297]

Goyer PF, Andreason PJ, Semple WE, Clayton AH, King AC, Compton-Toth BA, Schulz SC, Cohen RM. Positron-emission tomography and personality disorders. Neuropsychopharmacology 1994;10:21–28. [PubMed: 8179791]

Grafman J, Litvan I. Importance of deficits in executive functions. Lancet 1999;354:1921–1923. [PubMed: 10622291]

Hadfield MG. Dopamine: mesocortical versus nigrostriatal uptake in isolated fighting mice and controls. Behavioral Brain Research 1983;7:269–281.

Harrison AA, Everitt BJ, Robbins TW. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology (Berl) 1997;133:329–342. [PubMed: 9372531]

Hawton K, Houston K, Haw C, Townsend E, Harris L. Comorbidity of axis I and axis II disorders in patients who attempted suicide. American Journal of Psychiatry 2003;160:1494–1500. [PubMed: 12900313]

Heinrichs RW. Frontal cerebral lesions and violent incidents in chronic neuropsychiatric patients. Biological Psychiatry 1989;25:174–178. [PubMed: 2930801]

Heinz AJ, Dee Higley JG, Gorey RC, Saunders DW, Jones D, Hommer K, Zajicek SJ, Suomi, Klaus-Peter Lesch DR, Weinberger, Markku Linnoila. In vivo association between alcohol intoxication, aggression, and serotonin transporter availability in nonhuman primates. American Journal of Psychiatry 1998;155:1023–1028. [PubMed: 9699688]

Henriksson MM, Aro HM, Marttunen MJ, Heikkinen ME, Isometsä ET, Kuoppasalmi KI, Lönnqvist JK. Mental disorders and comorbidity in suicide. American Journal Psychiatry 1993;150:935–940.

Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ. Family transmission and heritability of externalizing disorders: a twin-family study. Archives of general psychiatry 2004;61(9):922–92. [PubMed: 15351771]

Higley JD, Bennett AJ. Central nervous system serotonin and personality as variables contributing to excessive alcohol consumption in non-human primates. Alcohol and Alcoholism 1999;34:402–418. [PubMed: 10414617]

Higley JD, King ST, Hasert MF, Champoux M, Suomi SJ, Linnoila M. Stability of interindividual differences in serotonin function and its relationship to severe aggression and competent social behavior in rhesus macaque females. Neuropsychopharmacology 1996;14:67–76. [PubMed: 8719031]

Higley JD, Linnoila M. Low central nervous system serotonergic activity is traitlike and correlates with impulsive behavior: a nonhuman primate model investigating genetic and environmental influences on neurotransmission. Alcohol and Wine In Health and Disease 1997;836:39–56.

Hirono N, Mega MS, Dinov ID, Mishkin F, Cummings JL. Left frontotemporal hypoperfusion is associated with aggression in patients with dementia. Archives of Neurology 2000;57:861–866. [PubMed: 10867784]

Hodge GK, Butcher LL. Catecholamine correlates of isolation-induced aggression in mice. European Journal of Pharmacology 1975;31:81–93. [PubMed: 1168580]

Horesh N, Gothelf D, Ofek H, Weizman T, Apter A. Impulsivity as a correlate of suicidal behavior in adolescent psychiatric inpatients. Crisis 1999;20:8–14. [PubMed: 10365500]

Hurd YL, Ungerstedt U. Cocaine: an in vivo microdialysis evaluation of its acute action on dopamine transmission in rat striatum. Synapse 1989;3:48–54. [PubMed: 2537539]

Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annual Review of Neuroscience 2006;29:565–98.

Ikemoto S, Panksepp J. The role of nucleus accumebs dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Research Reviews 1999;31:6–41. [PubMed: 10611493]

Kamali M, Oquendo MA, Mann JJ. Understanding the neurobiology of suicidal behavior. Depression and Anxiety 2001;14:164–76. [PubMed: 11747126]

Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. American Journal of Psychiatry 1996;153:436–476.

Kelland, MD.; Chiodo, LA. Serotoninergic modulation of midbrain dopamine systems. In: Ashby, CR., Jr, editor. The modulation of dopaminergic neurotransmission by other neurotransmitters. New York: CRC Press; 1996. p. 87-122.

Koller G, Preuß UW, Bottlender M, Wenzel K, Soyka M. Impulsivity and aggression as predictors of suicide attempts in alcoholics. European Archives of Psychiatry and Clinical Neurosciences 2002;252:155–160.

Kuikka JT, Tiihonen J, Bergstrom KA, Karhu J, Rasanen P, Eronen M. Abnormal structure of human striatal dopamine re-uptake sites in habitually violent alcoholic offenders: a fractal analysis. Neuroscience Letters 1998;253:195–197. [PubMed: 9792244]

Lapierre D, Braun CMJ, Hodgings S. Ventral frontal deficits in psychopathy: neuropsychological test findings. Neuropsychologia 1995;33:139–151. [PubMed: 7746360]

Lawrence AD, Calder AJ, McGowan SW, Grasby PM. Selective disruption of the recognition of facial expressions of anger. Neuroreport 2002;13:881–884. [PubMed: 11997706]

Lidberg L, Tuck JR, Asberg M, Scalia-Tomba GP, Bertilsson L. Homicide, suicide and CSF 5-HIAA. Acta Psychiatrica Scandinavica 1985;71:230–236. [PubMed: 2580421]

Linnoila VM, Virkkunen M. Aggression, suicidality, and serotonin. Journal of Clinical Psychiatry 1992;53:46–51. [PubMed: 1385390]

Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sciences 1983;33:2609–2614. [PubMed: 6198573]

Malone KM, Corbitt EM, Li S, Mann JJ. Prolactin response to fenfluramine and suicide attempt lethality in major depression. British Journal of Psychiatry 1996;168:324–329. [PubMed: 8833686]

Mammen OK, Kolko DJ, Pilkonis PA. Negative affect and parental aggression in child physical abuse. Child Abuse and Neglect 2002;26:407–24. [PubMed: 12092806]

Mann J, Malone K, Diehl D, Perel J, Nichols T, Mintun MA. Positron emissions tomographic imaging of sertonin activation effects on prefrontal cortex in healthy volunteers. Journal of cerebral blood flow and metabolism 1996;16(3):418–426. [PubMed: 8621746]

Mann JJ, Huang YY, Underwood MD, Kassir SA, Oppenheim S, Kelly TM, Dwork AJ, Arango V. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. Archives of General Psychiatry 2000;57:729–738. [PubMed: 10920459]

Mann JJ, Malone KM. Cerebrospinal fluid amines and higher-lethality suicide attempts in depressed inpatients. Biological Psychiatry 1997;41:162–71. [PubMed: 9018386]

Mann JJ, Stoff DM. A synthesis of current findings regarding neurobiological correlates and treatment of suicidal behavior. Abdominal Aortic Aneurysm: Genetics, Pathophysiology, and Molecular Biology 1997;836:352–63.

Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. American Journal of Psychiatry 1999;156:181–9. [PubMed: 9989552]

Mehlman PT, Higley JD, Faucher I, Lilly AA, Taub DM, Vickers J, Suomi SJ, Linnoila M. Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. American Journal of Psychiatry 1994;152:1698–1699.

Michaelis BH, Goldberg JF, Davis GP, Singer TM, Garno JL, Wenze SJ. Dimensions of impulsivity and aggression associated with suicide attempts among bipolar patients: a preliminary study. Suicide and Life Threatening Behavior 2004;34:172–6. [PubMed: 15191273]

Miczek KA, DeBold JF, Van Erp AM. Neuropharmacological characteristics of individual differences in alcohol effects on aggression in rodents and primates. Behavioral Pharmacology 1994;5:407–421.

Miczek KA, Fish EW, DeBold JF, de Almeida RMM. Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and y-aminobutyric acid systems. Psychopharmacology 2002;163:434–458. [PubMed: 12373445]

Miczek KA, Haney M. Psychomotor stimulant effects of d-amphetamine, MDMA and PCP: aggressive and schedule-controlled behavior in mice. Psychopharmacology (Berl) 1994;115:358–365. [PubMed: 7871076]

Miczek KA, Weerts E, Haney M, Tidey J. Neurobiological mechanisms controlling aggression: preclinical developments for pharmacotherapeutic interventions. Neuroscience Biobehavioral Review 1994;18:97–110.

Miczek KA, Yoshimura H. Disruption of primate social behavior by d-amphetamine and cocaine: differential antagonism by antipsychotics. Psychopharmacology (Berl) 1982;76:163–171. [PubMed: 6123132]

Millan MJ, Dekeyne A, Gobert A. Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NAD), but not 5-HT, release in the frontal cortex in vivo. Neuropharmacology 1998;37:953–955. [PubMed: 9776391]

Moore T, Scarpa A, Raine A. A Meta-Analysis of Serotonin Metabolite 5-HIAA and Antisocial Behavior. Aggressive Behavior 2002;28:299–316.

Mulder RT, Porter RJ, Joyce PR. The prolactin response to fenfluramine in depression: effects of melancholia and baseline cortisol. Journal of Psychopharmacology 2003;17:97–102. [PubMed: 12680745]

Nader MA, Morgan D, Gage HD, Nader SH, Calhoun TL, Buchheimer N, Ehrenkaufer R, Mach RH. PET imaging of dopamine D_2 receptors during chronic cocaine self-administration in monkeys. Nature Neuroscience 2006;9:1050–1056.

Netter P, Rammsayer T. Reactivity to dopaminergic drugs and aggression related personality traits. Personality and Individual Differences 1991;12:1009–1017.

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Reynolds D, Mitropoulou V, Sprung L, Shaw RB Jr, Koenigsberg H, Platholi J, Silverman J, Siever LJ. Blunted prefrontal cortical 18fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. Archives of General Psychiatry 2002;59(7):621–629. [PubMed: 12090815]

Newman ME, Shapira B, Lerer B. Evaluation of central serotonergic function in affective and related disorders by the fenfluramine challenge test: a critical review. International Journal of Neuropsychopharmacology 1998;1:49–69. [PubMed: 11281946]

Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 2004;2:483–499. [PubMed: 15488398]

Oquendo MA, Placidi GP, Malone KM, Campbell C, Keilp J, Brodsky B, Kegeles LS, Cooper TB, Parsey RV, Van Heertum RL, Mann JJ. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. Archives of General Psychiatry 2003;60:14–22. [PubMed: 12511168]

Ossowska G, Kenk-Majewska B, Zebrawska-Lupina L. Acute effect of dopamine agonists and some antidepressants in stress-induced deficit of fighting behavior. Polish Journal of Pharmacology 1996;48:403–408. [PubMed: 9112680]

Parsey RV, Oquendo MA, Simpson NR, Ogden RT, Van Heertum R, Arango V, Mann JJ. Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT1A receptor binding potential measured by PET using [C-11]WAY-100635. Brain Research 2002;954:173–182. [PubMed: 12414100]

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. Biological Psychiatry 2005;57(3):210–219. [PubMed: 15691521]

Pietrini P, Guazzelli M, Basso G, Jaffe K, Grafman J. Neural correlates of imaginal aggressive behavior assessed by positron emission tomography in healthy subjects. American Journal of Psychiatry 2000;11:1772–1781. [PubMed: 11058474]

Placidi GP, Oquendo MA, Malone KM, Huang YY, Ellis SP, Mann JJ. Aggressivity, suicide attempts, and depression: relationship to cerebrospinal fluid monoamine metabolite levels. Biological Psychiatry 2001;50:783–91. [PubMed: 11720697]

Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. Journal of Neuroscience 2000;20:6225–6231. [PubMed: 10934272]

Raine A, Lencz T, Bihrle S, LaCasse L, Colletti P. Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. Archives of General Psychiatry 2000;57:119–29. [PubMed: 10665614]

Raine A, Mellingen K, Liu J, Venables P, Mednick SA. Effects of environmental enrichment at ages 3–5 years on schizotypal personality and antisocial behavior at ages 17 and 23 years. American Journal of Psychiatry 2003;160:1627–35. [PubMed: 12944338]

Raine A, Meloy JR, Bihrle S, Stoddard J, LaCasse L, Buchsbaum MS. Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behavioral Science and the Law 1998;16:319–32.

Raine A, Stoddard J, Bihrle S, Buchsbaum M. Prefrontal glucose deficits in murderers lacking psychosocial deprivation. Neuropsychiatry Neuropsycholpgy Behavioral Neurology 1998;11:1–7.

Raleigh MJ, McGuire MT, Brammer GL, Pollack DB, Yuwiler A. Serotonergic mechanisms promote dominance acquisition in adult male vervet monkeys. Brain Research 1991;559:181–190. [PubMed: 1794096]

Robinson W, Galetta SL, McCluskey L, Forman MS, Balcer LJ. Retinal findings in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (cadasil). Survey of Ophthalmol 2001;45:445–8.

Rocca P, Marchiaro L, Cocuzza E, Bogetto F. Treatment of borderline personality disorder with risperidone. Journal of Clinical Psychiatry 2002;63:241–244. [PubMed: 11926724]

Rujescu D, Giegling I, Bondy B, Gietl A, Zill P, Moller HJ. Association of anger-related traits with SNPs in the TPH gene. Molecular Psychiatry 2002;7:1023–9. [PubMed: 12399958]

Schulz SC, Camlin KL, Berry SA, Jesberger JA. Olanzapine safety and efficacy in patients with borderline personality disorder and comorbid dysthymia. Biological Psychiatry 1999;46:1429–1435. [PubMed: 10578457]

Sher L. Alcohol and suicide: neurobiological and clinical aspects. Scientific World Journal 2006;6:700–706. [PubMed: 16799741]

Sher L, Oquendo MA, Galfalvy HC, Grunebaum MF, Burke AK, Zalsman G, Mann JJ. The relationship of aggression to suicidal behavior in depressed patients with a history of alcoholism. Addictive Behaviors 2005;30:1144–1153. [PubMed: 15925124]

Shi WX, Nathaniel P, Bunney BS. Ritanserine, a 5-HT2A/2C antagonist, reverses direct dopamine agonist-induced inhibition of midbrain dopamine neurons. Journal of Pharmacology Experimental Therapeutics 1995;274:735–740.

Siever LJ, Buchsbaum MS, New AS, Spiegel-Cohen J, Wei CT, Hazlett E, Sevin E, Nunn M, Mitropoulou V. D1-Fenfluramine response in impulsive personality disorder assessed with 18F-deoxyglucose positron emission tomography. Neuropsychopharmacology 1999;20:413–423. [PubMed: 10192822]

Siever LJ, Torgersen S, Gunderson JG, Livesley WJ, Kendler KS. The borderline diagnosis III: identifying endophenotypes for genetic studies. Biological Psychiatry 2002;51:964–968. [PubMed: 12062879]

Sigvardsson S, Bohman M, Cloninger CR. Replication of the Stockholm Adoption Study of alcoholism. Confirmatory cross-fostering analysis. Archives of General Psychiatry 1996;53(8):681–687. [PubMed: 8694681]

Soderstrom H, Blennow K, Manhem A, Forsman A. CSF studies in violent offenders: 5-HIAA as a negative and HVA as a positive predictor of psychopathy. Journal of Neural Transmission 2001;108:869–78. [PubMed: 11515752]

Soderstrom H, Blennow K, Sjodin AK, Forsman A. New evidence for an association between the CSF HVA:5-HIAA ratio and psychopathic traits. Journal of Neurology Neurosurgery and Psychiatry 2003;74:918–921.

Soloff PH, Meltzer CC, Greer PJ, Constantine D, Kelly TM. A fenfluramine-activiated FDG-PET study of borderline personality disorder. Biological psychiatry 2000;47(6):540–547. [PubMed: 10715360]

Sorensen SM, Kehne JH, Fadayel GM, Humphreys TM, Ketteler HJ, Sullivan CK, Taylor VL, Schmidt CJ. Characterization of the 5-HT2 receptor antagonist MDL100907 as a putative atypical antipsychotic: behavioral, electrophysiological and neurochemical studies. Journal of Pharmacology Experimental Therapeutics 1993;266:684–691.

Sostek AJ, Buchsbaum MS, Rapoport JL. Effects of amphetamine on vigilance performance in normal and hyperactive children. Journal of Abnormal Child Psychology 1980;8:491–500. [PubMed: 7462528]

Swann AC. Neuroreceptor mechanisms of aggression and its treatment. Journal of Clinical Psychiatry 2003;64:26–35. [PubMed: 12672262]

Tedlow J, Fava M, Uebelacker L, Nierenberg AA, Alpert JE, Rosenbaum J. Outcome definitions and predictors in depression. Psychotherapy and Psychosomatics 1998;67:266–70. [PubMed: 9693355]

Tidey JW, Miczek KA. Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. Brain Research 1996;721:140–149. [PubMed: 8793094]

Tiihonen J, Kuikka J, Bergstrom K, Hakola P, Karhu J, Ryynanen OP, Fohr J. Altered striatal dopamine re-uptake site densities in habitually violent and non-violent alcoholics. Nature Medicine 1995;1:654–657.

Traskman-Bendz L, Asberg M, Schalling D. Serotonergic function and suicidal behavior in personality disorders. Abdominal Aortic Aneurysm: Genetics, Pathophysiology, and Molecular 1986;487:168–74.

Tupala E, Hall H, Mantere T, Rasanen P, Sarkioja T, Tiihonen J. Dopamine receptors and transporters in the brain reward circuits of type 1 and 2 alcoholics measured with human whole hemisphere autoradiography. Neuroimage 2003;19:145–55. [PubMed: 12781734]

Tupala E, Hall H, Halonen P, Tiihonen J. Cortical dopamine D_2 receptors in type 1 and 2 alcoholics measured with human whole hemisphere autoradiography. Synapse 2004;54:129–137. [PubMed: 15452867]

Tupala E, Halonen P, Tiihonen J. Visualization of the cortical dopamine transporter in type 1 and 2 alcoholics with human whole hemisphere autoradiography. European Neuropsychopharmacology 2006;16(8):552–560. [PubMed: 16626947]

Turecki G. Dissecting the suicide phenotype: the role of impulsive-aggressive behaviours. Journal of Psychiatry and Neuroscience 2005;30:398–408. [PubMed: 16327873]

Van Erp AM, Miczek KA. Aggressive Behavior, Increased Accumbal Dopamine, and Decreased Cortical Serotonin in Rats. Journal of Neuroscience 2000;20:9320–9325. [PubMed: 11125011]

Virkkunen M, Nuutila A, Goodwin FK, Linnoila M. Cerebrospinal fluid monoamine metabolites in male arsonists. Archives of General Psychiatry 1987;44:241–247. [PubMed: 2435256]

Virkkunen M, De Jong J, Bartko JJ, Goodwin FK, Linnoila M. Relationship of psychobiological variables to recidivism in violent offenders and impulsive fire setters: a follow-up study. Archives of General Psychiatry 1989;46:600–603. [PubMed: 2472122]

Virkkunen M, Linnoila M. Brain serotonin, type II alcoholism and impulsive violence. Journal of Studies on Alcohol 1993;11:163–169.

Virkkunen M, Rawlings R, Tokola R, Poland RE, Guidotti A, Nemeroff CB, Bissette G, Kalogeras K, Karonen SL, Linnoila M. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. Archives of General Psychiatry 1994;51:20–27. [PubMed: 7506515]

Volavka J. The neurobiology of violence: an update. Journal of Neuropsychiatry and Clinical Neurosciences 1999;11:307–314. [PubMed: 10440006]

Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP. Decreased dopamine D_2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 1993;14:169–77. [PubMed: 8101394]

Volkow ND, Fowler JS, Wang GJ, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. Molecular Psychiatry 2004;9:557–69. [PubMed: 15098002]

Volkow ND, Wang GJ, Hitzemann R, Fowler JS, Wolf AP, Pappas N, Biegon A, Dewey SL. Decreased cerebral response to inhibitory neurotransmission in alcoholics. American Journal of Psychiatry 1993;150:417–422. [PubMed: 8382010]

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. Journal of Neuroscience 2006;26:6583–6588. [PubMed: 16775146]

Westergaard GC, Suomi SJ, Chavanne TJ, Houser L, Hurley A, Cleveland A, Snoy PJ, Higley JD. Physiological correlates of aggression and impulsivity in free-ranging female primates. Neuropsychopharmacology 2003;28:1045–1055. [PubMed: 12700686]

William SM, Goldman-Rakic PS. Widespread origin of the primate mesofrontal dopamine system. Cerebral Cortex 1998;8(4):321–345. [PubMed: 9651129]

Wong PT, Feng H, Teo WL. Interaction of the dopaminergic and serotonergic systems in the rat striatum: effects of selective antagonists and uptake inhibitors. Neuroscience Research 1995;23:115–9. [PubMed: 7501296]

Yan Z. Regulation of GABAergic inhibition by serotonin signaling in prefrontal cortex: molecular mechanisms and functional implications. Molecular Neurobiology 2002;26:203–216. [PubMed: 12428756]

Zanarini MC, Frankenburg FR, Prachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. Journal of Clinical Psychiatry 2004;65:903–7. [PubMed: 15291677]