



Evaluation of behavioral impulsivity and aggression tasks as endophenotypes for borderline personality disorder

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ABSTRACT

Borderline personality disorder (BPD) is marked by aggression and impulsive, often self-destructive behavior. Despite the severe risks associated with BPD, relatively little is known about the disorder's etiology. Identification of genetic correlates (endophenotypes) of BPD would improve the prospects of targeted interventions for more homogeneous subsets of borderline patients characterized by specific genetic vulnerabilities. The current study evaluated behavioral measures of aggression and impulsivity as potential endophenotypes for BPD. Subjects with BPD ($N = 127$), a non cluster B personality disorder (OPD $N = 122$), or healthy volunteers (HV $N = 112$) completed self report and behavioral measures of aggression, motor impulsivity and cognitive impulsivity. Results showed that BPD subjects demonstrated more aggression and motor impulsivity than HV (but not OPD) subjects on behavioral tasks. In contrast, BPD subjects self-reported more impulsivity and aggression than either comparison group. Subsequent analyses showed that among BPD subjects behavioral aggression was associated with self-reported aggression, while behavioral and self-report impulsivity measures were more modestly associated. Overall, the results provide partial support for the use of behavioral measures of aggression and motor impulsivity as endophenotypes for BPD, with stronger support for behavioral aggression measures as an endophenotype for aggression within BPD samples.

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1. Introduction

Borderline personality disorder (BPD) is a chronic, debilitating mental illness that affects approximately 2% of individuals in the community (Coid et al., 2006; Samuels et al., 2002) and up to 20% of psychiatric inpatient samples (Skodol et al., 2002). Marked by an unstable self-concept, poor impulse control and emotional dysregulation, individuals with BPD often show severe distress and impairment in interpersonal functioning that result in significant suffering for the patient and their loved ones. Roughly three-quarters of all BPD patients report engaging in suicidal behavior at some point (Paris et al., 2004; Paris and Zweig-Frank, 2001; Zanarini et al., 2004) with up to 10% eventually committing suicide (Lieb et al., 2004).

Currently, there are few efficacious treatments for BPD, with the most effective treatments (e.g., Dialectical Behavioral Therapy) providing only moderate symptom relief (Lieb et al., 2004). Identification of genetic correlates of BPD would improve the prospects of targeted interventions for more homogeneous subsets of border-

line patients characterized by specific genetic vulnerabilities. However, despite the prevalence and severity of BPD, its genetic underpinnings have only recently begun to receive significant attention (New et al., 1998; New and Siever, 2003; Ni et al., 2006, 2007; Pascual et al., 2007; Schmahl et al., 2002; Zetzsche et al., 2008) and are hampered by the heterogeneity and complexity of the BPD diagnosis, which is based on symptom-clustering, not underlying neurobiology (APA, 1994). This has led to a call for alternative methodological approaches including identification of endophenotypes (Siever et al., 2002).

Endophenotypes are measurable characteristics associated with a phenotype (e.g., a disease or disorder) that are more closely related to an underlying genotype than the phenotype itself (Gottesman and Gould, 2003). Though the term "endophenotype" was originally limited to phenotypes that were not visible (e.g., microscopic or biochemical), it has been expanded to refer to any measurable phenotype below the level of a diagnosis. The underlying beliefs are; (a) the endophenotype lies along a developmental pathway between genes and disorder, and (b) because the endophenotype is less complex than the disorder phenotype, it will be dependent on fewer genes and thus more amenable to genetic analysis. This approach of searching for endophenotypes is being

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employed with some success for a number of severe mental illnesses including schizophrenia (Greenwood et al., 2007; Hong et al., 2008; Leppanen et al., 2008; Smesny et al., 2007) and bipolar disorder (Savitz et al., 2005).

Several criteria must be met for a biological marker to classify as an endophenotype. First and foremost, it should be associated with the illness in the relevant population, occurring at a higher level among individuals with the disorder than among the general population. Ideally, this would include having the putative endophenotype differentiate between the disorder of interest (in our case BPD) and other psychiatric disorders. The endophenotype should also be largely state independent, occurring during both active and residual phases of the disorder (though it may require challenge or provocation). Furthermore, the putative endophenotype should be heritable (Gottesman and Gould, 2003).

Measures of aggression and impulsivity may serve as endophenotypes for BPD as both traits vary within the general population and are strongly associated with BPD. Patients with BPD report more anger, aggression and impulsivity than healthy volunteer or Axis I control subjects (Gardner and Cowdry, 1986; Jacob et al., 2007; Snyder and Pitt, 1985). In fact, impulsive behavior, anger dyscontrol/aggression and self-aggression (i.e., self-mutilation and suicidal behavior) represent three of the nine BPD criteria (APA, 1994). Furthermore, results of twin and family studies have shown impulsivity and aggression to be partially heritable (Coccaro et al., 1993; Dougherty et al., 2003; Hines and Saudino, 2004; Pedersen et al., 1988; Seroczynski et al., 1999). Impulsivity and aggression are also associated with underlying biological deficits including serotonergic dysregulation and functional impairment of frontal-limbic circuits (Brown et al., 1982; Coccaro et al., 1997a; Haberstick et al., 2006; Manuck et al., 1999) that are also present in BPD (Coccaro et al., 2007; Donegan et al., 2003; McCloskey et al., 2005; Minzenberg et al., 2007; New et al., 2004).

Behavioral (laboratory) measures of aggression and impulsivity are promising candidates to evaluate as potential endophenotypes for BPD as they obtain an observable sample of the behavior of interest, albeit under an experimenter controlled context (Siever et al., 2002). The point subtraction aggression program (PSAP) is one of the few validated laboratory measures of aggression (Cherek et al., 2003). In the PSAP, subjects are provoked by having money indirectly taken from them by a (unbeknownst to the subject) fictitious opponent during a money acquisition task (Cherek et al., 1992). The PSAP has been shown to discriminate between violent and non-violent groups, including criminals and drug abusers (Allen et al., 1997; Cherek et al., 2000, 1997). Furthermore, preliminary data from the authors suggest that aggressive responding on the PSAP is partially heritable. Support for the PSAP as an endophenotype for BPD comes from a finding that a group of 14 hospitalized female BPD subjects were more aggressive on the PSAP than a comparison group of 17 healthy controls (Dougherty et al., 1999).

Impulsivity is a multifaceted construct that can include concepts as varied as sensation-seeking, lack of planning, lack of persistence, inability to delay gratification, insensitivity to delayed consequences, alteration in the perception of time, urgency, and risk taking (de Wit et al., 2002; Reynolds et al., 2006; Smith et al., 2007). However, most major theories of impulsivity include dimensions of motor impulsivity (the inability to delay or inhibit a proponent motor response) and cognitive impulsivity (impulsive decision making such as the inability to shift sets or delay gratification despite negative or less than optimal consequences) (Reynolds et al., 2006; Winstanley et al., 2004). Behavioral measures of both motor impulsivity (e.g., the Immediate Memory Task in which you have to inhibit a prepotent motor response) as well as cognitive impulsivity (e.g., the Passive Avoidance Task in which subjects have to discriminate numbers associated with monetary reward from those associated with monetary loss) are shown to

discriminate between impulsive and non-impulsive groups including adults with attention deficit hyperactivity disorder (Malloy-Diniz et al., 2007), bipolar disorder (Christodoulou et al., 2006), substance abusers (Hanson et al., 2008) and pathological gamblers (Forbush et al., 2008). Behavioral measures of cognitive and motor impulsivity also appear to discriminate individuals with BPD from healthy controls. (Chapman et al., 2008; Dougherty et al., 1999; Grootens et al., 2008; Hochhausen et al., 2002; Rentrop et al., 2008), though negative findings for motor impulsivity have also been found (Lampe et al., 2007). Finally, there is evidence of familial transmission for commission errors on the Immediate Memory Task, supporting the heritability of this task (Dougherty et al., 2003).

As stated, optimally an endophenotype would discriminate BPD from other psychiatric diagnoses as well. However, impulsivity and aggression are not specific to BPD. Other Axis I (e.g., intermittent explosive disorder) and Axis II (e.g., paranoid personality disorder) disorders are associated with increased levels of impulsivity and aggression, even when not co-morbid with BPD (McCloskey et al., 2008; Moeller et al., 1997). Furthermore, impulsivity and aggression are not pathognomonic for BPD, with other traits (i.e., emotion regulation) also central to the disorder. For other disorders (e.g., schizophrenia) investigators have had considerable difficulty finding endophenotypes that discriminate them from different psychiatric disorders (Burdick et al., 2006). If behavioral measures of impulsivity and aggression are found not to be specific for BPD, they may still represent an endophenotype for aggression or impulsivity within BPD, which would have considerable utility for case control and gene mapping studies of BPD. The possibility of identifying endophenotypes that reflect key dimensions of the disorder would provide an opportunity to potentially identify and study the underlying genetics of that dimension, e.g. aggression and its contribution to the genetics of BPD. The utility of behavioral tasks as endophenotypes of impulsivity and aggression in BPD would be supported if these tasks were found to be associated with the underlying construct among individuals with BPD. In other words, if behavioral and self-report trait measures of aggression or impulsivity were correlated among subjects with BPD.

Previous research suggests that behavioral measures of impulsivity and aggression are associated with BPD; however, these studies have been limited in that they have generally used relatively small sample sizes and low level control groups (e.g., healthy volunteers) without controlling for other psychopathology. The current study evaluated behavioral measures of impulsivity and aggression as candidate endophenotypes for BPD in a large sample of individuals with varying levels of psychopathology. Specifically, individuals with BPD were compared to two control groups, a psychopathology free group that does not control for other psychopathology (healthy volunteers) and a second comparison group that controls for the presence of Axis II psychopathology. This latter control group consists of individuals with a non cluster B personality disorders (i.e., personality disorders other than borderline, antisocial, histrionic and narcissistic). All participants completed self-report measures of anger, aggression, and impulsivity and then completed behavioral measures of motor impulsivity (the Immediate Memory Task), cognitive impulsivity (the Passive Avoidance Task and the Bechara Gambling Task) and aggression (the Point Subtraction Aggression Paradigm).

We hypothesized that subjects with BPD would show greater impulsivity and affective aggression on behavioral measures than either comparison group. We also hypothesized that patients with BPD would endorse higher levels of anger, aggression and impulsivity on self-report measures than either comparison group. Finally, we hypothesized that behavioral and self-report measures of aggression/impulsivity would be associated with each other among subjects with BPD.

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