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Archival Report

Losing Control: Prefrontal Emotion Regulation Is Related to Symptom Severity and Predicts Treatment-Related Symptom Change in Adolescent Girls With Conduct Disorder

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ABSTRACT

BACKGROUND: Emotion regulation skills are linked to corticolimbic brain activity (e.g., dorsolateral prefrontal cortex [dlPFC] and limbic regions) and enable an individual to control their emotional experiences, thus allowing healthy social functioning. Disruptions in emotion regulation skills are reported in neuropsychiatric disorders, including conduct disorder or oppositional defiant disorder (CD/ODD). Clinically recognized means to ameliorate emotion regulation deficits observed in CD/ODD include cognitive or dialectical behavioral skills therapy as implemented in the START NOW program. However, the role of emotion regulation and its neural substrates in symptom severity and prognosis following treatment of adolescent CD/ODD has not been investigated.

METHODS: Cross-sectional data including functional magnetic resonance imaging responses during emotion regulation (N = 114; average age = 15 years), repeated-measures assessments of symptom severity (pretreatment, posttreatment, long-term follow-up), and functional magnetic resonance imaging data collected prior to and following the START NOW randomized controlled trial (n = 44) for female adolescents with CD/ODD were analyzed using group comparisons and multiple regression.

RESULTS: First, behavioral and neural correlates of emotion regulation were disrupted in female adolescents with CD/ODD. Second, ODD symptom severity was negatively associated with dlPFC/precentral gyrus activity during regulation. Third, treatment-related symptom changes were predicted by pretreatment ODD symptom severity and regulatory dlPFC/precentral activity. Additionally, pretreatment dlPFC/precentral activity and ODD symptom severity predicted long-term reductions in symptom severity following treatment for participants who received the START NOW treatment.

CONCLUSIONS: Our findings demonstrate the important role that emotion regulation skills play in the characteristics of CD/ODD and show that regulatory dlPFC/precentral activity is positively associated with treatment response in female adolescents with CD/ODD.

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Emotion regulation skills describe a person's ability to control the intensity, length or extent of an emotional experience through explicit and implicit regulatory processes (1,2). In line with a multilevel framework, emotion regulation may be conceptualized in terms of emotion regulatory goals (implicit to explicit) or the emotion change processes ranging from more automatic to controlled (3). Higher-order emotion regulation skills, including cognitive reappraisal, are typically attained in the period from adolescence to young adulthood (2,4,5). An increase in emotion regulatory control is thereby paralleled by age-appropriate behavioral and social development. However, emotion regulation deficits are linked to different neuropsychiatric disorders, such as adolescent conduct disorder (CD) or oppositional defiant disorder (ODD) (6–8).

Adolescent CD is characterized by severe antisocial and aggressive behavior and violates the rights of others through actions that are clearly beyond age-appropriate norms (6,9). Disruptive behaviors range from oppositional and defiant symptoms, which are characterized as a form of acting out (e.g., temper outbursts, arguing, or becoming easily annoyed with others), to more severe antisocial tendencies (e.g., theft, violence, or other crimes) (9,10). ODD manifests as a recurrent pattern of developmentally inappropriate defiant and disobedient behaviors, although it is considered less severe in its antisocial nature and more strongly characterized by reactive and impulsive tendencies (8,9). While some studies have found that ODD symptoms preceded later diagnoses of CD (11–14), others have not found this pattern (14). The lifetime prevalence

of ODD and CD ranges between 2% and 14% and 2% and 16%, respectively (8). CD/ODD is more prevalent in males than females [with a ratio of ∼3:1 (15)] and can lead to significant personal (e.g., academic disruptions, increased likelihood for comorbidity, relationship problems), societal (e.g., conflicts with the law), and economic (e.g., societal costs) consequences (6,16). While the prevalence is higher in males, symptom progression and associated psychosocial adjustment problems are often more severe in females (17). However, research findings, particularly intervention research, has been dominated by knowledge generated by studying males with CD/ODD (18). Notably, up to 60% of all adults receiving any mental health diagnosis report a prior history of ODD or CD (19).

Disruptive behaviors associated with CD/ODD are a leading cause of referral to mental health clinics among adolescents (20). This highlights the urgent need for evidence-based treatments to ameliorate associated behavioral emotion regulation deficits. Clinically recognized means of supporting emotion regulation skills are at the core of different treatment programs, including parental coaching, cognitive behavioral skills training, and dialectical behavioral therapy (21–23). Their effectiveness for the treatment of disruptive behaviors has been confirmed by randomized controlled trials (RCTs) and meta-analytic evidence (10,18,24,25). One exemplary skills training program that integrates aspects of cognitive behavioral and dialectical behavioral therapy is START NOW (18,22). This program has been successfully implemented to support populations struggling with antisocial and disruptive behaviors (22,26) and was specifically adapted for female adolescents with CD/ODD (18). A fundamental idea that is included in the START NOW program training builds on Dodge's social information-processing model, which describes how children process different experiences (27). Emotional, physiological, and behavioral reactions to emotion-eliciting events are processed by a sequence of cognitive processes, which may include cognitive reappraisal [i.e., altering the interpretation of an emotional situation by changing one's thinking about the event (27,28)]. It has been suggested that adolescents who show disruptive behaviors perceive, interpret, and act on social situations through means that increase the likelihood of aggression (29). Cognitive behavioral approaches, including START NOW, aim to cause change in individuals' disruptive behaviors by facilitating increased use of emotion regulation–related mental strategies, including cognitive reappraisal (30).

Mastery of higher-order emotion regulatory skills has been linked to the functional and structural maturation of the corticolimbic circuitry (4,31,32). The corticolimbic circuitry forms the brain's emotion processing and regulatory system and includes limbic, middle temporal, and prefrontal brain regions. While emotion evaluation and integration are commonly linked to limbic regions (e.g., amygdala, ventral striatum, hippocampus), emotion regulation and higher-order control are more strongly associated with prefrontal brain areas [e.g., dorsolateral prefrontal cortex (dlPFC)] or temporoparietal regions (5,33,34). Meta-analytic studies that have investigated the neural correlates of emotion regulation have confirmed that across different tasks and stimuli, the prefrontal cortex (middle, ventral, and dlPFC) and left temporoparietal regions are most consistently recruited (31,35–37). The reactivity of limbic emotion evaluation regions is thereby modulated as a consequence of the employed regulatory control (36,38). Emotion regulation deficits have been associated with alterations in corticolimbic brain structure, function, or connectivity. Alterations have been reported for different childhood psychopathologies [e.g., depression, anxiety, or bipolar disorder (10,39–41)], including disruptive behaviors (8) or adolescent CD/ODD (7,10,42). For example, we previously demonstrated hypoactivation in the dlPFC and middle temporal regions and reduced prefrontal-limbic connectivity during emotion regulation in girls with CD (7).

To summarize, behavioral and neural correlates of emotion regulation skills are at the core of healthy socioemotional development, and altered emotion regulation has been reported in different neuropsychiatric disorders, including CD/ODD (2,4–9). The development of effective treatment programs for CD/ODD is of utmost importance to reduce the exceptionally high risk of short- and long-term negative outcomes (43). However, the precise interplay between behavioral and neural characteristics associated with emotion regulatory deficits observed in adolescents with CD/ODD and possible therapy-induced neural and behavioral changes have not been investigated. We used cross-sectional behavioral and neuroimaging data obtained from a European multisite study including female adolescents with CD/ODD and typically developing (TD) adolescents and capitalized on an RCT that was designed to improve emotion regulation ability (https://cordis.europa.eu/project/id/602407/reporting/de).

First, previously identified neural correlates and alterations during emotion regulation in girls with CD/ODD compared with TD control participants (7) were tested and described for the current, extended sample (N = 114), including overlap with past participants (7), but with almost double the number overall (Figure 1). Consistent with Raschle *et al.* (7), emotion regulation difficulties and neural hypoactivation were expected when comparing girls with CD/ODD to TD girls. We predicted that TD adolescents would display activation increases in dlPFC/precentral and mid-temporal/angular gyrus regions during emotion regulation, while adolescent girls with CD/ODD would recruit the same regions to a lesser extent. Our own work and past and recent meta-analytic findings that have synthesized the neural correlates of emotion regulation (7,35,36,44,45) particularly highlight the role of dlPFC/precentral regions. Here, we aimed to further test (main aim 1) (Figure 1) whether CD or ODD symptom severity is associated with neural activity during emotion regulation in left hemisphere dlPFC/precentral regions in females with CD/ODD. We expected that symptom severity would be negatively associated with neural activity in these regions.

Secondly, we have previously tested the efficacy of the cognitive behavioral skills training program START NOW, which aims to increase emotion regulation skills and decrease symptom severity in female participants with CD/ODD. Results in 127 females with CD/ODD demonstrated symptom severity reductions in all participants who completed treatment (START NOW or treatment as usual [TAU]) directly following treatment (T2). At a 12-week follow-up after the end of treatment (T3), only participants who received START NOW training continued to display lower symptom severity (18). Here, CD/ODD symptom severity changes following an RCT were re-evaluated for a subgroup of 44 participants who also completed functional

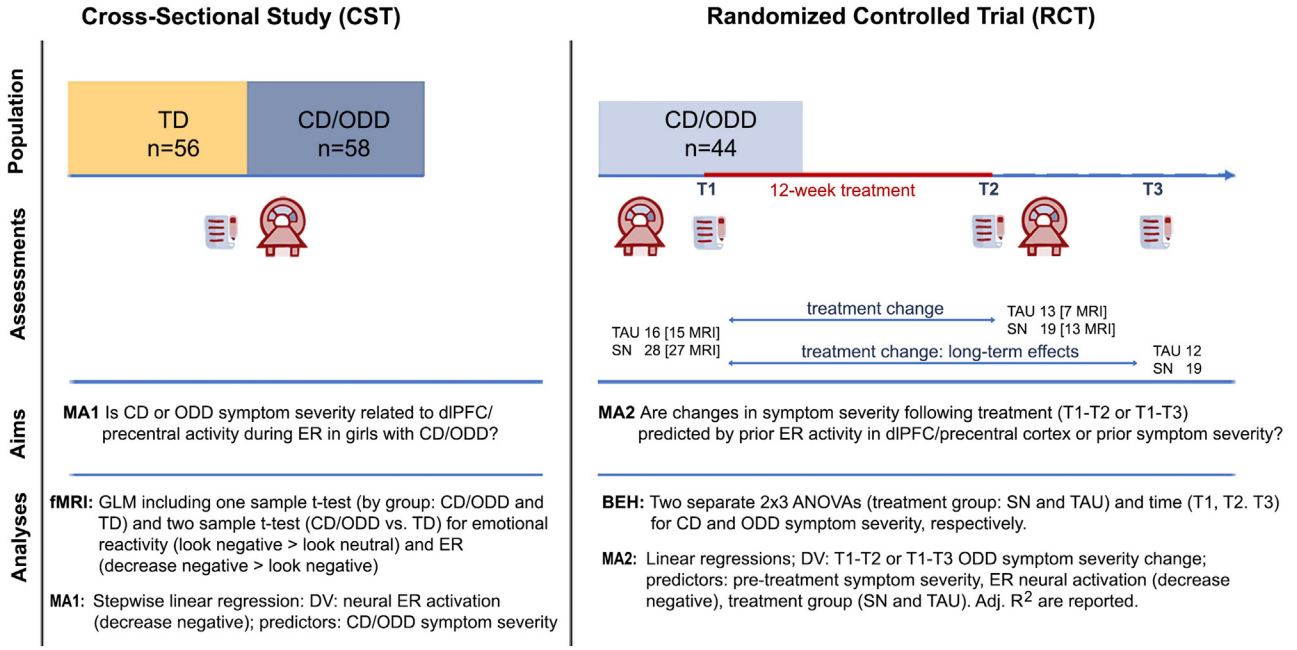

Figure 1. Overview of the research design, including study population, behavioral, and neuroimaging data obtained in the cross-sectional study (CST) (*N* = 114 participants, 58 of whom had conduct disorder [CD] or oppositional defiant disorder [ODD]) and randomized controlled trial (RCT) study subgroup (*n* = 44, all with CD/ODD), main aims (MAs), and analytic approach. The CST and RCT populations were derived from the FemNAT-CD consortium study and include mid- to postpubertal females who completed a functional magnetic resonance imaging (fMRI) emotion regulation (ER) task and behavioral assessments. For a subgroup of adolescents with CD/ODD, fMRI data was further available prior to or following an RCT that also included repeated-measures clinical testing for symptom severity during treatment [consistent with Stadler *et al.* 2023 (18); T1: CD/ODD participants' clinical and fMRI data prior to RCT treatment; T2: clinical and fMRI data acquired directly following RCT treatment; and T3: clinical data acquired 12 weeks following the end of RCT treatment. The data reported are the number of participants for whom behavioral/clinical data (population count) or fMRI data (as listed in brackets for START NOW (SN) and treatment as usual (TAU) were available. Adj, adjusted; ANOVA, analysis of variance; dlPFC, dorsolateral prefrontal cortex; DV, dependent variable; GLM, general linear model; TD, typically developing.

magnetic resonance imaging (fMRI) during an emotion regulation task prior to or following the RCT. Here, we aimed to follow up on significant group by time treatment effects for our second main aim of testing whether pretreatment CD/ODD symptom severity, pretreatment dlPFC/precentral activation during emotion regulation, or treatment group (START NOW/TAU) would predict symptom severity changes from pretreatment levels to scores obtained directly following (T1–T2) and 12 weeks posttreatment (T1–T3). We hypothesized that pretreatment regulatory dlPFC/precentral activity would represent a biomarker that would be positively related to treatment response in addition to pretreatment symptom severity. Moreover, we hypothesized that the explained variance would be higher for individuals receiving START NOW than for individuals receiving TAU (Figure 1).

METHODS AND MATERIALS

Ethics

Local ethics committees reviewed and approved the study at each of the 3 sites (Ethics Committees of Northwest and Central Switzerland in Basel, the Medical Faculty of Goethe University Frankfurt, and the Medical Faculty of RWTH Aachen University). Adolescents and their parents or caregivers provided informed assent and consent, respectively.

Study Groups

Cross-Sectional Study Group. Data from 114 mid- to postpubertal (46) female adolescents (58 CD/ODD; age range: 13–18 years) (see design in Figure 1 and group characteristics in Table 1) were obtained using an adapted fMRI emotion regulation by cognitive reappraisal task (7,47). Behavioral testing and clinical interviews were conducted in line with previous work (18,22). Fifty-nine (30 CD/ODD) cross-sectional study participants were included in the previous article by Raschle *et al.* (7), and clinical scores obtained during the RCT (i.e., symptom severity) were included in Stadler *et al.* (18). Present and past CD/ODD symptom severity and comorbidities were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (48), which was completed by both the participant and a parent or youth welfare social workers (18). Psychopathic and callous-unemotional traits were assessed using the self-report Youth Psychopathic Traits Inventory (49), while habitual use of cognitive reappraisal and expressive suppression were tested using the Emotion Regulation Questionnaire (50). Participants' socioeconomic status was close to population average levels, with mean ± SD = 0.055 ± 1.033 and 0.345 ± 0.967

Table 1. Group Characteristics of TD Adolescents and Adolescents With a Diagnosis of CD/ODD Included in the CST and RCT (Including SN and TAU Subgroups)

	CST			RCT			
Characteristic	TD, *n* = 56	CD/ODD, *n* = 58	CD/ODD vs. TD, *p* Value	CD/ODD at T1, *n* = 44	CD/ODD, SN, *n* = 28	CD/ODD, TAU, *n* = 16	SN vs. TAU, *p* Value
Age, Years	15.48 ± 1.45 (56)	15.12 ± 1.16 (58)	.144	15.02 ± 1.3 (44)	15.46 ± 1.17 (28)	14.25 ± 1.24 (16)	.003
IQ							
Performance IQ	103.7 ± 14.41 (56)	102.93 ± 15.67 (58)	.746	99.9 ± 15.7 (43)	100.93 ± 16.00 (27)	98.13 ± 15.59 (16)	.578
Verbal IQ	106.02 ± 14.93 (56)	94.83 ± 14.26 (58)	<.001	91.05 ± 12.5 (43)	87.96 ± 9.73 (27)	96.25 ± 15.00 (16)	.033
Total IQ	105.06 ± 11.66 (56)	99.10 ± 12.89 (58)	.010	95.7 ± 11.5 (43)	94.74 ± 10.70 (27)	97.31 ± 13.03 (16)	.486
CD/ODD and Comorbidity, DSM-5							
CD	–	55/58 (94.8%)		35/44 (79.5%)	22/28 (78.6%)	13/16 (81.3%)	.837
ODD	–	52/58 (89.7%)		33/44 (75%)	21/28 (75%)	12/16 (75%)	>.999
Attention-deficit/hyperactivity disorder	–	15/58 (25.9%)		12/38 (31.6%)	7/23 (30.4%)	5/15 (33.3%)	.926
Major depressive disorder	–	13/53 (24.5%)		8/37 (21.6%)	7/22 (30.4%)	1/15 (6.7%)	.107
Generalized anxiety disorder	–	2/54 (3.7%)		2/38 (5.3%)	0/28 (0%)	2/15 (13.3%)	.075
Posttraumatic stress disorder	–	7/55 (12.7%)		6/39 (14.3%)	5/24 (20.8%)	1/15 (6.7%)	.105
Alcohol abuse	–	3/53 (5.6%)		1/22 (4.5%)	1/15 (6.7%)	1/15 (6.7%)	.533
Substance dependence	–	4/53 (7.5%)		4/37 (10.8%)	3/22 (13.6%)	1/15 (6.7%)	.620
Symptom Severity[a]							
ODD, current	N/A	4.88 ± 2.31		4.91 ± 2.11	3.57 ± 1.73 (28)	3.06 ± 1.77 (16)	.947
CD, current	N/A	5.24 ± 2.70		3.38 ± 1.74	4.89 ± 2.06 (28)	4.94 ± 2.27 (16)	.357
YPI							
Callousness, sum	8.07 ± 2.35 (54)	9.36 ± 2.71 (50)	.005	8.7 ± 2.4 (35)	9.23 ± 2.54 (22)	7.77 ± 1.96 (13)	.085
Unemotionality, sum	10.17 ± 2.73 (54)	11.38 ± 2.71 (50)	.013	11.4 ± 2.6 (35)	11.27 ± 2.66 (22)	11.54 ± 2.63 (13)	.776
Total, sum	89.83 ± 17.78 (54)	106.68 ± 21.31 (50)	<.001	103.4 ± 20.4 (35)	104.32 ± 21.08 (22)	101.92 ± 20.02 (13)	.743
ERQ							
Reappraisal	27.8 ± 5.6 (54)	21.7 ± 8.1 (32)	<.001	20.5 ± 9.6 (15)	19.71 ± 13.02 (7)	21.13 ± 6.29 (8)	.789
Suppression	13.9 ± 4.8 (54)	15.4 ± 5.7 (32)	.197	13.9 ± 4.4 (15)	14.00 ± 4.47 (7)	13.75 ± 4.65 (8)	.917
In-Scanner Performance							
Reactivity	1.25 ± 0.59 (56)	0.89 ± 0.65 (58)	.002	1.07 ± 0.66 (44)	0.96 ± 0.69 (28)	1.19 ± 0.68 (16)	.293
Regulation success	0.60 ± 0.49 (56)	0.27 ± 0.34 (58)	<.001	0.31 ± 0.39 (44)	0.23 ± 0.36 (28)	0.34 ± 0.30 (16)	.329

Values are presented as mean ± SD (*n*) or *n* (%).

CD, conduct disorder; CST, cross-sectional study; ERQ, Emotion Regulation Questionnaire; ODD, oppositional defiant disorder; RCT, randomized controlled trial; SN, START NOW; T1, pretreatment; TAU, treatment as usual; TD, typically developing; YPI, Youth Psychopathic Traits Inventory.

[a]Current, referring to the past 6 months.

for TD participants and participants with CD/ODD, respectively (for details on the socioeconomic status construct, see Supplement 1).

Randomized Controlled Trial. A subgroup of 44 participants from a prospective, confirmatory, cluster-randomized, multicenter, international phase III trial with 2 parallel CD/ODD patient groups (N = 127), including a START NOW intervention versus standard care/TAU group, were included in this study. The completed preregistered clinical study aimed to test the efficacy of START NOW, a cognitive behavioral and dialectical behavior therapy–oriented skills training program that targets enhancement of emotion regulation skills. TAU corresponded to standard care, excluding any group-based psychotherapeutic programs [e.g., cognitive behavioral or dialectical behavioral therapy according to the RCT protocol (18,22)]. Participants were recruited for the treatment study from youth welfare institutions and were included when fMRI data pre- or post-RCT were available. Recruitment and retention of participants with CD/ODD is highly challenging, and a primary focus was placed on the RCT study rather than the optional fMRI study. Data from the RCT participants with CD/ODD who completed fMRI in addition to the RCT study should be considered with caution because self-selection biases may have occurred. Forty-two neuroimaging datasets were available prior to the start of the RCT (T1; n = 42; 15 TAU/27 START NOW) (Figure 1), and 20 were available following treatment (T2; n = 20; 7 TAU/13 START NOW). Continuous reports on CD/ODD symptom severity were available for all 44 participants.

For DSM-5 diagnostic criteria and CD/ODD symptom severity, see Table 2.

Neuroimaging

fMRI Task. Participants completed an adapted version of the fMRI emotion regulation task by use of cognitive reappraisal as developed by Ochsner *et al.* (1,47,51) and previously described in Raschle *et al.* (7). Each trial started with an instruction cue that indicated whether participants had to look at the presented picture (neutral or negative) or downregulate the emotions evoked by a negative picture. Emotion regulation required participants to reduce the intensity of the emotional experience during negative image processing by using reappraisal techniques [see (7)]. During a training session prior to fMRI scanning, participants learned to use cognitive reappraisal to reinterpret the observed scenes and practiced this strategy in real-time with a trained study team member. Following each of 12 (50% decrease/50% look) practice trials, participants were asked to verbalize their reappraisal strategy to verify that no alternative strategy (e.g., looking away or active avoidance) was used. Additionally, to reduce potential expectation-based response bias, the research team members assured the participants that there were no right or wrong answers during the affect rating phase and asked the participants to try to indicate their actual feelings and not what they thought was expected given a specific picture or instruction. During the experiment, each trial started with a 2500-ms instruction cue (to look at an image or decrease-negative affect) followed by a negative or neutral image presented for 10,000 ms, in-scanner self-report rating for 5000 ms, and a 2500-ms relaxation period that concluded the trial. Participants reported on the strength of the negative affect following each trial (Likert scale from 1 = lowest to 4 = highest). Data from 48 trials (16 trials per task condition: look-neutral, look-negative, decrease-negative) were collected over 2 runs, with each trial lasting about 8 minutes.

fMRI In-Scanner Affect Ratings. Affect ratings reflecting experienced emotion intensity by condition (look-negative, look-neutral, decrease-negative) were reported inside the scanner on a 1- to 4-point Likert scale following each trial. Within-group differences between look-negative versus look-neutral and look-negative versus decrease-negative trials were assessed to test emotional reactivity and emotion regulation success through paired-samples t tests within the CD/ODD and TD groups. Independent t tests (CD/ODD vs. TD) were used to evaluate group differences in emotional reactivity and emotion regulation success.

fMRI Analyses. Standard fMRI acquisition protocols were implemented. Site-specific scanner details, qualification procedures, and standard preprocessing, including fMRI quality control, are described in Supplement 2. Regressors of interest

Table 2. Criteria for DSM-5 Diagnosis of CD and ODD

	No. of Possible Symptoms	Symptoms	No. of Symptoms Required	
			Past 6 Months	Past 12 Months
CD	15	Lies; truant; initiates physical fights; bullies, threatens, or intimidates; nonaggressive stealing; vandalism; breaking and entering; aggressive stealing; fire setting; often staying out at night; run away overnight; use of a weapon; physical cruelty to persons; forced sexual activity; cruelty to animals	1	3 or more
ODD	8	Loses temper; argues a lot with adults; disobeys rules; easily annoyed or angered; angry or resentful; spiteful and vindictive; annoys people on purpose; blames others for own mistakes	4	–

Criteria for a DSM-5 diagnosis of CD were met when at least 3 or more CD symptoms were present consistently over the past 12 months, with at least 1 present during the past 6 months, while the criteria for a DSM-5 diagnosis of ODD were met when at least 4 ODD symptoms were present for the past 6 months [based on K-SADS (49)].

For each time point and participant, the raw number of current CD and ODD symptoms were combined to yield CD and ODD severity scores, respectively. Items were rated from 0 = "no information," 1 = "not present," 2 = "subthreshold," to 3 = "threshold" by participant and primary caregiver and the combined raters' score was dichotomized to 0 = "symptom not present" (rating 0, 1, 2) vs. 1 = "symptom present" (rating 3) and summed for symptom severity.

CD, conduct disorder; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; ODD, oppositional defiant disorder.

were created by condition using a boxcar function for look-neutral, look-negative, and decrease-negative trials. Consistent with previously presented data from a smaller subgroup of girls with CD/ODD and TD participants (n = 59; 30 CD/ODD) (7) and to facilitate future meta-analytic efforts, the original contrasts including look-negative > look-neutral (emotional reactivity), decrease-negative > look-negative (emotion regulation without automatic baseline processes), and modulation by emotion regulation (decrease-negative < look-negative) were built and are reported for the extended group of 114 participants whose data were analyzed for the current study.

Regions of Interest. Mean parameter estimate in regions of interest (ROIs) including the left dlPFC/precentral gyrus and left mid-temporal/angular gyrus region were extracted for contrasts and regressors of interest using the MarsBaR toolbox (http://marsbar.sourceforge.net/). Using the procedure described in our previous publication (7), 10-mm spherical ROIs centered around the left middle temporal/angular gyrus (Montreal Neurological Institute coordinates: −42, −60, 44) and left dlPFC/precentral gyrus (Montreal Neurological Institute coordinates: −44, 10, 46) were created (7,35). Following the whole-brain findings, the left precuneus was added as a post hoc anatomically defined ROI using the Automated Anatomical Labeling atlas (52). Notably, the choice of ROIs, particularly the dlPFC/precentral gyrus, followed our 2019 publication (7), which included half of the participants from the current article, but this choice is also consistent with more recent meta-analytic work that has investigated the neural correlates of emotion regulation and cognitive reappraisal (36,44,45).

All neuroimaging analyses included site, age, and IQ (total score) as covariates of no interest (associations between IQ, emotion regulation, emotional reactivity, and CD/ODD symptom severity are reported in more detail in Supplement 4). Whole-brain results are presented using a $p < .001$ cluster-building threshold and $p < .05$ cluster-level familywise error correction. For regressions, adjusted R^2 values are reported (thus considering addition of predictors to the model), and covariates of no interest included group, site, age, and IQ.

RESULTS

Behavioral Performance and Neural Correlates of Emotion Regulation in CD/ODD and TD Adolescents

fMRI In-Scanner Affect Ratings. Females with CD/ODD had significantly lower scores than TD adolescents on behavioral ratings of emotional reactivity and regulation success (both ps < .001) (Table 1). However, paired t-test within-group comparisons for CD/ODD and TD adolescents' emotional reactivity and regulation success revealed higher valence ratings following negative than neutral stimuli and lower valence reports following regulation than in the control condition (look-negative) in each group individually. Thus, both groups experienced stronger emotions when viewing negative than neutral images and reported successful downregulation of negative affect during decrease-negative trials (Figure 2).

Whole-Brain Findings. One-sample t tests confirmed that emotion regulation (based on the contrast look-negative < decrease-negative) in TD adolescents was associated with activation increases in regulatory control regions (1,7,34–36), including dlPFC/precentral areas (superior, inferior, and middle frontal gyri) and middle temporal (including angular gyrus) and parietal regions (including precuneus and posterior cingulate gyrus). Adolescents with CD/ODD did not show significant

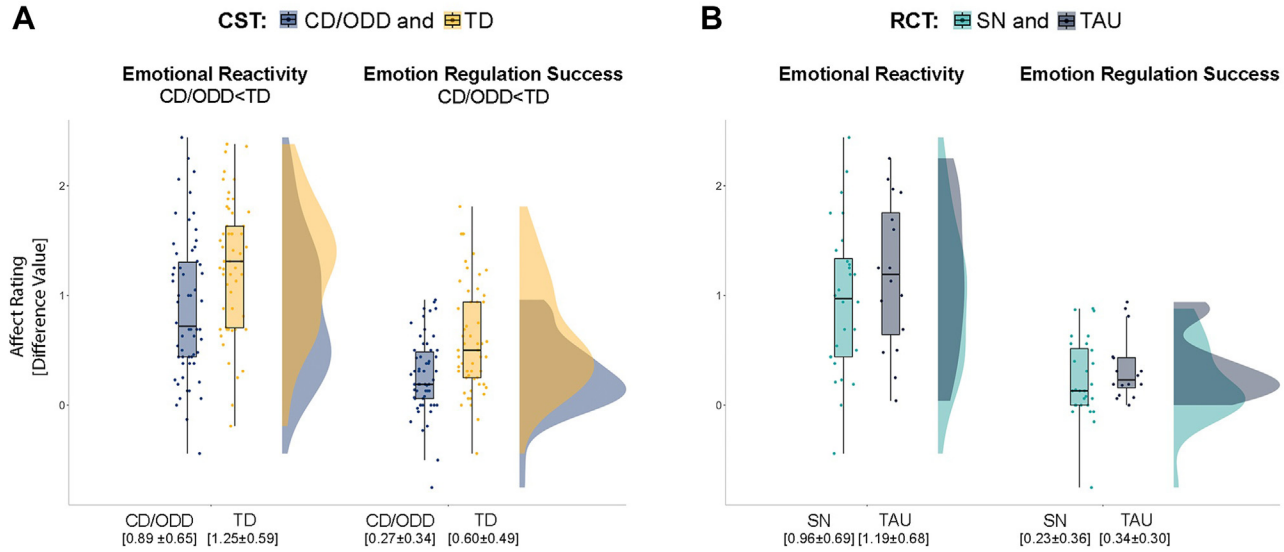

Figure 2. Self-reported in-scanner affect ratings (emotion intensity) for conduct disorder (CD) or oppositional defiant disorder (ODD) and typically developing (TD) participants. Raincloud plots (53) for **(A)** cross-sectional study (CST) participants, including CD/ODD and TD participants, and for **(B)** randomized controlled trial (RCT) participants at T1, including CD/ODD participants in the START NOW (SN) or treatment-as-usual (TAU) groups, with respect to emotional reactivity (difference score between look-negative and look-neutral trials) and emotion regulation success (difference score between look-negative and decrease-negative trials).

neural activation for the look-negative < decrease-negative contrast in these areas; significant clusters were restricted to visual areas. Modulation by emotion regulation (i.e., look-negative > decrease-negative) in TD participants and participants with CD/ODD was only observed in occipital areas. Group comparisons revealed significant differences for emotion regulation (i.e., look-negative < decrease-negative for CD/ODD < TD) in the left dlPFC/precentral gyrus, mid-temporal/angular gyrus, and posterior cingulate/precuneus (Table 3 and Figure 3). Comparable with earlier reports in a smaller subgroup (7), emotional reactivity (look-negative > look-neutral) was reflected by the engagement of prefrontal and limbic regions for the TD and CD/ODD groups, and there were no regions that were more active in TD participants than in participants with CD/ODD (Supplement 5). Significant interaction effects for group (CD/ODD and TD) by condition (emotional reactivity and emotion regulation) are also reported using an *F* test in Supplement 6.

All whole-brain neuroimaging findings are provided through neurovault: https://identifiers.org/neurovault.collection:17764.

ROI-Based Findings. ROI extractions and visualizations for left dlPFC/precentral, middle temporal/angular gyrus, and precuneus confirmed hypoactivations in these regions for participants with CD/ODD compared with TD participants during emotion regulation (decrease-negative > look-negative) (Figure 3C–E). Within-group findings for the individual regressors look-negative and decrease-negative confirmed significantly greater activation in all emotion regulatory ROIs during decrease-negative trials than look-negative trials in TD participants but not in participants with CD/ODD. Additionally, testing between-group differences for individual regressors indicated that left middle temporal/angular gyrus activity was significantly lower for participants with CD/ODD than for TD participants during emotion regulation (decrease-negative) trials (Figure 3D).

Table 3. Peak Activations During Emotion Regulation (Decrease-Negative > Look-Negative) and Modulation by Emotion Regulation (Decrease-Negative < Look-Negative) for Female TD and CD/ODD Adolescents

Brain Region Lobe	Area	Side	p_{FWE}	Cluster Size, *k*	*t* (*df*)	MNI Coordinates, mm		
						x	y	z
TD: Activation by ER (Decrease-Neg > Look-Neg)								
Frontal/temporal	Superior/middle/inferior frontal grus, SMA, pre-/postcentral, temporal pole, OFC, insula, ACC, cingulate	Right/Left	<.001	8418	6.21 (1,52)	−42	18	−14
Frontal/temporal	Inferior/middle frontal gyrus, OFC, insula, temporal pole	Right	<.001	944	6.05 (1,52)	38	16	−22
Temporal/occipital/parietal	Middle/superior/inferior temporal, angular, middle/superior/inferior occipital lobe, inferior/superior parietal gyrus, precuneus, cuneus, supramarginal	Left	<.001	4825	5.85 (1,52)	−46	−66	4
Temporal/parietal/occipital	Middle temporal, angular gyrus, inferior parietal, supramarginal, middle occipital, inferior/superior temporal	Right	<.001	1576	5.76 (1,52)	50	−58	0
Parietal	Middle/posterior cingulate, precuneus, pre-/post-/paracentral, SMA	Left/Right	<.001	1781	5.59 (1,52)	−8	−18	40
Temporal	Middle/superior temporal gyrus	Right	.001	288	4.70 (1,52)	58	−32	−4
Temporal	Caudate	Right	.015	166	4.53 (1,52)	20	12	12
Temporal	Caudate, pallidum, thalamus	Left	.011	176	4.31 (1,52)	−14	4	14
TD: Modulation by ER (Decrease-Neg < Look-Neg)								
Occipital	Inferior/middle occipital, calcarine	Right	.043	129	5.31 (1,52)	30	−94	−4
CD/ODD: Activation by ER (Decrease-Neg > Look-Neg)								
Temporal/occipital	Middle/inferior temporal, middle occipital gyrus	Right	.002	252	5.60 (1,54)	50	−74	14
Occipital/temporal	Middle/inferior occipital, middle/inferior temporal gyrus	Left	<.001	473	5.48 (1,54)	−52	−72	6
CD/ODD: Modulation by ER (Decrease-Neg < Look-Neg)								
Occipital	Inferior/middle occipital, furisorm, calcarine	Right	.037	134	4.74 (1,54)	28	92	−6
Occipital	Cuneus, superior occipital, calcarine	Right	.017	161	4.51 (1,54)	14	−90	18
Occipital	Fusiform, cerebellum	Right	.045	127	4.24 (1,54)	24	−48	−24
CD/ODD < TD: Activation by ER (Decrease-Neg > Look-Neg)								
Frontal	Middle/superior frontal gyrus	Left	.001	278	5.03 (1,109)	−26	14	46
Temporal	Middle/superior temporal, Heschl, insula, thalamus	Left	<.001	344	4.69 (1,109)	−30	−30	4
Parietal/limbic	Precuneus, posterior cingulate	Left	.010	344	4.66 (1,109)	−8	−54	28
Parietal/limbic	Mid/posterior cingulate, precuneus	Left	.032	141	4.18 (1,109)	−10	−32	42

All reports based on a cluster-building $p < .001$ and cluster-level FWE–corrected $p < .05$.

ACC, anterior cingulate cortex; CD, conduct disorder; ER, emotion regulation; FWE, familywise error; MNI, Montreal Neurological Institute; Neg, negative; ODD, oppositional defiant disorder; OFC, orbitofrontal cortex; SMA, supplementary motor area; TD, typically developing.

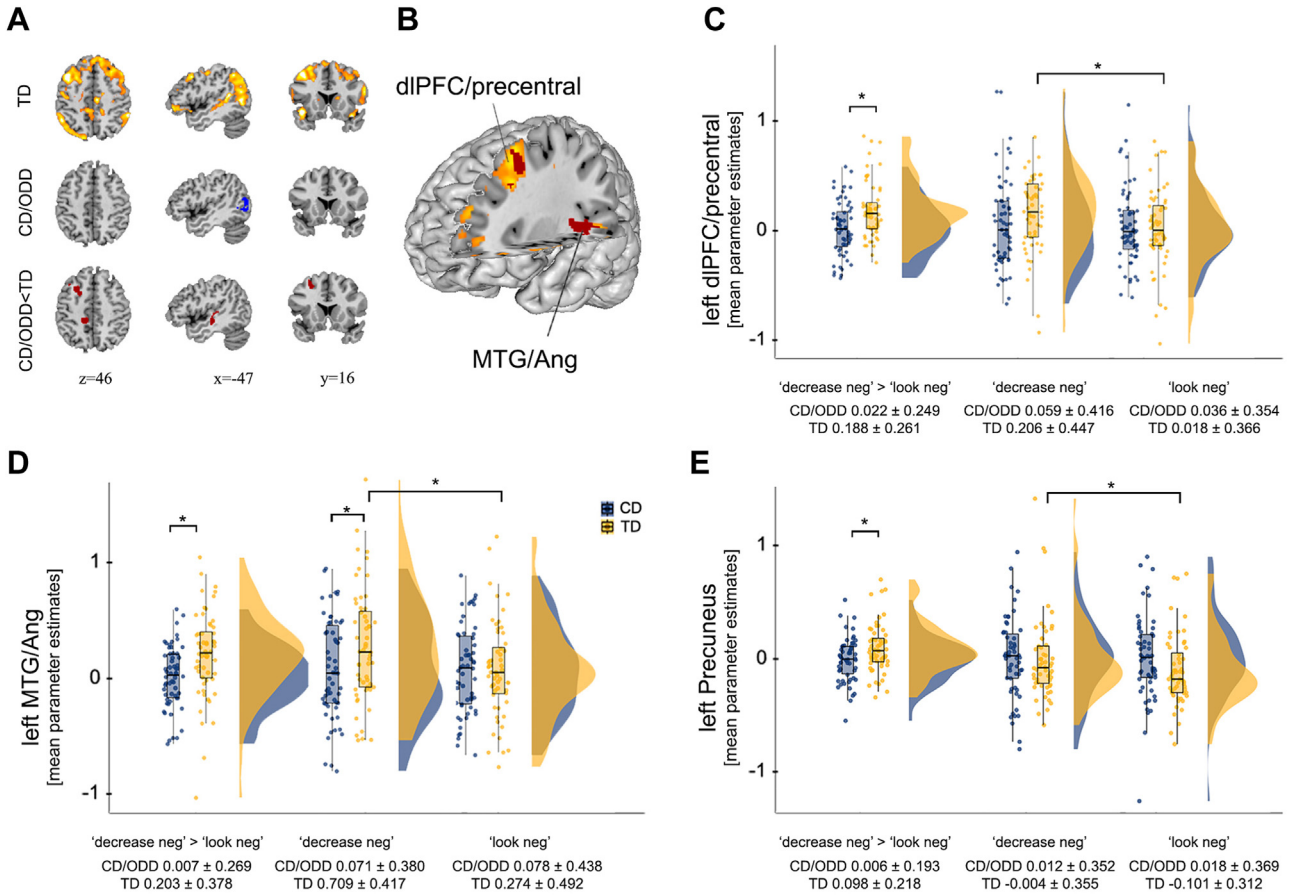

Figure 3. Neural correlates of emotion regulation (decrease-negative > look-negative) in **(A)** typically developing (TD) adolescents, adolescents with conduct/oppositional defiant disorder (CD/ODD), and the direct group contrast (CD/ODD < TD). **(B)** Three-dimensional (3D) rendering of whole-brain results, including sagittal and coronal cuts. Neural activation during emotion regulation (decrease-negative > look-negative) in TD adolescents is represented in yellow-orange colors, and hypoactivations in CD/ODD (from the group comparison CD/ODD < TD) are displayed in red. **(C–E)** Raincloud plots for the **(C)** left dorsolateral prefrontal cortex (dlPFC)/precentral gyrus, **(D)** middle temporal/angular gyrus (MTG/Ang), and **(E)** precuneus. Blue bars and symbols correspond to participants with CD/ODD, and yellow bars and symbols correspond to TD participants, with asterisks indicating significant between-group or within-group differences as indicated by the results of independent-samples *t* tests and paired-samples *t* tests, respectively. The findings were obtained using clusterwise familywise error correction ($p < .05$; cluster-building threshold of $p < .001$).

dlPFC/Precentral Gyrus Activity and CD/ODD Symptom Severity (Main Aim 1)

The stepwise linear regression model used to test main aims 1 and 2 included dlPFC/precentral emotion regulatory activation scores during decrease-negative trials as the dependent variable. This decision was based on evidence of reduced emotion regulatory control in CD/ODD for the contrast decrease-negative > look-negative (removing automatic processes occurring during look-negative) and more variability in the selected regressor (for more on regressor selection, see Supplement 3).

T1 ODD symptom severity was the only significant negative regression-based predictor of T1 dlPFC/precentral gyrus activation related to emotion regulation: decrease-negative, significant at $p = .020$, explained 13.5% of the variance in dlPFC/precentral activation ($F_{1,54} = 4.918$, $p = .031$, $R^2_{adjusted} = 0.135$).

Effects of Time and Treatment Group on CD/ODD Symptom Severity

A 2 × 3 analysis of variance revealed a significant main effect of time but not of group or the interaction between group and time on CD symptom severity (Table 4). Participants demonstrated significant T1 to T2 and T1 to T3 symptom decreases (both *p*s < .001) (Figure 4A).

A 2 × 3 analysis of variance revealed significant main effects of time (T1–T2 decrease [$p < .001$] and T1–T3 decrease [$p = .033$]) and treatment group (START NOW [mean = 3.284 ± 0.268] < TAU [mean = 4.351 ± 0.332]; $p = .014$) and a significant interaction between treatment group and time on ODD symptom severity ($F_{2,104} = 3.549$, $p = .032$, $\eta_p^2 = 0.064$) (Figure 4A and Table 4). This interaction was driven by lower ODD symptoms at T3 for START NOW participants than for TAU participants ($F_{1,104} = 11.530$, $p < .001$, $\eta_p^2 = 0.100$).

Table 4. Variation in CD/ODD Symptom Severity as a Factor of Treatment Group and Time

Source of Variation	SS	MS	*F* (*df*)	*p* Value	η^2
CD Symptom Changes					
Treatment group	0.548	0.548	0.267 (1)	.606	0.003
Time	98.009	49.005	23.911 (2)	<.001[a]	0.315
Interaction	6.582	3.291	1.606 (2)	.206	0.030
ODD Symptom Changes					
Treatment group	29.201	29.201	6.251 (1)	.014[a]	0.057
Time	74.637	37.319	7.989 (2)	<.001[a]	0.133
Interaction	33.158	16.579	3.549 (2)	.032[a]	0.064

CD, conduct disorder; MS, mean square; ODD, oppositional defiant disorder; SS, sum of squares.
[a]Significant effects.

dlPFC/Precentral Activity and Prior ODD Symptom Severity Predict Symptom Change (Main Aim 2)

T1 to T2. Linear regression models tested whether treatment effects (ODD symptom T1–T2 change) were predicted by prior symptom severity and neural dlPFC/precentral regulation or depended on group status (START NOW/TAU). Pretreatment ODD symptom severity predicted treatment-related change in ODD symptom severity (34.9% of variability; $p < .001$), while group status did not explain any outcome. Adding dlPFC/precentral regulatory activity increased the explained variance in treatment outcome by an additional 5%, resulting in 39.9% of total variance explained overall ($p = .049$). Both prior symptom severity and dlPFC/precentral regulatory activity were positively associated with treatment outcome (Figure 4C).

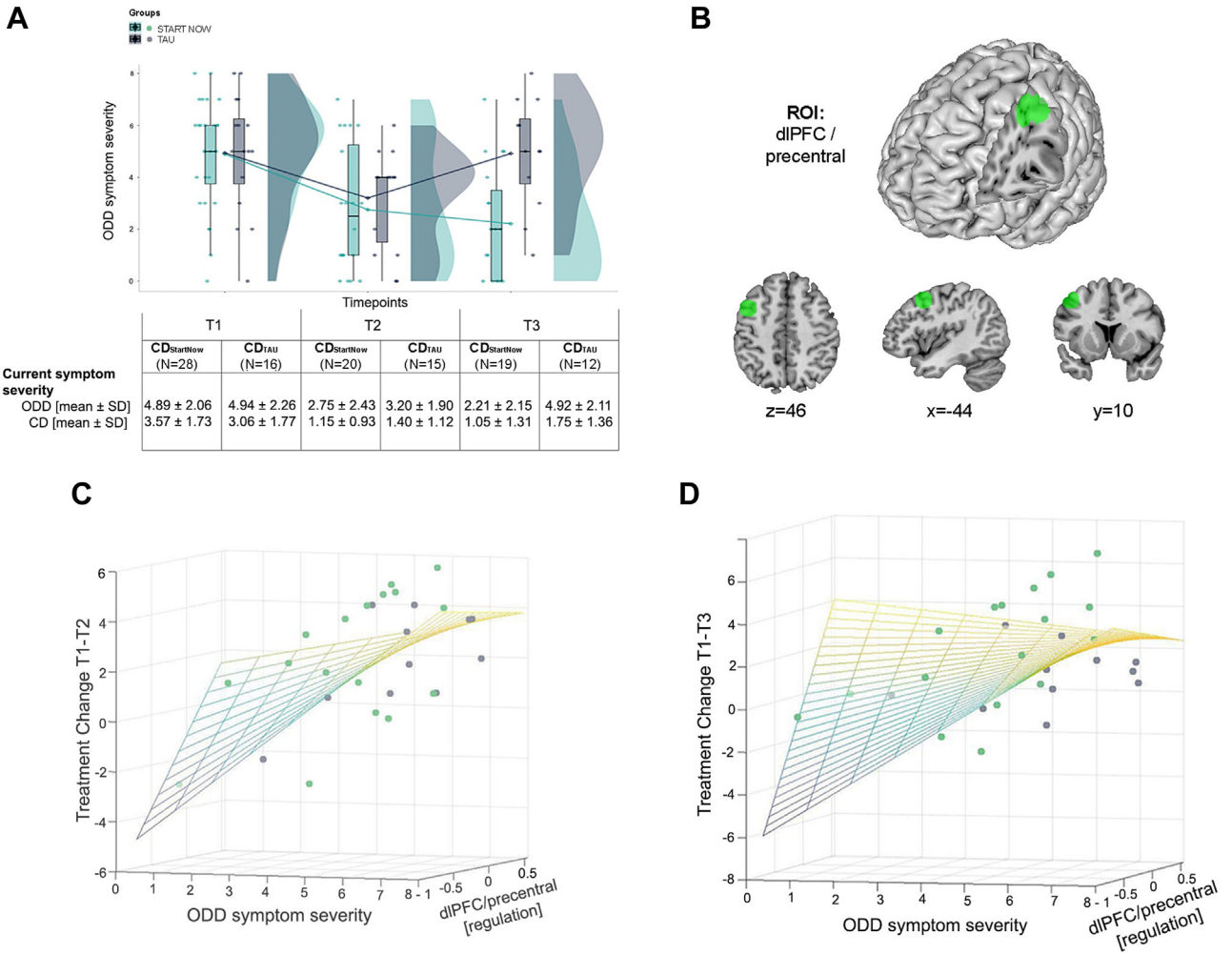

Figure 4. Variations in symptom severity by time and predictors of treatment effect. Raincloud plots **(A)** showing variations in oppositional defiant disorder (ODD) symptom severity by time (T1, T2, T3) for START NOW (green-blue color) and treatment as usual (TAU) participants (gray) are displayed, including descriptive statistics for conduct disorder (CD) and ODD symptom severity below the raincloud plots. **(B)** Green sphere depicting the dorsolateral prefrontal cortex (dlPFC)/precentral region of interest. Three-dimensional (3D) scatterplot for **(C)** short-term ODD symptom severity change (T1–T2; z-axis), which was positively predicted by pretreatment ODD symptom severity (x-axis) and positively predicted by pretreatment neural dlPFC/precentral emotion regulatory activity (y-axis; both at T1) in both START NOW (green dots) and TAU (gray dots) participants (independent of group). **(D)** Long-term ODD symptom severity change (T1–T3; z-axis), which was positively associated with pretreatment ODD symptom severity (T1; x-axis) and positively associated with neural dlPFC/precentral regulatory activity (T1; y-axis), which remained significant for START NOW (green dots), but not TAU (gray dots) participants. ROI, region of interest.

T1 to T3. Reductions in ODD symptoms were significantly predicted by pretreatment ODD symptom severity, group status, and neural dlPFC/precentral regulatory activity. Previous symptom severity explained 23.1% of the variance in the outcome, and group status added another 6.3% (p = .034 and p = .021). Including pretreatment dlPFC/precentral activity increased the explained variance by 16.1% to 45.5% (p = .003). All associations were positive (Figure 4D). Post hoc investigations revealed that pretreatment ODD symptom severity and emotion regulatory dlPFC/precentral activity were significantly associated with long-term treatment outcomes in START NOW only (57.4%; p = .007; with 9.6% of added variance through dlPFC/precentral marker in addition to pretreatment ODD symptom severity alone, which explained 47.8% of the variance with p = .013).

Exploratory Post Hoc Assessments Including fMRI Data Following Treatment (T2)

In Stadler *et al.* (18), we stated that future studies would aim to investigate changes in dlPFC/precentral gyrus functioning following RCT treatment. However, it was challenging to retain participants in the study to complete an additional fMRI session following the RCT. Due to low power, analyses involving fMRI data at T2 (n = 20) are only reported in Supplement 7.

DISCUSSION

Through a cross-sectional investigation in female adolescents with a diagnosis of CD/ODD compared with TD adolescents and by inclusion of repeated measurements during an RCT, we demonstrated several key outcomes. First, neural activation increases for emotion regulation by cognitive reappraisal in female TD adolescents were observed in a network of regulatory control regions, but hypoactivations were detected in girls with CD/ODD. Secondly, cross-sectional assessments revealed that in female adolescents with CD/ODD, ODD symptom severity was negatively associated with dlPFC/precentral emotion regulatory activity. Third, CD and ODD symptom severity was reduced directly following RCT treatment (for both START NOW, a cognitive behavioral skills program, and TAU). However, only girls with CD/ODD who completed START NOW remained low in ODD symptoms as measured 3 months posttreatment. Pretreatment symptom severity and pretreatment dlPFC/precentral emotion regulatory activity predicted ODD symptom severity reductions following treatment. Three months following the end of the RCT, this association only remained significant for girls with CD/ODD who completed START NOW. Overall, our findings demonstrate the important role that emotion regulatory skills play in the phenotype associated with adolescent CD/ODD. Furthermore, our results are consistent with evidence that supports the effectiveness of cognitive behavioral skills training for ameliorating symptoms observed in CD/ODD (18) and suggests regulatory dlPFC/precentral activity as a potential biomarker of treatment responsiveness, including cognitive behavioral skills training.

Adolescents' Emotion Regulatory Control and Neural Alterations in CD/ODD

During emotion regulation (i.e., when decreasing affect evoked by negative images as compared to looking at a negative image), TD adolescents employed a network of brain regions including prefrontal, middle temporal, and parietal areas, consistent with previous work with healthy participants (1,4,5,34,47). Compared with TD control participants, neural activation during cognitive reappraisal was reduced in girls with CD/ODD. Our findings extend previous work in a smaller sample (7) and are consistent with data from different neuropsychiatric populations characterized by emotion regulation difficulties, including depression or anxiety (39,40), bipolar disorder (41), and externalizing disorders (6,42).

Our findings reiterate the importance of dlPFC/precentral regions during emotion regulatory control (1,7,33,36,47). It has been suggested that dlPFC and ventral PFC regions conjointly integrate affect and value representations that guide emotion regulatory behaviors (54). During adolescence, emotion regulation skills improve significantly, a process that is paralleled by prefrontal cortical maturation and increased prefrontal-subcortical connectivity (4,5,33,55). Such plastic adaptations allow the refinement of complex skills; however, some adolescents struggle more than others (e.g., CD/ODD). Prefrontal cortex development is influenced by positive and negative experiences, including adverse childhood experiences, which are common in CD/ODD (6,8). Sex-specific hormones may further affect the development of the PFC and its vulnerability to stress (56).

Next to dlPFC/precentral regions, task-related neural activity in middle temporal/angular gyrus and posterior cingulate/precuneus regions was observed for TD but was hypoactivated in females with CD/ODD. Middle temporal/angular gyrus and cingulate/precuneus regions have been associated with emotion regulatory processes in the past (36,44,45). The angular gyrus is further implicated in episodic memory formation and associative semantic processes (34,35,57), including the simulation of past, remembered, or future, expected situations (35). Similarly, the precuneus is further linked to visuospatial imagery, episodic memory, perspective taking, and self-agency (58), and the cingulate gyrus is relevant for emotional awareness and internally directed cognition (59,60). Overall, our data support the notion that the generation, perception, and regulation of emotions is likely performed by the dynamic interplay of different larger-scale neural networks (34,61). Local or connectivity-related alterations in any functional or structural features of such emotion regulatory networks may all lead to similar characteristics, as has been observed across different populations with emotion regulation difficulties (62). Future studies may test network alterations that lead to similar emotion regulatory deficits across different neuropsychiatric disorders more directly.

ODD Symptom Severity Is Linked to dlPFC/Precentral Regulatory Activation in CD/ODD

ODD symptom severity was negatively associated with regulatory dlPFC/precentral gyrus activity in females with CD/ODD (i.e., when decreasing affect evoked by negative images). This indicates that lower dlPFC/precentral activity was present in participants with CD/ODD who had the most severe impulse control problems (e.g., participants who struggled with anger control or regulation of behaviors in social contexts). Overall,

13.5% of emotion regulatory dlPFC/precentral signaling was explained by ODD symptom severity.

dlPFC/precentral regulation was explained by ODD symptom severity, reflecting on behaviors that are associated with impulse control problems, but not by CD symptoms, which are linked to more severe forms of antisocial behaviors (e.g., physical fights, cruelty to animals or people, vandalism, or theft). Notably, this finding occurred when testing emotion regulation overall (i.e., when decreasing affect evoked by negative images), and was not observed following removal of baseline automatic processes (i.e., when decreasing affect evoked by negative images as compared to looking at a negative image). Thus, this neural correlate encompasses both automatic and more explicit higher-order processes (3) to which dlPFC has been linked in previous studies (63,64). It is possible that in the current study, we mostly tested variations in automatic neural emotion regulation processes, which drove the significant association with ODD symptom severity.

RCT-Related Changes in CD/ODD Symptom Severity

Consistent with previous findings from studies that investigated the effectiveness of the START NOW treatment (18), we observed significant reductions in CD and ODD symptom severity in all participants following the RCT, but only the group who underwent START NOW treatment showed persistent reductions in ODD symptoms at a 12-week follow-up. More specifically, we identified an interaction of time and treatment group, with ODD symptom severity reductions being greater for participants who underwent START NOW as opposed to TAU. Participants with CD/ODD who completed START NOW remained lower in ODD symptom severity only for the long-term follow-up (3 months posttreatment). Consequently, treatment-related changes may initially generalize across treatment modalities. However, long-term treatment-related benefits for ODD symptoms only resulted from START NOW, a program that includes cognitive and dialectical behavioral therapy.

Previous research suggests that ODD symptoms may precede the development of CD, thus possibly increasing the risk for more severe behavioral problems later in life (11–14). However, the precise order of emergence and more specifically the question of whether ODD symptoms develop earlier and precede the onset of CD symptoms or whether CD and ODD symptoms develop together, remains debated (13). In females, the presence of ODD symptoms has previously been shown to increase risk for additional emotional disorders (65), including anxiety and depression (11,66). Furthermore, adolescent ODD symptom severity has previously been associated with later adult antisocial behaviors independent of whether the CD component was present or not (67). If such distinct contributions of adolescent ODD and CD symptoms to adult antisocial behavior exist, it may be of further interest to examine whether changes in one may impact the other and how this may be linked to remission following treatment.

While the findings reported here in a smaller RCT subgroup (n = 44) are consistent with behavioral data published in the full trial group (19), the low power in the current study warrants caution in the interpretation of findings. Moreover, the conceptual difference between ODD and CD symptom categories might have made it more likely to observe reductions in ODD symptom severity at the end of treatment followed by increases in ODD but not CD symptoms 12 weeks posttreatment in the TAU group. ODD symptoms include more habitual, repeated, and impulsive behaviors as opposed to more serious antisocial acts that make up the CD diagnostic criteria (i.e., physical violence) and that generally occur across a longer time period and not necessarily at a high frequency. Future studies may further investigate the contributions of CD/ODD severity to treatment-based changes in larger groups and use a longer time window following the end of treatment. Furthermore, additional variables, such as behavioral observations reported by the affected person, their caretakers, or social partners, will be valuable additions to future research that examines treatment impact (68).

Regulatory dlPFC/Precentral Activity Predicts Treatment-Based Symptom Change

We demonstrated that pretreatment ODD symptom severity and neural dlPFC/precentral activity during emotion regulation (i.e., when decreasing affect evoked by negative images) positively predicted symptom change measured directly following and 12 weeks after RCT treatment ended for participants who received START NOW. Individuals who were higher in ODD symptom severity gained the most from the treatment, and higher dlPFC/precentral regulatory activation prior to treatment preceded greater change.

Our findings are consistent with research that has demonstrated that pretreatment symptom severity predicted treatment outcomes, with the largest gain occurring among participants who were the most severely affected (69–71). Moreover, we showed that the inclusion of dlPFC/precentral biomarkers substantially outperformed regression models that included pretreatment symptom severity alone, increasing the regression-based prediction by 5% to a total of 39.9%. Results revealed that 45.5% of the variation in ODD symptom severity 3 months after the end of treatment was explained by a combination of pretreatment symptom severity, dlPFC activation during emotion regulation, and group status.

Across different psychopathologies, cognitive behavioral therapy may target remediation of the function of affected brain areas by the respective disorder [e.g., PFC in phobia (72); prefrontal (73), limbic areas (74), or hippocampus in depression (75); occipital/temporal regions in social anxiety (69)]. Behaviorally, cognitive therapy programs support individuals' gain of emotional control and thus increase emotion regulation skills and possibly neural functions. Timely interventions, including those that address aggression and impulse control problems, are critical and may impact the course and prognosis of an individual's diagnosis (76). Especially during adolescence, treatment programs may harness the brain's heightened plasticity at a time when neural networks are still being formed (55,76). Given known variations in treatment responses among adolescents with disruptive behavior problems (10), identification of individuals with an increased likelihood of responding well to a certain therapy may promise the greatest benefit in return (69,73,75). Specifically, patients with a heightened neural propensity for emotion regulation [e.g., stronger

pretreatment activation (73)] may display beneficial network requirements for successfully implementing regulatory tools taught in cognitive behavioral skill–like treatments.

Several limitations of the current study need to be mentioned. First, the findings were part of comprehensive assessments undertaken as part of the wider FemNAT-CD project, and the possibility cannot be ruled out that repeated testing and task demands posed a challenge to the population that we investigated. Because the fMRI study was optional for RCT participants, self-selection effects may have occurred. Secondly, we reported on female participants with CD/ODD only, and different findings may be observed in males with CD/ODD (6,17). It would also be interesting to test participants with a pure CD or ODD diagnosis; however, recruitment of such groups may be challenging due to high comorbidity (17). Third, notably, both the participants in the TD and CD/ODD groups and the participants with CD/ODD who received START NOW as opposed to TAU differed in aspects of IQ. While we included IQ as a covariate in all analyses, future studies could compare IQ-matched CD/ODD and TD groups. Fourth, although we took great care in training the participants to cognitively reappraise, evaluated task compliance, tried to ensure that participants understood the reappraisal task prior to fMRI scanning, and aimed to reduce expectancy bias, we cannot fully rule out the possibility that group differences in these variables might have influenced the results. Fifth, power considerations underline the importance of caution in the interpretation of smaller subgroup findings (e.g., group-specific treatment effects).

Conclusions

Replication in larger groups of participants with CD/ODD or populations with similar neurocognitive profiles is warranted. Ideally, our findings should be replicated in an independent group of participants with CD/ODD undergoing an evidence-based treatment.

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The study protocol was published in Kersten *et al.* (22) and the RCT trial was registered in German Clinical Trials Register (DRKS): Group-Based Treatment of Adolescent Female Conduct Disorders: The Central Role of Emotion Regulation; https://drks.de/search/en/trial/DRKS00007524; DRKS00007524 and in the International Clinical Trials Registry Platform (WHO) trial number NL-OMON44782.

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