

Dopamine Dysfunction in Borderline Personality Disorder: A Hypothesis

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Research on the biological basis of borderline personality disorder (BPD) has focused primarily on the serotonin model of impulsive aggression. However, there is evidence that dopamine (DA) dysfunction may also be associated with BPD. Pertinent research and review articles, identified by Medline searches of relevant topics, books, references from bibliographies, and conference proceedings from 1975 to 2003, were reviewed. Evidence of DA dysfunction in BPD derives from the efficacy of traditional and atypical antipsychotic agents in BPD, and from provocative challenges with amphetamine and methylphenidate of subjects with the disorder. In addition, human and animal studies indicate that DA activity plays an important role in emotion information processing, impulse control, and cognition. The results of this review suggest that DA dysfunction is associated with three dimensions of BPD, that is, emotional dysregulation, impulsivity, and cognitive-perceptual impairment. The main limitation of this hypothesis is that the evidence reviewed is circumstantial. There is no study that directly demonstrates DA dysfunction in BPD. In addition, the therapeutic effects of antipsychotic agents observed in BPD may be mediated by non-DA mechanisms of action. If the stated hypothesis is correct, DA dysfunction in BPD may result from genetic, developmental, or environmental factors directly affecting specific DA pathways. Alternatively, DA dysfunction in BPD may be a compensatory response to alterations in the primary neural systems that control emotion, impulse control, and cognition, and that are mediated by the brain's main neurotransmitters, glutamate, and GABA, or in one or more other neuromodulatory pathways such as serotonin, acetylcholine, and norepinephrine.

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INTRODUCTION

BPD is characterized by: (1) emotional dysregulation; (2) impulsivity; (3) cognitive-perceptual impairment; and (4) disturbed relationships (American Psychiatric Association, 2001). Research on the biological basis of BPD has focused primarily on the relationships between impulsive aggression and serotonin (5-HT) dysfunction (Silk, 2000; Skodol *et al*, 2002). To a lesser degree, emotional dysregulation has been correlated with imbalances in cholinergic, noradrenergic, and GABAergic neurotransmission (Skodol *et al*, 2002; Gurvits *et al*, 2000). A recent integration of the biological, psychosocial, and clinical findings in BPD does not mention

a potential role of DA dysfunction in the disorder (Schmahl *et al*, 2002).

This body of work leaves unexplained the efficacy of low doses of traditional neuroleptics and atypical antipsychotic agents in the treatment of patients with BPD (American Psychiatric Association, 2001; Table 1). The most commonly cited models of the mechanisms of action of antipsychotic agents in other mental disorders specify their capacity to block D2 (Kapur and Seeman, 2001), or D2 and 5-HT₂ (Meltzer, 1989) receptors. In addition, this body of work does not consider evidence from animal and human studies that implicate DA activity in emotion information processing, impulse control, and cognition (Table 2). For example, DA modulates emotional responses to salient positive and negative events and arousal-producing stimuli (Everitt *et al*, 2000; Horvitz, 2000; Liberzon *et al*, 2003), and modulates working memory and cognition (Arnsten *et al*, 1994; Goldman-Rakic, 1996; Arnsten and Goldman-Rakic, 1998). There is evidence that CSF HVA levels may be related to impulsive behavior in patients with BPD (Coccaro, 1998; Chotai *et al*, 1998). Therefore, this review evaluated data relevant to the hypothesis that DA dysfunction in specific neural pathways is associated with one or more of the behavioral dimensions of BPD.

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Table 1 Summary of Effects of Traditional and Atypical Antipsychotic Agents in Placebo-Controlled Trials on Behavioral Dimensions of Borderline Personality Disorder

Agent studied	Mean dose (mg)	Sample size (AA/P)	Study period (weeks)	Results		References
				Drug-placebo differences	Net effect size (%) ⁺	
<i>Emotional dysregulation</i>						
Thiothixene	8.7/day	24/26	12	Phobic anxiety*** Obsessive-compulsive*	IWS IWS	Goldberg <i>et al</i> (1986)
Haloperidol	4.8/day	28/28	5	Depression HAM-D-24* Beck** HSCL-90*	21 30 24	Soloff <i>et al</i> (1986, 1989)
Trifluoperazine	7.8/day	7/15	6	Obsessive-compulsive* Anxiety** Depression*	24 43 36	Cowdry and Gardner (1988)
Olanzapine	5.33/day	19/9	26	Anxiety**	35 37	Zanarini and Frankenberg (2001)
<i>Impulsivity</i>						
Flupenthixol	20 im q 4 weeks	14/16	26	Suicide attempts**	73	Montgomery and Montgomery (1982)
Haloperidol				Hostility** Hostile belligerence** Excitement* Impulsivity patterns* Impulse control**	45 62 51 67 19	Soloff <i>et al</i> (1986, 1989)
Trifluoperazine				Suicidality**	40	Cowdry and Gardner (1988)
Olanzapine				Anger/hostility*	NA	Zanarini and Frankenberg (2001)
<i>Cognitive perceptual impairment</i>						
Thiothixene				Illusions*** Ideas of reference* Psychoticism***	IWS IWS IWS	Goldberg <i>et al</i> (1986)
Haloperidol				Psychoticism* Paranoid ideation*** Paranoid projection*	25 45 35	Soloff <i>et al</i> (1986, 1989)
Olanzapine				Paranoia*	NA	Zanarini and Frankenberg (2001)
<i>Disturbed relationships</i>						
Haloperidol				Global functioning* Interpersonal sensitivity**	12 30	Soloff <i>et al</i> (1986, 1989)
Trifluoperazine				Rejection sensitivity**	36	Cowdry and Gardner (1988)
Olanzapine				Interpersonal sensitivity**	NA	Zanarini and Frankenberg (2001)
Haloperidol	4/d	30/28	5	No drug effects detected		Soloff <i>et al</i> (1993)

AA—antipsychotic agent; +—effect sizes were calculated from data presented; IWS—increases with severity; NA—data not available; *—less than or equal to .05; **—less than or equal to 0.01; ***—less than or equal to 0.001.

METHODS

Pertinent research and review articles, identified by Medline searches of relevant topics, books, references from bibliographies, and conference proceedings from 1975 to 2003 were reviewed.

RESULTS

Two main lines of evidence appear to implicate DA dysfunction in BPD: (1) pharmacological studies of patients and subjects with BPD; and (2) animal and human research

Table 2 Summary of Evidence from Human and Animal Studies of Dopamine Dysfunction in the Behavioral Dimensions of Borderline Personality Disorder

Emotional dysregulation	Impulsivity	Cognitive-perceptual impairment
Effects of amphetamine and methylphenidate in subjects with BPD (Schulz <i>et al</i>, 1985, 1988; Lucas <i>et al</i>, 1987)		
Produce affective changes	Produce impulsivity	Produce psychosis and thought disturbance
Other human and animal studies		
DA modulates responses to positive/negative rewards, salient events and arousal-producing stimuli (Everitt <i>et al</i> , 2000; Liberzon <i>et al</i> , 2003; Horvitz, 2000)	CSF HVA levels are related to impulsivity in BPD (Coccaro, 1998; Chotai <i>et al</i> , 1998); to self-injurious and violent behavior (Winchel and Stanley, 1991; Soderstrom <i>et al</i> , 2001)	DA receptor activity in the DLPFC modulates working memory and cognition (Amsten <i>et al</i> , 1994; Goldman-Rakic, 1996; Amsten and Goldman-Rakic, 1998)
DA modulates emotional responses mediated by the amygdala-VTA-PFC circuits (Horvitz, 2000)	DA dysfunction is involved in drug addiction (Modell <i>et al</i> , 1993; Volkow and Fowler, 2000)	PCP-induced cognitive impairment correlates with DA levels in the DLPFC (Jentsch <i>et al</i> , 1997)
Stress alters DA activity in the amygdala and PFC (Finlay and Zigmond, 1997; Doherty and Gratton, 1999)	DA mediates aggression and attack in rats (Wade <i>et al</i> , 2000; Vukhac <i>et al</i> , 2001)	DA modulates cognitive processes at NMDA receptors (Williams and Goldman-Rakic, 1995)
DA modulates conditioned fear responses (Guarraci <i>et al</i> , 1999)	DA stimulates impulsive behavior in rats (Harrison <i>et al</i> , 1997)	DI agonist dihydrexidine enhances cognitive performance and stimulates Ach release in the PFC (Steele <i>et al</i> , 1997; Schneider <i>et al</i> , 1994)
	Microdialysates of the PFC and the NAC suggest DA dysfunction is a risk factor for impulsivity (Van Erp and Miczek, 2000; Dalley <i>et al</i> , 2002)	DA dysfunction in the DLPFC is related to cognitive impairment in SCZ, SPD, and normal subjects (Goldberg <i>et al</i> , 2003; Siever <i>et al</i> , 2002)

DA—dopamine; CSF HVA—spinal fluid homovanillic acid; DLPFC—dorsolateral prefrontal cortex; PCP—phencyclidine; VTA—ventral tegmental area; PFC—prefrontal cortex; Ach—acetylcholine; NAC—nucleus accumbens; SCZ—schizophrenia; SPD—schizotypal personality disorder.

implicating DA activity in emotion information processing, impulse control, and cognition.

Pharmacological Evidence

Placebo-controlled clinical trials of antipsychotic agents in BPD. Five of six placebo-controlled studies testing the efficacy of traditional and atypical antipsychotic agents in BPD have demonstrated significant drug effects (Table 1). As would be expected, the drugs tested consistently reduced the psychotic features of BPD. However, significant improvement was also noted in the areas of emotional dysregulation and impulsivity in four of the trials, respectively.

A number of open label trials of atypical antipsychotic agents in the treatment of BPD have been reported, including risperidone (Szigethy and Schulz, 1997; Rocca *et al*, 2002), clozapine (Frankenburg and Zanarini, 1993; Benedetti *et al*, 1998; Chengappa *et al*, 1999), and olanzapine (Schulz *et al*, 1999), uniformly suggesting efficacy in one or more of the dimensions of BPD.

Traditional and atypical antipsychotic agents are thought to act primarily through the blockade of D2 receptors (Kapur and Seeman, 2001). However, there is evidence that other mechanisms of action may also be important, such as 5-HT₂ receptor blockade (Meltzer, 1989).

Amphetamine and methylphenidate challenge studies in BPD. Three placebo-controlled studies of agents that mainly

challenge the DA system have been reported in subjects with BPD (Table 2). Amphetamine (AMPH) produced symptoms of psychosis in four of eight subjects with BPD, and a significant increase in global well being (Schulz *et al*, 1985). AMPH produced a greater increase in BPRS scores in subjects with BPD and schizotypal personality disorder (SPD) than in subjects with only BPD (Schulz *et al*, 1988). Subjects with BPD and SPD typically rated themselves worse after AMPH, while those with BPD alone usually reported themselves improved. Finally, in two of three subjects with BPD, methylphenidate caused affective symptoms, excitation, decreased impulse control, and cognitive disturbances similar to those experienced under stress (Lucas *et al*, 1987). It should be noted that although AMPH and methylphenidate are known to exert significant effects on CNS DA activity, they also affect other neurotransmitter systems, such as norepinephrine.

The Effects of Dopamine in Human and Animal Studies

DA effects on emotion. The extended amygdala plays a central role in the determination of positive and negative affects and the generation of species-specific responses (Davidson, 2001; Amaral, 2002; Liberzon *et al*, 2003). Information from sensory pathways and from stored experiences enters and is processed in the lateral and basal nuclei of the amygdala (Figure 1) (Pitkanen, 2000). The central nucleus of the amygdala provides the main efferents from the amygdala to the ventral tegmental area (VTA), the

primary source of DA fibers to corticolimbic structures. Connections between the amygdala and the VTA directly link emotional states with CNS DA activity. Therefore, it is possible that reciprocal DA projections from the VTA to the amygdala (Figure 1) may not properly modulate DA effects on emotional reactivity in individuals with BPD.

Motivation/reward: Dopamine activity in the nucleus accumbens (NAC) appears to play a major role in the positive reinforcement of conditioned, goal-directed behaviors and the experience of pleasure (Everitt *et al*, 2000), as well as salient non-reward events and arousal-producing environmental changes (Horvitz, 2000; Liberzon *et al*, 2003). The rich innervation of the NAC by the amygdala directly, and indirectly through the VTA (Figure 1) (Pitkanen, 2000), suggests that the amygdala exerts significant influence over the activity of these DA-modulated behavioral systems. A recent report indicates that cAMP-dependent protein kinase (PKA) activity in the amygdala can facilitate reward-related learning (Jentsch *et al*, 2002). PKA regulates DA- and cAMP-regulated phosphoprotein (DARPP-32) (Greengard, 2001). Dysphoric symptoms common in BPD may be related in part to DA dysfunction in these neural circuits.

Stress responses: The connections between the amygdala and the orbitomedial wall of the prefrontal cortex (PFC), including the anterior cingulate cortex (ACC), are critical in the conscious recognition, learning, and modulation of emotional responses to important external and internal

stimuli (Figure 1) (Bechara *et al*, 2000; Davidson, 2002), and are modulated by DA activity (Rosenkranz and Grace, 2001). Stress induces release of DA in the NAC, but more strongly in the medial PFC (Finlay and Zigmond, 1997). This results in increased activation of local GABA transmission in the PFC that ultimately inhibits the DA response of the NAC to stress (Doherty and Gratton, 1999). Compared to controls, subjects with BPD demonstrate a decrease in amygdala volume (Rusch *et al*, 2003), an increase in amygdala activation bilaterally (Herpertz *et al*, 2001), and frontal and prefrontal hypermetabolism (Juegling *et al*, 2003). DA dysregulation in these neural circuits could result in an inappropriate balance of amygdala and prefrontal cortical activity in response to affect-inducing stimuli. A specific example of how this could operate in BPD is the conditioned fear response.

Conditioned fear responses: Fear-evoking stimuli processed in the amygdala are projected to subcortical structures to initiate rapid, organized, automatic conditioned fear responses (Figure 1) (LeDoux, 1996; Iversen *et al*, 2000). Sensory information is also transmitted to the cortical component of the conditioned fear neural system for processing, integration, and modulation of the rapid, conditioned responses initiated by the amygdala. Though slower than the amygdala component, the cortical component is more specific and brings conditioned emotional responses under a measure of conscious control through inhibitory feedback loops from the PFC to the amygdala, striatum, and critical brain stem nuclei. There is evidence

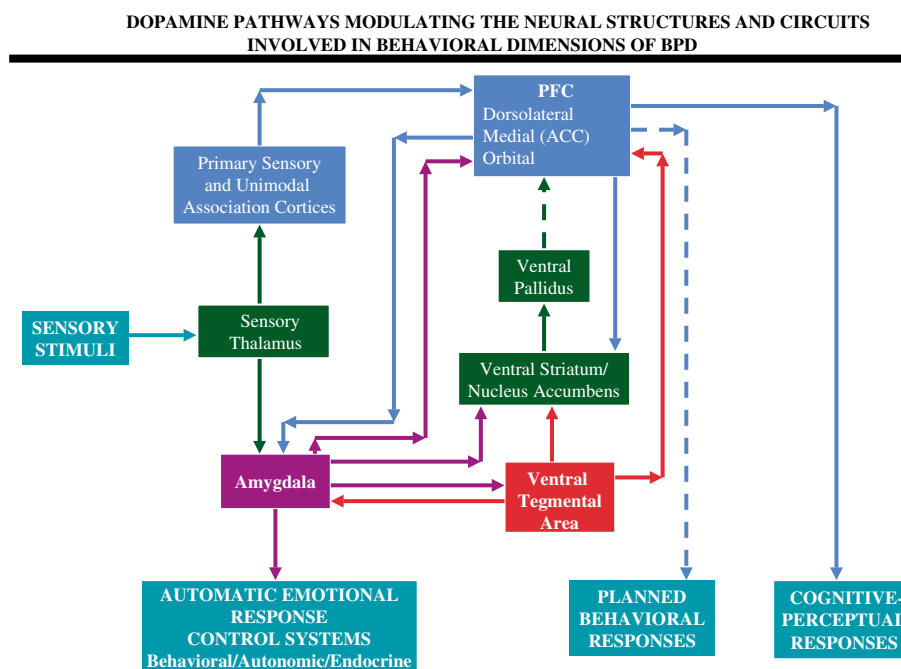


Figure 1 Sensory information is split at the thalamus and processed rapidly by the amygdala (AMG) to determine emotional valence. The AMG then initiates automatic, species-specific responses, signals the VTA to stimulate DA release when indicated, and projects information to the PFC, either directly or indirectly through the ventral striatum/nucleus accumbens (VS/NAC). The PFC also receives sensory stimuli directly from the thalamus for processing, resulting in a measure of cognitive control over emotional responses generated by subcortical systems via projections back to the AMG and the VS/NAC from the medial and orbital PFC, especially from the ACC. The dorsolateral PFC receives information from other PFC regions and from subcortical structures, including the VTA, and mediates the processes of working memory and components of executive function. Finally, integration of the functions of the different regions of the PFC may result in planned behavioral actions mediated by the pre-motor and motor cortices. DA pathways in red; - - - - -, intermediate structures not represented in pathways.

that DA activity in the amygdala is involved in fear conditioning (Guarraci *et al*, 1999). Dysregulated DA activity in the neural system regulating conditioned fear could result in the abnormal fear and anxiety responses prominent in BPD. In support of this is the finding that traditional and atypical antipsychotic agents significantly reduce anxiety in subjects with BPD (Table 1).

Anger: Evidence in support of critical roles of the extended amygdala and medial and lateral orbital PFC in the mediation and modulation of anger are derived from studies involving damage to these areas of the brain (Davidson *et al*, 2000), and from neuroimaging studies (Dougherty *et al*, 1999). The involvement of DA and 5-HT activity in the control of anger and aggression are discussed in the next section. In some studies, antipsychotic agents decrease anger in patients with BPD (Table 1).

Affect-driven memory: Strong connections between the amygdala and hippocampal formation establish part of the neuroanatomical framework for the processes of affect-driven memory formation and recall. As noted above, reward-related learning has been linked to activity in the amygdala of PKA, a modulator of DA signal transduction cascade pathways (Jentsch *et al*, 2002). Dysregulation of DA activity in the amygdala could account for the affect-related dissociative episodes observed in BPD.

Neuroimaging studies and emotion in BPD: There is evidence of structural and functional disturbances in the extended amygdala and related structures in subjects with BPD. Decreased volumes of the amygdala and hippocampus determined by MRI (Driessen *et al*, 2000; Rusch *et al*, 2003), and enhanced responses to emotionally aversive visual stimuli in the amygdala and medial and lateral orbital PFC measured by fMRI (Herpertz *et al*, 2001) have been reported in subjects with BPD. Facial expressions of emotion elicit significantly greater activation in the left amygdala in subjects with BPD compared with normal controls (Donegan *et al*, 2003). Levels of pessimistic attitudes correlate directly with 5-HT₂ receptor binding potential in depressed subjects, but not in those with BPD (Meyer *et al*, 2003). This does not rule out 5-HT dysfunction in BPD mediated by other 5-HT receptors. These and other neuroimaging studies demonstrate abnormalities in the structure and function in brain regions that mediate emotion information processing, impulsivity, and cognition. However, there are no published neuroimaging studies that evaluate DA turnover or DA-binding potential in subjects with BPD. This issue will be addressed further in the discussion section of this review.

DA effects on impulse control. Impulsive aggression appears to be directly related to a deficiency in CNS 5-HT activity across a wide range of ages, psychiatric diagnoses, and normative personality types (Silk, 2000; Skodol *et al*, 2002). Recent evidence supporting the role of 5-HT dysfunction in impulsive aggression in BPD has been provided by neuroimaging studies (Soloff *et al*, 2000; Leyton *et al*, 2001). However, the 5-HT hypothesis of impulsive aggression may be limited in scope (Oquendo and Mann,

2000). Four of six controlled trials of subjects with BPD treated with antipsychotic agents have shown a decrease in impulsive behavior (Table 1). In addition, there is evidence of a significant interaction between DA and 5-HT activity in impulsive behaviors.

CSF HVA and 5-HIAA levels in impulsive aggression and BPD: Most studies have not demonstrated a correlation of CSF HVA and impulsive aggression (Brown *et al*, 1982; Virkkunen *et al*, 1994; Coccaro, 1998). However, when CSF HVA levels are adjusted for CSF 5-HIAA, Coccaro (1998) reports a significant inverse relationship between aggression and CSF HVA levels in subjects with personality disorders. The complex relationship between 5-HT and DA in impulsive behavior is further demonstrated in a recent study of the correlation between CSF 5-HIAA and HVA levels and scores on the Diagnostic Interview for Borderlines (DIB) in a large sample of patients with BPD (Chotai *et al*, 1998). Patients with an intermediate score on the impulse action subscale of the DIB had significantly higher levels of 5-HIAA and HVA than patients with low and with high scores. There is also evidence that patients with disorders other than BPD, who demonstrate severe self-injurious behavior, have low CSF HVA levels and increased DA receptor sensitivity (Winchel and Stanley, 1991). In violent offenders, interpersonal and behavioral measures of psychopathy are related to high CSF HVA and low CSF 5-HIAA (Soderstrom *et al*, 2001).

DA dysfunction in alcoholism: Studies suggest that impulsivity in drug abuse results from decreased frontostriatal inhibitory responses to drugs that reinforce the DA-mediated motivation/reward system (Modell *et al*, 1993; Kuikka *et al*, 1998; Jentsch and Taylor, 1999). VTA DA projection neurons are under inhibitory control by 5-HT, mediated by 5-HT_{2C} receptors (Di Matteo *et al*, 2002). 5-HT_{2A} and 5-HT_{2C} receptors modulate DA release induced by amphetamine and morphine, respectively, in the NAC and striatum, and 5-HT_{2C} receptors selectively modulate the impulse-flow-dependent release of DA (Porras *et al*, 2002).

Volkow and Fowler (2000) provide evidence that the orbital PFC is hypoactive relative to the levels of DA D₂ receptors in the ventral striatum in addicted individuals during protracted withdrawal. However, during drug-induced craving, the orbital PFC is hypermetabolic. This suggests that the high co-morbidity of drug abuse and BPD (Zanarini *et al*, 1998) may be partly related to an imbalance of DA activity in the ventral striatum and reciprocal orbital PFC inhibitory responses.

DA dysfunction and impulsive behaviors in animals: Recent evidence suggests that the NAC, well innervated by DA neurons, plays an important role in impulsive choice in rats (Cardinal *et al*, 2001). Aggressive and impulsive behaviors in rodents are modulated, in part, by DA activity at D₁ and D₂ receptors (Harrison *et al*, 1997; Vukhac *et al*, 2001). Dopamine-stimulated impulsive responses in rats are increased by central 5-HT depletion (Harrison *et al*, 1997). Microdialysates of the NAC and the medial PFC collected during behaviors measuring impulse control suggest that

both DA and 5-HT dysfunction are risk factors of impulsivity (Van Erp and Miczek, 2000; Dalley *et al*, 2002).

DA effects on cognition.

DA dysfunction in psychotic features of BPD: Psychotic features in subjects with BPD respond well to antipsychotic agents (Table 1), and are induced in some subjects with BPD by AMPH and methylphenidate provocative challenges (Table 2).

DA dysfunction in nonpsychotic cognitive symptoms of BPD: Neuropsychological testing demonstrates nonpsychotic cognitive deficits in BPD, including impairments in reasoning, learning, memory, and executive functions (O'Leary, 2000). Neuroimaging studies in subjects with BPD indicate structural and functional changes in brain regions critical to cognitive activity, such as decreases in frontal lobe and hippocampal volumes (Driessen *et al*, 2000; Lyoo *et al*, 1998; Rusch *et al*, 2003), and changes in frontal lobe glucose metabolism (Goyer *et al*, 1994; De la Fuente *et al*, 1997; Juengling *et al*, 2003). Tebartz van Elst *et al* (2001) report a significant reduction of *N*-acetylaspartate concentration (a proposed measure of neuronal integrity) in the dorsolateral prefrontal cortex (DLPFC) measured by ¹H-MRS in patients with BPD compared to controls. Memories of abandonment were associated with greater blood flow in the DLPFC bilaterally and in the right cuneus in women with BPD than in women without BPD (Schmahl *et al*, 2003). Evidence suggests that nonpsychotic cognitive disturbances in schizophrenia and normal subjects (Goldberg *et al*, 2003), and in schizotypal personality disorder (Siever *et al*, 2002), are due to hypodopaminergic activity in the PFC.

Animal studies provide the bulk of the evidence that cognitive function is modulated by DA activity in specific prefrontal cortical areas (Table 2). The DLPFC is important in the implementation of cognitive control, and the ACC in responding to incongruent stimuli, the monitoring of responses and initiating mid-course corrections in behavior (MacDonald *et al*, 2000; Shima and Tanji, 1998). D1 receptors predominate in the human cortical mantle (Hurd *et al*, 2001), and there is strong evidence that DA neurons projecting from the VTA to the DLPFC (Figure 1) serve to modulate working memory and cognition through their effects on D1 receptors (Arnsten *et al*, 1994; Goldman-Rakic, 1996). The effect is bimodal. At low levels of DA activity, working memory is enhanced, while at moderate to high DA levels, working memory is impaired (Arnsten *et al*, 1994).

In monkeys, the performance of routine tasks is typically enhanced by stress, while even low to moderate levels of uncontrollable stress impair cognitive function through a hyperdopaminergic mechanism that is blocked by haloperidol, a mixed D1 and D2 receptor antagonist, and SCH 23390 (Arnsten and Goldman-Rakic, 1998). Cognitive impairment in monkeys can be produced by repeated treatment with phencyclidine (PCP) (Jentsch *et al*, 1997). The impairment produced by PCP, a glutamatergic antagonist, correlates significantly with a decrease in DA levels only in the DLPC and in the prelimbic cortex, and is reversed by clozapine.

Brembs *et al*, (2002) have demonstrated in *Aplysia* a cellular model of DA enhanced instrumental conditioning.

DA modulates cognitive processes in the PFC by gating glutamate activity at NMDA receptors (Williams and Goldman-Rakic, 1995). Glutamate upregulates DA D1 receptors by NMDA receptor activation (Scott *et al*, 2002). Any alteration in these mechanisms could cause an impairment of DA-modulated cognitive function (Jentsch *et al*, 1997). In addition, the D1 agonist dihydrexidine releases acetylcholine in the PFC and enhances cognitive performance in rats (Steele *et al*, 1997) and in monkeys (Schneider *et al*, 1994), effects blocked by SCH 23390. Of interest in this regard is the recent finding that atypical, but not traditional antipsychotic drugs increase cortical acetylcholine release in the PFC with no effect in the nucleus accumbens or striatum (Ichikawa *et al*, 2002).

DISCUSSION

Pharmacological Evidence

The strongest evidence supporting DA dysfunction in BPD derives from the therapeutic effects of antipsychotic agents on emotional dyscontrol, impulsivity, and cognitive impairment in controlled clinical trials (Table 1). There is evidence that disturbed relationships in BPD result from the social impairments caused by the other behavioral dimensions of the disorder (Koenigsberg *et al*, 2001). Effect sizes are clinically significant in all the three behavioral dimensions. They are comparable to those typically demonstrated in antidepressant clinical trials (Khan *et al*, 2000), and the percentage of trials showing efficacy (> 80%) is superior to results reported in standard antidepressant and anxiolytic clinical trials (~ 50%) (Khan *et al*, 2002). As these agents are thought to exert their therapeutic effects in other patient populations mainly by D2 (Kapur and Seeman, 2001), or by D2 and 5-HT₂ (Meltzer, 1989) receptor blockade, it is reasonable to consider similar mechanisms of action in BPD, thereby implicating DA dysfunction in these three dimensions of the disorder. Owing to the methodological limitations mainly involving sample size and diagnostic heterogeneity of subjects, the stimulant challenge studies (Table 2) add only a modest increment of support to the hypothesis.

DA Effects on Emotion in Human and Animal Studies

The neural circuits connecting the amygdala, NAC, and PFC areas associated with recognition and control of emotion (Pitkanen, 2000; Amaral, 2002) provide the neural pathways by which DA dysfunction could play a significant role in the dimension of emotional dysregulation in BPD. This proposal is supported by the relationships of DA activity in the extended amygdala, NAC, and PFC to fear conditioning (Guarraci *et al*, 1999), motivation, reward, and stress (Horvitz, 2000; Finlay and Zigmond, 1997), and of DA and 5-HT activity in these structures in anger (Swann, 2003). Of interest is the recent report by Jentsch *et al* (2002) that cAMP-dependent protein kinase (PKA) activity in the amygdala can facilitate reward-related learning. PKA regulates the activity of DA- and cAMP-regulated phosphoprotein (DARPP-32) (Greengard, 2001).

These findings raise the possibility that DA dysfunction affecting the motivation/reward neural circuits may be related to impaired motivation and positive behavioral reinforcement in BPD, and suggest a biochemical mechanism of action.

Finally, neuroimaging studies demonstrate structural abnormalities in the amygdala (Driessen *et al*, 2000, Schmahl *et al*, 2003), and enhanced responses to emotionally aversive stimuli in the amygdala and medial and lateral orbital PFC in subjects with BPD (Herpertz *et al*, 2001; Donegan *et al*, 2003). In sum, the studies of subjects with BPD and the animal and human studies on the neural basis of emotion and reward suggest a link between the pathophysiology of the neural circuits affected in BPD to DA dysfunction. However, more definitive studies establishing this relationship are indicated as noted below.

DA Effects on Impulsivity in Human and Animal Studies

There is strong evidence of 5-HT dysfunction in impulsive aggression across a broad population range including BPD (Silk, 2000; Skodol *et al*, 2002). Neuroimaging studies consistently demonstrate a decrease in 5-HT function in the medial PFC of subjects with BPD, which correlates with the degree of impulsive aggression (Soloff *et al*, 2000; Leyton *et al*, 2001). However, the evidence from human and animal studies reviewed above suggests a reciprocal interaction of DA hyperactivity and 5-HT hypoactivity in this dimension of BPD (Table 2). A possible biochemical mechanism of this interaction will be discussed below.

DA Effects on Cognition in Human and Animal Studies

The most robust evidence of DA dysfunction affecting cognition in BPD is the effect of antipsychotic agents on psychotic features of the disorder (Table 1). Current hypotheses and evidence suggesting the roles of DA (Kapur and Seeman, 2001), and DA and 5-HT (Meltzer, 1989) dysfunction in psychotic symptoms support this contention. Other evidence cited (Table 2) suggest that DA dysfunction may also be involved in more subtle cognitive disturbances manifested by subjects with BPD (O'Leary, 2000), consistent with similar findings in schizophrenia (Goldberg *et al*, 2003) and SPD (Siever *et al*, 2002).

Numerous animal studies also indicate that DA activity plays a significant role in cognitive processes (Table 2), and present sites in DA signal transduction cascades as potential loci of genetic vulnerability in BPD. However, there are no published studies evaluating DA activity and cognitive function, including working memory, in subjects with BPD. Such studies in schizophrenia (Goldberg *et al*, 2003) and in schizotypal personality disorder (Siever *et al*, 2002) have demonstrated a correlation between DA dysfunction and cognitive impairment. Similar studies seem warranted in BPD.

Mechanisms of Action

It is now generally accepted that the prefrontal and temporal regions of the brain operate as part of architecturally and functionally discrete, parallel closed loop

circuits that link cortical regions with subcortical structures, such as the basal ganglia, thalamus, extended amygdala, and hippocampus (Masterman and Cummings, 1997; Trimble *et al*, 1997). These circuits interface with one another in a manner referred to as parallel distributed processing to produce neural systems with specific functions (Trimble *et al*, 1997). These neural systems are mediated by glutamate and GABA, the primary stimulatory and inhibitory brain neurotransmitters, and are modulated by DA, 5-HT, and other neuromodulators. Recent studies suggest the involvement of DA activity in some of the circuits that are associated with the behavioral dimensions of BPD. For example, it has been suggested that the *Aplysia* cellular model of DA-enhanced instrumental conditioning recently demonstrated by Brembs *et al* (2002) may be conserved in higher animal forms, and may provide the basis for the learning of reward-seeking behaviors mediated by DA in the NAC (Rankin, 2002).

At the molecular level, the facilitation of reward-based learning by PKA activity in the amygdala may operate by the regulation of DARPP-32 phosphorylation (Jentsch *et al*, 2002). A recent report indicates that, in addition to DA, 5-HT also regulates DARPP-32 phosphorylation (Svenningsson *et al*, 2002a), an effect modified by fluoxetine (Svenningsson *et al*, 2002b). Some of the effects of diverse psychotomimetics on DA, 5-HT, and glutamate activity in humans and in animals appear to be mediated by the DARPP-32 signal transduction pathway (Svenningsson *et al*, 2003). This mechanism may also mediate a portion of the reciprocal interactions of DA and 5-HT on the specific behavioral dimensions of BPD.

If DA dysfunction is associated with BPD, it may be the result of genetic, developmental, or environmental factors directly affecting specific DA pathways. Alternatively, DA dysfunction in BPD may be a compensatory response to the effects of these factors either on the primary neural systems that control emotion, impulse regulation, and cognition that are mediated by the main neurotransmitters of the brain, glutamate, and GABA, or on one or more of the other neurotransmitter pathways that modulate activity in these neural systems such as serotonin, acetylcholine, and norepinephrine.

Implications

The data presented in this review are consistent with the stated hypothesis that DA dysfunction plays an important role in three behavioral dimensions of BPD. This hypothesis has at least three heuristic implications. First, it broadens the conceptual framework for investigations of the neural mechanisms that operate as risk factors for BPD. More specifically, the data suggest complex interactions of the neural systems that mediate these behavioral dimensions, as shown in Figure 1. For example, in the dimension of emotional dysregulation, hyper-reactive response to salient stimuli by the amygdala may result in enhanced conditioned fear responses in individuals with BPD. These enhanced responses could result from an increase in DA activity in the amygdala (Guarraci *et al*, 1999) that is inadequately modulated by medial prefrontal cortical inhibition (Rosenkranz and Grace, 2001).

At this point, it would be tempting to generate a general hypothesis of hyperdopaminergic and hyposerotonergic activity in those neural circuits mediating emotion information processing, impulsivity, and cognitive-perceptual activity in individuals with BPD. However, the high degree of architectonic specificity, the heterogeneity of neurotransmitter receptors and signal transduction cascade pathways in the circuits, the compensatory capacity of the circuits, and the meager amount of data from all sources require restraint from doing so. These factors may be responsible for the failure to find clear relationships between CSF DA and 5-HT metabolites in subjects with BPD (Chotai *et al*, 1998; Coccaro, 1998). If only a few specific DA and 5-HT pathways are involved in modulating the circuitry responsible for the behaviors present in BPD, we are searching for very small changes in CSF metabolites among a large amount of background data.

In addition, it is not proposed that DA dysfunction is involved in all symptoms in each of the three dimensions of BPD focused on in this review. For example, the identity disturbance commonly observed in individuals with BPD may be regarded as a cognitive-perceptual impairment. However, I know of no data that relates this disturbance to DA dysfunction in any subject population.

The hypothesis does suggest areas of investigation of the nature of BPD that have not been pursued. To date, there are no reported studies that utilize a PET tracer that images both striatal and extrastriatal behavior-related DA binding in subjects with BPD and in controls. For example, relationships between DA activity and cognitive dysfunction have been demonstrated in both schizophrenia (Goldberg *et al*, 2003) and in schizotypal personality disorder (Siever *et al*, 2002). Similar studies appear to be warranted in BPD in order to determine the presence of DA dysfunction in BPD and the specific cognitive and other behavioral impairments of BPD related to this dysfunction.

AMPH-induced changes in ^{11}C -raclopride DA D2/D3 binding potential (BP) observed in the anterior ventral striatum, but not in the dorsal caudate, correlate inversely with euphoria scale changes in normal subjects (Drevets *et al*, 2001). Yasuno *et al* (2001) have demonstrated that the BP in the amygdala of the extrastriatal D2 radiotracer ^{11}C -FLB 457 correlates significantly with personality trait scores of harm avoidance, a personality trait related to BPD (Svrakic *et al*, 1993). These studies suggest that studies utilizing analogous methodologies in subjects with BPD may provide tests of the proposed relationships between DA dysfunction and symptoms of BPD.

Second, the hypothesis suggests new directions in the selection of candidate genes for analysis of the genetic basis of BPD, and for genetic manipulation in the development of animal models of the disorder. Even if DA dysfunction were demonstrated in neuroimaging studies, it would not necessarily indicate primary defects in DA pathways related to the behavioral dimensions of BPD. Abnormalities in DA function in BPD demonstrated by such studies might reflect compensatory changes to basic flaws in other neurotransmitter systems. Genetic and other studies would be required to provide direct evidence of dysfunction in DA transporter and DA signal transduction cascade pathways.

The hypothesis does not consider DA dysfunction to be the only risk factor for BPD. There is evidence that

oligogenic, developmental, and environmental risk factors operate and interact to produce the full phenotypic expression of BPD (Silk, 2000; Skodol *et al*, 2002). Consequently, it would seem likely that disturbances at other chemical nodal points in the neural systems mediating the dimensions of BPD, such as the glutamate, GABA, and 5-HT signal transduction cascade pathways, may serve as additional risk factors for the disorder.

Third, the hypothesis provides a scientific rationale for the expanded study and use of antipsychotic agents in patients with BPD. The first controlled study of an atypical antipsychotic agent in subjects with BPD has recently been reported (Table 1) (Zanarini and Frankenburg, 2001).

Limitations

The main limitation of the proposed hypothesis is that the evidence reviewed is circumstantial. As noted, there are no studies that directly demonstrate DA dysfunction in subjects with BPD. The therapeutic effects of antipsychotic agents in BPD may operate through non-DA pathways, or result from nonspecific decreases in symptom severity not related directly to DA mechanisms. However, the two leading models of the mechanism of action of antipsychotic agents both involve the effect of these agents on DA activity (Meltzer, 1989; Kapur and Seeman, 2001), and a molecular mechanism of action of these agents through a signaling pathway common to DA, 5-HT and glutamate has recently been proposed (Svenningsson *et al*, 2003). Also, I know of no existing, credible models of non-DA mediated reductions in symptom severity by antipsychotic agents in any mental disorder. Finally, it may be argued that the hypothesis attempts to attribute too many of the behavioral dimensions of BPD to a single neurotransmitter disturbance. This issue has been addressed in the above sections on mechanisms of action and implications. Ultimately, genetic studies, behavior-related neuroimaging studies evaluating CNS DA function, and other research strategies in subjects with BPD and in animal models of the disorder, will be required to test the validity of the hypothesis.

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