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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 Probands compared with relatives of Non-IED Probands. This familial signal of IED was not affected by comorbidity in the IED Probands of comorbidity in the relatives of the IED Probands.
Conclusions: IED, as defined by research criteria, appears to be familial and may not be an artifact of other co-morbid conditions.

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 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_1) 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_2) 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_1, b, c, d; Coccaro et al., 1998) with current DSM-IV Criteria (i.e., a_2). 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 Controls 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 ± 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 ± 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

reached or interviewed. Diagnostic interviews were primarily conducted in-person but also by telephone where necessary. Inter-rater reliability for IED-IR in Probands ($k = .87$) and in Relatives ($k = .90$), at this point in the process, was excellent. Sensitivity and specificity for the IED-IR diagnosis, comparing direct interview with the family history method employed in this study, were 57% and 81%, respectively, for the IED-IR diagnosis. All available information from these sources was summarized and presented by the third rater to a Best Estimate Board composed of one psychiatrist, two doctoral-level psychologists and up to four pre-doctoral psychologists. Diagnoses were then assigned by the Best Estimate Board at three levels: a) DSM-IV diagnosis (full DSM-IV criteria for the disorder); b) FHx-Definite (e.g., one less criterion than DSM-IV criteria); c) FHx-Probable (e.g., two less criterion than full DSM-IV criteria). A diagnosis was considered present in relatives if the disorder was given at least a "probable" level or higher.

2.4. Assessment of aggression in probands

History of actual aggressive behavior was assessed with the Aggression Scale from the Life History of Aggression (Coccaro et al., 1997b). Aggressive tendencies were assessed with the Aggression Scale of the self-report Buss-Durkee Hostility Inventory (BDHI; Buss and Durkee, 1957).

2.5. Statistical analysis

Differences between subject groups were tested by *t*-test for continuous variables and by Chi-Square (X^2), or Fishers Exact Test (FET), for categorical variables. The primary statistic for familiality was morbid risk (MR). MR for a disorder in first-degree relatives of a proband group was assessed using the Weinberg Abridged Method (Slater and Cowie, 1971). MR is the proportion of the "number of cases with the disorder" to the "number of individuals at risk for developing the disorder". The figure for the "individuals at risk" is corrected by the "age of risk". Individuals with the disorder in question, or individuals beyond the "age of risk" were counted as a single (American Psychiatric Association, 1994) "lifetime of risk"; individuals within the "age of risk" and without the disorder in question were counted as one-half (1/2) a "lifetime of risk". The age of risks employed were 15–39 years for IED-IR (Coccaro et al., 2005), and for substance dependence and psychotic disorders (Silverman et al., 1991), and 15–59 years for mood and anxiety disorders (Silverman et al., 1991). Differences in the relative morbid risks were assessed using the "Test of the Difference Between Two Proportions" as described by Fleiss (1981): $z = MR_1 - MR_2/\text{sqrt}\ [p \times q\ (1/n_1 + 1/n_2)$ where p = number of "cases" in the total sample divided by the number of "lifetimes of risk" in the total sample; $q = 1 - p$; and n_1 and n_2 = the number of relatives in the two samples respectively. An alpha of .05 was used for pre-planned analyses. All reported p values are two-tailed and corrected for multiple testing in follow-up analyses.

3. Results

3.1. Characteristics of the probands

Healthy Control Probands did not differ from Psychiatric Control Probands in age, gender, ethnicity, or in socioeconomic status. They did differ, as expected, in GAF scores (HC: 83.6 ± 3.3 *vs.* PC: 61.0 ± 8.5; $t_{30} = 10.36$, $p < .001$), in LHA (HC: 4.1 ± 3.1 *vs.* PC: 8.8 ± 7.0; $t_{29} = 2.36$, $p < .05$) and BDHI (HC: 14.2 ± 5.4 *vs.* PC: 20.0 ± 6.2; $t_{26} = 2.65$, $p < .02$) aggression scores, and in lifetime psychiatric morbidity (see above). Despite this, the two groups of controls displayed the same degree of morbid risk for IED-IR in their relatives (HC: .090 *vs.* PC: .114; $z = .55$, $p = .58$). Accordingly, the two control groups were combined as a single control group for further analysis.

IED-IR and Control Probands did not significantly differ in age, gender, ethnicity, or socioeconomic status (Table 1). IED-IR Probands, as expected, had lower GAF Scores, and higher LHA Aggression and BDHI Aggression scores, than Control Probands. IED-IR Probands had 184 relatives, compared with 144 relatives for Control Probands. The number of relatives and informants per family, and the percentage of informants per family was marginally higher in the IED-IR Probands.

3.2. Morbid risk (MR) of IED-IR in relatives of IED-IR and control probands

MR for IED-IR in first-degree relatives of IED-IR Probands was significantly greater than that seen in first-degree relatives of Control Probands (.342 *vs.* .103; $z = 5.22$, $p < .00001$). MR for IED-IR in relatives among IED-IR Probands, who did not have co-morbid Borderline (BPD) and/or Antisocial Personality Disorder (AsPD), was also significantly greater than that among Control Probands (.273 *vs.* .103; $z = .353$, $p < .0005$).

3.3. MR as a function of IED diagnosis in probands

While all IED Probands met criteria for IED-IR, thirteen probands did not meet DSM-IV criteria for IED. Instead, these probands met the original research criteria for IED-R (Coccaro et al., 1998) which meant that these individuals had a history of frequent episodes of low intensity aggressive outbursts but not a history of the high intensity aggressive outbursts involving significant physical assault or destruction of property required to meet DSM-IV Criteria for IED.

Table 1
Demographic, Functional, Behavioral, and Family Data for Proband Subjects.

Variable	IED Probands ($n = 32$)	Control Probands ($n = 32$)	Statistic	*P*
Demographic				
Age	37.8 ± 8.8	35.0 ± 9.4	$t_{62} = 1.23$	.225
Gender (M/F)	22/10	23/9	Fishers exact	1.00
Race (White/Non-White)	22/10	14/18	Fishers exact	.077
SES (I/II/III/IV/V)	1/4/12/10/5	0/3/10/7/12	$X^2 = 4.74$, df = 4	.315
Functional				
GAF	54.7 ± 7.2	73.3 ± 12.9	$t_{48.5} = 7.29$	< .001
Behavioral				
LHA aggression	19.2 ± 4.3	6.2 ± 5.6	$t_{59} = 10.12$	<.001
BDHI aggression	29.2 ± 8.3	16.7 ± 6.4	$t_{53} = 6.32$	<.001
Family study variables				
Number of relatives per family	5.8 ± 2.8	4.5 ± 2.3	$t_{62} = 1.98$	.052
Number of informants per family	2.4 ± 1.0	1.7 ± .8	$t_{62} = 3.11$	<.005
Informants per family as percentage of family size	36%	31%	$Z = 2.08$	.038

The MR for IED-IR in relatives of probands who met IED-R (but not DSM-IV) Criteria, was higher than that among relatives of probands who met DSM-IV IED Criteria (.489 *vs.* .286; $z = 2.81$, $p < .005$). This result was not altered by removal of probands with co-morbid BPD/AsPD.

3.4. MR of IED-IR as a function of other co-morbid features of IED-IR probands

Among IED-IR Probands no differences in familial risk of IED-IR were observed as a function of the proband's gender, or as a function of the presence (or absence) of a life history of Mood Disorder, Anxiety Disorder, Alcohol/Drug Dependence, Non-IED impulse Control Disorder, or history of suicide attempt.

3.5. MR of non-IED disorders or features in relatives of IED-IR probands

Among IED-IR Probands no differences were observed in the familial risk of life history of Mood Disorder, Anxiety Disorder, Alcohol/Drug Use Disorders, Psychosis, Non-IED Impulse Control Disorders, or history of suicide attempt.

4. Discussion

In this family history study of IED-IR we compared the morbid risks of IED-IR (by research criteria) of first-degree relatives of IED-IR Probands with those observed in first-degree relatives of Control Probands without IED-IR or any other history of recurrent, problematic, impulsive aggression. Analysis of the family history data revealed significantly elevated morbid risk for IED-IR in relatives of IED-IR Probands compared to relatives of Control Probands. While this is consistent with previous reports (Mattes and Fink, 1987; McElroy et al., 1998), this is the first study to use a controlled and blinded, family history assessment using semi-structured interviews to estimate the familiarity of IED.

It is noteworthy that the elevation of morbid risk for IED-IR in relatives of IED-IR probands remained after IED-IR probands with co-morbid BPD/AsPD were removed from analysis. This indicates that this finding was not due to the co-morbid presence of BPD/AsPD in the IED-IR probands. This is important because there remains some controversy as to whether IED, or its influence, exists in the absence of BPD/AsPD, two personality disorders, often (though not exclusively) characterized by frequent impulsive aggressive behavior. Examination of other co-morbid conditions among the IED-IR Probands revealed no significant differences in the familial risk of IED-IR in IED-IR Probands as a function of presence or absence of a life history of Mood disorder, Anxiety disorder, Alcohol and/or Drug dependence, Non-IED Impulse Control disorders, or history of a suicide attempt. Similar examination of co-morbidity among the relatives of IED-IR Probands also revealed no significant differences in the lifetime rate of Mood disorder, Anxiety disorder, Alcohol and/or Drug Use disorders, Non-IED Impulse Control disorders, Psychosis, or history of a suicide attempt. These findings suggest strongly that IED-IR runs in families of IED-IR Probands and that it is not affected by co-morbidity in the IED-IR Probands nor by co-morbidity in the relatives themselves. Accordingly, while these co-morbid conditions aggregate in relatives of IED probands, the aggregation of IED is not due to an epiphenomenon of the liability to have these co-morbid conditions. These findings support the hypothesis that IED, as defined by research criteria, is familial and is independent of other co-morbid conditions.

The observation of a greater morbid risk for IED-IR in relatives of probands who met IED-R, but not DSM-IV, criteria for IED suggests that individuals who display frequent, low intensity, aggressive outbursts (i.e., "A" Criteria for IED-R), also have a significantly increased aggregation of IED-IR in their families compared to the families of control probands. This supports the proposal that such individuals should also be included in the overall construct of IED as proposed by the IED-IR Criteria. Results from several other studies involving analog measures of aggression (McCloskey et al., 2008), hormonal responses to serotonergic probes (Coccaro et al., 2010a), Platelet 5-HT Transporter Binding (Coccaro et al., 2010b), and anti-aggressive treatment responses to fluoxetine (Coccaro et al., 2009), or Cognitive-Behavioral Therapy (McCloskey et al., 2008), in IED-IR subjects, also support the proposal that the even the presence of frequent, low intensity, aggressive outbursts, alone, separates such individuals from non-aggressive controls.

There are a number of limitations that require acknowledgement. First, the sample is relative modest in size and there is a possibility of Type 1 error. However, these findings are similar to those in previous studies with similarly modest sample sizes but much less rigorous methods (Bach-y-Rita et al., 1971; Maletsky, 1973). Second, many of the relatives were not interviewed directly. Other limitations include the sensitivity and specificity of the IED-IR assessment used with informants, the nature of the Control Probands, differences between the groups in the proportion of informants per family, and the inherent limitations of family studies. This was a family history study and about a third (35.5%) of all relatives were not directly interviewed about themselves. It is possible that cases of IED-IR in relatives were missed using this methodology. The sensitivity of our measures to identify IED-IR with the informant method was moderate suggesting that about 40% of cases of IED-IR in relatives could have been missed. However, this should apply equally for relatives from both groups of probands. Specificity for detecting true cases of IED-IR in relatives was 81%, however, and so there is a good degree of confidence concerning the validity of the true-positive cases of IED-IR in relatives. In addition, control probands were not recruited in a population-based fashion. They were recruited in a similar manner to that of the IED-IR Probands and may not reflect a true cross-section of the general population which appears to have a lower lifetime rate of IED (Kessler et al., 2006) than that reported in relatives of control probands in this study. If so, the relative risk (RR) of IED-IR in relatives of IED-IR Probands may be nearly twice as high as that seen in this study [e.g., RR = 6.33 using the rate of 5.4% for IED by "Narrow" Criteria (Kessler et al., 2006) *vs.* RR = 3.32 using the data in this study] and suggests a much stronger genetic component for IED-IR than appears considering only the present data. The fact that this study had a greater proportion of informants per family size for IED, compared with Control, families is also a limitation of this study since the sensitivity for the target diagnoses should increase as the proportion of informants increases. The actual difference in this variable between the groups, however, was only about 16% and so the effect of this difference would be expected to be very small. Finally, this study only estimates the familiality, not the heritability, of IED-IR. That said, twin studies of the core behavioral correlate of IED (e.g., aggression) report heritabilities of BDHI Assault, (Coccaro et al., 1997a) and LHA Aggression (Yeh et al., 2010) in the 40–50% range suggesting that the familiarity of IED observed in this study is under substantial genetic influence.

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Conflict of interest statement

None declared.

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