Atypical Dorsolateral Prefrontal Activity in Females With Conduct Disorder During Effortful Emotion Regulation

Supplemental Information

fMRI Task

Task Design: Emotion Regulation Task (fMRI)

fMRI task design illustrating the trial structure. Each neutral or negative trial commences with a picture cue indicating the trial instruction ['look' versus 'decrease'] presented for 2.5s, an emotional image [negative/neutral] presented for 10s for which the cued strategy is being applied, followed by an affect rating phase lasting 5s [on a Likert scale 1-4] and an additional 2.5s of relaxation time. Prior to neuroimaging, participants were extensively trained using videos, standardized verbal instructions and feedback.

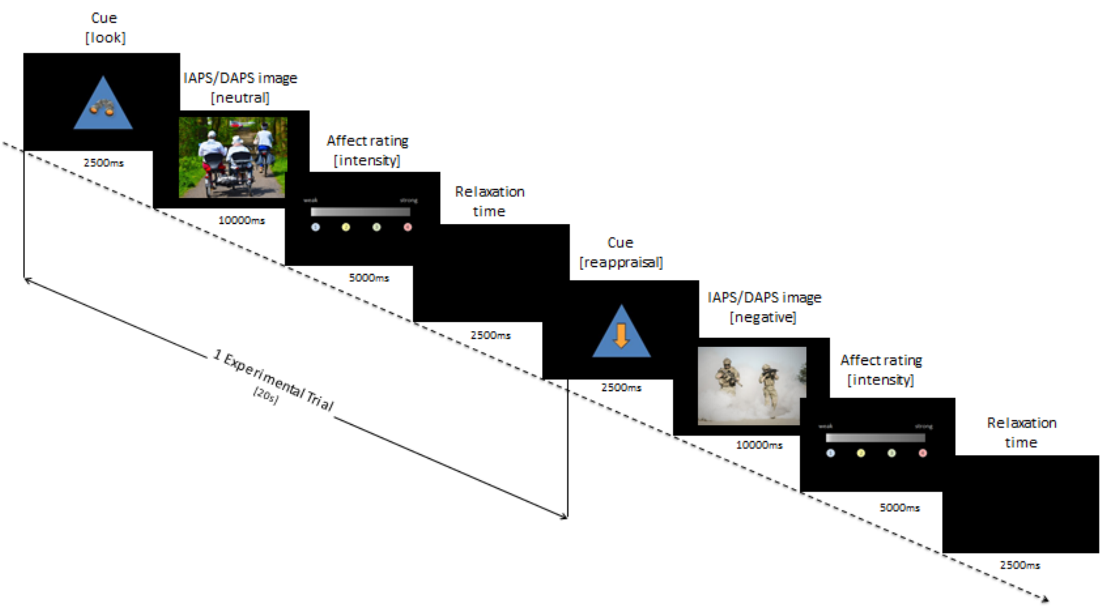

Figure S1. fMRI task.

Stimuli: Emotion Regulation Task (fMRI)

All images presented were selected from the International Affective Picture System (IAPS; (1)). However, aversive images were only drawn from those also included in the

Developmental Affective Photo System series (DAPS; (2)) in order to ensure age-appropriateness for children and adolescents. There were three sets of pictures (16 per condition: look neutral, look negative, decrease negative). Negative images had a reported IAPS mean normative valence rating of 2.66 (for look negative) and 2.77 (for decrease negative) and mean arousal ratings of 5.80 (look negative) and 5.70 (decrease negative; based on a 9-point rating scale where 1=most negative and 9=most positive or 1=low arousal and 9=high arousal, respectively). Negative images for both sets (look negative and decrease negative) were deliberately matched for content (e.g., presence of humans, animals, object, scene complexity), valence and arousal. Neutral images had a mean normative valence rating of 6.20 and mean arousal ratings of 3.62. We further ensured that the negative images in the first and second runs did not significantly differ in terms of valence or arousal. Likewise, the neutral images in the first and second runs did not differ in valence or arousal.

All images were presented using a stochastic randomized design in order to reduce the effects of idiosyncratic picture characteristics in relation to the instruction assignments and picture order. The order of the instruction conditions and picture types were pseudo-randomized to prevent the possibility that any more than three trial or picture types would be presented consecutively.

* The IAPS images used were: 1410, 2053, 2091, 2156, 2191, 2205, 2273, 2274, 2278, 2299, 2374, 2383, 2384, 2390, 2506, 2691, 2800, 3160, 3180, 3230, 3530, 5210, 5390, 6190, 6211, 6260, 6300, 6370, 6510, 6830, 7026, 7175, 8480, 9050, 9120, 9140, 9180, 9421, 9430, 9440, 9490, 9530, 9600, 9620, 9622, 9910, 9911, 9912.

Training protocol: Emotion Regulation Task (fMRI)

During practice trials, participants were further asked to verbalize their reappraisal strategy to ensure correct use of the instructed strategy of reinterpreting affects/dispositions, outcomes and contexts depicted in the images and to verify that they were not using alternative distraction strategies, such as actively avoiding (looking away from/or only attending to non-emotional aspects of) the images. Participants completed 12 (50% look/50% decrease condition) practice trials, mirroring the scanner task employed later on. However, these images were not included in the actual fMRI experiment.

In order to decrease potential expectation-based response-bias, the research team members assured the participants that there is no right or wrong answer 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. Finally, the team members mentioned that reappraisal is the attempt to decrease feelings associated with the negative images. However, this may not necessarily lead to the experience of a decreased negative affect for each person.

Site Procedures

Similar scanning parameters and image acquisition sequences were adapted at each site in order to ensure comparability of the neuroimaging assessments. Both sites additionally underwent site qualification procedures which tested the implemented sequences. More specifically an American College of Radiology phantom (ACR; designed to assess structural MRI sequences (3)), a Functional Biomedical Informatics Research Network phantom (FBIRN; designed to verify scanning stability during functional MRI sequences (4)), and a human volunteer were tested at each site. The resulting data of each site was compared and reviewed by a qualified MR physicist and adjusted until the sites' scanning procedures were comparable. Data acquisition only started once each site had successfully passed this site qualification procedure.

Table S1. Effects of site on demographic/clinical data

	CD				TD			
	Mean ± SD		N	*p*	Mean ± SD		N	*p*
	Basel	**Frankfurt**	[BSL/FFM]		**Basel**	**Frankfurt**	[BSL/FFM]	
Age (in years)	16.39 ± 0.91	15.85 ± 0.34	[24/6]	.029 *	16.78 ± 1.05	16.67 ± 0.94	[17/12]	.784
Handedness (right/left/both)	(17/2/2)	(5/0/1)	[21/6]	.881	(12/5/0)	(9/3/0)	[17/12]	.802
Puberty status	4.22	4.17	[23/6]	.794	4.47	4.25	[17/12]	.233
Age of onset (childhood/adolescence)	(8/16)	(2/3)	[24/5]	.785				
IQ								
Matrix reasoning	103.54 ± 13.55	104.17 ± 15.30	[24/6]	.922	102.65 ± 9.37	109.17 ± 12.94	[17/12]	.127
Vocabulary	95.63 ± 16.04	95.83 ± 20.84	[24/6]	.979	106.18 ± 9.77	107.50 ± 16.86	[17/12]	.791
Total score	99.75 ± 12.20	100.50 ± 16.96	[24/6]	.902	104.59 ± 7.27	108.58 ± 12.23	[17/12]	.280
Comorbidities (DSM-5)								
ADHD	8	2	[23/6]	.719	0	0	[0/0]	
MDD	5	1	[22/6]	.936	0	0	[0/0]	
GAS	0	0	[23/6]	--	0	0	[0/0]	
PTBS	4	0	[24/6]	.083	0	0	[0/0]	
Alc. abuse	2	2	[22/6]	.284	0	0	[0/0]	
Alc. dep.	1	1	[22/6]	.611	0	0	[0/0]	
Subs. abuse	1	2	[22/6]	.237	0	0	[0/0]	
Subs. dep.	4	2	[22/6]	.566	0	0	[0/0]	
YPI								
GM dimension	39.13 ± 10.11	39.67 ± 12.63	[23/6]	.913	32.97 ± 8.90	32.97 ± 8.90	[17/12]	.818
CU dimension	29.70 ± 7.05	31.67 ± 7.00	[23/6]	.547	24.52 ± 5.16	24.52 ± 5.16	[17/12]	.423
II dimension	40.39 ± 7.90	38.17 ± 7.36	[23/6]	.539	30.93 ± 6.48	30.93 ± 6.48	[17/12]	.947
Total score	109.22 ± 19.49	109.50 ± 25.26	[23/6]	.976	88.41 ± 15.30	88.41 ± 15.30	[17/12]	.666
CBCL								
Int. subscale	68.00 ± 9.87	59.40 ± 9.45	[12/5]	.119	48.38 ± 10.85	50.64 ± 10.63	[16/11]	.596
Ext. subscale	71.50 ± 6.17	70.20 ± 5.51	[12/5]	.690	44.50 ± 8.17	50.64 ± 5.94	[16/11]	.043 *
Total score	70.67 ± 7.67	67.20 ± 4.71	[12/5]	.367	45.06 ± 10.50	52.27 ± 8.32	[16/11]	.069

Furthermore, we repeated our neuroimaging analysis for participants from Basel only (CD=24/TD=17). The main finding of reduced neuronal correlates during emotion regulation in CD compared to TD individuals remained unchanged and significant using a cluster-building threshold of $p<0.001$ and a small-volume family wise error correction of $p<0.05$ (see statistical map and rendering below).

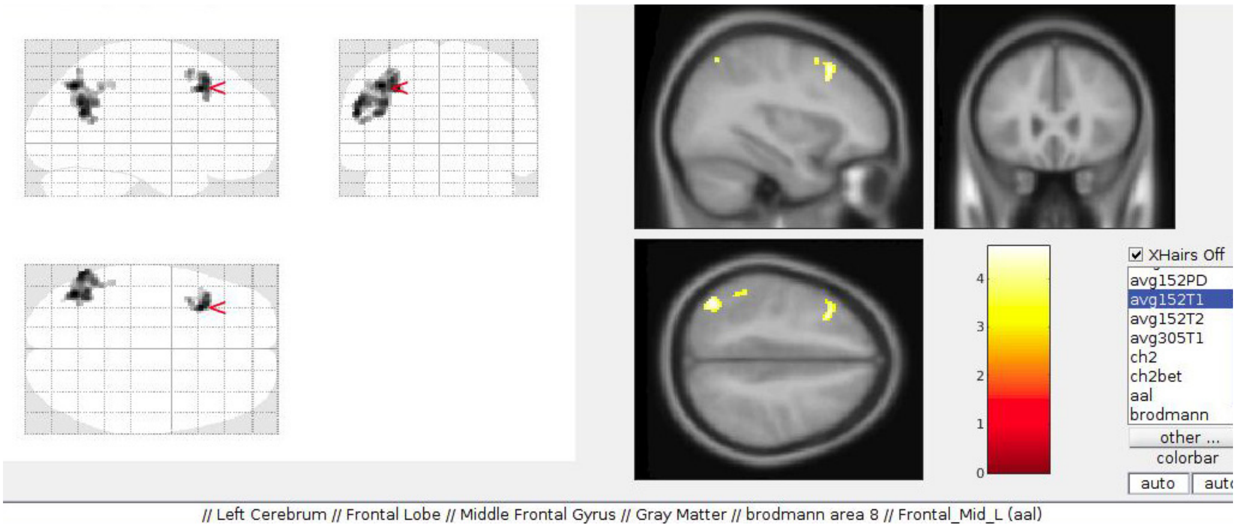

Figure S2. Statistical map for participants from Basel only.

Regions of Interest

All ROIs were defined based on networks reported by meta-analytic evidence (5). Cognitive control ROIs were defined as 10mm spherical ROIs centered around the following coordinates: bilateral vlPFC (left peak MNI: -42, 22, -6/right peak MNI: 50, 30, -8), anterior middle cingulate gyrus (peak MNI: -2, 14, 58), dlPFC (left peak MNI: -44, 10, 46/right peak MNI: 48, 8, 48), angular gyrus (left peak MNI: -42, -60, 44/right peak MNI: 60, -54, 40) and left middle temporal cortex (peak MNI: -38, 22, 44) using the MarsBaR toolbox (http://marsbar.sourceforge.net/). Affective regions of interest with clear anatomical boundaries (i.e. bilateral insula and bilateral amygdala) were defined according to the AAL atlas (6). Bilateral ventral striatum regions of interest were created using a 10mm spherical ROI centered around a left peak MNI: -12, 12, -2 and a right peak MNI: 10, 12, -2).

Supplemental Table S2. Cortical brain regions with peak activation scores in female typically-developing (TD) and conduct disorder (CD) youths for the emotional reactivity condition (look negative > look neutral).

Brain Region			***T***	P_{FWE}	P_{FWE}	**k**	**MNI coordinates**		
Lobe	Area	Side		[svc]	[wb]		x	y	z
TD:	**Look Neg > Look Neu**								
Frontal	superior/medial gyrus, SMA, anterior/middle cingulum	R/L	6.87	0.001		307	0	10	54
Occipital	occipital, superior/inferior parietal, inferior/middle temporal, fusiform gyrus, cuneus, lingual, angular gyrus	R	6.82		0.000	4864	46	-78	-2
Occipital	inferior occipital, fusiform, parietal, occipital, temporal, calcarine and lingual gyrus	L	6.81		0.000	2513	-46	-78	-8
Frontal	inferior/middle frontal, precentral gyrus	R	5.13		0.022	260	50	10	36
TD:	**Look Neg > Look Neu**								
Occipital	occipitotemporal, fusiform, calcarine gyrus, cuneus	R/L	8.71		0.000	9416	32	-80	-10
TD:	**Look Neg > Look Neu**								
	ns								

k = cluster size

Follow-up Analyses

For follow-up evaluations we also conducted all analyses: ***1. Using CU-traits as a covariate.*** There is considerable heterogeneity within CD youths (7-11) and prior evidence indicates that CU-traits (indexed here using the YPI callous-unemotional dimension) influence brain structure and function (12-15). In addition to performing regression analyses and in order to assess the impact of CU-traits on our findings, we included CU-traits (callous-unemotional dimension of the YPI) as a covariate of no interest, with similar main results. ***2. For an IQ-matched subsample.*** Neuronal differences in emotion regulation (look negative vs. decrease negative) after removal of one CD individual with the lowest IQ scores remained significant for neuronal differences in emotion regulation (CD<TD) in dorsolateral prefrontal cortex and angular gyrus (both findings are displayed in **Figure S3**).

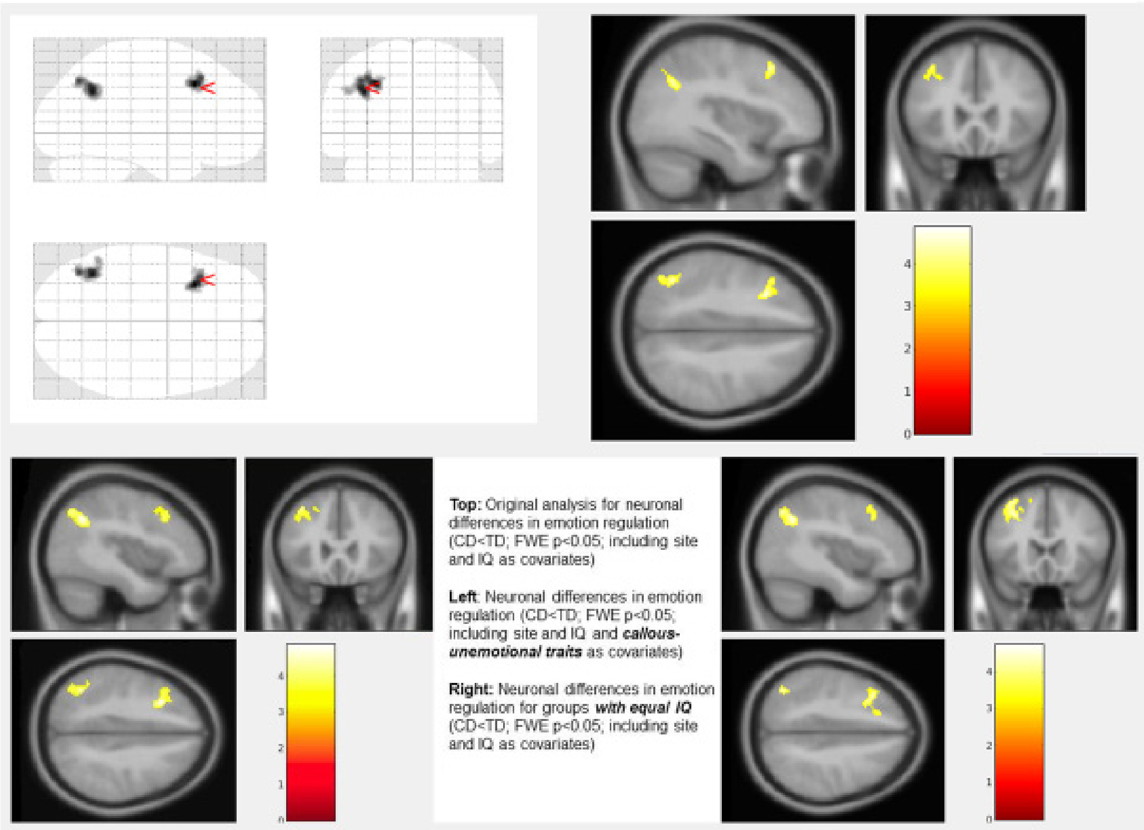

Figure S3. Neuronal differences in emotion regulation (CD<TD) within the original analysis (top), when including CU-traits as a covariate (bottom left) and for an IQ-matched subgroup (bottom right; *p*<0.05, small-volume FWE-corrected).

Connectivity Analysis

We imported the analyzed first-level models including movement and outlier regressors for each individual into the CONN toolbox. Additional preprocessing steps included denoising of the functional data (linear regression and band-pass filtering in order to remove motion, physiological or further artifacts before functional connectivity scores are calculated), first and second-level analyses. We employed analyses of covariance (ANCOVA), testing effects between the two groups (CD vs. TD) during reappraisal (decrease negative > look negative) while controlling for site/IQ for left dlPFC and left angular seeds. Both areas were implicated during emotion regulation previously and seeds were based on a priori defined ROIs. There was a main effect of group for the left dlPFC, but not angular seed of interest. Masked follow-up analyses for group effects based on left dlPFC seed indicate that CD show less connectivity between left dlPFC and bilateral putamen as well as right-hemispheric, prefrontal brain regions and amygdala compared to TD. Connectivity reports are reported as significant based on a cluster-building threshold of $p<0.001$ and a two-tailed cluster level inference of $p<0.05$ FDR-corrected.

Table S3. Condition specific group findings.

H	Region	x	y	z	size	cluster-size	size	T
L dlPFC Seed: ***TD>CD Dec Neg***								
R	putamen, caudate, pallidum	18	10	8	108	0.001	0.22	5.69
R	vlPFC, frontal pole, inferior frontal gyrus, OFC	54	34	-10	98	0.001	0.39	5.83
L	putamen	-24	-6	0	49	0.025	0.19	4.88
L dlPFC Seed: ***TD>CD Dec Neg***								
	non significant at p<0.05, FDR-corrected							

H=hemisphere; OFC=orbitofrontal cortex; vlPFC=ventrolateral prefrontal cortex

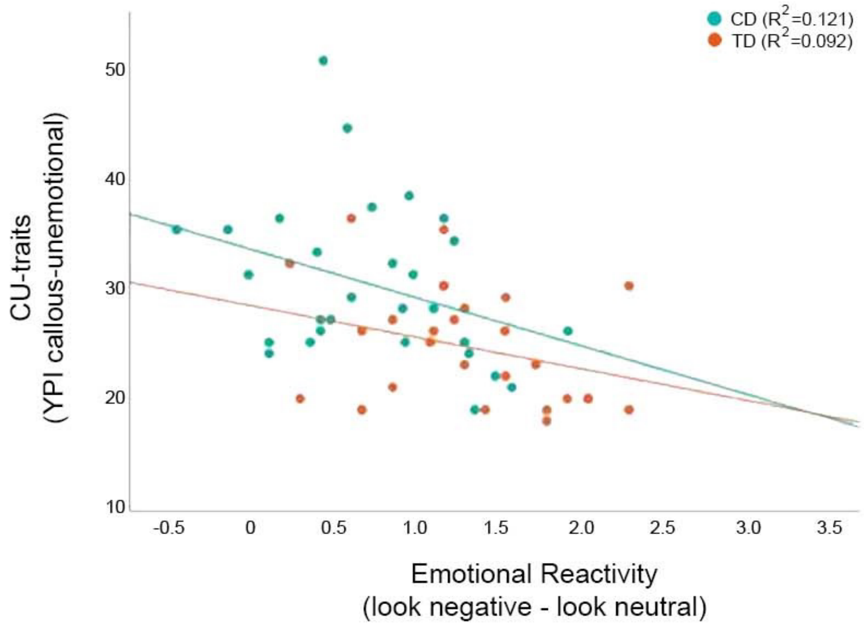

Figure S4. Correlational analyses between CU-traits and behavioral scores of emotional reactivity (difference for look negative – look neutral) show a negative correlation in CD (r=-.390, p=0.044), but not the TD group (r=-.269, p=0.184).

Supplemental References

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