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Validity of the new A_1 and A_2 criteria for DSM-5 intermittent explosive disorder

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Abstract

A disorder of impulsive aggression has been in the Diagnostic and Statistical Manual for Mental Disorders (DSM) since the first edition. In DSM-III, this disorder was codified as Intermittent Explosive Disorder (IED) and was thought to be rare. However, DSM criteria for IED were poorly operationalized and empiric research in IED was limited until the past decade when research criteria were developed. Subsequently, renewed interest in disorders of impulsive aggression led to a recent series of community based studies that have now documented IED to be as common as many other psychiatric disorders. Recent research indicates that the core of IED (A criteria) can be captured with new criteria that identify high frequency/low intensity aggressive outbursts (A_1) and low frequency/hi intensity outbursts (A_2). This paper presents new data regarding the phenomenology, comorbidity/life course of IED as a function of A_1 and A_2 criteria. Together with reanalysis of previously published data regarding family history, biomarkers, and treatment response in individuals with recurrent, problematic, impulsive aggression, these data provide empirical support for both A_1 and A_2 criteria for DSM-5 IED.

1. Introduction

The construct for Intermittent Explosive Disorder (IED) has been in the Diagnostic and Statistical Manual of Mental Disorders (DSM) from its first edition in 1956 [1]. In DSM-I and DSM-II, excessive reactivity to threat/environmental pressures was at the core of this disorder construct. In DSM I, this disorder was called "Passive–Aggressive Personality (Aggressive Type)" and was characterized as *"persistent reaction to frustration with irritability, temper tantrums and destructive behavior"*. In DSM-II, this disorder became "Explosive Personality" in DSM-II (1968) and such individuals were characterized as *"aggressive individuals"* who displayed *"intermittently violent behavior"* and who were *"generally excitable, aggressive, and over-responsive to environmental pressures"* with *"gross outbursts of rage or of verbal or physical aggressiveness different from their usual behavior."* Despite these vivid descriptions, little empiric data existed on either "Passive–Aggressive Personality (Aggressive Type)" or on "Explosive Personality". This was also the case when DSM-III and DSM-IV Work Groups drew up, and then revised, operational criteria for IED, later, in the 1970s and 1990s, respectively.

In 1980, the DSM-III Work Group changed the name of Explosive Personality to IED and assigned it to the "Impulse Control Disorders" (ICD) section. DSM-III's IED Workgroup focused on "low-frequency/high intensity" aggressive acts that were "out of character" for the individual and not associated with "generalized aggression and impulsivity" in between aggressive outbursts. DSM-III conceptualized IED as a "Jekyll and Hyde" type behavioral disorder where an otherwise normal, well behaved, person abruptly goes from being "mild-mannered" to being a "full of rage" and then, back to being "mild-mannered", as if nothing had happened. The members of the IED Work Group were clinical psychiatrists who were highly influenced by the hypothesis that intermittently aggressive individuals had a "limbic seizure-like" disorder referred to as "Episodic Dyscontrol" [2], a hypothesis that has not been supported by empiric data. Ultimately, DSM-III (and DSM-III-R) criteria were found to

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be problematic because very few individuals with recurrent, problematic, aggression could actually be given a diagnosis of IED. This was because the "C" criteria in DSM-III/III-R excluded people who were *"generally impulsive or aggressive"* in between the "aggressive outbursts". The report that led to this conclusion [3] was one of the very few empirical studies on IED until the late 1990s.

The next edition of the DSM (DSM-IV) made two changes to the IED Criteria Set in 1994 [4]. The first was to remove the "C" criterion from DSM-III/III-R that excluded an IED diagnosis in those individuals with *"generalized aggression and impulsivity"* because of the realization that DSM-III/III-R criteria could not properly identify individuals with recurrent, problematic, aggressive behavior (whether or not it was impulsive in nature) [3]. The second was to relax the exclusion criteria so that IED could be diagnosed in the presence of other disorders as long as the aggression seen in the subject was not fully explained by the presence of a comorbid disorder. This change was DSM-IV wide and reflected the realization that as long as psychopathology was not solely due to a comorbid disorder the DSM-IV diagnosis in question could be made.

Over the course of time, during the DSM-III/IIIR/DSM-IV eras, investigators studying the biology and treatment of aggression demonstrated inverse correlations between measures of central serotonin (5-HT) and aggression, impulsivity, and irritability [5]. This work led to treatment trials with SSRIs that demonstrated that SSRIs could reduce impulsive aggressive behavior in aggressive individuals (who would now be called IED) [6]. Two important empiric insights came from this data-driven work. First, IED subjects have "high frequency/low intensity" impulsive aggressive outbursts alone, or in addition to, the "low frequency/high intensity" impulsive aggressive outbursts characteristic of the "A Criterion" for DSM-IV IED [7]. Second, it was just these "high frequency/low intensity" impulsive aggressive outbursts that responded to SSRI and to CBT treatment with a reduction in the number and severity of impulsive aggressive outbursts [6,8,9]. This did not mean that "low frequency/high intensity" aggressive outbursts do not, ultimately, respond to these treatments but, simply, that the frequency of these behaviors is too low to see sufficient change in 8–12 week clinical trials.

This psychobiologic and treatment response work led to the development of Research Criteria that aimed to clarify the nature of IED so that it would more accurately describe, and categorize, individuals with recurrent, impulsive aggressive behavior that was associated with significant distress and/or impairment [1,7]. Unlike other attempts to craft criteria for IED, this work was based on empiric data. In addition, Research Criteria went back to DSM's "roots" to conceptualize IED as a disorder in which *excessive reactivity to threat/environmental stimuli/pressures is expressed by aggressive behavior*. Aggressive behavior, in fact, includes all forms of aggression ranging from verbal assault (e.g., screaming or verbal arguments), non-damaging/non-destructive physical aggression to objects (e.g., throwing things around, slamming doors), animals or other individuals (e.g., physical assault *without* injury), to damaging/destructive physical aggression against objects (e.g., breaking things) or animals or other individuals (e.g., physical assault *with* injury). This conceptualization is consistent with findings reported in the biology and treatment of impulsive aggression in human and animal studies [10].

Based on this work, the framers of Research Criteria posited that recurrent, problematic, impulsive aggression *was not due* to the presence of a "limbic seizure-like" focus in the brain, as posited by the DSM-III/III-R criteria *but was due* to abnormalities in central neurotransmitter function (e.g., low 5-HT associated with disinhibition of aggressive impulses) and imbalance of inhibitory (e.g., orbitofrontal cortex) and excitatory (e.g., amgydala) neuronal systems that underlie the type of recurrent, problematic, impulsive aggression [11] present in the community [12–14] and in clinical settings [7,15].

The most recent version of Research Criteria for IED divided the A criterion into A_1 (high frequency/low intensity) and A_2 (low frequency/high intensity) criteria to document the nature of the aggressive behavior, and time frame, of aggressive behaviors in order to further operationalize the core feature of IED based on empiric data [7]. While the A_1 criterion was not part of the formal diagnostic criteria in DSM-IV, "high frequency/low intensity" aggressive outbursts were acknowledged as an "associated feature" of IED in the Text-Revision of DSM-IV [16]. Thus the formal creation of an A_1 and A_2 criteria brings this out of the text into the diagnostic criteria for IED.

This paper focuses on the empirical data that support the creation of A_1 and A_2 criteria for DSM-5 IED. We hypothesized the following: a) A_1 and A_2 criteria are both characteristic of most individuals with IED; b) IED subjects with *only* A_1 aggressive outbursts are little, if no, different than individuals with *only* A_2 aggressive outbursts, c) IED subjects with only A_1 aggressive outbursts are little, or no, different than individuals with *both* A_1 and A_2 aggressive outbursts and, d) IED subject with *only* A_1 aggressive outbursts are significantly different than "controls" in terms of levels of aggression, anger, impulsivity, psychosocial function, family history of aggression, biomarkers, and treatment response.

2. Methods

2.1. Subjects

Nine-hundred and three, new, physically healthy subjects participated in the phenomenological aspect of this study. In addition, a total of one-hundred-fifty-six, non-overlapping, subjects participated in previously published studies of family history [17], biomarkers [10,18], and treatment response [8,9] in IED that were re-analyzed for this paper.

All subjects were systematically evaluated in regard to impulsive aggressive and other personality-related behaviors

in human subjects. Subjects were recruited from clinical settings and through newspaper advertisements seeking out individuals who: a) reported psychosocial difficulty related to one or more Axis I and Axis II conditions (Axis I/II subjects) or b) had little evidence of psychopathology (Healthy Controls). All subjects gave informed consent and signed the informed consent document approved by the Institutional Review Board (IRB). Subjects with a life history of bipolar disorder, schizophrenia (or other psychotic disorder), or mental retardation were excluded from this study. Medical health of all subjects was documented by medical history and exam that also included a drug screen for illicit drugs of abuse (no one testing positive for any substance entered this study).

2.2. Diagnostic Assessment

Axis I and Axis II Personality Disorder diagnoses were made by DSM-IV criteria [4] (APA 1994). The diagnosis of Intermittent Explosive Disorder was made by Research Criteria as previously described [7,11]. Diagnoses were made using information from: (a) the Structured Clinical Interview for DSM Diagnoses (SCID-I) [19] for Axis I disorders and the Structured Interview for the Diagnosis of DSM Personality Disorder [20] for Axis II disorders; (b) clinical interview by a research psychiatrist; and, (c) review of all other available clinical data. The research diagnostic interviews were conducted by individuals with a masters or doctorate degree in Clinical Psychology after a rigorous training program including lectures on DSM diagnoses and rating systems, videos of expert raters conducting SCID/SIDP interviews, and practice interviews/ratings until the raters were deemed reliable with the trainer. This process resulted in good to excellent inter-rater reliabilities (mean kappa of .84 ± .05; range: .79 to .93) across anxiety, mood, substance use, impulse control, and personality disorders. Final diagnoses were assigned by team best-estimate consensus procedures [21,22] involving research psychiatrists and clinical psychologists as previously described [7]. This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone [23].

A total of three-hundred-fifty-four subjects met Research Criteria for current Intermittent Explosive Disorder (IED), four-hundred-three met DSM-IV criteria for current or lifetime history of an Axis I and/or Axis II, disorder (Psychiatric Controls: PC), and three-hundred-thirty-eight had no evidence of any DSM-IV Axis I or II psychopathology (Healthy Controls: HC).

Among the IED and PC subjects, 474 (62.6%) had a current history of an Axis I disorder, 721 (95.2%) had a lifetime history of an Axis I disorder, and 479 (63.3%) had an Axis II Personality Disorder. Among IED subjects, current Axis I disorders were present in all subjects by definition since all IED subjects met criteria for current IED. Other current Axis I disorders were as follows: Any Mood Disorder (n = 64); Any Anxiety Disorder (n = 120); Any Non-IED Impulse Control Disorder (n = 10); Adjustment Disorder (n = 5); Eating Disorder (n = 19); Somatoform Disorder (n = 7). Aside from IED, lifetime Axis I disorders were as follows: Any Mood Disorder (n = 218); Any Anxiety Disorder (n = 158); Alcohol Dependence (n = 71), Drug Dependence (n = 79); Any Non-IED Impulse Control Disorder (n = 19); Adjustment Disorder (n = 22); Eating Disorder (n = 40), Somatoform Disorder (n = 8). Two-hundred-twenty IED subjects met DSM-IV criteria for specific personality disorder as follows: Cluster A (n = 63); Cluster B (n = 172); Cluster C (n = 86). The remaining 97 subjects were diagnosed Personality Disorder-Not Otherwise Specified (PD-NOS). These subjects met DSM-IV general criteria for personality disorder, had pathological personality traits from a variety of personality disorder categories and had evidence of impaired psychosocial functioning [25]. Among PC subjects, current Axis I disorders were present in 120 subject (29.8%) as follows: Any Mood Disorder (n = 28); Any Anxiety Disorder (n = 70); Any Non-IED Impulse Control Disorder (n = 3); Adjustment Disorder (n = 11); Eating Disorder (n = 6); Somatoform Disorder (n = 2). Lifetime Axis I disorders, present in 367 subjects (91.1%), were as follows: Any Mood Disorder (n = 156); Any Anxiety Disorder (n = 106); Alcohol Dependence (n = 93), Drug Dependence (n = 25); Any Non-IED Impulse Control Disorder (n = 9); Adjustment Disorder (n = 45); Eating Disorder (n = 30), Somatoform Disorder (n = 2). Eighty-eight PC subjects also met DSM-IV criteria for a specific personality disorder as follows: Cluster A (n = 12); Cluster B (n = 34); Cluster C (n = 55). The remaining 74 PC subjects were diagnosed Personality Disorder-NOS.

Table 1
A_1 and A_2 Criteria for DSM-5 IED.

A1. Verbal aggression (e.g. temper tantrums, tirades, verbal arguments or fights) or physical aggression towards property, animals or other individuals, occurring twice weekly, on average, for a period of 3 months. The physical aggression does not result in damage or destruction of property and does not result in physical injury to animals or other individuals.
OR
A2. Three behavioral outbursts involving damage or destruction of property and/or physical assault involving physical injury against animals or other individuals occurring within a 12-month period.

2.3. Creation of A_1 and A_2 Criteria for IED (Table 1)

The A_1 threshold was set at two (2) aggressive outbursts involving verbal aggression and/or physical, but non-damaging, non-destructive, non-injurious, aggression, per week for one month, because this level of frequency was documented as the lower threshold for this form of aggression, in impulsive aggressive individuals taking part in clinical trials with SSRIs [6]. The A_2 threshold was set at three (3) severe aggressive outbursts a year because this level distinguishes individuals who display damaging, destructive, or injurious, physical aggressive behavior, on several

Table 2
Aggression/Anger/Impulsivity Measures (Mean + SEM) A1-Only *vs*. A2-Only & A1-Only *vs*. "All A2".

	Ncs (n = 268)	PCs (n = 297)	"A1-Only" (n = 72)	"A2-Only" (n = 35)	"All A2" (n = 273)	P* for "A1-Only" vs. NCs or PCs	P* for "A1-Only" vs. "A2-Only"	P* for "A1- Only" vs. "All A2"
LHA Aggression	5.2 ± 0.3	8.2 ± 0.3	15.7 ± 0.5	16.9 ± 0.7	19.6 ± 0.3	< .001** (Vs. NC/PC)	.65	< .001**
BPA Aggression	56.8 ± 1.4	66.7 ± 1.4	89.6 ± 3.1	83.6 ± 5.8	96.8 ± 1.8	< .001** (Vs. NC/PC)	.9	.18
Trait Anger	13.2 ± 0.6	16.7 ± 0.7	24.9 ± 1.2	25.6 ± 2.1	28.0 ± 0.7	< .001** (Vs. NC/PC)	.99	.14
LHIB Impulsivity	49.6 ± 3.0	63.8 ± 2.9	116.8 ± 6.2	108.7 ± 11.4	131.4 ± 3.6	< .001** (Vs. NC/PC)	.91	.17
BIS Impulsivity	56.3 ± 0.7	63.0 ± 0.7	66.5 ± 1.6	71.5 ± 2.8	70.3 ± 0.9	< .001** (Vs. NC Only)	.54	.15

*P by Tukey Honestly Significant Difference (Tukey-HSD) after significant ANOVA ($p < .001$) for each measure.
** Significant after correcting for sixteen comparisons ($p < .0032$ required).

parameters (i.e., years of aggressive outbursts, highest number of outbursts in any year, number of outbursts and weeks of outbursts in the past year, number of outbursts resulting in injury requiring medical attention, dollars in property damage resulting from these outbursts, and severe role impairment due to these outbursts) compared with those with a lower frequency (i.e., three or more over the lifetime but never as frequent as three or more in any single year) of these aggressive outbursts [11].

2.4. Psychometric Measures Relevant Aggression, Anger, Impulsivity, and Related Behavioral Dimensions

Aggression was assessed by the Aggression Factor from the Life History of Aggression (LHA) [24] and the Buss–Perry Aggression Questionnaire (BPAQ) [25]. The LHA-Aggression instrument assesses the number of times a person has engaged in aggressive behavior while the BPAQ assesses the person's tendency to act aggressively as a personality trait. Anger was assessed by the Trait Anger scale from the State–Trait Anger and Expression of Anger (STAXI) scales [26]. Impulsivity was assessed by the Life History of Impulsive Behavior (LHIB) [27] and Barratt Impulsivity Scale (BIS-11) [28]. The LHIB assesses the number of times a person has engaged in impulsive behavior while the BIS-11 assesses the person's tendency to act impulsively as a personality trait. Global psychosocial functioning of subjects was assessed by the Global Assessment of Function scale (GAF) [4].

2.5. Statistical Analysis and Re-Analysis of Published Data

For data from our Chicago Studies (n = 903), comparisons between groups were performed by t-test, with correction for unequal variances where necessary, analysis of covariance (ANCOVA and MANOVA), and by χ^2 tests. Correlational analyses included Pearson correlation, partial correlation, and multiple regression. A two-tailed alpha value of 0.05 was used to denote statistical significance for all analyses with Bonferroni correction for multiple comparisons. Finally, previously published data was re-analyzed [8–10,17,18] to explore potential differences in outcome measures as a function of meeting the A_1 criterion only, compared to those who met the A_2, or both A_1 and A_2, criterion.

3. Results

3.1. Demographic Features and Psychosocial Function (Table 2)

No significant differences were seen between "A_1-Only", "A_2-Only", or "All A_2" subjects with regard to gender, race, socioeconomic status, or general level of current psychosocial function (GAF Scores). In addition, there is little difference in the age of onset, or in lifelong course between "A_1-Only" *vs*. "A_2-Only", or "A_1-Only" *vs*. "All A_2" subjects.

3.2. Frequency and Duration of A_1 vs. A_2 Criteria in IED Subjects

In this sample, the frequency of IED subjects meeting the "A_1" and/or "A_2" criteria was nearly 20% for "A_1-Only", nearly 10% for "A_2-Only", and about 70% for "$A_{1+}A_2$" criteria. Duration of the A_1 criterion in these subjects ranged from less than one month to greater than 10 years, with nearly all IED subjects (94.4%) having an A_1 duration of three months or more. The few IED subjects meeting the A_1 criterion for less than three months did not differ in measures of aggression, trait anger, or impulsivity, from those meeting the A_1 criterion for three months or more.

3.3. Aggression, Anger, and Impulsivity (Table 3)

Analysis of scores assessing history of "actual aggressive behavior" (i.e., Life History of Aggression) and on "aggressive tendencies" (i.e., Buss–Perry Aggression) demonstrates that "A_1-Only" subjects have significantly higher aggression scores compared with both NC and PC subjects. In addition, the aggression scores of "A_1-Only" subjects are as high as that in "A_2-Only" subjects and only modestly lower (by 19%) than the aggression scores of "All A_2" subjects (regardless of whether these subjects also met the "A_1"criteria). Similar analysis of scores assessing trait anger demonstrate that "A_1-Only" subjects have significantly higher trait anger scores compared with both NC and PC subjects and that trait anger scores of "A_1-Only" subjects are as high as that in "A_2-Only", and in All A_2", subjects. Analysis of scores for history of "actual impulsive behavior" (i.e., Life History of Impulsive Behavior) and on "impulsive tendencies" (i.e., Barratt Impulsiveness Scale) also

Table 3
IED-Demographics: A1-Only *vs*. A2-Only & A1-Only *vs*. "All A2".

	"A1-Only" (n = 72)	"A2-Only" (n = 35)	P* for "A1-Only" *vs*. "A2-Only"	"All A2" (n = 273)	P* for "A1-Only" *vs*. "All A2"
Age (years)	36.6 ± 1.2	33.6 ± 1.8	.15	35.3 ± 0.6	.33
Gender (% Male)	44%	51%	.54	47%	.69
Race W/AA/H/Other (By Percent)	45/44/9/3	58/23/13/6	.21	47/36/12/13	.51
SES (HH) I + II/III/IV + V (By Percent)	67/14/19	58/26/16	.38	56/22/23	.20
GAF Score	57.1 ± 0.9	58.7 ± 1.2	.32	54.0 ± 0.5	.01**
Age of Onset (Years)	13.5 ± 0.9	12.1 ± 1.3	.31	12.2 ± 0.4	.15
Duration of IED (Years)	24.8 ± 2.1	23.3 ± 2.7	.69	27.8 ± 1.0	.17

* = P by Fisher Exact Test.
**Not significant after correcting for fourteen comparisons (corrected p < .0036).

demonstrates that "A_1-Only" subjects have significantly higher LHIB and BIS Impulsivity scores compared with NC subjects and significantly higher LHIB Impulsivity (though not BIS) scores compared with PC subjects. In addition, both LHIB and BIS Impulsivity scores of "A_1-Only" subjects are as high as those in "A_2-Only" subjects and as high as those in "All A_2" subjects.

3.4. Comorbidity (Table 4)

No significant differences were seen between "A_1-Only", A_2-Only, or among "All A_2" on current or lifetime Axis I disorders (Table 4). From these analyses, it is clear that adding the A_1 criterion to the DSM-5 Criteria Set allows for about 20% more individuals to receive a DSM-5 diagnosis of IED and be candidates for treatment with psychopharmacological or psychotherapeutic interventions.

3.5. Re-Analysis of Family History and Biomarker Data (Table 5)

Reanalysis of Family History data [17], 5-HT Challenge Studies [10] and Platelet 5-HT Transporter Studies [18] yielded the same findings regarding the comparability of "A_1-Only" subjects *vs*. "All A_2" subjects.

3.6. Family History

Reanalysis of the Family History Study [17] data found that "A_1-Only" subjects made up 22% of "All IED" subjects in the study; this is consistent with the "A_1- Only" *vs*. "All A_2" frequency data presented above. "A_1-Only" Probands (7 Probands, 36 Relatives, 5.1 Relatives/Proband) had a significantly higher Age-Adjusted Morbid Risk (MR) for Familial IED compared with that for "All A_2" subjects (25 Probands, 149 Relatives, 6.0 Relatives/Proband), and compared with 0.10 for "Control" subjects (32 probands, 144 relatives, 4.5 Relatives/Proband). Differences in MR between "A_1-Only" *vs*. "Control" and "All A_2" *vs*. "Control" were statistically significant ($z = 5.30$, $p < .0001$ and $z = 3.97$, $p < .0001$, respectively). The difference in MR between "A_1-Only" *vs*. "All A_2" was statistically significant *before* correction for three comparisons ($z = 2.21$, $p = .027$) and a statistical trend when corrected for these three comparisons ($p = .081$).

Table 4
IED-Comorbidity - A1-Only *vs*. A2-Only & A1-Only *vs*. "All A2".

	"A1- Only" (n = 72)	"A2- Only" (n = 35)	P* for "A1-Only" *vs*. "A2-Only"	"All A2" (n = 273)	P* for "A1-Only" *vs*. "All A2"
Current Axis I Dx					
Mood Disorder	18.1%	5.7%	.17	18.7%	.99
Anxiety Disorder	30.6%	17.1%	.17	35.2%	.49
Non-IED Impulse Control Disorder	0.0%	0.0%	.99	3.7%	.13
Adjustment Disorder	2.8%	0.0%	.99	1.1%	.28
Past Axis I Dx					
Mood Disorder	50.0%	51.4%	.99	65.2%	.02**
Anxiety Disorder	40.3%	22.9%	.09	45.8%	.43
Non-IED Impulse Control Disorder	1.4%	0.0%	.99	6.6%	.14
Adjustment Disorder	12.5%	5.7%	.34	4.8%	.03**
Alcohol Dependence	13.9%	25.7%	.18	21.2%	.32
Drug Dependence	19.4%	14.3%	.60	23.8%	.53

* P by Fisher Exact Test.
** Not significant after correcting for twenty comparisons (p < .0025 required).
*** Significant after correcting for twenty comparisons (p < .0025 required).

Table 5
Family History, 5-HT Biomarkers, Clinical Trial Response (Mean + SEM) "All IED" vs. "Control" *and* "A1-Only" *vs*. "All A2".

	"Control"	"A1-Only"	"All A2"	P* for "All IED" *vs*. "Control"	P* for "A1-Only" *vs*. "All A2"
Family History Study (Morbid Risk)	0.10	0.47	0.28	.001	.028**
5-HT Transporter Study (Platelet 5-HTT)	1414 ± 54	1198 ± 146	1073 ± 69	.001	.73
5-HT Challenge Study (PRL[d-FEN])	0.42 ± 0.14	−0.28 ± 0.23	−0.23 ± 0.17	.001	.98
SSRI Clinical Trial Endpoint OAS-M Aggression	1.19 ± 0.11	0.85 ± 0.10	0.84 ± 0.8	.003	.93
CBT Clinical Trial Endpoint OAS-M Aggression	1.17 ± 0.16	0.72 ± 0.20	0.67 ± 0.13	.017	.75

* P by Tukey-HSD after significant ANOVA ($p < .05$) for each study except for Family History Study.
** Not significant after correcting for five comparisons ($p < .01$ required).

3.7. Biomarkers (Table 5)

3.7.1. Physiological Response to Acute Pharmaco-Challenge with 5-HT Agents

Reanalysis of the 5-HT Challenge Study [10] data found that "A_1-Only" subjects made up 36% of IED subjects in the study. In this study, the outcome measure was a Z score that represented the prolactin response to acute challenge with d-Fenfluramine (PRL[d-FEN]), a 5-HT releasing agent, after all relevant covariates (age, weight, gender, etc.) were accounted for. Both "A_1-Only" and "All A_2" subjects had a similarly ($p = .98$) reduced PRL[d-FEN] responses compared with "NC" subjects ($p < .001$).

3.7.2. Platelet 5-HT Transporters

Reanalysis of the Platelet 5-HT Transporter Study [18] data found that "A_1-Only" subjects made up 34% of "All IED" subjects in the study. "All IED" subjects had significantly reduced mean numbers of Platelet 5-HT Transporters (Bmax) compared with "Non-IED" subjects. The mean number of Platelet 5-HT Transporters for "A1-Only" subjects was the same as that for "All A2" subjects ($p = .73$).

3.8. Re-Analysis of Response to Treatment Interventions (Table 5)

3.8.1. Clinical Trial with Fluoxetine

Reanalysis of the SSRI-Fluoxetine study [8] data found that "A_1-Only" subjects made up 21% of "All IED" subjects in the study. The outcome measure for this study was the log-transformed endpoint score for "Overt Aggression" on the Overt Aggression Scale — Modified for Outpatient Subjects (OAS-M; 29) *controlled* for baseline OAS-M Aggression scores [29]. For both "A_1-Only" and "All A_2" groups, Fluoxetine was superior to Placebo Control ($F[1,95] = 9.03$, $p = .003$) on OAS-M Aggression, with no effect of "A_1-Only" *vs*. "All A_2" ($F[1,95] = 0.05$, $p = .83$) and no effect for an interaction between Drug Condition and "A_1-Only" *vs*. "All A_2" Group ($F[1,95] = 1.49$, $p = .23$). For "A_1-Only" subjects treated with Fluoxetine ($n = 14$), the mean endpoint score was the same ($p = .93$) as that for "All A2" subjects treated with Fluoxetine ($n = 51$).

3.8.2. Clinical Trial with CBT

Re-analysis of the CBT Study [9] data found that "A_1-Only" subjects made up 31% of "All IED" subjects in the study. For the CBT Study the outcome measure was the same as in the SSRI Study above. For both "A_1-Only" and "All A_2" groups, CBT was superior to Wait-List Control ($F[1,40] = 6.23$, $p < .02$) on OAS-M Aggression, with no effect of "A_1-Only" *vs*. "All A_2" group condition ($F[1,40] = 0.10$, $p = .75$) and no effect for an interaction between Treatment Condition and "A_1-Only" *vs*. "All A_2" Group ($F[1,40] = 0.01$, $p = .95$). For "A_1-Only" subjects treated with CBT ($n = 9$), the mean endpoint score was the same ($p = .75$) compared with that of "All A_2" subjects treated with CBT ($n = 21$).

4. Discussion

These analyses were conducted in the context of revising the DSM-IV criteria for Intermittent Explosive Disorder for the Fifth Edition of the DSM. As discussed above, DSM-IV criteria for IED were poorly defined, with few guidelines to assist clinicians in making a diagnosis. Accordingly, research criteria were developed to offer specific operationalized criteria for diagnosis that would allow the appropriate identification of individuals with recurrent, problematic, impulsive aggressive behavior. This included specific proposals for the quantification of aggressive behavior and for the time frames in which these behaviors took place. Close clinical observation revealed that individuals with recurrent, problematic, impulsive aggressive behavior displayed two forms of this behavior. One, "high frequency/low intensity" (A_1) aggressive behavior and, two, "low frequency/high intensity" aggressive behavior (A_2). Because the first set of behaviors was new to the criteria set for IED, it was critical to assess the equivalency of "high frequency/low intensity" aggressive behaviors with those of "low frequency/high intensity" aggressive behaviors, and this was done. In addition, it was important to assess the validity of the proposed time frame for the proposed A_2 behaviors.

For "low frequency/high intensity" aggressive outbursts (A_2), reanalysis of data from the NCS-Replication study reveals that individuals with at least three "high intensity" aggressive outbursts in any one year are quite different than those who never have three "high intensity" aggressive outbursts in any one year [12]. Since there is evidence of some role impairment in this latter group, such individuals might be given a diagnosis of IED-NOS when using DSM-5. However, it is also possible that many of these individuals had enough "low intensity" aggressive outbursts to meet the proposed A_1 criteria for IED and that this explains the role impairment, associated with aggressive outbursts observed in this group. While this remains, as the NCS-R study did not record numbers of "low intensity" aggressive outbursts [13], the clinical research data set presented above, suggests that at least 20% of all recurrent, problematic, impulsive aggressive individuals had "high frequency/low intensity", even if they did not have enough "low frequency/high intensity", aggressive behaviors. If so, many in this very low frequency/high intensity" aggressive group might meet criteria for DSM-5 IED by meeting the A_1 criteria.

Overall, data from this and a previous clinical study [7] demonstrate that about 70% of subjects with recurrent, problematic, impulsive aggression (e.g., candidates for a diagnosis of IED) have *both* "high frequency/low intensity" (A_1 Criterion) *and* "low frequency/high intensity" (A_2 Criterion) episodes of impulsive aggressive outbursts. An additional 20% have only "high frequency/low intensity" (A1-Only), and 10% have only "low frequency/high intensity" (A2-Only), impulsive aggressive outbursts. Respectively, A1 was present in about 90%, and A2 was present in about 80%, of all individuals with clinically significant, recurrent, problematic, impulsive aggressive behavior in these studies. Individuals with either (or both) A1 and/or A2 criteria differ from normal controls in terms of aggression, anger, impulsivity, psychosocial function, family history of impulsive aggression, and biomarkers of impulsive aggression. In addition, there were no meaningful differences between subjects who meet the A_1 Criterion *only* and subjects who meet the A_2 Criterion *only*. Further, there are few, if any, meaningful differences between subjects who meet the A_1 criterion *only* and subjects who *meet* A_2 (with or without meeting A_1) Criteria. Most importantly, clinical trial data provide evidence that "A_1-Only" and "All A_2" subjects have equivalent anti-aggressive responses to treatment with SSRIs, or with CBT, strongly suggesting subjects meeting "A_1-Only", "A_2-Only", *or* "$A_1 + A_2$" Criteria should be considered a single group under the diagnosis of IED.

Adopting the A_1 criterion brings this "associated feature" in DSM-IV up into the formal diagnostic criteria set and allows up to an additional 20% of individuals with clinically significant, recurrent, problematic, impulsive aggressive behavior to receive a diagnosis of DSM-5 IED and, thus, be referred for treatment of these behaviors with psychopharmacological and/or psychotherapeutic interventions. This consideration, coupled with observations that "A_1-Only" subjects are significantly different than "NC" (and "PC") subjects on phenomenological variables and the same or nearly the same to "All A_2" subjects in terms of phenomenological variables, life course, family history, biological markers, and treatment response, supports the inclusion of A_1, in addition to A_2, as a criteria for IED in DSM-5.

These data were presented to the DSM-5 Work Group for "Conduct and Disruptive Behavior Disorders" and then reviewed and endorsed by the Scientific Review and Clinical Psychopathology and Health, Committees for the DSM-5. The APA Board of Trustees then approved the adoption of the A_1 and A_2 criteria for DSM-5 IED in November 2012. In addition to approving these criteria for DSM-5 the recommendation that A_1 be present for at least three months was also adopted to prevent an individual from getting a diagnosis of IED simply because he or she "had a bad month". As noted in this study, duration of the A_1 criterion for at least three months was present in nearly 95% of our IED subjects. While IED subjects with less than three months of A_1, at index evaluation, did not differ from those with three months of A_1 in the most important ways, few subjects are likely to be diagnosed IED-NOS given a DSM-5 required A_1 criterion duration of three months or more.

In summary, these data provide empirical support for the inclusion of both A_1 and A_2 criteria for IED in the DSM-5. Given the relative frequency of IED in the US and elsewhere [11], it is likely that these new DSM-5 criteria will properly identify individuals with recurrent, problematic, impulsive aggression for further evaluation and treatment. This is a critical step because the vast majority of such individuals are not currently diagnosed and relatively few are treated for it [12,13] despite evidence of the efficacy of both pharmacologic and psychotherapeutic approaches to reducing impulsive aggression [8,9,30–35].

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