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Journal
Psychiatry Research, 205(3)

ISSN
0165-1781

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Publication Date
2013-02-01

DOI
10.1016/j.psychres.2012.09.029

Peer reviewed

Published in final edited form as:
Psychiatry Res. 2013 February 28; 205(3): 269–275. doi:10.1016/j.psychres.2012.09.029.

Prevalence and clinical correlates of explosive outbursts in Tourette Syndrome

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Abstract

The aim of this study was to examine the prevalence and clinical correlates of explosive outbursts in two large samples of individuals with TS, including one collected primarily from non-clinical sources. Participants included 218 TS-affected individuals who were part of a genetic study (N=104 from Costa Rica (CR) and N=114 from the US). The relationship between explosive outbursts and comorbid attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), tic severity, and prenatal and perinatal complications were examined using regression analyses. Twenty percent of participants had explosive outbursts, with no significant differences in prevalence between the CR (non-clinical) and the US (primarily clinical) samples. In the overall sample, ADHD, greater tic severity, and lower age of tic onset were strongly associated with explosive outbursts. ADHD, prenatal exposure to tobacco, and male gender were significantly associated with explosive outbursts in the US sample. Lower age of onset and greater severity of tics were significantly associated with explosive outbursts in the CR sample. This study

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Financial Disclosures of all authors (for the preceding 12 months): none

Conflicts of Interest of all authors (for the preceding 3 years): none

confirms previous studies that suggest that clinically significant explosive outbursts are common in TS and associated with ADHD and tic severity. An additional potential risk factor, prenatal exposure to tobacco, was also identified.

Keywords

impulse control; tic disorders; prenatal maternal smoking; rage; co-morbidity

1. Introduction

Explosive outbursts (also referred to as “rage attacks”) are sudden, dramatic, repetitive episodes of verbal and/or physical aggression that are developmentally ageinappropriate and disproportionate to the putative trigger (Budman et al., 1998). These symptoms can be classified under the DSM-IV-TR diagnostic category of Intermittent Explosive Disorder (IED) as an independent disorder, but have also been described in a variety of neuropsychiatric conditions, including obsessive compulsive disorder (OCD), mood disorders, non-OCD anxiety disorders, and disruptive behavioral disorders such as oppositional defiant disorder (APA DSM-IV, 1994; Kessler et al., 2006; Storch et al. 2012). Data from the National Comorbidity Survey (NCS) suggest that the lifetime prevalence of explosive outbursts that meet criteria for DSM-IV IED is 5.4% (Kessler et al., 2006). It is common for symptoms of IED to first emerge during childhood; the mean age of onset for IED among participants in the NCS study was 14 years with almost 40% meeting diagnostic criteria by age 10 years (Kessler et al., 2006). Epidemiological data on 6483 youth ages 13–17 years from the National Comorbidity Survey Replication Adolescent Supplement indicated that two-thirds of adolescents experience significant anger attacks; of these, 7.8% met DSM-IV criteria for lifetime IED. In this study, 6.2% of all adolescent respondents met 12-month criteria for IED with a mean age of onset at 12 years (McLaughlin et al. 2012).

According to the NCS, 81% of participants with explosive outbursts in the general population have been diagnosed with at least one other DSM-IV disorder, most commonly mood disorders (37.4%), anxiety disorders (58.1%), impulse control disorders (44.9%), and substance abuse disorders (35.1%) (Kessler et al., 2006). Explosive outbursts have been reported to occur with significant frequency in Tourette Syndrome (TS), a phenomenologically heterogeneous disorder characterized by the childhood onset of chronic multiple motor and vocal tics (APA DSM-IV, 1994). Previous studies among clinically-referred samples suggest that approximately 25% to 70% of TS-affected individuals report problems with explosive anger and that, when present, such symptoms are a leading cause of morbidity (Budman et al., 1998; Stephens and Sandor, 1999; Budman, et al., 2000; Zhu et al., 2006; Budman et al., 2008; Cavanna et al., 2011, Kano et al., 2008, Wright et al., 2012). However, the relationship, if any, between explosive outbursts and the underlying tic diathesis has been difficult to untangle (Goodman et al., 2006; Wright et al., 2012).

Previous clinical studies have reported a strong association between the presence of explosive outbursts in TS and comorbid obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD) (Budman et al., 2000; Freeman et al, 2000; Sukhdolsky et al., 2003; Mol Debes et al., 2008; Cavanna et al. 2011; Wright et al. 2012). However, confirmation of these associations, further exploration and clarification of the possible relationship of explosive outbursts in TS with demographic characteristics such as gender, socioeconomic status and ethnicity, as well as clinical characteristics such tic severity, tic type, and severity of obsessions and compulsions, are needed. Earlier clinical studies of explosive outbursts in TS were limited by relatively small sample sizes and sample composition, consisting of patients recruited

primarily from TS specialty clinics (Budman et al., 1998; Stephens and Sandor, 1999; Budman et al., 2000; Budman et al., 2003; Kano et al., 2008). Therefore, in this study we examined the prevalence and demographic and clinical correlates (including potential pre- and perinatal risk factors, tic severity, and obsessive-compulsive symptom severity) of explosive outbursts in two separate populations of individuals with TS who were initially recruited for participation in TS genetic studies. The first study sample included individuals with TS who were living in the United States (US) and who were recruited primarily from TS specialty clinics. The second sample was derived from individuals with TS living in Costa Rica (CR) and who, in most cases, were recruited from the community rather than from clinics. The aim of this investigation was to first examine the prevalence of explosive outbursts in this large (combined) sample of individuals with TS and compare it to previously reported rates. We then sought to identify specific characteristics highly correlated with explosive outbursts in the overall sample. Next, we examined the prevalence and clinical characteristics of explosive outbursts in each of the two samples separately. We hypothesized that the prevalence of explosive outbursts would be at the lower end of the previously reported range of frequencies, and that explosive outbursts would, as previously described, be associated with comorbid OCD and/or ADHD (Budman et al., 1998; Stephens and Sandor, 1999; Cavanna et al., 2011; Wright et al., 2012). However, we also hypothesized that pre-or perinatal risk factors such as maternal tobacco or alcohol use during pregnancy or hypoxia at birth would be associated with increased rates of explosive outbursts in TS-affected individuals, based partly on our previous findings relating these risk factors to increased risk for OCD (Mathews et al., 2006).

2. Methods

2.1. Participants

The study sample consisted of 218 individuals diagnosed with TS (ages 5 to 75 years) recruited for genetic studies between 1996 and 2009, including a genetic study of individuals with TS from the genetically isolated Central Valley of Costa Rica (N = 104) and a genetic study among individuals of Ashkenazi Jewish descent in the US (N = 114). Costa Rican (CR) participants were ethnically Hispanic; US participants were Caucasian. 65% of participants were under 18 at the time of interview, and 21% of participants were female. Participants from the US were recruited primarily from TS specialty clinics and by referral from the National Tourette Syndrome Association (TSA). CR participants were recruited from healthcare professionals, media advertisements, elementary schools, and friends or family members. Written informed consent (and assent, for children between 5 and 17 years) was obtained for all participants, and all studies were approved by the relevant Institutional Review Boards.

2.2. Diagnostic Assessments

Diagnostic information was systematically gathered using structured instruments administered by two psychiatrists (CAM and LDH) who were blinded to IED diagnosis. Lifetime symptom prevalence and worst-ever symptom severity were assessed in all cases. Interviews were videotaped for confirmation of tics. Information about explosive outbursts was elicited using a questionnaire that probed for the diagnostic criteria for Intermittent Explosive Disorder (IED) according to the DSM-IV (APA DSM-IV, 1994; Budman et al., 2000). The Yale Global Tic Severity Scale (YGTSS) was used to assess worst-ever lifetime severity (Leckman et al., 1989). Socioeconomic status was measured using the Hollingshead scale, a 5 point scale assessing parental income, education, and profession, with 1 being the lowest socioeconomic class and 5 being the highest (Hollingshead, 1975). Other demographic, medical, social, and clinical characteristics, including pre-and perinatal history, developmental history, school performance, medical history, and family history of

tics and obsessive-compulsive symptoms (OCS), were assessed using a semi-structured clinical interview.

Information about motor and vocal tics, OCD, obsessive-compulsive symptoms (OCS), ADHD, and self-injurious behavior (SIB) was elicited using a self-report questionnaire that was designed for genetic studies of TS and is in use globally for genetic and other etiological studies (TSAICG, 1999; TSAICG, 2007). For all child cases and for 43% of the adult cases in CR and 10% of the adult cases in the US (74% of total, 91% CR group, 58% US group), parents were present during the interview, allowing for confirmation of childhood symptoms, and providing detailed information on prenatal, perinatal and early childhood history. When parents were not present for the interview, adult participants were asked to confirm their prenatal, perinatal, and childhood history with their parents, if still living. Additionally, when possible, this information was confirmed by the research staff via telephone. Diagnoses of TS, OCD, and ADHD were made according to DSM-IV criteria by experienced clinicians using a best-estimate consensus diagnosis approach (CAM, VIR, TLL, and NW) (Leckman et al., 1982). The inter-rater agreement was 95% for TS ($k = 0.62$), 94% for OCD ($k = 0.88$), and 91% for ADHD ($k = 0.82$).

2.3. Outcome and Predictor Variables

The primary outcome measure was presence or absence of clinically significant explosive outbursts, defined as meeting full symptomatic criteria for Intermittent Explosive Disorder (IED). Predictor variables included gender, ethnicity (Costa Rican/Hispanic or US/Caucasian), age at interview, comorbid diagnoses of OCD and ADHD, and presence of moderate or severe SIB. Moderate SIB was defined as behaviors that resulted in moderate tissue damage, such as skin picking that led to profuse bleeding, scarring, or infections requiring treatment. Severe SIB was defined as extreme behaviors that had permanent potentially impairing outcomes such as self-cutting, or deliberate eye enucleation (Mathews et al. 2004). Other predictor variables included YGTSS scores (motor and phonic tics), age of onset of tics, family history of tics, socioeconomic status, referral source, birth weight, prenatal problems, perinatal problems, medication exposure in utero, and prenatal maternal smoking. Perinatal problems assessed included history of traumatic delivery, fetal respiratory distress, nuchal cord, forceps or suction delivery, hypoxia at birth, jaundice, emergency or unplanned cesarean section, premature delivery (greater than two weeks pre-term), or twin births. Prenatal problems included pre-eclampsia, hyperemesis of pregnancy, threatened abortion, and gestational diabetes. Information was also obtained about medication use (prescribed and over the counter), tobacco (any regular or repeated but episodic cigarette or tobacco use during pregnancy), regular alcohol (≥ 5 glasses of wine or equivalent during pregnancy) or any illicit drug exposure in utero. Medication use included assessment of the use of pitocin and fenoterol, as well as fertility drugs. Referral sources included referral into the study by the National Tourette Syndrome Association, health care providers (including TS specialists), newspaper or other media advertisements, school screening for TS, or referral by family members or friends. For the purposes of the analysis, referral source was grouped into referral by a medical professional vs. community (or other) referral.

2.4. Analyses

Statistical analyses were generated using Stata 11.0 (Statistical Software, 2010). Univariate analyses were conducted for each predictor and potential confounder variable and presence or absence of explosive outbursts using either chi square analyses (for categorical variables) or t-tests (for continuous variables). These analyses were done separately for the CR and US groups as well as for the overall sample. Variables with positive associations ($p \leq 0.10$) with explosive outbursts were then entered into a logistic regression separately for each ethnic

group, as the CR and US groups had significant differences in baseline characteristics. For the overall sample, any variable with a positive association in either the CR or the US sample was included in a logistic regression, followed by a backwards stepwise regression analysis that sequentially removed variables with p-values >0.10 in the overall model until the best fit was obtained. Potential confounding variables (gender, age at interview, and referral source) were included in all regression analyses.

3. RESULTS

78% of participants in the overall sample were male. The mean age at assessment was 17.8 years (SD = 12.8 years) (Table I). 66% of participants were under age 18 years. 56% of the participants had a current diagnosis of ADHD (mean age of onset of 4.7 years, SD = 2.3 years), and 49% had a current diagnosis of OCD (mean age of onset of 7.1 years, SD = 4.2 years). 53% of participants were referred to the study by medical professionals (Table I). Other referral sources included the Tourette Syndrome Association (17%), media (19.7%), family members and relatives (6.6%) and others (3.8%).

There were several demographic and clinical differences between the US and CR groups. CR participants were significantly younger at the time of assessment, and were less likely to have OCD, prenatal exposure to tobacco, and self-injurious behaviors (Table I). CR participants also had a later age of onset for tics, lower tic severity scores, and parents of lower socioeconomic status. Compared with the US group, the CR group had a later age of onset for OCD, higher rates of family history of tics, more prenatal complications overall, and higher rates of traumatic delivery at birth (Table I).

3.1. Explosive Outbursts

Twenty percent of the overall sample had explosive outbursts. US participants were more likely than CR participants to report these symptoms (24.6% versus 15.4%, $\chi^2 = 2.84$, df = 2, p = 0.09) but this finding did not reach statistical significance. Male participants were more likely to report experiencing explosive outbursts than females (males = 22.8% versus females = 10.6%), although again these differences were not statistically significant. Conversely, 89% of individuals with explosive outbursts were male, compared to 76% of those without explosive outbursts. There were no significant associations between explosive outbursts and age at interview, referral source, or socioeconomic status (Table II). In the overall sample, explosive outbursts were significantly associated with current OCD and ADHD diagnoses ($\chi^2 = 4.99$, df =2, p = 0.025 and $\chi^2 = 13.37$, df =2, p <0.001, respectively). 26.7% of individuals with OCD had explosive outbursts, compared to 14.4% of those without OCD, while 28.7% of individuals with ADHD had explosive outbursts, compared to 9.6% of those without ADHD. In order to further parse the relationship between these frequently co-occurring conditions and explosive outbursts, we next compared individuals with neither OCD nor ADHD to those with OCD alone, ADHD alone, and those with OCD+ADHD. Individuals with both OCD and ADHD had the highest rates of explosive outbursts (32.3%), followed by those with ADHD alone (24.5%), and OCD alone (17.5%), with the lowest rates in those with neither OCD nor ADHD (3.7%) ($\chi^2 = 15.78$, df 3, p = 0.001). The same pattern was seen in the US sample, but not in the CR sample. In the CR sample, only 6.7% of individuals with both OCD and ADHD had explosive outbursts, compared to 22.7% of those with ADHD alone, 50% of those with OCD alone, and 5.1% of those with neither OCD nor ADHD ($\chi^2 = 11.37$, df 3, p = 0.01). However, due to the relatively small number of individuals with explosive outbursts in this sample, as well as the low number of individuals with OCD, these results must be interpreted with caution.

Explosive outbursts were also significantly associated with a younger age of onset for tics (4.8 years, SD = 1.9 versus 6.1 years, SD = 2.5, t = 3.17, df = 213, $p < 0.001$) and with total tic severity, with IED-affected individuals exhibiting higher YGTSS total tic severity (motor + phonic) scores (37.3, SD = 7.2 versus 33.2, SD = 8.4, t = −2.98, df = 214, $p < 0.001$). Comparison of demographic and clinical information within each sample separately suggested that explosive outbursts were significantly associated with maternal tobacco use during pregnancy in the US sample ($\chi^2 = 3.83$, df = 2, p = 0.05) and maternal alcohol and illicit drug use during pregnancy in the CR sample ($\chi^2 = 5.49$, df = 2, p = 0.02). Additionally, the US sample with explosive outbursts showed associations with fertility drugs ($\chi^2 = 6.25$, df = 2, p = 0.01), twin birth ($\chi^2 = 2.95$, df = 2, p = 0.09), and ADHD diagnosis ($\chi^2 = 13.2$, df = 2, $p < 0.0001$) (Table III).

We then examined univariate associations of explosive episodes within each study group (CR and US) separately and within the total sample. We entered all predictor variables significantly associated with explosive outbursts (p value < 0.10) into a logistic regression model, along with the potential confounding variables (age at assessment, OCD/ADHD diagnosis, gender, and referral source) for the two study groups separately (Tables IV and V). Because of power limitations, the combined variable of OCD alone, ADHD alone, and OCD+ADHD was not included in the multivariable analyses for the US and CR subgroups; instead, OCD and ADHD were entered individually into the model. For the total sample, we initially included OCD and ADHD as separate variables, and subsequently substituted these variables with the combined variable (OCD alone, ADHD alone, OCD+ADHD, neither) in a secondary analysis. Predictor variables included age at onset of tics, tic severity, OCD and ADHD, emergency or unplanned cesarean section birth, and maternal tobacco use during pregnancy. For the US group, ADHD and maternal tobacco use during pregnancy were significantly and independently associated with explosive outbursts, and there was a trend for male gender (Table IV). ADHD was associated with roughly a 6- fold increased risk of explosive outbursts, while individuals with prenatal maternal tobacco exposure had a 5-fold increased risk for explosive outbursts. In addition, male gender was associated with a 77% (or 8-fold) increased risk of explosive outbursts. For the CR group, tic severity was significantly associated with explosive outbursts, and there was a trend for an association with age at onset of tics, but not for comorbid diagnosis or pre/perinatal risk factors (Table V). Among the CR participants, each point increase in the YGTSS tic severity score was associated with roughly a 19% increased risk of explosive outbursts, and each year decrease in the age of onset of tics was associated with approximately a 22% increased risk of explosive outbursts (Table V). The results of the logistic regression analyses in the overall sample indicated that only age of onset of TS (OR = 0.83, SE = 0.08, 95% CI = 0.68–1.00, z = − 1.92, p = 0.06), presence of ADHD (OR = 2.78, SE = 1.23, 95% CI = 1.17– 6.61, z = 2.31, p = 0.02), and maternal tobacco use during pregnancy (OR = 3.57, SE = 2.60, 95% CI = 0.86– 14.89, z = 1.79, p = 0.08), were associated with presence of explosive outbursts. The total model accounted for 10% of the overall variance (LR $\chi^2 = 31.58$, df = 13, p = 0.003, pseudo $R^2 = 0.15$) (Table VI). The secondary analysis that substituted the combined ADHD/OCD variable for the independent variables showed the same pattern as the primary analysis —ADHD alone and ADHD+OCD was significantly associated with explosive outbursts, but OCD alone was not. The association between explosive outbursts and ADHD alone and ADHD+OCD was similar (odds ratios =7.0, p=0.018 for ADHD, odds ratio=7.1, p=0.018 for OCD+ADHD), and the rest of the model did not change with this substitution.

DISCUSSION

The aim of this study was to examine the prevalence and demographic and clinical correlates of explosive outbursts in a sample of 218 individuals with TS recruited from a variety of sources. We found that the overall prevalence of explosive outbursts in our sample

was 20%, which is significantly higher than the reported prevalence of IED (5.4%) in the general population, but comparable to the lower range of prevalence rates that have been previously reported for TS in clinical samples (Budman et al., 1998; Stephens and Sandor, 1999; Budman et al., 2000; Budman et al., 2003; Kessler et al., 2006; Kano et al., 2008; Wright et al., 2012).

We hypothesized that the prevalence of explosive outbursts would be significantly higher in the US study group when compared to the CR study group due to differences in recruitment strategies between these two groups. In fact, although we did find differences in the rates of explosive outbursts between the US and CR samples, these differences were not statistically significant, suggesting that either the two groups had insufficient power to identify such differences or that the differences we detected between the CR and US participants were due to stochastic variation. Interestingly, we found that different variables appeared associated with different outcomes when comparing the two groups. In the US group, ADHD was independently and significantly associated with explosive outbursts. This finding is consistent with other clinical studies investigating aggressive behaviors in TS, including a study by the National Comorbidity Survey (NCS) which links ADHD, along with other impulse disorders, with explosive outbursts (Stephens and Sandor, 1999; Budman et al., 2000; Sukhodolsky et al., 2003; Zhu et al., 2006; Cavanna et al., 2011). We also found an association between ADHD and explosive outbursts among the CR participants, but this association did not reach statistical significance.

We did not find a statistically significant association between OCD and explosive outbursts, in the multivariable models that also included ADHD, although there was a trend in this direction among US participants, and US participants were more likely to report OCD in general. This is in contrast to the earlier findings ofBudman et al. (1998), and to the NCS findings that show an association between OCD and explosive outbursts (Kessler et al., 2006). These differences may be due to the fact that in TS-affected individuals, ADHD and OCD are often jointly comorbid; in studies that recruit from tertiary care or specialty clinics, where participants are likely to have both comorbidities, there may not be sufficient sample sizes available to distinguish independent relationships between OCD, ADHD and explosive outbursts in TS-affected individuals. When we examined the effects of comorbid ADHD +OCD directly in the overall sample, the results indicated that ADHD accounted for all of the association with explosive outbursts, as the odds ratios and p values were the same for ADHD alone as for ADHD+OCD. However, note that in this study, OCD was treated as a categorical variable, yet many individuals with TS suffer from subthreshold OC symptoms. It is still possible that OC symptoms may have been significantly associated with explosive outbursts but could not be addressed using current methodology.

Perhaps of most interest is the association that we identified in the US participants between explosive outbursts and fetal exposure to tobacco (prenatal maternal smoking), which has previously been linked to attention problems, hyperactivity, reduced impulse control, and irritability (Henry et al., 2007; Johansson et al., 2008; Nair et al., 2008; Pulsifier et al., 2008; Chae and Covington, 2009). Although we did not see the same association in the CR group, the rates of maternal tobacco use during pregnancy was significantly lower among CR participants (N=2), suggesting there was insufficient power to identify such an association in the CR group.

These findings suggest that explosive outbursts are not only common among TS-affected individuals, including those who do not necessarily come to the attention of medical professionals, but also that these symptoms may be mediated by multiple factors, including prenatal risk factors, psychiatric comorbidity, and increased tic severity/early age of onset of tics. The differences in associated clinical and demographic characteristics between the two

study samples also suggest the possibility that ethnic, cultural, or genetic differences may interact with clinical variables to create differential risk patterns for specific individuals, which underscores the complex and multifaceted nature of explosive outbursts.

This study has several potential limitations. Firstly, and perhaps most important, is that we do not have clinical data available on psychiatric comorbidities other than OCD and ADHD. It is possible that, in addition to the risk factors that we identified, explosive outbursts are associated with additional risk factors, such as mood disorders or other psychiatric comorbidities, and this should be further examined. Further, this is not an epidemiological study but rather is based on a sample of TS-affected individuals recruited for genetic studies, potentially introducing a referral bias. Similarly, all data were retrospective and based on either self- and parent-report plus available medical records; a prospective study would be important to pursue in the future. The presence of self-report measures uncorroborated by other sources may also potentially limit this study. Additionally, an age and ethnically matched control sample without comorbid TS/tics was not available to compare explosive outburst frequency and prevalence. It is noteworthy, however, that the lifetime prevalence of IED in the general population is significantly lower than that found in either of our TS groups or in our overall TS sample (Kessler et al., 2006). Lastly, this study's findings are less likely to apply to the overall TS population due to the fact that both the US and CR sample were obtained from genetically isolated populations. A similar study in the worldwide TS population would further elucidate these findings.

Despite such limitations, this study, in conjunction with previously published work, confirms that explosive outbursts are quite common in TS-affected individuals, and suggests that they likely develop from a complex network of factors, including psychological, biological, and environmental conditions (Budman et al., 2003). As such, these findings have potential implications for diagnosis and treatment planning in TS-affected individuals. For example, educating parents that a child with TS plus ADHD has an increased risk for explosive outbursts or other types of aggressive behaviors early in the course of treatment may facilitate early behavioral interventions. Similarly, the finding that at least for the US group, tic severity alone does not predict explosive outbursts is valuable information to share with parents.

Acknowledgments

We are grateful for the children and families who participated in this study, as well as the support of the Tourette Syndrome Association, school staff and other medical professionals who were instrumental in our recruitment of participants for this study. This research was supported by U.S. government grants from the NCRR (K23 RR015533) and the NINDS (R01 444653).

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Table I

Clinical Information for US and CR Participants with TS

	Total (N=218)	US (N=114)	CR (N=104)	(X^2/t, P-value)*
Percent Male	78.4%	73.7%	83.7%	(3.20, 0.07)
Mean age at assessment (SD)	17.8 (12.8)	23 (14.7)	12.2 (6.6)	(6.83, <0.001)
Age Range (yrs)	5−75	6−75	5−41	
Socioeconomic status				(19.92, <0.001)
Hollingshead score = 1	9.5%	13.0%	7.5%	
Hollingshead score = 2	31.1%	50.0%	20.2%	
Hollingshead score = 3	29.7%	13.0%	39.4%	
Hollingshead score = 4	23.7%	18.5%	26.6%	
Hollingshead score = 5	6.1%	5.6%	6.4%	
Percent with explosive outbursts	20.2%(N=44)	24.6%(N=28)	15.4%(N=16)	(2.84,0.09)
OCD diagnosis	48.6% (N=105)	75% (N=84)	20.2% (N=21)	(64.8, <0.001)
ADHD diagnosis	56.5%(N=122)	56.3% (N=63)	56.7% (N=59)	(0.01,0.94)
OCD+ADHD diagnosis	30.1% (N=65)	44.6% (N=50)	14.4% (N=15)	(65.8, <0.001)
Mean age at onset of tics (SD)	5.9(2.4) (N=13)	5.4 (2.4) (N=6)	6.3 (2.4) (N=7)	(−2.66, 0.01)
Mean age at onset of OC symptoms (SD)	7.1 (4.2) (N=15)	6.8 (4.0) (N=8)	8.6 (4.7) (N=9)	(−1.80, 0.08)
Mean age at onset of ADHD symptoms (SD)	4.7 (2.3) (N=10)	4.5 (2.4) (N=5)	4.9 (2.2)(N=5)	(−0.83, 0.41)
Self injurious behavior (moderate or severe)	21.8%(N=48)	33.3%(N=38) *8*	8.8%(N=9)	(19.00, <0.001)
Severe self injurious behavior *1*	2.3%(N=5)	3.5%(N=4)	1.0%(N=1)	(F, 0.37)*
Maternal family history of tics	48.8%(N=106)	47.1%(N=54)	51.7% (N=54)	(0.32, 0.57)
Family history of tics	77.9%(N=170)	70.0%(N=80)	87.6%(N=91)	(8.89, <0.001)
Paternal family history of tics	56.9%(N=124)	45.1%(N=51)	72.2%(N=75)	(13.29), <0.001)
Mean birth weight (lbs) (SD)	7.2(1.3) (N=16)	7.2(1.2) (N=8)	7.1 (1.4) (N=7)	(0.75, 0.45)
Mean total tic severity (motor and phonic tics YGTSS scores)	34.0	38.9	28.5 (6.7)	
(SD)	(8.3) (N=74)	(6.3) (N=44)	(N=30)	(11.59, <0.001)
Referred to study by medical professional	52.8%(N=115)	66.7%(N=76)	37.5%(N=39)	(18.56, <0.001)
Drugs during pregnancy	19.7%(N=43)	16.2%(N=18)	23.5%(N=24)	(1.80,0.18)
Maternal tobacco use during pregnancy	5.5%(N=12)	8.8%(N=10_	1.9%(N=2)	(F, 0.03)*
Maternal alcohol and illicit drug use during pregnancy	1.8%(N=4)	2.6%(N=3)	1.0%(N=1)	(F, 0.35)*
Prenatal Complications *2*	12.0%(N=26)	7.9%(N=9)	16.5%(N=17)	(3.80, 0.05)
Nuchal-cord or Hypoxia	9.2%(N=20)	11.4%(N=13)	6.8%(N=7)	(1.37, 0.24)
Forceps or Suction	8.8%(N=19)	11.4%(N=13)	5.8%(N=6)	(2.11,0.15)
Emergency C-Section	20.3%(N=44)	21.9%(N=25)	18.5%(N=19)	(0.41,0.52)
Traumatic Delivery	11.6%(N=25)	6.2%(N=7)	17.5%(N=18)	(6.70, 0.01)
Jaundice	17.1%(N=37)	19.3%(N=22)	14.6%(N=15)	(0.86, 0.35)
Premature Labor	10.1%(N=22)	11.4%(N=13)	8.7%(N=9)	(0.42, 0.52)
Fertility Drugs	2.9%(N=6)	1.8%(N=2)	2.9%(N=3)	(F, 0.67)*
Twin birth	1.8%(N=4)	2.6%(N=3)	1.0%(N=1)	(F, 0.62)*

*F=Fisher’ s exact test used in place of chi-square.

[1] See Methods for definition of severe vs. moderate Self Injurious behavior.

[2] Prenatal complications include preeclampsia, threatened abortion, gestational diabetes, and hyperemesis.

Table II

Comparison of Demographic and Clinical Information for Participants in Total Sample With and Those Without Explosive Outbursts

	Do Not Have Explosive Outbursts(N=174)	Have Explosive Outbursts(N=44)	(X^2/t, P-value)*
Percent US participants	75.4%(N=86)	24.6%(N=28)	
Percent CR participants	84.6%(N=88)	15.4%9N=16)	(2.84, 0.09)
Percent Male	75.9% (N=132)	88.6% (N=39)	(3.39, 0.07)
Mean age at interview (SD)	18.1 (13.2)	16.9 (10.9)	(0.57, 0.57)
Socioeconomic status (Hollingshead score = 1)	10.4%(N=18)	4.4%(N=2)	
Socioeconomic status (Hollingshead score = 2)	30.4%(N=53)	34.8%(N=15)	
Socioeconomic status (Hollingshead score = 3)	28.8%(N=50)	34.8%(N=15)	
Socioeconomic status (Hollingshead score = 4)	24.0%(N=42)	21.7%(N=9)	
Socioeconomic status (Hollingshead score = 5)	6.4%(N=11)	4.4%(N=2)	(1.28, 0.6)
Referred to study by medical professional	50% (N=85)	63.6% (N=28)	(2.62, 0.11)
Mean age at onset of tic symptoms (SD)	6.1 (2.5)	4.8 (1.9)	(3.17, <0.001)
Mean age at onset of OC symptoms (SD)	6.9 (4.0)	7.7 (4.5)	(−0.94, 0.35)
Mean age of onset of ADHD symptoms (SD)	4.9 (2.1)	4.3 (2.6)	(1.31, 0.19)
Family history of tics (N=199)	76.1%(N=121)	85% (N=34)	(1.47, 0.23)
Maternal family history of tics (N=164)	46.2% (N=61)	59.4% (N=19)	(1.79, 0.18)
Paternal family history of tics (N=181)	55.2% (N=79)	63.2% (N=24)	(0.77, 0.38)
Self injurious behavior	19.8% (N=34)	29.6% (N=13)	(1.97, 0.16)
Severe self injurious behavior	1.8% (N=3)	4.6% (N=2)	(F, 0.27)*
Mean tic severity (motor and phonic tic YGTSS scores) (SD)	33.2 (8.4)	37.3 (7.2)	(−2.98, 0.001)
Maternal tobacco use during pregnancy	4.1% (N=7)	11.4% (N=5)	(3,60, 0.058)
Maternal alcohol and illicit drugs during pregnancy	1.7% (N=3)	2.3% (N=1)	(F, 1.00)*
Medications during pregnancy	21.2% (N=36)	14.0% (N=6)	(1.13, 0.29)
Prenatal complications	12.7% (N=22)	9.1% (N=4)	(0.44, 0.51)
Nuchal cord/Hypoxia	9.3% (N=16)	9.1% (N=4)	(F,1.00)*
Forceps/Suction delivery	9.3% (N=16)	6.8% (N=3)	(F, 0.77)*
Emergency C−Section	17.9% (N=31)	29.6%(N=13)	(2.93, 0.09)
Traumatic delivery	10.5% (N=18)	15.9% (N=7)	(1.01, 0.31)
Jaundice	17.3% (N=30)	15.9% (N=7)	(0.05, 0.82)
Premature labor	9.8% (N=17)	22.7%(N=5)	(F, 0.78)*
Fertility drugs	1.7% (N=3)	4.6% (N=2)	(F, 0.27)*
Twin birth	50.0%(N=87)	50.0%(N=22)	(F, 0.18) *
Birth weight (lbs)	7.14(1.3)	7.2 (1.3)	(−0.26, 0.80)

Table III

Comparison of Demographic and Clinical Information for Participants With and Those Without Explosive Outbursts in CR and US samples

	Costa Rican Sample			US Sample		
	EO- (N=88)	**EO+ (N = 16)**	***(X²/t, P-value***	**EO- (N=86)**	**EO+N= 28)**	***(X²/t, P-value)***
Percent Male	83.0%	87.5%	0.20, 0.65	68.6%	89.3%	**4.66, 0.03**
Mean age at interview (SD)	12.2 (0.7)	11.9 (1.4)	0.17, 0.87	24.1 (1.7)	19.7 (2.3)	1.37, 0.17
Socioeconomic status (Hollingshead score = 1)	7.5% (N=7)	7.1% (N=1)		15.6%(N=13)	0%(N=0)	
Socioeconomic status (Hollingshead score = 2)	20.0%(N=18)	21.4%(N=3)		48.9%(N=42)	55.6%(N=16)	
Socioeconomic status (Hollingshead score = 3)	37.5%(N=33)	50.0%(N=8)		13.3%(N=11)	11.1%(N=3)	
Socioeconomic status (Hollingshead score = 4)	27.5%(N=24)	21.4%(N=3)		17.8%(N=15)	22.2%(N=6)	
Socioeconomic status (Hollingshead score = 5)	7.5%(N=7)	0%(N=0)	1.70, 0.79	4.4%(N=4)	11.1%(N=3)	2.18, 0.70
Referred to study by medical professional	36.4%(N=32)	43.8%(N=7)	0.32, 0.58	63.9%(N=55)	75.0%(N=21)	1.16, 0.28
OCD	19.3%(N=17)	25.0%(N=4)	0.27, 0.60	71.4%(N=61)	85.7%(N=24)	2.28, 0.13
ADHD	54.6%(N=48)	68.8%(N=11)	1.11, 0.29	46.4%(N=40)	85.7%(N=24)	**13.2, <0.0001**
Mean age at onset of tic symptoms (SD)	6.5 (0.3)	5.2 (0.6)	**2.06, 0.04**	5.7 (0.3)	4.6 (0.3)	**2.08, 0.04**
Mean age at onset of OC symptoms (SD)	8.8 (1.3)	7.8 (1.1)	0.40, 0.70	6.4 (0.5)	7.7 (1.0)	−1.4, 0.16
Mean age of onset of ADHD symptoms (SD)	5.1 (0.3)	3.9 (0.8)	1.55, 0.12	4.6 (0.4)	4.4 (0.6)	0.28, 0.78
Family history of tics	85.5%(N=75)	100.0%(N=16)	2.15, 0.14	67.5%(N=58)	77.8%(N=22)	1.03, 0.31
Self injurious behavior	9.3%(N=8)	6.3%(N=1)	0.16, 0.69	30.2%(N=26)	42.9%(N=12)	1.52, 0.22
Mean tic severity (motor and phonic tic YGTSS scores) (SD)	26.0 (8.3)	28.7(1.2)	−0.87, 0.39	38.5(0.7)	39.6 (1.1)	−0.71, 0.76
Maternal tobacco use during pregnancy	2.3%(N=2)	0%(N=0)	0.38, 0.54	5.8%(N=5)	17.9%(N=5)	**3.83, 0.05**
Maternal alcohol and illicit drugs during pregnancy	0%(N=0)	6.25%(N=1)	**5.49, 0.02**	3.5%(N=3)	0%(N=0)	1.00, 0.32

	Costa Rican Sample			US Sample		
	EO- (N=88)	**EO+ (N = 16)**	***(X^2/t, P-value***	**EO- (N=86)**	**EO+N= 28)**	***(X^2/t, P-value)***
Drugs during pregnancy	25.6%(N=23)	12.5%(N=2)	1.28, 0.26	16.7%(N=14)	14.8%(N=4)	0.39, 0.82
Prenatal complications	17.2%(N=15)	12.5%(N=2)	0.22, 0.64	8.1%(N=7)	7.1%(N=2)	0.03, 0.87
Nuchal cord/Hypoxia	5.8%(N=5)	12.5%(N=2)	0.97, 0.32	12.8%(N=11)	7.1%(N=2)	0.67, 0.41
Forceps/Suction delivery	5.6%(N=5)	6.3%(N=1)	0.01, 0.94	12.8%(N=11)	7.1%(N=2)	0.67, 0.41
Emergency C-Section	16.1%(N=14)	31.3%(N=5)	2.06, 0.15	19.8%(N=17)	28.6%(N=8)	0.96. 0.33
Traumatic delivery	14.9%(N=13)	31.3%(N=5)	2.49, 0.11	5.8%(N=5)	7.1%(N=2)	0.05, 0.81
Jaundice	17.2%(N=15)	0%(N=0)	**3.22, 0.07**	17.4%(N=15)	25.0%(N=7)	0.77, 0.38
Premature labor	9.2%(N=8)	6.3%(N=1)	0.15, 0.70	10.5%(N=9)	14.3%(N=4)	0.31, 0.58
Fertility drugs	3.5%(N=3)	0%(N=0)	0.57, 0.45	0(N=0)	7.1%(N=2)	**6.25, 0.01**
Twin birth	1.2%(N=1)	0%(N=0)	0.19, 0.67	1.2%(N=1)	7.1%(N=2)	**2.95 0.09**
Birth weight (lbs)	7.2 (0.3)	7.3 (1.0)	−0.05, 0.95	7.2 (0.2)	7.1 (0.1)	0.77, 0.44

Table IV

Logistic Regression Model for Explosive Outbursts in TS, US Model

	Odds Ratio (Standard Error)	95% CI	Z	p value
Gender (Female)	0.23 (0.17)	0.06–0.99	−1.98	0.06
ADHD	6.81 (4.22)	2.02–22.93	3.10	0.002
OCD	1.66 (1.08)	0.47–5.93	0.78	0.43
Maternal tobacco use during pregnancy	5.52 (4.59)	1.08–28.19	2.06	0.04
Twin birth	4.93 (8.51)	0.17–145.32	0.92	0.36

* N = 110, LR X^2 = 23.31, p =0.0003, pseudo R^2 = 0.19

* Note: use of fertility drugs was dropped from the model because it perfectly predicted presence or absence of the outcome variable: both of the two individuals with the exposure had explosive outbursts, and none of the individuals without explosive outbursts had the exposure.

Table V

Logistic Regression Model for Explosive Outbursts in TS, CR Model

	Odds Ratio (Standard Error)	95% CI	Z	p value
Gender (Female)	0.51 (0.45)	0.09–2.83	−0.77	0.44
Tic severity	1.19 (0.09)	1.03–1.40	2.33	0.02
Age of onset of tics	0.78 (0.12)	0.57–1.06	−1.60	0.11
ADHD	1.03 (0.68)	0.28–3.76	0.04	0.97
OCD	0.99 (0.70)	0.25–3.94	−0.02	0.98

* N = 86, LR X^2 = 10.98, df=5, p = 0.05, pseudo R^2 = 0.14

* Note: use of alcohol and/or drugs during pregnancy was dropped from the model because it perfectly predicted presence or absence of the outcome variable: the only individual with the exposure had explosive outbursts and none of the individuals without explosive outbursts had the exposure. Similarly, jaundice was dropped from the model because it perfectly predicted presence or absence of the outcome: all 15 individuals with jaundice did not have explosive outbursts.

Table VI

Logistic Regression Model for Explosive Outbursts in TS, Total Sample

	Odds Ratio (Standard Error)	95% CI	Z	p value
Age	1.00 (0.02)	0.96–1.04	−0.11	0.91
Gender (Female)	0.38 (0.22)	0.12–1.20	−1.65	0.10
Age at onset of TS	0.83 (0.08)	0.68–1.00	−1.92	0.06
Referred by medical professional	1.58 (0.64)	0.72–3.48	1.13	0.25
Tic severity	1.03 (0.44)	0.95−1.12	0.77	0.44
ADHD	2.78 (1.23)	1.17–6.61	2.31	0.02
OCD	1.46 (0.66)	0.61–3.52	0.85	0.40
Cesarean section	1.70 (0.75)	0.71–4.05	1.19	0.23
Maternal tobacco use during pregnancy	3.57 (2.60)	0.86–14.89	1.75	0.08
Twin birth	0.34 (0.54)	0.02–7.65	−0.68	0.50
Jaundice	0.72 (0.40)	0.25–2.11	−0.60	0.55
Alchol/drug use during pregnancy	3.94 (5.20)	0.30–52.25	1.04	0.30
Use of fertility drugs	4.31 (5.13)	0.42–44.37	1.23	0.22

*N = 201, LR X^2 = 31.58, p = 0.003, pseudo R^2 = 0.15