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Neural Responses to Intranasal Oxytocin in Youths With Severe Irritability

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Abstract

Objective: The authors investigated the neural impact of intranasal oxytocin on emotion processing areas in youths with severe irritability in the context of disruptive mood and behavior disorders.

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Methods: Fifty-two participants with severe irritability, as measured by a score ≥4 on the Affective Reactivity Index (ARI), with diagnoses of disruptive behavior disorders (DBDs) and/or disruptive mood dysregulation disorder (DMDD) were randomly assigned to treatment with intranasal oxytocin or placebo daily for 3 weeks. Assessments were conducted at baseline and at the end of the trial; the primary outcomes were measures of irritability on the ARI and ratings on the Clinical Global Impressions severity scale (CGI-S) focusing on DBD and DMDD symptoms, and secondary outcomes included the CGI improvement scale (CGI-I) and ratings of proactive and reactive aggressive behavior on the Reactive-Proactive Aggression Questionnaire. Forty-three participants (22 in the oxytocin group and 21 in the placebo group) completed pre- and posttreatment functional MRI (fMRI) scans with the affective Stroop task.

Results: Youths who received oxytocin showed significant improvement in CGI-S and CGI-I ratings compared with those who received placebo. In the fMRI data, blood-oxygen-level-dependent (BOLD) responses to emotional stimuli in the dorsomedial prefrontal cortex and posterior cingulate cortex were significantly reduced after oxytocin compared with placebo. These BOLD response changes were correlated with improvement in clinical severity.

Conclusions: This study provides initial and preliminary evidence that intranasal oxytocin may induce neural-level changes in emotion processing in youths with irritability in the context of DBDs and DMDD. This may lead to symptom and severity changes in irritability.

Irritability is a significant mental health issue in children and adolescents (1) and is one of the most common reasons children are referred for psychiatric treatment (2, 3). Children with chronic irritability are at increased risk for long-lasting mental health problems, including anxiety and depressive disorders, suicide, and substance use disorders (4, 5).

There are few evidence-based pharmacologic treatment options for irritability in children and adolescents. Furthermore, very few studies have explored how any treatment modality impacts neural areas implicated in the pathophysiology of irritability (6). Several studies have suggested that the neuropeptide hormone oxytocin may be effective in inducing neural changes in youths with irritability. Oxytocin has been used in clinical trials of psychiatric diagnoses associated with elevated risk for irritability, such as borderline personality disorder (7) and autism spectrum disorder (8). Several studies implicate changes in oxytocin levels related to irritability in children and adolescents, especially in the context of disruptive behavior disorders (DBDs) (9). Decreased oxytocin levels have been reported in saliva or serum of children with DBDs (oppositional defiant disorder or conduct disorder) (10, 11). Notably, lower levels of serum oxytocin in children with attention deficit hyperactivity disorder (ADHD) correlate with their degree of aggressive behavior (12).

In neuropsychiatric studies, emphasis is placed on the ability to measure both symptom change and the engagement of the neural target of the intervention (13). However, relatively little work has focused on the actual neural impact of oxytocin, especially in youths with irritability (13, 14). Notably, one form of neurocognitive dysfunction in adolescents with irritability is an atypically increased activation of neural regions to emotional cues, including the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and amygdala (1, 15). Previous work with oxytocin (both single-dose administration and clinical trials) has indicated that oxytocin reduces neural responsiveness

to emotional cues in areas including amygdala and mPFC in healthy individuals as well as in patients with borderline personality disorder, anxiety disorders, and posttraumatic stress disorder (16, 17). Hence, a potential treatment target for irritability, atypically increased neural responsiveness of areas including mPFC to emotional cues, may be modulated by oxytocin.

Our goal in this study was to determine the impact of 3 weeks of daily intranasal oxytocin on 1) irritability symptom severity in youths with severe irritability in the context of disruptive behavior (in DBDs) and mood disorders (in disruptive mood dysregulation disorder [DMDD]), since these disorders seem to share a common neurobiological mechanism of irritability (compared to, for example, autism spectrum disorder) (1, 18); and 2) the neural profile relating to emotional responding as indexed by a task (the affective Stroop task) previously demonstrated to identify dysfunction in neural responsiveness associated with irritability (mainly increased response to emotional stimuli in the dorsomedial prefrontal cortex [dmPFC] and PCC in youths with significant levels of irritability) (15). The study used clinical measurements of severity before and after oxytocin intervention in the context of randomized, double-blind administration for 3 weeks. Based on previous work, we hypothesized that intranasal oxytocin would reduce the severity of irritability in youths with DBDs and DMDD and that the level of symptom severity would be associated with the level of reduction of neural responses in the mPFC and PCC to emotional stimuli under the affective Stroop task.

METHODS

Participants

The study was conducted at an outpatient child and adolescent psychiatry clinic at a large academic medical center in the Midwest from January 2016 until August 2021. The center's institutional review board reviewed and approved the study. The participants were between 10 and 18 years of age, had diagnoses of ADHD, oppositional defiant disorder, conduct disorder, and/or DMDD, and had significant levels of irritability, as indicated by a score ≥4 on the Affective Reactivity Index (ARI). All participants provided written assent, and their parents written informed consent. Participants were recruited by referrals from outpatient clinic providers and the surrounding community by local advertisements. The study was registered at ClinicalTrials.gov (NCT02824627) with two primary outcomes (the ARI and the Clinical Global Impressions severity scale; see below). A data safety monitoring board was formed at the medical center to monitor the integrity of the conduct of the study. Figure 1 illustrates the flow of participant screening and recruitment.

Screening

Psychiatric diagnoses were confirmed using the semistructured Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version, administered by a licensed and board-certified child and adolescent psychiatrist and/or an advanced practice psychiatric nurse. For inclusion and exclusion criteria, see the online supplement.

Assessments

The clinical severity of irritability was assessed with the ARI at the screening and at the final assessment session after 3 weeks of study treatment. Additional outcome measures, including the Inventory of Callous-Unemotional Traits and the Reactive-Proactive Aggression Questionnaire (RPAQ), were completed at both time points. For descriptions of the symptom profile measurements, see the online supplement. The Clinical Global Impressions severity and improvement scales (CGI-S and CGI-I) (19) as well as the Children's Global Assessment of Severity (CGAS) (20) documented the clinicians' global assessment of the youths' symptoms of DBDs and DMDD, including irritability, and were completed at screening and at the final assessment session (the CGI-I was completed only at the final assessment session). The CGI was administered by a psychiatrist with extensive experience in providing assessment and treatment in this population, blinded to the participants' treatment assignment. (For details on the randomized double-blind administration of intranasal oxytocin, see the online supplement.)

Statistical Analysis of Clinical Trial Data

We first examined group differences in symptom profiles (ARI, irritability, Inventory of Callous-Unemotional Traits, proactive aggressive behavior, reactive aggressive behavior, and total aggressive behavior in the RPAQ) and clinical severity (CGI-S and CGAS, focused on symptoms of DBDs and DMDD) at baseline by t test. We then conducted 2×2 repeated-measures analyses of covariance (ANCOVAs) (group [oxytocin, placebo] by time [pre- and posttreatment]) on the symptom profile and clinical severity measures. T tests were conducted on the CGI-I scores at the final assessment, after 3 weeks of treatment, between participants in the oxytocin and placebo groups.

Functional MRI Scans

Functional MRI (fMRI) sessions took place after the initial assessment session but before initiation of intranasal oxytocin or placebo (average time between first MRI scan and initiation of treatment, 1.4 days [SD = 0.52]) and after the final postintervention assessment session 3 weeks later (average time between end of treatment and second MRI scan, 2.8 days [SD = 0.74]). The research personnel who performed the MRI procedure were also blinded to participants' treatment assignment. For the youths with DBDs, psychiatric treatment continued at the outpatient clinic or with their local providers after study completion. For more details on the fMRI scans, see the online supplement.

Twenty-two participants in the oxytocin treatment group and 21 in the placebo group completed both the pre- and posttreatment fMRI scans. Two participants in the oxytocin group and three in the placebo group completed only one scan, as a result of scheduling conflicts, machine malfunctioning, or lack of interest. One participant in the oxytocin group and three in the placebo group were excluded from the analyses because of excessive in-scanner motion. We included only the data from these 39 participants (21 in the oxytocin group and 18 in the placebo group) in the final MRI data analyses.

Statistical Analysis of fMRI Data

Behavioral data.—We conducted a full 2×2×3×3 repeated-measures ANCOVA (group [oxytocin, placebo] by time [pre- and posttreatment] by condition [incongruent, congruent, view] by emotion [negative, positive, neutral]) on the accuracy and reaction time data, with sex as a covariate.

MRI data.—We selected two approaches to the data analyses of blood-oxygen-level-dependent (BOLD) responses. First, we conducted a 2×2×3×3 ANCOVA (group [oxytocin, placebo; between-subject variable] by time [pretreatment and follow-up; within-subject variable] by condition [incongruent, congruent, and view] by emotion [negative, positive, and neutral]) on the whole-brain BOLD response data, using the 3dMVM program in AFNI, with sex as a covariate. Correction for multiple comparisons was performed using a spatial clustering operation in AFNI's 3dClustSim program, utilizing the auto-correction function -acf) with 10,000 Monte Carlo simulations for a whole-brain gray matter mask. The initial significance threshold was set at a p value of 0.001 (21). This procedure yielded an extent threshold (k) of 25 voxels, which then resulted in a cluster-level false positive probability of 0.05, corrected for multiple comparisons. To facilitate future meta-analytic work, effect sizes (partial η^2) for all clusters are reported.

Second, we focused on the ACC region of interest (ROI). As noted, previous work with the same affective cognitive task (the affective Stroop task) has indicated atypical ACC response to negative emotional stimuli in youths with severe levels of irritability. The ACC ROI was generated from our previous study (15) of a large number of youths with severe levels of irritability (N = 155, none of whom participated in the present study) (59 voxels; coordinates: −7.5, 28.5, 11.5), following a common approach (22). Similar to the method we implemented in a previous work (23), this approach would allow us to focus on the role of the ACC in the treatment response with oxytocin but be unbiased with respect to pre-to-posttreatment differences among participants in the present study.

Relationship of treatment-related BOLD response changes to symptom-level changes.—These were examined via correlational analyses. Differential BOLD responses (posttreatment minus pretreatment) in the neural areas showing a significant group-by-time interaction and in the ACC ROI were correlated against changes in symptom levels (posttreatment minus pretreatment).

RESULTS

Clinical Characteristics

Twenty-eight participants were assigned to treatment with intranasal oxytocin and 30 participants to placebo. Twenty-five participants in the oxytocin group completed the 3 weeks of study treatment. One participant withdrew because of an adverse event, and two were lost to follow-up. Twenty-seven participants in the placebo group completed the 3 weeks of study treatment. Two participants withdrew because of adverse events, and one was lost to follow-up. Table 1 summarizes the participants' demographic and clinical characteristics, and Table 2 lists the treatment groups' mean scores on assessment

instruments at baseline and follow-up. None of the participants had any changes in their psychiatric medication regimens or required higher levels of care (such as inpatient psychiatric hospitalization) during their participation in the study. (For a list of the psychiatric medications participants were taking during the study period, see Table S1 in the online supplement.)

Symptom Profile Changes

Our repeated-measures ANCOVA revealed that there was a significant group-by-time interaction in CGI-S scores ($F = 5.14$, $p=0.028$; $\eta^2_p = 0.093$) and that clinical severity was significantly decreased for the oxytocin group compared with the placebo group (4.44–3.40 and 4.59–4.04, respectively; the scale ranges from 1 [normal, not at all ill] to 7 [the mostly extremely ill]). The t test for CGI-I scores also showed significant improvement in the oxytocin group (mean = 2.72, SD = 0.79) compared with the placebo group (mean = 3.33, SD = 1.07) ($t=2.33$, $p = 0.024$) (the scale ranges from 1 [very much improved] to 4 [no change] to 7 [very much worse]). The number needed to treat, calculated from CGI-I scores with the criterion for significant change as a score of 1 (very much improved) or 2 (much improved), was 3.4, with an absolute risk reduction of 29.5%.

However, irritability as measured on the youth-reported ARI did not reach statistical significance in the group-by-time interaction ($F = 2.57$, $p = 0.115$; $\eta^2_p = 0.049$). In addition, self-reported reactive aggression ($F = 2.79$, $p = 0.101$; $\eta^2_p = 0.053$), self-reported total aggression ($F = 2.13$, $p = 0.151$; $\eta^2_p = 0.041$), and CGAS score ($F = 3.85$, $p = 0.055$; $\eta^2_p = 0.072$) showed reductions in the oxytocin group compared with the placebo group, but the differences were not statistically significant. The number needed to treat, calculated from the youth-reported ARI with the criterion of significant reduction as ≤ -4, was 5.7, with an absolute risk reduction of 17.5%. There was no significant difference in symptom reductions in callous-unemotional traits or proactive aggression. For details, see Table 2.

Adverse Events

There were no significant differences in types of adverse events between participants who received intranasal oxytocin and those who received placebo ($\chi^2 = 10.81$, $p = 0.37$) (for adverse event profiles, see Table S2 in the online supplement). All three participants who discontinued the trial as a result of adverse events experienced mood changes (two in the placebo group became more irritable, and one in the oxytocin group became more anxious), which were completely resolved when assessed by telephone follow-up 2–3 weeks after their withdrawal. Of the adverse events more broadly described, drowsiness was the most common (oxytocin group, 40.0%; placebo group, 40.7%), followed by headache (oxytocin group, 12.0%; placebo group, 18.5%) and mood changes (oxytocin group, 4.0%; placebo group, 22.2%).

Behavioral Data

For the results of the behavioral data analyses, see the online supplement.

MRI Data

Whole-brain analysis.—Regions showing significant group-by-time-by-condition interactions included the left dmPFC, left PCC, right fusiform gyrus, left and right caudate, and left thalamus/anterior nucleus (see Table 3). Within all these regions, participants in the oxytocin group showed a significantly greater decrease in activation in response to view trials after treatment relative to those in the placebo group (t values, 2.20–3.71; p values, <0.001–0.02).There were no regions showing group-by-time-by-emotion or group-by-time-by-condition-by-emotion interactions.

ROI analysis.—Our ROI analysis of the ACC showed a significant time-by-group-by-condition-by-emotion interaction; participants in the oxytocin group showed a significantly greater decrease in activation in response to negative view trials after treatment relative to those in the placebo group ($t = 3.13$, $p = 0.002$) (Figure 2).

Correlation between BOLD response changes and symptom improvement.—We examined the correlation between BOLD response changes (posttreatment vs. pretreatment) and symptom changes (posttreatment vs. pretreatment reduction) among youths with DBDs, using the symptom profiles and the signal in the neural areas that exhibited significant group-by-time-by-condition interactions and in the ACC ROI (Table 3). These revealed consistent significant associations between BOLD response changes in the dmPFC, PCC, and ACC and changes (reduction) in irritability, reactive aggression, and total aggression (ρ values, 0.32–0.64; p values, <0.001–0.038) (for details, see Table S4 and Figure S3 in the online supplement).

DISCUSSION

To our knowledge, this is the first study reporting the neural impact of intranasal oxytocin intervention for youths with significant levels of irritability in the context of disruptive mood and behavior disorders. There were three main findings. First, of two primary outcomes (the ARI and the CGI), youths with significant levels of irritability who received intranasal oxytocin showed significant improvement in clinical severity, as measured by the CGI-S and the CGI-I. However, the reduction in irritability (on the ARI) in the oxytocin group compared with the placebo group did not reach statistical significance ($p = 0.115$). In addition, there were greater improvements in reactive aggression, total level of aggression, and level of daily functioning in the oxytocin group compared with the placebo group, although the differences were not statistically significant (p values, 0.055–0.151). Second, youths in the oxytocin group, compared with those in the placebo group, showed greater reductions in BOLD responses in the dmPFC, PCC, and fusiform gyrus in response to emotional stimuli, and in the ACC in response to negative emotional stimuli. Third, there were significant correlations among the reductions in BOLD responses to emotional stimuli in the dmPFC, PCC, and ACC and symptom improvements in irritability, reactive aggression, and overall clinical severity of illness.

Intranasal oxytocin administration for 3 weeks yielded significant reductions in overall clinical severity of illness as measured by the CGI-S, and overall improvement in functioning as measured by the CGI-I, compared with placebo, although this finding

could be a preliminary result given the small sample size. Although irritability (on the ARI) showed only a nonsignificant improvement, this may reflect type II error, given the relatively short period of administration (3 weeks) and the relatively small number of participants. Both the ARI and the RPAQ, used to measure irritability and aggressive behavior, were designed for trait measurement rather than assessing changes by intervention, whereas the CGI-S and CGI-I have been widely used for changes or improvement in clinical trials. Consequently, the ARI or RPAQ may have not been as effective as the CGI-S or CGI-I in capturing the actual changes from the intranasal oxytocin intervention (for a similar argument, see reference 24). It is also possible that the aggregation of subthreshold improvement in each disruptive mood and behavioral psychopathology (especially irritability and aggressive behavior) led to overall statistically significant improvement in clinical severity (25). Indeed, the aggregated standardized scores (Z scores) of irritability and total aggression as well as irritability and reactive aggression showed significant differences between the two treatment arms (see the online supplement).

The effect of intranasal oxytocin on aggressive behavior has shown mixed results thus far. There have been reports that oxytocin increased aggression in healthy adults (26) but decreased aggression in women with higher baseline state anxiety (27). However, most previous work investigating this treatment has indexed aggression via computer-based tasks (28) rather than reported symptoms. It will be important for future work to consider aggression in contexts beyond the laboratory.

Studies of intranasal oxytocin in pediatric populations with autism spectrum disorder (ASD) have also reported increased irritability and/or aggressive behavior as adverse events (8). Irritability and emotional dysregulation in ASD are a prominent clinical issue, but little is known of their neurobiological mechanisms and etiology (29). It is possible that intranasal oxytocin affects children with ASD significantly differently than it does neurotypical children, which will need to be explored in future work. It is possible, too, that the impact of oxytocin differs depending on the target population and the type of dependent measure used to index aggression.

More importantly, intranasal oxytocin significantly modulated BOLD responses within regions implicated in emotional response and regulation. Specifically, the dmPFC and PCC showed significantly greater reductions in BOLD responses to view trials after the intranasal oxytocin intervention compared with placebo. In our previous study using the same task (the affective Stroop task) in youths with irritability, we observed increased activation of a proximal area of the mPFC (coordinates: 4.5, 17.5, 52.5 vs. −13.5, 25.5, 41.5 in this study) and PCC (coordinates: 4.5, −28.5, 33.5 vs. −1.5, −40.5, 14.5 in this study), and the degree of activation to view trials in the mPFC area was correlated with level of irritability (15). Previous studies have also demonstrated abnormal responsiveness within these areas related to irritability (30, 31) as well as reactive aggression (32). The ACC ROI, which showed decreased activation to negative stimuli in our previous study (15), showed significantly greater reductions in BOLD responses to negative view trials after intranasal oxytocin intervention compared with placebo. We might have expected an increase in activation with oxytocin in this area, given that it showed decreased baseline activation in our previous study. However, it is also possible that the previous study’s finding

reflected only a population with high levels of both irritability and anxiety. In fact, our more recent study showed that irritability was associated with increased activation of the ACC to threat cues (31). Many previous studies have suggested the role of the ACC in emotional stimulus processing (e.g., 33–35), and the degree of reduction of BOLD response in this area was correlated with the degree of symptom improvement (see Table S4 and Figure S2 in the online supplement), supporting the notion that this was indeed a target engagement of the intervention.

We have a few caveats to offer on interpretation of the results. First, the duration of treatment with oxytocin or placebo was relatively short (3 weeks). This may have contributed to the subthreshold improvements in irritability and aggressive behavior in the oxytocin group. However, the duration of the majority of previous oxytocin clinical trials for psychiatric disorders has been between 1 and 6 weeks (28). Currently, there is no clear consensus on the recommended duration of an oxytocin trial or determination of the pharmacodynamic and pharmacokinetic model of oxytocin for behavioral effects (the latter is, however, under investigation in our ongoing study; ClinicalTrials.gov identifier, NCT03863288). Second, the small sample size was a limitation of the present study. The small number of participants in each categorical diagnosis meant that we could not conduct any separate analyses based on categorical diagnoses. Although it has been suggested that the neurobiological mechanism of irritability is commonly shared among the disruptive behavior and disruptive mood disorder diagnoses (1), it is possible that the effect of intranasal oxytocin differs between youths with ADHD and irritability and those with conduct disorder and irritability, for example. Lastly, sex differences were not statistically significant between the groups, but there was an imbalance between the groups ($p = 0.07$). To overcome this, we used sex as a covariate in both symptom profile and BOLD response analyses. Clinical trials with larger groups of youths with a greater variety of psychiatric diagnoses are warranted.

In summary, we report the result of the impact of intranasal oxytocin on youths with DBDs and high levels of irritability. We found that youths with DBDs and irritability showed significant improvement in clinical severity of illness and subthreshold improvement of irritability symptoms and aggressive behavior. Moreover, we observed target engagement of neural areas implicated in emotion processing (emotional responding and emotion regulation) with intranasal oxytocin. Notably, there were significant correlations between improvements in core DBD symptoms and neural-level changes. Although this may be a preliminary result given the small sample size, it may provide guidance for the future direction of clinical trials and treatment for this challenging population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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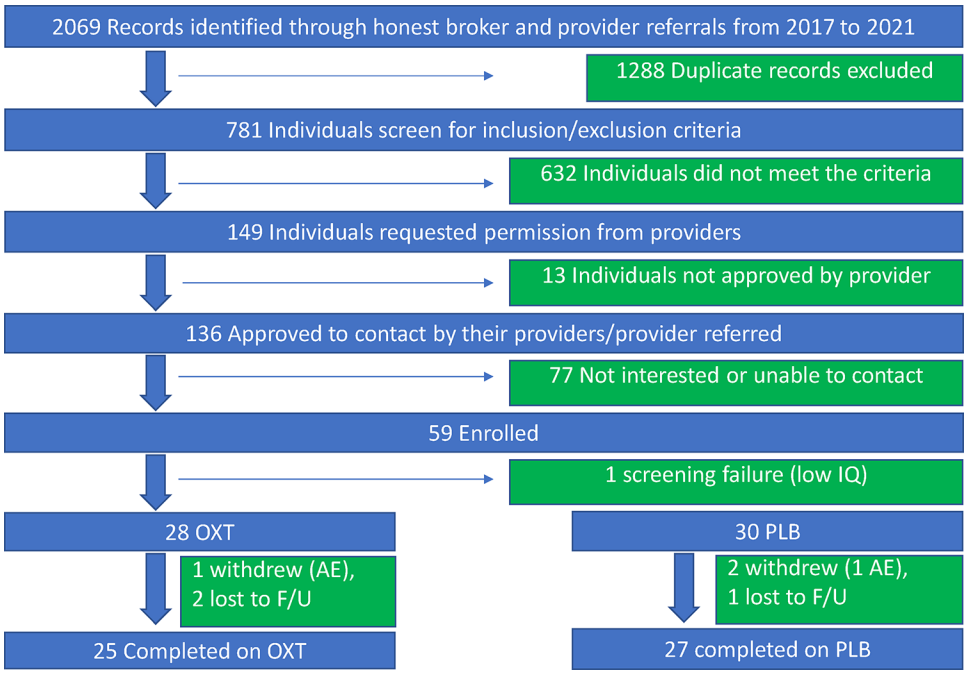

FIGURE 1. Participant flow in a study of intranasal oxytocin treatment for youths with disruptive behavior disorders

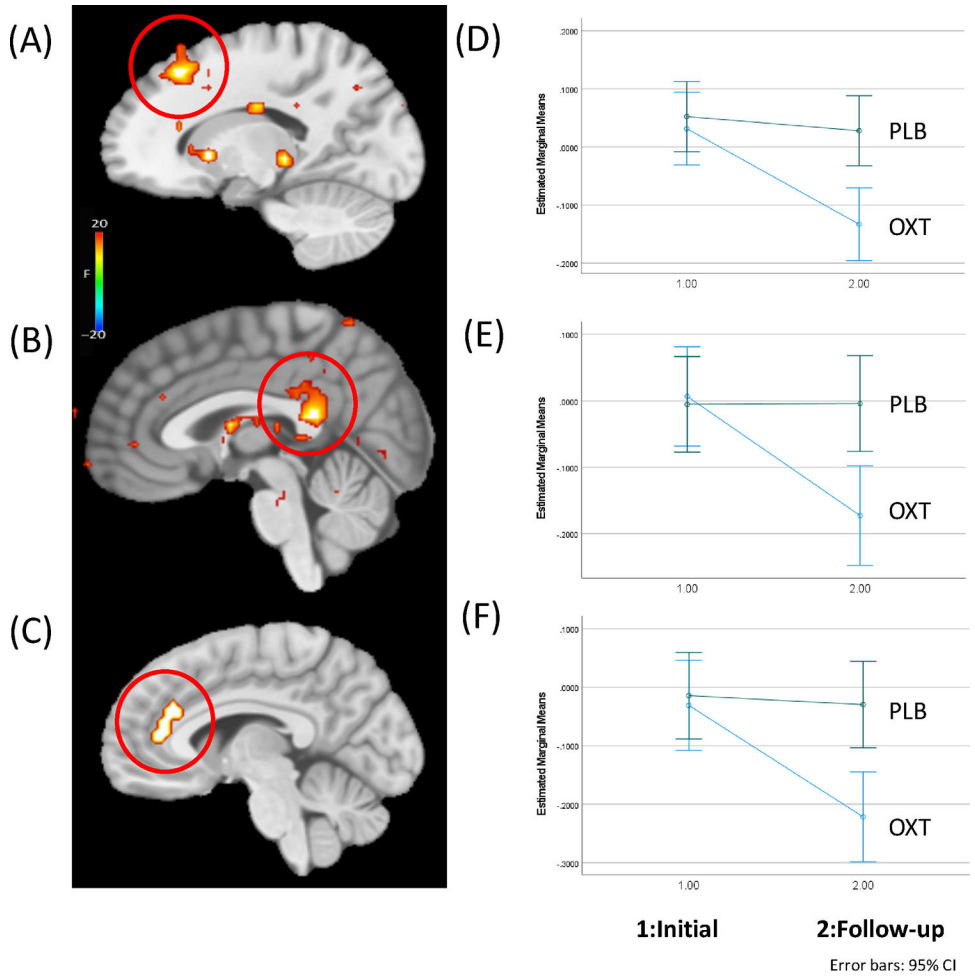

FIGURE 2. Neural level changes with oxytocin intervention[a]

[a]The regions of interest (ROIs) shown are as follows: in panel A, the dorsomedial prefrontal cortex (dmPFC) (coordinates: −13.5, 25.5, 41.5); in panel B, the posterior cingulate cortex (PCC) (coordinates: −1.5, 40.5, 14.5); and in panel C, the anterior cingulate cortex (ACC) (coordinates: −7.5, 28.5, 11.5). The dmPFC and PCC showed significant reduction of blood-oxygen-level-dependent (BOLD) responses to emotional stimuli with intranasal oxytocin compared with placebo, and the ACC showed a significant reduction of BOLD responses to negative emotional stimuli. Panels D–F show the BOLD response parameters.

TABLE 1.

Demographic and clinical characteristics of participants in a study of oxytocin treatment for youths with disruptive behavior disorders[a]

	Oxytocin Treatment Group (N = 25)		Placebo Group (N = 27)		
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**p**
Age (years)	14.5	2.2	14.8	1.9	0.53
IQ	100.7	17.3	99.8	14.5	0.85
	N	**%**	**N**	**%**	**p**
Sex					0.07
Male	17	68.0	24	88.9	
Female	8	32.0	3	11.1	
Primary diagnosis					
ADHD	15	60.0	14	51.9	
DMDD	6	24.0	7	25.9	
Conduct disorder	2	8.0	0	0.0	
Other[b]	2	8.0	6	22.2	
Secondary diagnosis					
ADHD	6	24.0	6	22.2	
Oppositional defiant disorder	13	52.0	15	55.6	
Conduct disorder	3	12.0	1	3.7	
DMDD	5	20.0	7	25.9	
Other[b]	8	32.0	12	44.4	

[a]ADHD=attention deficit hyperactivity disorder; DMDD=disruptive mood dysregulation disorder.

[b]The “other” category includes mood disorder not otherwise specified, bipolar disorder not otherwise specified, anxiety disorder not otherwise specified, generalized anxiety disorder, social phobia, panic disorder, and social anxiety disorder.

TABLE 2.

Symptom profiles at baseline and follow-up among youths with disruptive behavior disorders in a study of intranasal oxytocin treatment[a]

	Oxytocin Treatment Group (N = 25)				Placebo Group (N = 27)					
	Baseline		Follow-Up		Baseline		Follow-Up			
Scale or Subscale	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p	η_p^2
Affective Reactivity Index										
Youth-reported	6.64	2.22	4.24	3.09	6.52	2.67	5.37	3.12	0.12	0.049
Parent-reported	7.52	2.73	4.32	2.67	8.67	1.98	6.07	3.44	0.53	0.008
Inventory of Callous-Unemotional Traits										
Youth-reported	27.14	10.07	25.55	9.44	27.39	9.35	25.89	9.92	0.96	0.000
Parent-reported	35.13	12.25	32.24	11.67	35.14	8.93	32.85	12.52	0.80	0.001
Reactive-Proactive Aggression Questionnaire										
Youth-reported	15.40	5.78	9.92	7.43	16.38	7.71	13.00	6.51	0.15	0.041
Parent-reported	20.64	7.09	12.08	6.95	22.33	6.45	15.87	10.25	0.37	0.016
Reactive aggression										
Youth-reported	12.36	3.97	8.08	5.26	12.56	5.25	10.30	4.52	0.10	0.053
Parent-reported	15.25	3.76	9.52	4.45	16.04	3.71	11.78	6.46	0.29	0.023
Proactive aggression										
Youth-reported	3.04	2.73	1.82	2.66	3.80	2.82	2.69	3.37	0.86	0.001
Parent-reported	5.40	3.82	2.60	2.96	6.30	3.11	4.11	4.41	0.59	0.006
Children's Global Assessment of Severity	40.00	7.31	48.60	7.84	38.67	4.46	43.59	6.73	0.06	0.072
CGI severity score	4.44	0.58	3.40	0.65	4.59	0.69	4.04	0.81	0.03	0.093
CGI improvement score			2.72	0.79			3.33	1.07	0.024	

[a]CGI=Clinical Global Impressions scale.

TABLE 3.

Brain regions showing significant interactions

Interaction and Region[a]	Coordinates of Peak Activation[b]							
	Side	BA	x	y	z	F	Voxels	η^2
Group×time×condition								
Dorsomedial frontal gyrus	Left	8	−13.5	25.5	41.5	15.63	98	0.183
Posterior cingulate cortex	Left	29	−1.5	−40.5	14.5	15.25	102	0.136
Fusiform gyrus	Right	37	31.5	−46.5	−9.5	12.65	27	0.102
Caudate	Right		16.5	19.5	8.5	12.65	38	0.100
Caudate	Left		−10.5	10.5	2.5	18.97	36	0.098
Thalamus/anterior nucleus	Left		−1.5	−1.5	11.5	18.00	46	0.172
Group×time×condition×emotion								
Anterior cingulate cortex ROI	Left	24	−7.5	28.5	11.5	6.68	59	0.164

[a]Regions are based on the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/). BA=Brodmann area; ROI = region of interest.

[b]Based on the Tournoux and Talairach standard brain template.