



## A family history study of intermittent explosive disorder

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### ABSTRACT

**Background:** Intermittent Explosive Disorder (IED) is newly appreciated as a commonly occurring disorder of impulsive aggression. Since aggression and impulsivity are under genetic influence, IED may be familial.

**Methods:** Blinded and controlled family history study of IED and co-morbid conditions in an outpatient clinical research center for impulsive aggression. The subjects were first-degree relatives of individuals who did and did not meet criteria for IED by DSM-IV and Research Criteria.

**Results:** Elevated Morbid Risk of IED was observed in relatives of IED Proband compared with relatives of Non-IED Proband. This familial signal of IED was not affected by comorbidity in the IED Proband of comorbidity in the relatives of the IED Proband.

**Conclusions:** IED, as defined by research criteria, appears to be familial and may not be an artifact of other co-morbid conditions.

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### 1. Introduction

Intermittent Explosive Disorder (IED), in DSM-IV (American Psychiatric Association, 1994), is characterized by recurrent episodes of serious aggressive outbursts that are out of proportion to psychosocial stressors/provocation and that are not better accounted for by another mental disorder, co-morbid medical conditions, or the physiological effects of a pharmacological agent. Over the past several years, efforts to refine the DSM-IV IED criteria have resulted in IED Research Criteria that operationalize the type and frequency of aggression and the degree to which the aggressive behavior impacts on psychosocial function (Coccaro et al., 1998, 2004). Current IED Research Criteria require the frequency of aggressive behavior to be at least three episodes of serious assault (or destruction of property) in a one-year period, or at least two outbursts per week, for no less than one month, involving verbal aggression or aggression against objects (Coccaro et al., 2004). These IED Research Criteria also require criteria-meeting aggressive episodes to be impulsive, as opposed to premeditated, in nature and require the aggressive behavior to be associated with significant psychosocial impairment and/or distress.

Using either DSM-IV or IED Research Criteria, recent epidemiologic data suggests that from about 4 to 7% of the general

population in the United States (Coccaro et al., 2004; Kessler et al., 2006) and about 2–10% of the population of other countries (Bromet et al., 2005; Fincham et al., 2009) have IED over the course of their lifetime. About 70% of these individuals have at least three aggressive outbursts per year and average more than twenty-seven aggressive outbursts per year (Kessler et al., 2006). While DSM-IV does not formally define relevant aggressive outbursts as impulsive, all the epidemiologic studies, to date, required the aggressive acts to occur “all of a sudden” and, thus, be impulsive in nature.

Data from twin, adoption, and family studies suggest genetic influence on impulsivity and aggression (Bergeman and Seroczynski, 1998; Seroczynski et al., 1999). In adults, heritability estimates ranging from 44% to 72% have been reported (Rushton et al., 1986; Tellegen et al., 1988; Cates et al., 1993; Coccaro et al., 1993, 1997) and a meta-analysis study confirmed a substantial genetic influence for aggression (Miles and Carey, 1997). The later study found that heritability estimates were most pronounced for aggression measures reflecting anger and hostility and/or anger, impulsiveness and irritability (Rushton et al., 1986; Tellegen et al., 1988; Cates et al., 1993; Coccaro et al., 1993, 1997). These are the same phenomena associated with the clinical profile of IED and, thus, it is likely that IED is heritable and runs in families.

While there are no twin or adoption studies of IED, existing family history data suggests that IED or IED-type behavior may be familial. The first-degree relatives of patients with histories of violent behavior have a high incidence of violent behavior (Bach-y-Rita et al., 1971; Maletsky, 1973). An increased frequency

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of first-degree relatives with history of temper outbursts and a strong trend for familial aggregation of IED (defined as the first two DSM-III criteria for IED) was reported in psychiatric patients with history of temper outbursts compared to other patients (Mattes and Fink, 1987). While neither a blinded nor controlled study, McElroy et al. (1998) reported that 32% of first-degree relatives of IED probands met criteria for IED.

In this paper we report the results of a blinded, controlled, family history study of IED by research criteria (IED-IR) using reliable and comprehensive assessments of psychopathology and DSM-IV disorders. IED-IR criteria include the essence of DSM-IV IED criteria but are more precise and valid in terms of analog behavioral studies (McCloskey et al., 2005) or serotonergic biomarkers (Coccaro et al., 2010a, 2010b). We hypothesized that there would be a significantly elevated morbid risk of IED-IR in first-degree relatives of IED-IR Probands compared to Control Probands was found. We further hypothesized that Familial IED-IR would not be affected by co-morbidity in IED-IR probands and that co-morbidity of Non-IED disorders in relatives would also not be affected by presence of IED-IR in those relatives.

## 2. Methods and materials

### 2.1. Subjects

Sixty-four (64) proband subjects, with and without Axis I and/or Axis II disorders, were included in this study. Thirty-two probands met DSM-IV (American Psychiatric Association, 1994) and/or Integrated Research Criteria for IED (IED-IR; Coccaro et al., 2004); thirty-two control probands did not meet either criteria set for IED and had little or no life history of significant outwardly-, or inwardly-, directed aggression. Subjects were recruited by newspaper and public service announcements seeking subjects with, and without, self-reported problems of personality disorder for studies of personality traits. All subjects signed the informed consent document approved by the Institutional Review Board (IRB) before engaging in any study procedures.

### 2.2. Diagnostic assessment of probands

Axis I and Axis II Personality Disorder (PD) diagnoses were made according to DSM-IV criteria (American Psychiatric Association, 1994). The diagnosis of Intermittent Explosive Disorder (IED) was made by DSM-IV, IED-R (Coccaro et al., 1998), and by Integrated Research Criteria for IED (IED-IR; Coccaro et al., 2004). Integrated Research Criteria for IED differ from DSM-IV criteria in that they require: a<sub>1</sub>) one month (or more) period of aggressive outbursts (including verbal outbursts only, or outbursts in which property is not destroyed) occurring twice a week on average or, a<sub>2</sub>) at least three episodes of serious assaultive or destructive behavior (even when there are not recurrent aggressive outbursts within the one-month time frame); b) aggressive outbursts to be primarily impulsive in nature; c) aggressive outbursts to be associated with significant subjective distress or psychosocial impairment and, d) that they allow for co-morbid diagnoses of Borderline and/or Antisocial Personality Disorder. The IED-IR criteria, thus, “integrates” the originally proposed Research Criteria (IED-R: a<sub>1</sub>, b, c, d; Coccaro et al., 1998) with current DSM-IV Criteria (i.e., a<sub>2</sub>). In addition, it is noteworthy that IED-IR criteria are more sensitive in detecting differences, among IED vs. Non-IED subjects, on measures of serotonergic system function (Coccaro et al., 2010a; Coccaro et al., 2010b) Data collection leading to all diagnoses were made using information from: (a) clinical research interviews conducted by trained masters, or doctoral, level clinicians; (b) clinical interview by a research psychiatrist; and, (c) review of all other available

clinical data as previously described (Bunce et al., 2005). The interviews consisted of: (a) Structured Clinical Interview for DSM Diagnoses (SCID-I; First et al., 1997) for Axis I disorders; (b) Structured Interview for the Diagnosis of DSM-IV Personality Disorder (SIDP-IV; Pfohl et al., 1997) for Axis II Personality Disorders and, (c) Intermittent Explosive Disorder-Module (IED-M) for the diagnosis of IED by IED-IR criteria (inter-rater reliability: kappa = .83). Final diagnoses, and Global Assessment of Function (GAF) in the past year (American Psychiatric Association, 1994), were assigned by team best-estimate consensus procedures as previously described (Bunce et al., 2005).

All IED Probands met IED-IR Criteria. Among the IED-IR Probands, all had a history of another Axis I and/or Axis II disorder. Lifetime Axis I disorders were as follows: Any Mood Disorder ( $n = 26$ ): Major Depression ( $n = 17$ ); Any Anxiety Disorder ( $n = 13$ ); Substance Use Disorders: Alcohol Dependence ( $n = 16$ ), Drug Dependence ( $n = 16$ ); Intermittent Explosive Disorder: DSM-IV IED ( $n = 19$ ), IED-R ( $n = 13$ ), IED-IR ( $n = 32$ ); Non-IED Impulse Control Disorders: ( $n = 2$ ). Twenty-two subjects met DSM-IV criteria for a specific personality disorder as follows: a) Cluster A ( $n = 12$ ): Paranoid ( $n = 12$ ), Schizoid ( $n = 1$ ), Schizotypal ( $n = 1$ ); b) Cluster B ( $n = 16$ ): Borderline ( $n = 6$ ), Antisocial ( $n = 5$ ), Narcissistic ( $n = 3$ ), Histrionic ( $n = 3$ ); c) Cluster C ( $n = 7$ ): Obsessive–Compulsive ( $n = 4$ ), Avoidant ( $n = 4$ ). The remaining ten subjects met general DSM-IV criteria for Personality Disorder (i.e., PD-NOS), had pathological personality traits from a variety of personality disorder categories, and had clear evidence of impaired psychosocial functioning (mean GAF score =  $57.7 \pm 5.1$ ).

Control Probands either had no lifetime history of any Axis I or II disorder (i.e. Healthy Control Probands:  $n = 18$ ) or had a lifetime history of Axis I or Axis II disorders (i.e. Psychiatric Control Probands:  $n = 14$ ). Axis I disorders in Psychiatric Control Probands were as follows: Any Mood Disorder ( $n = 6$ ): Major Depression ( $n = 6$ ); Any Anxiety Disorder ( $n = 3$ ); Substance Use Disorders: Alcohol Dependence ( $n = 2$ ); Non-IED Impulse Control Disorders ( $n = 1$ ). Specific Personality Disorders in this group ( $n = 9$ ) were as follows: a) Cluster A ( $n = 4$ ): Paranoid ( $n = 3$ ), Schizoid ( $n = 2$ ), Schizotypal ( $n = 2$ ); b) Cluster B ( $n = 3$ ): Narcissistic ( $n = 3$ ); c) Cluster C ( $n = 1$ ): Avoidant ( $n = 1$ ). The five remaining subjects met general DSM-IV criteria for Personality Disorder (i.e., PD-NOS) and had clear evidence of impaired psychosocial functioning (mean GAF score =  $61.0 \pm 8.9$ ) similar to that of the IED subjects with PD-NOS.

### 2.3. Diagnostic assessment for family history of psychiatric disorders in probands

Axis I diagnoses were similarly made according to DSM-IV criteria (American Psychiatric Association, 1994). Ratings for Axis I Disorder were made through use of a Family History Interview updated for DSM-IV diagnoses (Klein et al., 1994) and modified to include the information necessary to make diagnoses of IED-IR. Diagnostic data on all first-degree relatives was collected, first, from probands (90% of all families) by a second rater who did not assess the diagnoses of the proband and who was blind to the proband's diagnoses. Further diagnostic data was collected on the relatives of probands from up to three to four additional informants, 64.5% of whom were first-degree relatives of the probands (i.e., parents: 36.8%; siblings: 28.0%; offspring: 16.1%) by a third rater also blind to the proband's diagnoses and blind to any data from the proband about the relatives' diagnoses. Overall, 71% of families of probands had a first-degree relative as an informant. While all potential informants were contacted, after permission from the proband, by mail or telephone by the research staff, not all could be

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