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Impulsivity, gender, and response to fenfluramine challenge in borderline personality disorder☆

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Abstract

Behavioral impulsivity in borderline personality disorder (BPD) is associated with indices of diminished central serotonergic function, independent of suicidal behavior, depression or alcohol use disorder. Many of these studies have been conducted among males in specialized settings. Studies of BPD females, who constitute the majority of BPD patients, are generally conducted in community settings and report inconsistent findings. We studied gender differences in behavioral impulsivity and the prolactin response to D,L-fenfluramine (FEN) in BPD subjects in a community setting. A FEN challenge study was conducted with 64 BPD subjects (20 male, 44 female), and 57 controls (36 male, 21 female). Axis I and II disorders, including BPD, and suicidal histories were assessed by structured interviews. Controls were free of Axis I and II disorders. Impulsivity and aggression were assessed by the Buss–Durkee Hostility Inventory, Barratt Impulsiveness Scale, Minnesota Multiphasic Personality Inventory-Psychopathic Deviate subscale, and the Brown–Goodwin Lifetime History of Aggression. Male, but not female, BPD subjects had significantly diminished prolactin responses compared to controls. Impulsivity and aggression each predicted prolactin responses. A significant effect of BPD diagnosis on prolactin response was eliminated when impulsivity was co-varied. Impulsivity and aggression were inversely related to delta-prolactin and peak-prolactin responses among male but not female subjects. Gender differences in central serotonergic function may contribute to variations in impulsivity in BPD.

Keywords: Serotonin; Suicide; Aggression; Prolactin

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1. Introduction

Borderline personality disorder (BPD) is an important clinical model for investigating impulsivity and suicidal behavior, and is defined, in part, by both behaviors (DSM-IV). BPD is one of the most lethal psychiatric disorders, with a suicide completion rate of 9–10% in long-term follow-up. (Stone, 1989; Paris, 2002). Suicide attempters and completers with BPD exhibit more impulsive behaviors than non-attempters (Soloff et al., 1994) or BPD control subjects (Kjelsberg et al., 1991). Impulsivity in patients with BPD is significantly associated with lifetime number of suicide attempts, even after controlling for co-morbid depression and substance use disorders (Brodsky et al., 1997; Soloff et al., 2000a). Borderline patients may commit suicide impulsively, in anger, often following a perceived rejection (Kullgren et al., 1986). In a stress–diathesis model of suicidal behavior, impulsivity constitutes a vulnerability involving temperament, increasing the likelihood of suicidal behavior in the presence of acute stressors such as depression, substance abuse, or perceived rejection (Mann et al., 1999).

Impulsivity and suicidal behavior are both associated with indices of diminished central serotonergic function, assessed by indirect methods such as CSF 5-HIAA, or neuroendocrine responses to challenge with serotonergic agonists such as D- or D,L-fenfluramine (FEN), meta-chlorophenylpiperazine (*m*-CPP), or buspirone (Oquendo and Mann, 2000; Coccaro et al., 1990; Stanley and Mann, 1988, for reviews). Diminished indices of central serotonergic function have been described in many studies of attempted or completed suicide, and across many, but not all, diagnoses. Åsberg et al. (1986) first reported an association between low CSF 5-HIAA and *violent* methods of suicide attempt. Other investigators have found relationships between low CSF 5-HIAA or blunted prolactin responses to FEN and high lethality attempts or impulsivity, rather than violence of method (Mann et al., 1996; Mann and Malone, 1997). In patients with BPD or other impulsive personality disorders (PD), diminished levels of CSF 5-HIAA are associated with violent attempts (Träskman-Benz et al., 1986), and non-violent, but 'genuine' attempts (Gardner et al., 1990), lifetime histories of aggression, (Brown et al., 1982) and impulsive–aggressive behavior *independent* of suicidal behavior (Linnoila et al., 1983, 1989; Virkkunen et al., 1987). A blunted prolactin response to serotonergic agonists, and an inverse relationship between prolactin response and behavioral impulsivity, has been described in patients with BPD or other impulsive PDs, independent of histories of suicidal behavior (Coccaro et al., 1989; O'Keane et al., 1992; Moss et al., 1990), co-morbid affective disorders, or alcohol use disorders (AUD) (Coccaro et al., 1989). Subjects with BPD and other impulsive PDs demonstrate a decreased uptake of [F-18] fluorodeoxyglucose on PET neuroimaging in response to FEN challenge in areas of prefrontal cortex associated with regulation of mood and impulse, especially in orbital and medial prefrontal cortex (Siever et al., 1999; Soloff et al., 2000b; Goyer et al., 1994; De La Fuenta et al., 1997; Raine et al., 1992, 1997; Oquendo et al., personal communication).

Many studies demonstrating serotonergic dysregulation in subjects with BPD or other impulsive PDs have been conducted in highly specialized settings. Brown et al. (1982) first demonstrated an inverse relationship between CSF 5-HIAA and Lifetime History of Aggression (LHA) in male military recruits with BPD, hospitalized for 'fitness to serve' assessments. Linnoila et al. (1983, 1989) and Virkkunen et al. (1987) used a forensic setting to compare CSF 5-HIAA levels in violent and non-violent, impulsive and non-impulsive, male offenders with BPD. Similarly, Lidberg et al. (1984, 1985) studied impulsive homicidal offenders who killed someone emotionally important to them, and suicide attempters who attempted to kill or actually killed their own children. Coccaro et al. (1989) recruited male patients with PD from a VA hospital setting. A second study advertised for male volunteers 'who considered themselves to have difficulty managing their aggressive behaviors' (Coccaro et al., 1996).

Studies of BPD subjects conducted in specialized settings or ascertained for impulsivity and aggression, have focused predominately on males, though 76–80% of BPD diagnoses are made in females (Widiger and Weissman, 1991). Studies