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ORIGINAL CONTRIBUTION

Childhood aggression, callous-unemotional traits and oxytocin genes

Joseph H. Beitchman · Clement C. Zai · Katherine Muir · Laura Berall · Behdin Nowrouzi · Esther Choi · James L. Kennedy

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Abstract Given the known behavior effects of oxytocin, and in particular its putative effect on trust, affiliation and anxiety, we hypothesized that oxytocin may be involved in the development and expression of callous-unemotional traits in children with aggressive antisocial behavior. We recruited 162 children between the ages of 6 and 16. The majority of subjects were Caucasian (84.0%) compared to African-Canadian (4.9%) and others (11.1%). The oxytocin and oxytocin receptor gene polymorphisms were genotyped and analyzed for possible association with child aggression in a case–control study design as well as with callous-unemotional traits in a within cases analysis. We did not have significant findings with our tested OXTR markers in the case–control analysis. We found the *OXTR*_rs237885 AA genotype carriers to score higher than AC or CC genotype carriers on the callous-unemotional traits. This result remained significant following correction for multiple testing. No other markers were found to be significant. However, the haplotype consisting of the *OXTR*_rs237885 A allele and *OXTR*_rs2268493 A allele was associated with significantly higher callous-unemotional scores than other haplotypes. This is the first known study to show a significant association between callous-unemotional traits in children and adolescents with extreme, persistent pervasive aggression and a polymorphism on the oxytocin receptor. Given the small sample size and the possibility of false positive effects, the need to replicate and verify these findings is required.

Keywords Childhood aggression · Oxytocin · Callous-unemotional trait · Genetics · Oxytocin receptor · Aggression

J. H. Beitchman (✉) · B. Nowrouzi · E. Choi
Child, Youth and Family Program, Centre for Addiction and Mental Health, 250 College Street, Room 125, Toronto, ON M5T 1R8, Canada
e-mail: Joe_Beitchman@camh.net

J. H. Beitchman · C. C. Zai · J. L. Kennedy
Department of Psychiatry, University of Toronto, Toronto, Canada

C. C. Zai · J. L. Kennedy
Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Canada

K. Muir
University of Toronto, Toronto, Canada

L. Berall
University of Western Ontario, London, Canada

Introduction

Aggressive and antisocial behaviors are the leading cause of all child and adolescent referrals to mental health clinicians [1, 2]. Children with aggressive behavior constitute a heterogeneous group, in terms of the specific types of behaviors they show and their course, prognosis and response to intervention. There have been ongoing efforts to identify subgroups or subtypes of aggressive antisocial children and youth. For instance, Moffitt et al. [3] has proposed the life course persistent versus the adolescent limited forms of aggressive antisocial youth. The identification of subgroups that share an underlying etiology, course and prognosis has the potential to advance the field by leading to targeted approaches to prevention and treatment. One strategy developed by Frick et al. [4] is to classify aggressive children on the basis of the psychopathic construct of callous-unemotional traits (CU) that include lack of empathy, lack of guilt, and shallow emotions.

Psychopathic tendencies in childhood involve both emotional dysfunction (CU traits) and overt antisocial behavior [5]. Only a subset of individuals with conduct disorder (CD) demonstrate high levels of CU traits and they represent a unique group of children who have earlier contacts with the juvenile justice systems and show a more severe pattern of aggressive behavior [5–7]. As well, adults with antisocial personality disorder (APD) with CU traits compared to those without, commit offenses at a younger age [5, 6].

A meta-analysis of twin and adoption studies revealed that 50% of the variance found in measures of antisocial behavior (AB) could be ascribed to genetic factors [8]. In addition, a recent twin study of 7-year antisocial children reported that CU traits are under strong genetic influence [9]. Although previous studies have reported associations between antisocial behavior and MAOA polymorphisms and childhood aggressive behavior [10, 11], and the serotonin transporter [12], to date, studies of CU traits and genetic polymorphisms have failed to demonstrate significant associations [13]. These findings suggest that multiple genetic variants of modest effect may be involved in antisocial and aggressive behaviors.

Callous-unemotional traits (e.g., poverty of emotions and lack of guilt) are a well-documented temperamental correlate of severe and persistent antisocial behavior in children and may increase the risk for developing psychopathy in adulthood [14]. Data from longitudinal studies have suggested that psychopathic traits, including CU, are moderately to highly stable during childhood [15, 16], adolescence [16], and adulthood [17], from childhood to adolescence, [18, 19] and from adolescence to adulthood [20]. Two twin studies have examined the etiology of stability and change in psychopathic traits using multivariate, longitudinal models, reporting substantial genetic contributions to CU stability [20].

Although oxytocin is implicated in a variety of "non-social" behaviors, such as learning, anxiety, feeding and pain perception, it is oxytocin's role in various social behaviors that has come to the fore recently. Oxytocin is important for social memory and attachment, sexual and maternal behavior, aggression, human bonding and trust [21]. It has also been implicated in fear reduction, with anxiolytic effects among its most commonly recognized characteristics [22, 23].

Given that difficulties in social bonding and affiliative responding are considered key symptoms in autism, oxytocin's role in the etiology of autism has been subject to scrutiny by several investigators. For example, Hollander et al. [24] found enhanced social comprehension in high functioning adult males with autism following OXT injections. Studies of the oxytocin gene and oxytocin receptor gene have found that SNPs and haplotypes in the OXTR gene confer risk for autism spectrum disorders [25, 26]. Evidence from Sala et al. [27] has compared the behavioral impact of disrupted oxytocinergic function in rodents to behavioral abnormalities observed in autism spectrum disorders. Lerer et al. [25] detected associations between an OXTR five-locus haplotype A–T–T–G–A (rs237897–rs13316193–rs237889–rs2254298–rs2268494) and autism spectrum disorder. Recently, Campbell et al. [28] reported an association of oxytocin receptor genetic polymorphisms (rs2268493, rs1042778 and rs7632287) with social aspects of autism spectrum disorder. However, none of their findings survived appropriate correction for multiple comparisons. Other groups have examined oxytocin and oxytocin receptor genes and their potential role in the symptom severity and clozapine treatment response in schizophrenia [29].

Although findings of the association of oxytocin receptor gene SNPs and autism spectrum disorders are consistent with the view that oxytocin has important biological and behavioral effects, the full extent of oxytocin's behavioral effects has yet to be explored. For instance, little is known about the role of oxytocin in human aggression. Higher levels of auto antibodies reactive for oxytocin are found in males with conduct disorder than in controls [30]. Oxytocin administration has been shown to reduce amygdalar activity in response to fear-inducing visual stimuli [31], and anxiety levels appear to be linked to aggression in several animal models [32–35]. In humans, oxytocin may act to decrease anxiety by increasing recognition [36] and modulate social behavior [37, 38], and feelings of affiliation [39, 40]. Oxytocin modulates the formation of memories, particularly social and spatial memory, as well as responses to emotionally latent stimuli, such as facial expressions. However, there has been limited but increasing interest in the affiliative role of oxytocin [41] in humans.

Oxytocin is central to affiliative behaviors, including bonding with parents or romantic partners [42, 43]. It also plays a key role in emotion regulation and stability. For example, a study by Bakermans-Kranenburg and van Ilzendoorn suggests independent effects on maternal sensitivity of 5-HTT and OXTR genes in humans. They found that mothers with variants of the serotonin transporter and the OXTR genes (the 5-HTTLPR SLC6A4 and OXTR rs53576 polymorphisms) had lower levels of sensitive responsiveness to their toddlers [44]. Thompson et al. [45] found that girls who were heterozygous for the rs2254298 polymorphism and who had a history of adversity early in life (e.g., a mother with a history of depression) had the highest levels of depression and anxiety. A recent study by Montag et al. [46] demonstrated a robust interaction effect of 5-HTTLPR and OXTR rs2268498 on fear and sadness. Other studies report that rs2254298A OXTR risk alleles are

associated with larger amygdala volume [47, 48]. Interestingly, Reuter et al. [49] found that self-report measures of anger and left amygdala volume were inversely correlated.

Despite the growing research interest and findings regarding oxytocin, studies linking oxytocin to aggression in animal and human research there are no genetic linkage or association studies exploring the relationship between the oxytocinergic system and aggression in children and adolescents. The current study aims to investigate the association between the oxytocin system and childhood aggression using single nucleotide polymorphisms (SNPs) in the oxytocin gene region.

Given the known behavior effects of oxytocin, and in particular its putative effect on trust, affiliation and anxiety, we hypothesized that oxytocin may be involved in the development and expression of CU in children with aggressive antisocial behavior. Consequently, utilizing a sample of pervasive, persistent and extreme aggressive children we tested the association between CU and the oxytocin (*OXT*) and oxytocin receptor (*OXTR*) genes.

Methods and materials

Subjects and measures

We recruited 162 children from the Greater Toronto Area through referral from the Center for Addiction and Mental Health or Youthdale Treatment Centers. These children are between the ages of 6 and 16 (106 boys and 56 girls; mean age ± SD, 11.81 ± 2.85 years) for the present study. The majority of subjects were Caucasian (83.9%) with African-Canadians (4.9%) and mixed ethnicity (11.1%). Inclusion criteria in the study included scoring at or above the 90th percentile on the aggression subscales of both the Child Behavior Checklist (mean *T* Score ± SD, 79.43 ± 10.39) and the Teacher's Report Form (mean *T* Score ± SD, 75.94 ± 10.55) [50], and an intelligence quotient of over 69 (mean ± SD, 99.13 ± 14.01) based on a two-subtest short form of the Wechsler Intelligence Scale for Children—3rd edition [51]. The included cases also have a minimum 2-year history of aggressive behavior according to parent report (including any of the following: losing temper, deliberately annoying people, being angry/resentful/spiteful/vindictive, bullying/threatening/intimidating others, initiating physical fights, being physically cruel to others, having forced someone into sexual activity, or having committed arson/vandalism). Any child with a chronic medical illness, neurological disorder, or diagnosis of schizophrenia, mania, autism, or pervasive developmental disorder based on clinical records from the referral sites was excluded from the study. Each child aggression case subject was matched based on ethnicity and gender with a healthy adult control with no reported history of severe aggressive behavior. The adult controls (average age = 25.64 ± 8.72 years) were screened for the absence of current and past major psychiatric disorders using semi-structured interview for DSM-IV diagnoses (SCID-I) [52, 53].

DSM-IV [54] diagnoses for disruptive behavior disorders were obtained through administration of the Diagnostic Interview Schedule for Children (DISC) [55] checklist to the participant's primary caretaker and reviews of the participants' health records. Of the children for whom we had complete diagnostic information, 92% had a disruptive behavior disorder and 78% were comorbid for ADHD. Based on the Children's Depression Inventory [56], fewer than 12% of the subjects obtained clinically elevated depression scores (i.e., total *t* score >65). The *Psychopathy screening device* was used to identify dimensions integral to the description of childhood psychopathy. This instrument was developed as an extension of the adult Psychopathy Checklist—Revised for use in children. It is intended to assess three dimensions of psychopathy—a callous and unemotional interpersonal style, poor impulse control and narcissism [57].

This study was fully approved by the Research Ethics Board of the Center for Addiction and Mental Health and all subjects and their guardians provided written, informed consent before participating.

Genotyping

Peripheral blood, buccal cell or saliva samples were obtained from cases and controls. DNA extraction from whole blood was completed following the non-enzymatic, high-salt procedure [58], while extraction from cheek swab was performed using Qiagen DNA isolation kit (Qiagen Inc., CA, USA). DNA from saliva samples was collected and purified using Oragene 500 DNA kit and protocols supplied with the kit (DNA Genotek, Inc., ON, Canada).

Participants and gender- and ethnicity-matched adults were genotyped for six single-nucleotide polymorphisms (SNPs) in the *OXT* (20p13) and *OXTR* (3p25) genes: *OXT*_rs2740210 (3′ region), *OXT*_rs2770378 (3′ region), *OXT*_4813627 (3′ region), *OXTR*_rs237885 (intron 4), *OXTR*_rs2268493 (intron 4) and *OXTR*_rs237898 (intron 4). The oxytocin and receptor gene polymorphisms were genotyped using commercially available genotyping assays (ABI). The reaction mixtures were prepared according to the manufacturer's direction. This included 20 ng/μl of DNA, TaqMan Universal PCR Master Mix No AmpErase UNG (2X), and genotyping assays in a total volume of 10 μl. The Allelic Discrimination Program on ABI 7500 Prism Sequence Detection System was used to determine the genotypes of each individual.

Statistical analyses

All statistical tests were performed using SPSS 15.0 for Windows [59]. Analyses of allelic and genotypic distribution between child aggression cases versus adult controls were performed using the χ^2 test and/or Fisher's exact test. Within the sample of aggressive children, we compared the CU among genotypes of each polymorphism using ANOVA or the Kruskal–Wallis test (SPSS). Hardy–Weinberg equilibrium and linkage disequilibrium for the respective markers were assessed using Haploview version 4 [60]. Haplotype analyses were performed with two-marker sliding-window strategy using UNPHASED version 2 [61]. Haplotypes with frequencies of <5% were excluded from the analyses. Power calculations were carried out using QUANTO version 1.2.3 [62]. Our matched case–control sample has over 80% power to detect a genetic odds ratio of as low as 1.70 (minor allele frequency = 0.20, two-sided alpha = 0.05, additive model).

Results

The *OXT* and *OXTR* genotypes are in Hardy–Weinberg equilibrium ($p > 0.10$). Linkage disequilibrium values between the markers are shown in Fig. 1a and b.

Case control analysis

We did not find any of the three *OXT* and three *OXTR* markers to be significant in our matched case–control analysis (Table 1).

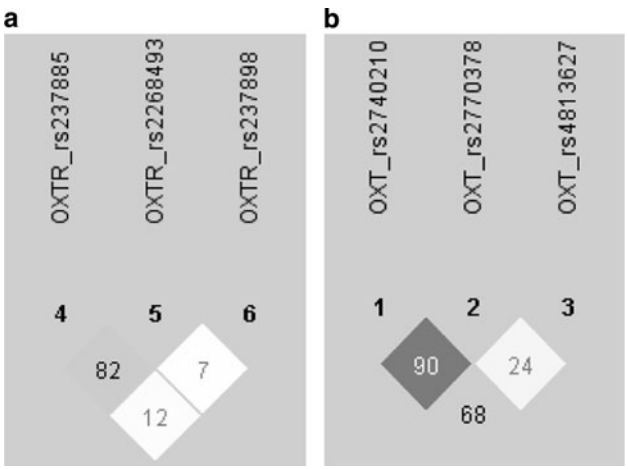

Fig. 1 Linkage disequilibrium plots are shown for *OXTR* (**a**) and *OXT* (**b**) SNPs. Shown are values for D′ between each SNP pair, and the intensity of *gray* indicates the r^2 values (*white* being 0% to *black* being 81–100%)

Within cases analysis

We compared callous-unemotional trait scores among genotypes of these six markers within our sample of our aggressive child cases (Table 2). We found the A allele to be associated with higher scores ($R = 0.256$), with the *OXTR*_rs237885 AA genotype carriers to score higher than AC or CC genotype carriers ($p = 0.014$; Table 2; Fig. 2—BOXPLOT). The other markers were not significant in this analysis. We tested two-marker haplotypes across the *OXT* and *OXTR* genes in a sliding-window approach to explore for possible association with child aggression and callous-unemotional trait scores. Haplotype analysis of *OXT* and *OXTR* did not yield significant findings in the case control analysis. However, the haplotype consisting of the *OXTR*_rs237885 A allele and *OXTR*_rs2268493 A allele was associated with significantly higher callous-unemotional trait scores than other haplotypes in this window (window $p = 0.043$, haplotype-specific $p = 0.012$). The results reported thus far have not been corrected for testing multiple markers. If we take into account the correlation of genotypes among the six markers, the adjusted alpha became 0.010 [63]. Nyholt's method for correction for multiple testing of single-nucleotide polymorphisms was used [63]. Our findings of *OXTR*_rs237885 in callous-unemotional trait would have survived this correction.

When we focused our analysis on the Caucasian cases ($n = 127$), the findings with *OXTR*_rs237885 remained nominally significant ($p = 0.017$) with AA genotype carriers having higher callous-unemotional trait scores than C-allele carriers (p = 0.04). The haplotype consisting of the *OXTR*_rs237885 A allele and *OXTR*_rs2268493 A allele among Caucasians was not significant (window $p = 0.310$, haplotype-specific $p = 0.060$).

Discussion

This is the first study to demonstrate a significant association between an oxytocin polymorphism and CU in children and youth. Previous studies have shown genetic polymorphisms are associated with prosocial behavior [38]. The hypothesized effect is thought to be mediated through greater trust, affiliation and improved facial recognition. In this study, we report the reverse effect of an oxytocin polymorphism. Given the hypothesis that oxytocin contributes to improved affiliation and facial recognition, any reduction in the amount of oxytocin produced, released, or recognized by the receptor(s) could conceivably contribute to a profile consistent with callous-unemotional traits.

It is of interest that none of the polymorphisms tested in the case control analysis for extreme, persistent, pervasive aggression were significant. Although our child cases were

Table 1 Results from analysis of genotypic and allelic distributions of *OXT* and *OXTR* single-nucleotide polymorphisms (SNPs) in aggressive child cases and matched non-aggressive adult controls

SNPs	Matched case-adult control pairs							
	Genotypes	All (162/162)	♂ (106/106)	♀ (56/56)	Alleles	All (162/162)	♂ (106/106)	♀ (56/56)
OXT_rs2740210	C/C	71/59	47/39	24/20	C	213/193	140/124	73/69
	C/A	71/75	46/46	25/29				
	A/A	14/22	9/17	5/5	A	99/113	64/80	35/39
	p	0.224	0.201	0.719	***P***	**0.093**	**0.097**	0.566
OXT_ rs2770378	G/G	49/40	31/29	18/11	G	178/160	118/106	60/54
	G/A	80/80	56/48	24/32				
	A/A	28/37	18/28	10/9	A	136/154	92/104	44/50
	p	0.340	0.240	0.236	***P***	0.150	0.240	0.403
OXT_rs4813627	G/G	34/32	22/19	12/13	G	141/141	89/86	52/55
	G/A	73/77	45/48	28/29				
	A/A	45/43	33/33	12/10	A	163/163	111/114	52/49
	p	0.899	0.854	0.887	***P***	1.000	0.762	0.677
OXTR_ rs237885	A/A	28/34	19/17	9/17	A	139/140	94/90	45/50
	A/C	83/72	56/56	27/16				
	C/C	40/45	25/27	15/18	C	163/162	106/110	57/52
	p	0.437	0.910	**0.062**	***P***	0.935	0.688	0.483
OXTR_rs2268493	A/A	86/84	58/58	28/26	A	228/221	151/147	77/74
	A/G	56/53	35/31	21/22				
	G/G	9/14	7/11	2/3	G	74/81	49/53	25/28
	p	0.551	0.568	0.897[a]	***P***	0.514	0.646	0.632
OXTR_ rs237898	A/A	23/30	17/18	6/12	A	115/124	76/81	39/43
	A/T	69/64	42/45	27/19				
	T/T	60/58	43/39	17/19	T	189/180	128/123	61/57
	p	0.564	0.849	0.174	***P***	0.455	0.611	0.565

Bold values indicate $0.05 < p < 0.10$

[a] Fisher's Exact test used

matched to normal adult controls for sex and ethnicity, it is unlikely that our control subjects would have had at least a 2-year history of aggression ≥90th percentile both at home and in school in their childhood. However, given our failure to reject the null hypothesis, any future case control comparisons would be better served to utilize contemporaneous age-matched control children and youth.

Significance, however, was found with the CU within the sample of aggressive children and youth. The findings were stronger among boys than among girls. The difference may partly be due to the smaller number of girls compared to boys in this sample (53 girls vs. 99 boys). The specific oxytocin receptor marker, rs237885, has not to our knowledge been previously shown to be associated with callous-unemotional behavior or alternatively prosocial behavior. Its exact role at this time is not known, also it is not known if it is functional or if the effect is due to a nearby unidentified marker. The possibility that the significant effect is due to a nearby, unidentified marker is supported by suggestive results from our haplotype analysis. Future studies, including deep re-sequencing of this gene region, will be needed to clarify this issue.

It is of interest that unlike the results reported here, the genome wide association study by Viding et al. [13] failed to find genes significantly associated with CU traits. Although there may be many explanations, one reason may be due to the different criteria by which the samples were selected. Our sample was selected to show extreme, persistent and pervasive aggression in contrast to Viding et al. in which the sample was selected from teachers report without the requirement for pervasive and persistent aggression.

Limitations

There are several limitations that should be noted. Although this sample represents one of the very few high aggression samples with genetically informative data, it is nevertheless a small sample and replication is necessary.

Table 2 Results from analysis of *OXT* and *OXTR* markers with PSD callous-unemotional trait scores within sample of aggressive children

Gene_polymorphisms	Genotypes	Aggressive child cases					
		N (all = 152)	*p*	♂ (*N* = 99)	*P*	♀ (*N* = 53)	*p*
OXT_rs2740210	C/C	1.15 ± 0.61		1.25 ± 0.65		0.94 ± 0.46	
	C/A	1.07 ± 0.45	0.188	1.13 ± 0.43	***0.045***	0.95 ± 0.46	0.754
	A/A	0.87 ± 0.43		0.75 ± 0.45		1.13 ± 0.25	
OXT_rs2770378	G/G	1.10 ± 0.53		1.19 ± 0.51		0.92 ± 0.55	
	G/A	1.08 ± 0.47	0.866	1.11 ± 0.50	0.640	1.03 ± 0.41	0.731
	A/A	1.15 ± 0.64		1.24 ± 0.75		0.97 ± 0.29	
OXT_rs4813627	G/G	1.04 ± 0.66		1.16 ± 0.75		0.83 ± 0.41	
	G/A	1.14 ± 0.46	0.404	1.23 ± 0.46	0.392	1.02 ± 0.43	0.463
	A/A	1.02 ± 0.49		1.05 ± 0.50		0.93 ± 0.48	
OXTR_rs237885	A/A	1.39 ± 0.68		1.52 ± 0.76		1.18 ± 0.48	
	A/C	1.05 ± 0.48	***0.003***	1.07 ± 0.50	***0.012***	1.01 ± 0.43	**0.055**
	C/C	0.96 ± 0.43		1.08 ± 0.40		0.73 ± 0.41	
OXTR_rs2268493	A/A	1.14 ± 0.54		1.18 ± 0.57		1.06 ± 0.45	
	A/G	0.97 ± 0.41	0.142	1.04 ± 0.39	0.435[a]	0.87 ± 0.43	0.304
	G/G	1.11 ± 0.47		1.21 ± 0.39		0.75 ± 0.71	
OXTR_rs237898	A/A	1.19 ± 0.50		1.23 ± 0.50		1.08 ± 0.52	
	A/T	1.00 ± 0.56	0.149	1.08 ± 0.62	0.514	0.87 ± 0.45	0.309
	T/T	1.16 ± 0.47		1.19 ± 0.49		1.08 ± 0.44	

Bold values indicate $0.05 < p < 0.10$

Bold, italics values indicate $p < 0.05$

[a] Kruskal–Wallis test used

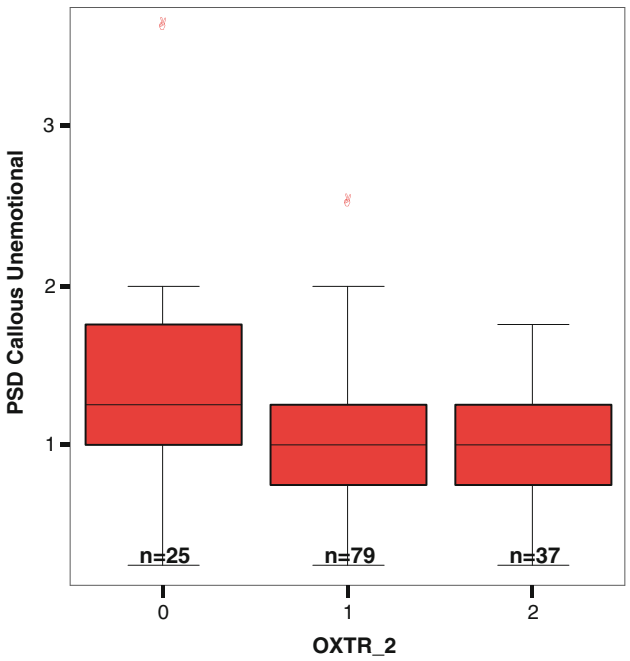

Fig. 2 *Boxplot* showing the comparison of PSD callous-unemotional mean scores among the three genotypes of the *OXTR*_rs237885 marker

Our findings survived correction for the number of markers we tested, but given the small sample size, the possibility of false positive findings cannot be dismissed.

When we redid the analysis focusing upon the Caucasian subset of the full sample, the results remained nominally significant. However, given the possibility that our full sample results are sample specific or that the nominally significant results with the Caucasians are due to the reduced sample size, it is important to test these findings in a larger sample.

The ratings of CU were completed by the mothers, without any independent objective verification of these characteristics in the children and youth. Consequently, future studies should include independent measures of CU in the children themselves. Although it is possible that the wide age range of the children and adolescents affected the results, studies suggest that callous and emotional traits show moderate stability from childhood to adolescence [19, 64, 65]. This stability is particularly strong for parent report [66] of callous and emotional traits.

While the control group was not specifically screened for childhood aggression, to the extent that our adult controls did have a 2-year history of aggressive behavior in childhood, this would tend to reduce differences between our cases and controls and decrease the likelihood of finding significant differences. Hence, these findings should be viewed as conservative. Therefore, their influence on our findings would have been minimal. Additionally, even though somatic mutations occur during life,

DNA sequence changes at the specific sites that we tested here are unlikely.

These findings were obtained within a sample of high aggressive children. It is not known to what extent these CU traits would show significant associations with oxytocin in a population sample in which aggression is normally distributed. However, from a therapeutic and prognostic point of view, it is important to note that there is evidence that for many children CU traits are modifiable across development [67] and potentially responsive to treatment and environmental changes.

As previously noted, accumulating evidence suggests that multiple gene systems each with weak effects contributes to risk of aggressive behavior. Consequently, other potential pathways to aggression warrant investigation. For example, reports of genetic variants in the arginine vasopressin receptor's (AVPR1a) relation to social deficits [37] and recent findings [35] showing associations between AVPR1a and preclinical studies of aggressive behavior, suggest that genetic variation in oxytocin's sister neuropeptide, vasopressin, and the vasopressin receptor gene, AVPR1a system is warranted.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kadzin AE (1995) Conduct disorders in childhood and adolescence, 2nd edn. Sage, Thousand Oaks
2. Steiner H (2000) Disruptive behavior disorders. In: Kaplan H, Sadock B (eds) Kaplan & Sadock's comprehensive textbook of psychiatry, vol 2. Lippincott Williams & Wilkins Publishers, New York, pp 2693–2703
3. Moffitt TE (2003) Life-course-persistent and adolescence-limited antisocial behavior. In: Lahey BB, Moffitt TE, Caspi A (eds) Causes of conduct disorder and juvenile delinquency. Guilford Press, New York
4. Frick PJ, O'Brien BS, Wootton JM, McBurnett K (1994) Psychopathy and conduct problems in children. J Abnorm Psychol 103(4):700–707
5. Blair RJR (2001) Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. J Neurol Neurosurg Psychiatry 71(6):727–731
6. Frick PJ, Ellis M (1999) Callous-unemotional traits and subtypes of conduct disorder. Clin Child Family Psychol Rev 2(3):149–168
7. Fisher L, Blair RJR (1998) Cognitive impairment and its relationship to psychopathic tendencies in children with emotional and behavioral difficulties. J Abnorm Child Psychol 26(6):511–519
8. Mason DA, Frick PJ (1994) The heritability of antisocial behavior: a meta-analysis of twin and adoption studies. J Psychopathol Behav Assess 16(4):301–323
9. Viding E, Blair RJR, Moffitt TE, Plomin R (2005) Strong genetic risk for psychopathic syndrome in children. J Child Psychol Psychiatry 46:592–597
10. Beitchman JH, Mik HM, Ehtesham S, Douglas L, Kennedy JL (2004) MAOA and persistent, pervasive childhood aggression. Mol Psychiatry 9(6):546–547
11. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002) Role of genotype in the cycle of violence in maltreated children. Science 297(5582):851–854
12. Beitchman JH, Baldassarra L, Mik H, De Luca V, King N, Bender D, Ehtesham S, Kennedy JL (2006) Serotonin transporter polymorphisms and persistent, pervasive childhood aggression. Am J Psychiatry 163(6):1103–1105
13. Viding E, Hanscombe KB, Curtis CJC, Davis OSP, Meaburn EL, Plomin R (2010) In search of genes associated with risk for psychopathic tendencies in children: a two stage genome wide association study of pooled DNA. J Child Psychol Psychiatry 51(7):780–788
14. Frick PJ, Viding E (2009) Antisocial behavior from a developmental psychopathology perspective. Dev Psychopathol 21(Special Issue 04):1111–1131
15. Barry TD, Barry CT, Deming AM, Lochman JE (2008) Stability of psychopathic characteristics in childhood. Crim Justice Behav 35(2):244–262
16. Dadds M, Fraser J, Frost A, Hawes D (2008) Disentangling the underlying dimensions of psychopathy and conduct problems in childhood: A community study. J Consul Clin Psychol 73(3): 400–410
17. Rutherford M (1999) The 2-year Test-Retest Reliability of the Psychopathy Checklist-revised in methadone patients. Assessment 6(3):285–291
18. Lynam DR, Charnigo R, Moffitt TE, Raine A, Loeber R, Stouthamer-Loeber M (2009) The stability of psychopathy across adolescence. Dev Psychopathol 21(04):1133–1153
19. Muñoz LC, Frick PJ (2007) The reliability, stability, and predictive utility of the self report version of the antisocial process screening device. Scand J Psychol 48(4):299–312
20. Forsman M, Lichtenstein P, Andershed H, Larsson H (2008) Genetic effects explain the stability of psychopathic personality from mid-to late adolescence. J Abnorm Psychol 117(3):606–617
21. Campbell A (2010) Oxytocin and human social behavior. Pers Soc psychol Rev 14(3):281–295
22. Engelmann M, Landgraf R, Wotjak CT (2004) The hypothalamic-neurohypophysial system regulates the hypothalamic-pituitary-adrenal axis under stress: an old concept revisited. Frontiers neuroendocrinol 25(3–4):132–149
23. Viviani D, Stoop R (2008) Opposite effects of oxytocin and vasopressin on the emotional expression of the fear response. Prog Brain Res 170:207–218
24. Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, Soorya L, Anagnostou E, Wasserman S (2007) Oxytocin increases retention of social cognition in autism. Biol Psychiatry 61(4):498–503
25. Lerer E, Levi S, Salomon S, Darvasi A, Yirmiya N, Ebstein RP (2008) Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. Mol Psychiatry 13(10):980–988
26. Israel S, Lerer E, Shalev I, Uzefovsky F, Reibold M, Bachner-Melman R, Granot R, Bornstein G, Knafo A (2008) Molecular genetics studies of the arginine vasopression 1a receptor (AVPR1a) and hte oxytocin receptor (OXTR) in human behaviour: from autism to altruism with some notes in between. In: Neumann I, Landgraf R (eds) Progress in Brain Research, vol 170. Elsevier, Amsterdam
27. Sala M, Braida D, Lentini D, Busnelli M, Bulgheroni E, Capurro V, Finardi A, Donzelli A, Pattini L, Rubino T, Parolaro D, Nishimori K, Parenti M, Chini B (2011) Pharmacologic rescue of impaired cognitive flexibility, social deficits, increased aggression, and seizure susceptibility in oxytocin receptor null mice: a neurobehavioral model of autism. Biol Psychiatry 69(9):875–882

28. Campbell DB, Datta D, Jones ST, Batey Lee E, Sutcliffe JS, Hammock EA, Levitt P (2011) Association of oxytocin receptor (OXTR) gene variants with multiple phenotype domains of autism spectrum disorder. J Neurodev Disord 3(2):101–112. doi: 10.1007/s11689-010-9071-2
29. Souza RP, de Luca V, Meltzer HY, Lieberman JA, Kennedy JL (2010) Schizophrenia severity and clozapine treatment outcome association with oxytocinergic genes. Int J Neuropsychopharmacol 13(06):793–798
30. Fetissov SO, Hallman J, Nilsson I, Lefvert AK, Oreland L, Hökfelt T (2006) Aggressive behavior linked to corticotropin-reactive autoantibodies. Biol psychiatry 60(8):799–802
31. Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, Gruppe H, Mattay VS, Gallhofer B, Meyer-Lindenberg A (2005) Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci 25(49):11489–11493
32. Bosch OJ, Meddle SL, Beiderbeck DI, Douglas AJ, Neumann ID (2005) Brain oxytocin correlates with maternal aggression: link to anxiety. J Neurosci 25(29):6807–6815
33. Winslow JT, Hearn EF, Ferguson J, Young LJ, Matzuk MM, Insel TR (2000) Infant vocalization, adult aggression, and fear behavior of an oxytocin null mutant mouse. Horm Behav 37(2):145–155
34. Bosch OJ, Sartori SB, Singewald N, Neumann ID (2007) Extracellular amino acid levels in the paraventricular nucleus and the central amygdala in high-and low-anxiety dams rats during maternal aggression: regulation by oxytocin. Stress: Int J Biol Stress 10(3):261–270
35. Veenema AH, Beiderbeck DI, Lukas M, Neumann ID (2010) Distinct correlations of vasopressin release within the lateral septum and the bed nucleus of the stria terminalis with the display of intermale aggression. Hormones Behav 58(2):273–281
36. Savaskan E, Ehrhardt R, Schulz A, Walter M, Schächinger H (2008) Post-learning intranasal oxytocin modulates human memory for facial identity. Psychoneuroendocrinology 33(3):368–374
37. Ebstein RP, Israel S, Lerer E, Uzefovsky F, Shalev I, Gritsenko I, Riebold M, Salomon S, Yirmiya N (2009) Arginine vasopressin and oxytocin modulate human social behavior. Ann NY Acad Sci 1167(1):87–102
38. Israel S, Lerer E, Shalev I, Uzefovsky F, Riebold M, Laiba E, Bachner-Melman R, Maril A, Bornstein G, Knafo A (2009) The oxytocin receptor (OXTR) contributes to prosocial fund allocations in the dictator game and the social value orientations task. PLoS One 4(5):5535
39. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005) Oxytocin increases trust in humans. Nature 435(7042):673–676
40. Lee H-J, Macbeth AH, Pagani JH, Young WS (2009) Oxytocin: the great facilitator of life. Prog Neurobiol 88(2):127–151
41. Stanley B, Siever LJ (2010) The interpersonal dimension of borderline personality disorder: toward a neuropeptide model. Am J Psychiatry 167(1):24–39
42. Gordon I, Zagoory Sharon O, Schneiderman I, Leckman JF, Weller A, Feldman R (2008) Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress. Psychophysiology 45(3):349–352
43. Grewen KM, Girdler SS, Amico J, Light KC (2005) Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. Psychosom Med 67(4):531
44. Bakermans-Kranenburg MJ, van Ijzendoorn MH (2008) Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. Soc Cogn Affect Neurosci 3(2):128–134
45. Thompson RJ, Parker KJ, Hallmayer JF, Waugh CE, Gotlib IH (2011) Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. Psychoneuroendocrinology 36(1):144–147
46. Montag C, Fiebach CJ, Kirsch P, Reuter M (2011) Interaction of 5-HTTLPR and a variation on the oxytocin receptor gene influences negative emotionality. Biol Psychiatry 69:601–603
47. Inoue H, Yamasue H, Tochigi M, Abe O, Liu X, Kawamura Y, Takei K, Suga M, Yamada H, Rogers MA (2010) Association between the oxytocin receptor gene and amygdalar volume in healthy adults. Biol Psychiatry 68(11):1066–1072
48. Furman DJ, Chen MC, Gotlib IH (2011) Variant in oxytocin receptor gene is associated with amygdala volume. Psychoneuroendocrinology 36(6):891–897
49. Reuter M, Weber B, Fiebach CJ, Elger C, Montag C (2009) The biological basis of anger: associations with the gene coding for DARPP-32 (PPP1R1B) and with amygdala volume. Behav Brain Res 202(2):179–183
50. Achenbach TM, Rescorla LA (2001) Manual for the ASEBA School-Age Forms and Profiles. University of Vermont, Research Center for Children, Youth and Families, Burlington
51. Weschsler D (1991) Manual for the Wechsler Intellgience Scale for Children. The Psychological Corporation, San Antonio
52. First MB, Spitzer RL, Gibbon M, Williams JBW (1997) Structured clinical interview for DSM IV-TR Axis I Disorders, research version, non-patient edition (SCID-I/NP). Biometrics Research, New York State Psychiatric Institute, New York
53. Maxwell E (1992) The Family Interview for Genetic Studies: Manual. Clinical Neurogenetics Branch, Intramural Research Program, National Institute of Mental Health, Washington
54. American Psychiatric Association (1994) Diagnostic and statistical manual of mental health disorders, 4th edn. American Psychiatric Association, Washington
55. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000) NIMH diagnostic interview schedule for children version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 39(1):28–38
56. Kovacs M (1985) The Children's Depression Inventory (CDI). Psychopharmacol Bull 21(4):995–998
57. Frick PJ, Hare RD (2001) Psychopathy screening device. Multi-Health Systems, Toronto
58. Lahiri DK, Nurnberger JI Jr (1991) A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic Acids Res 19(19):5444
59. SPSS (2007) SPSS Version 15 for Windows. SPSS Inc., Chicago
60. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21(2):263–265
61. Dudbridge F (2003) Pedigree disequilibrium tests for multilocus haplotypes. Genet Epidemiol 25(2):115–121
62. Gauderman WJ, Morrison JM (2006) QUANTO 1.1: a computer program for power and sample size calculations for genetic-epidemiology studies. http://hydra.usc.edu/gxe
63. Nyholt DR (2004) A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. AmJ Human Genet 74(4):765–769
64. Rutherford M, Cacciola JS, Alterman AI, McKay JR, Cook TG (1999) The 2-year test-retest reliability of the Psychopathy Checklist-revised in methadone patients. Assessment 6(3):285
65. Dadds MR, Fraser J, Frost A, Hawes DJ (2005) Disentangling the underlying dimensions of psychopathy and conduct problems in childhood: a community study. J Consult Clin Psychol 73(3):400
66. Frick PJ, Kimonis ER, Dandreaux DM, Farell JM (2003) The 4 year stability of psychopathic traits in non-referred youth. Behav Sci Law 21(6):713–736
67. Fontaine NMG, Rijsdijk FV, McCrory EJP, Viding E (2010) Etiology of different developmental trajectories of callous-unemotional traits. J Am Acad Child Adoles Psychiatry 49(7):656–664