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Exploring real-time functional magnetic resonance imaging neurofeedback in adolescents with disruptive behavior disorder and callous unemotional traits

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Research paper

Exploring real-time functional magnetic resonance imaging neurofeedback in adolescents with disruptive behavior disorder and callous unemotional traits

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ABSTRACT

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Conclusions: This exploratory study demonstrated feasibility and suggests clinical efficacy of individualized rtfMRI-NF comparable to active TAU for adolescents with DBD and increased CU traits. Further studies are needed to confirm efficacy, specificity and to clarify underlying learning mechanisms.

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1. Introduction

Disruptive behavior disorder (DBD) comprises conduct disorder (CD) and oppositional defiant disorder (ODD) and is a common condition in children and adolescents with an estimated prevalence rate of 6.1 % (O'Connell et al., 2009). DBD is marked by frequent aggression, deceitfulness, and defiance, which often persist through the lifespan. Individuals who engage in disruptive behavior represent a large population at risk for significant deleterious long-term outcomes, including family disruption, poor educational attainment, unemployment, substance abuse, and suicidal behavior (Colman et al., 2009; Fergusson et al., 2005; Odgers et al., 2008). Additionally, around 40 % of the individuals diagnosed with DBD display elevated callous-unemotional (CU) traits (Rowe et al., 2010). CU traits as a facet of DBD in youth are characterized by severe disregard for others, a lack of empathy and generally deficient affect (Pisano et al., 2017). As highlighted in meta-analytic studies, evidence-based psychological treatments for DBD only yield small to moderate effect sizes (Bakker et al., 2017; Erford et al., 2014; Fossum et al., 2008). Regarding the impact of CU traits on treatment outcome, findings are mixed but suggest that individuals with diagnosis of DBD and elevated CU traits may represent a more severe subtype with more stable behavior problems, more severe aggressive behavior and poorer response to treatment than their counterparts with low CU traits (Frick et al., 2014; Hawes et al., 2014).

In the context of precision medicine, individually tailored or subtype-specific treatment strategies aim to address heterogeneity across clinical disorders, target impaired functions in individuals or more homogenous subgroups to improve efficacy, and decrease variability in treatment outcomes. Such personalized treatment strategies appear particularly promising in DBD, as individuals with CD or ODD show prominent variability in affect-related neurophysiological responses related to subtype-specific aggressive behavior. Compared to controls, individuals diagnosed with DBD show altered affective processing in subcortical and cortical regions (Alegria et al., 2016; White et al., 2012) that varies with the presence and severity of CU traits. Specifically, decreased activity in the amygdala (AMG) was associated with increased CU traits (Aggensteiner et al., 2022; Viding and McCrory, 2018; Viding et al., 2012; White et al., 2012). Similarly, decreasing activity of the insula (INS) with increasing CU traits was observed in an empathy-eliciting task across individuals with conduct problems or diagnosis of DBD (Lockwood et al., 2013; Sethi et al., 2018). Besides these deficits in core-regions of affective processing, decreasing activity with increasing CU traits has also been observed in the anterior cingulate cortex (ACC) (Viding and McCrory, 2018), and altered activity in the orbitofrontal cortex (OFC), compared to controls, was indicated in adolescents with DBD during affective processing (Fairchild et al., 2014; Passamonti et al., 2010). Further, it has been suggested that treatment as usual which is less effective for individuals with high CU traits might be enhanced by new treatments such as emotion recognition training (Dadds et al., 2012). However, subtype-specific and customizable treatment options for adolescents with DBD are generally lacking and clinical efficacy of alternative, innovative treatment-strategies needs to be evaluated. Targeting brain regions implicated in severe DBD in a personalized fashion seems a particular promising approach to this end.

Recently, real-time functional magnetic resonance imaging neurofeedback (rtfMRI-NF) has become increasingly feasible and popular as a tool for the training of brain self-regulation, especially in emotion regulation (Paret and Hendler, 2020). Feasibility of rtfMRI-NF in adolescents has been tested in only two randomized controlled clinical trial (RCT) by Alegria et al. (2017) and Lam et al. (2022) targeting ADHD, and in one uncontrolled preliminary study addressing depression by Quevedo et al. (2019). So far, no study evaluated individualized rtfMRI-NF training in adolescents, or rtfMRI-NF in DBD. The AMG and INS have previously been implicated in emotion processing, DBD and increased CU traits (see above), so selecting that region (AMG or INS) with the most prominently reduced activation should represent a suitable target for the personalized treatment of adolescents with these conditions.

Thus, in this RCT, we explored the feasibility, clinical efficacy and specificity of individualized rtfMRI-NF of either AMG or INS activity compared to treatment as usual (TAU) in adolescents with DBD and elevated CU traits. We expected to observe superiority or non-inferiority of the rtfMRI-NF compared to TAU group and successful specific learning of self-regulation in the NF group to be correlated with clinical improvement.

2. Methods and materials

2.1. Participants

Participants in the current study were part of the EU-MATRICS project. Twenty-seven participants (12–18 years of age, 22 % female) were recruited from in- and outpatient facilities of the clinic of child and adolescent psychiatry and psychotherapy, as well as from local youth welfare institutions and via advertisement. Participants fulfilled diagnostic criteria of CD and/or ODD according to DSM-5 based on a clinical interview (Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) (Delmo et al., 2000) or scored above the clinical cut-off for aggressive behavior and/or rule-breaking behavior as measured with the Child Behavior Checklist (CBCL: Achenbach, 2000), Youth Self Report (YSR: Achenbach, 1991) or Teacher Report Form (TRF: Achenbach, 1991), and additionally displayed elevated CU scores (defined as ICU total score $>$ 20 in self-rating and/or $>$ 24 in parent-rating). The cut-off for high CU traits in our inclusion criteria were thus lower than the recently proposed cut-offs (34 for males; Kemp et al., 2021). However, the mean ICU score for our participants was 37.96, and six participants scored lower than the proposed cut-off. Exclusion criteria were any contraindications for MRI, an IQ $<$ 80 from four subtests (vocabulary, similarities, block design and picture completion/matrix reasoning) of the Wechsler Intelligence Scale for Children-IV (Petermann, 2011) and a primary DSM-5 diagnosis of psychosis, bipolar disorder, major depression and/or an anxiety disorder. Medication use of the participants had to be stable for at least two weeks prior to inclusion. The study was preregistered as a clinical trial (https://clinicaltrials.gov/ct2/show/NCT02563145). Patients were randomly assigned to either 6 sessions of TAU or 10 sessions of individualized rtfMRI-NF (see Table 1 and supplementary table S1 for

Table 1
Sample characteristics before treatment.

	NF	TAU	*p*-Value
N	12 (6 AMG / 6 INS)	13	
Female	25 % ($n = 3$)	15,4 % ($n = 2$)	0.645 (χ^2)
Completed treatment	75 % ($n = 9$)	72,7 % ($n = 8$)	0.901 (χ^2)
Medication	75 % (n = 9)	53,8 % ($n = 7$)	0.411 (χ^2)
Age	15.15 (1.622)	14.04 (1.527)	0.290
IQ	103.125 (13.106)	97.1154 (10.716)	0.220
CBCL ADHD (T-score)	66.92 (7.585)	66.42 (6.201)	0.861
CBCL ODD (T-score)	72.75 (4.413)	68.08 (4.00)	0.017
CBCL CD (T-score)	72.58 (4.757)	70.42(4.379)	0.258
ICU (parent)	37.67 (10.421)	38.25 (8.114)	0.880
ICU (self)	31.82 (9.745)	30.08 (7.633)	0.842
RPQ reactive	11.00 (5.568)	10.58 (4.542)	0.845
RPQ proactive	5.09 (5.262)	6.25 (5.242)	0.603
MOAS	7.08 (6.999)	7.23 (5.540)	0.954

Sample characteristics and group comparisons of demographic data for the NF and TAU groups. NF: real-time fMRI NF group. TAU: treatment as usual group. IQ: intelligence quotient. PDS: Pubertal development scale. CBCL ADHD: attention-deficit/hyperactivity disorder subscale of the child behavior checklist. CBCL-ODD: oppositional defiant disorder subscale of the child behavior checklist. CBCL-CD: conduct disorder subscale of the child behavior checklist. ICU: inventory of callous-unemotional traits. RPQ reactive: reactive subscale of the reactive-proactive aggression questionnaire. RPQ proactive: proactive subscale of the reactive-proactive aggression questionnaire. MOAS: modified overt aggression scale. M: mean. SD: standard deviation.

participant characteristics).

Ethical approval for the study was obtained from the local ethics committee. Written informed consent was given by the participants and their parents or legal representatives.

2.2. Clinical characterization and treatment outcome

As primary outcome, the Modified Overt Aggression Scale (MOAS: Kay et al., 1988) was assessed before and after treatment. Further outcome measures comprised the Inventory of Callous-Unemotional Traits (ICU: Frick, 2004) and the Reactive-Proactive Aggression Questionnaire (RPQ: Raine et al., 2006) in addition to the CBCL subscales CD and ODD to address important subtypes and dimensions of aggression. Further the Pubertal Development Scale (PDS: Carskadon and Acebo, 1993), was served to estimate dimensions of development at the pre assessment.

2.3. Intervention

2.3.1. Treatment as usual (TAU)

The active control group TAU consisted of six sessions within 10 weeks and included a comprehensive anamnesis by a clinical psychotherapist on the first day and parent interviews on the first and the last day of the intervention. Behavioral treatment consisted of selected elements of standardized manuals for the training of social competencies and aggression (Soziales Kompetenztraining (SKT), Anti-Aggressivitäts-Training (AAT: Weidner, 2011) and Assertiveness-Training-Program (ATP: Pfingsten, 2009)), which were individually combined to encounter the personal needs of each participant.

2.3.2. Real-time fMRI neurofeedback (rtfMRI-NF)

rtfMRI-NF training consisted of 10 sessions within 10 weeks. All rtfMRI-NF training sessions began with a high-resolution structural magnetization-prepared rapid gradient echo (MP-RAGE) scan, which was transformed into Talairach space to allow for intra-individual mapping between the NF-training sessions. Second, a brief implicit emotion-matching task (Hariri et al., 2000) was conducted. Finally, three NF training runs (simple feedback, video feedback, transfer feedback; 12.41 min. each) were performed (see Fig. 2 for paradigm overview).

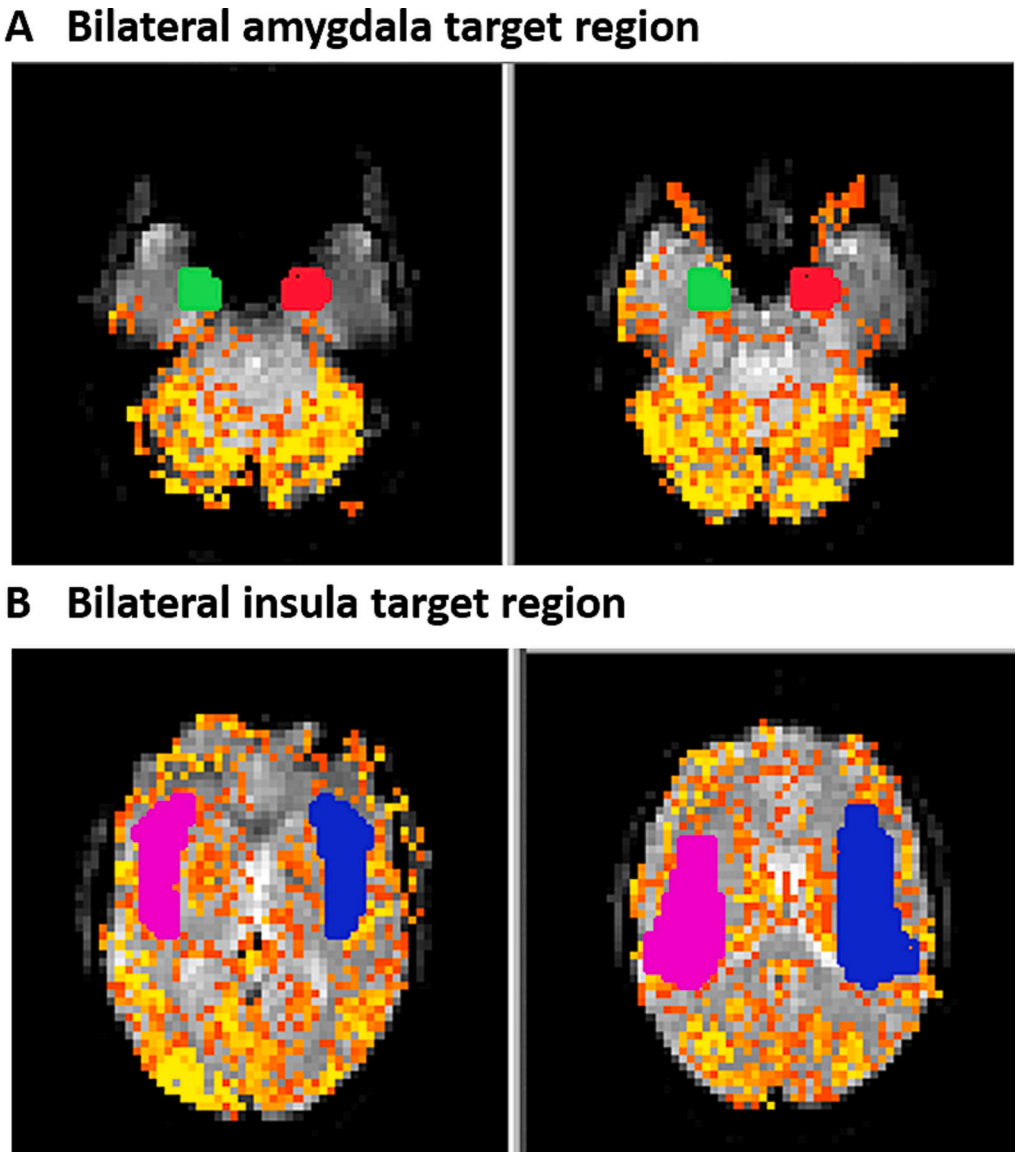

Fig. 1. Sample image of real-time functional localizer activation overlaid with target regions. A) Red = right amygdala, Green = left amygdala. B) blue = right insula, pink = left insula. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3.3. Individualized target region selection

The implicit emotion-matching task was used as a functional localizer at the first session. To determine the participant's individual activation within the anatomically defined regions of interest (ROIs: bilateral INS and the bilateral AMG, based on Talairach Demon, see Fig. 1), the data was compared to the activity levels in these regions from a healthy normative sample at the same task (sample characteristics are described in Holz et al. (2017)). The region which showed the most prominent hypoactivity (under-activation compared to the healthy sample) was selected as NF-target region for all upcoming sessions of the specific participant (amygdala, AMG-NF or insula, INS-NF).

2.3.4. Training runs and feedback presentation

Each NF-training run comprised up- and no-regulation condition trials (7 trials of 40s each). Condition was indicated by arrows, while two gauges (on the left and right side of the screen) were visualizing concurrent feedback of the mean activity within the individual target ROI. The condition sequence (up- and no-regulation trials) within each run was randomized. Baseline activity was assessed during an initial fixation period (30s) and updated during inter-trial fixation (7.5 s). To enhance performance, successful up-regulation trials (neural activity above the adapted baseline activity for 60 % of the duration of an up-regulation trial) were reinforced in all runs with a "thumb up" sign, while unsuccessful trials received no visual reinforcement (reinforcement period 3 s). Participants were instructed to move gauges in the requested direction or not move gauges, but received no instruction regarding regulation strategies. NF-training runs were presented in a fixed order. In the first run (*simple feedback*) only the gauges and arrows were displayed. In the second run (*video feedback*) video-clips showing either negative-affective or neutral scenes of social interaction were displayed additionally in the center of the screen for the duration of the trial (for more detail see supplementary material). The third run

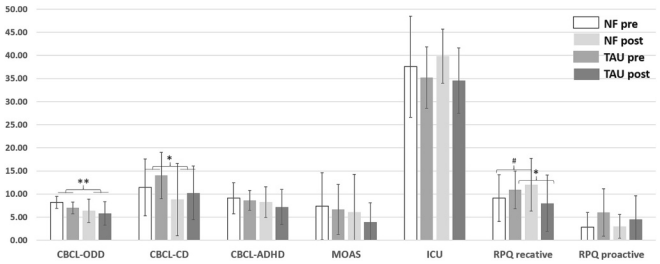

Fig. 3. Clinical outcome and symptom change for participants in the NF and TAU groups. NF: real-time fMRI NF group. TAU: treatment as usual group. CBCL-ODD: oppositional defiant disorder subscale of the child behavior checklist. CBCL-CD: conduct disorder subscale of the child behavior checklist. MOAS: modified overt aggression scale. RPQ reactive: reactive subscale of the reactive-proactive aggression questionnaire. RPQ proactive: proactive subscale of the reactive-proactive aggression questionnaire. M: mean. SD: standard deviation. $^{**}p < .01$, $^{*}p < .05$, $\#p < .07$.

(*transfer)* resembled the simple feedback, but gauges remained static so that no concurrent feedback of ROI activity was given. The intention of transfer trials within NF-studies is to ease the transfer of the regulation-skills into daily routine, which was additionally fostered in our study by a rewarded token-system (collecting thump ups) based on the principles of operant conditioning. Within this token system, points could be collected at each training day for successful performance (1 point equals three collected thumb ups / 80 points theoretically achievable in total) as well as treatment compliance (1 point/day for regular participation and 1 point/day for compliance during training) and were rewarded with a voucher of 10€ value at the participants choice for every unit of 40 collected points. Additionally, the cognitive self-regulation strategies, which the participants applied to move the gauges and according to

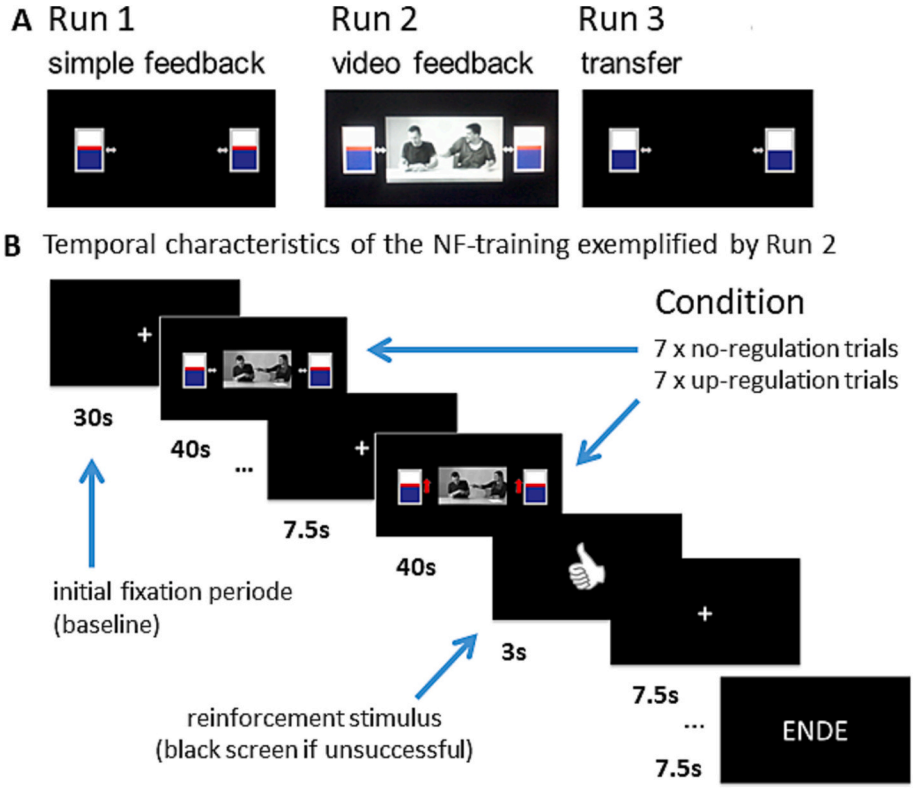

Fig. 2. Real-time fMRI neurofeedback design. A: The three different runs of the neurofeedback training. In the simple feedback run the gauges display activity of the individual target region. In the video feedback run the gauges display activity of the individual target region and affective video-clips are viewed in addition. In the transfer run the gauges are fixed at mid-level, no feedback is provided. B: Temporal characteristics of the NF-training exemplified by a video run. In each run positive reinforcement appears after successful up-regulation trials and a black screen appears if up-regulation was not successful. Total time of each run: 12.41 min.

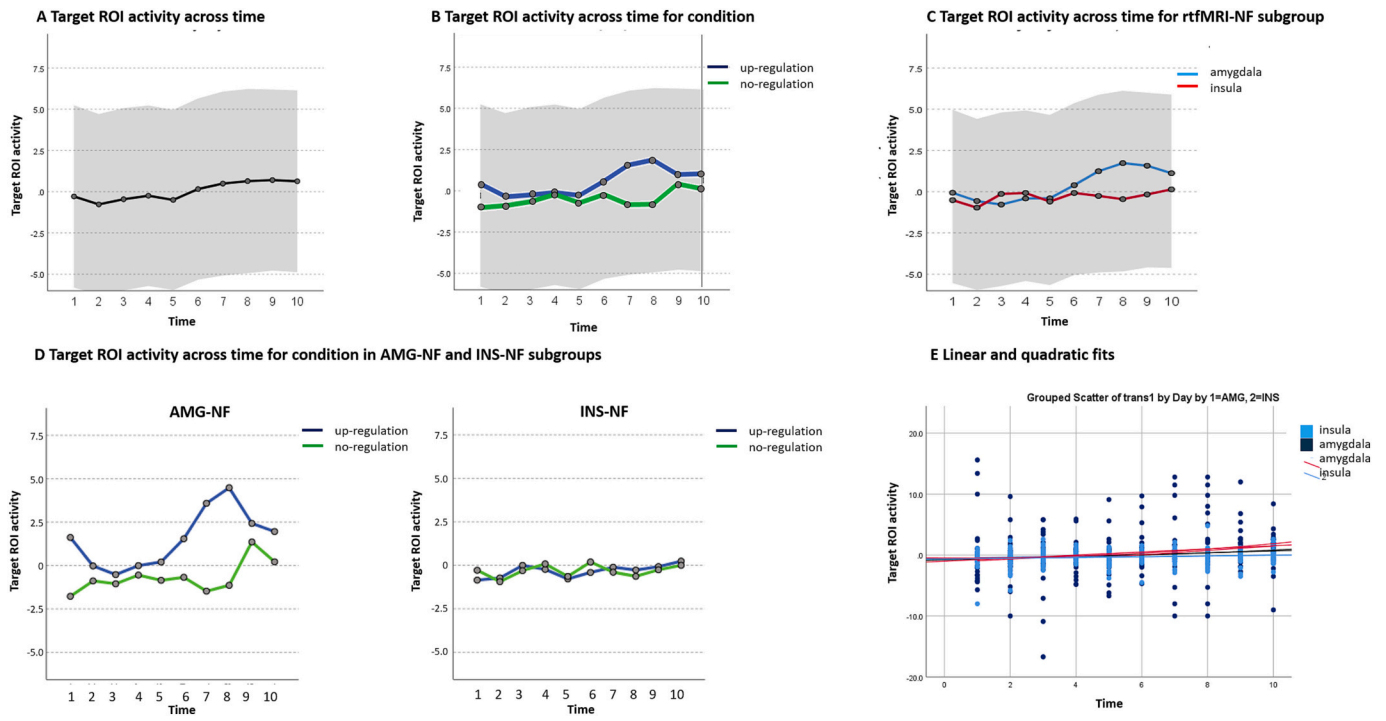

Fig. 4. Visualization of target ROI activity across time. A: Mean target ROI activity across time independent of subgroup, condition and run. B: Mean target ROI activity across time separately for the conditions (up-regulation in blue, no-regulation in green). C: Mean target ROI activity across time separately for the rtfMRI-NF subgroups (AMG-NF in blue, INS-NF in red). D: Mean target ROI activity across time separately for the conditions (up-regulation in blue, no-regulation in green) and the rtfMRI-NF subgroups. E: Quadratic and linear fits for total sample (black lines) and rtfMRI-NF subgroups (amygdala = red, insula = bright blue). RtfMRI-NF subgroups are indicated by colour (amygdala = dark blue, insula = bright blue). ROI: region of interest. RtfMRI-NF: real-time functional magnetic resonance imaging neurofeedback. Shaded areas show 1 standard deviation above and below the mean. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the conditions, were queried with a semi-structured interview after each training day.

The rtfMRI-NF training protocol was designed in cooperation with the Institute for Medical Psychology and Behavioral Neurobiology (University Tübingen) and implemented in *Presentation* software (Version 18.0, Neurobehavioral Systems Inc., Berkeley, CA). The real-time fMRI analysis was performed by *Turbo Brain Voyager (TBV)* software (Version 3.2, Brain Innovation B.V., Maastricht, Netherlands) supported by *Brain Voyager* software (Version 20.6, Brain Innovation B.V., Maastricht, Netherlands).

2.3.5. *fMRI data acquisition and offline preprocessing*

MRI scans were performed with a Magnetom TRIO (Siemens, Erlangen, Germany). For each self-regulation run, data of the individual NF-target regions were acquired using echo-planar imaging (EPI, 498 volumes á 16 axial slices, 5 mm thickness, repetition time 1500 ms, echo time 30 ms, voxel size: 3.3 × 3.3 × 5.0 mm, flipangle 70°, FOV = 210 mm). The anatomical scan was acquired at a resolution of 1.0 × 1.0 × 1.0 mm. Data was analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm/). The first four volumes were discarded to allow longitudinal magnetization to reach equilibrium. EPIs were interpolated in time to correct for slice time differences and realigned to the middle scan to correct for head movements. EPIs were co-registered and normalized to the standard EPI template in MNI space (Montreal Neurological Institute) using linear and non-linear transformations, and smoothed with a full-width-half-maximum Gaussian kernel of 8 mm. Realignment parameters were examined to ensure head movement did not exceed 5 mm (more lenient criteria to consider co-occurring hyperactivity in DBD). Please see supplementary material for further details.

2.4. *Statistical analyses*

2.4.1. *Demographics and treatment outcome analysis*

Demographic data between treatment groups were compared by two-sample *t*-tests and chi square tests. To evaluate and compare the impact of the interventions on symptom severity, pre-post comparisons were performed for all outcome measures using 2 × 2 repeated measures ANOVAs including a treatment group factor (NF vs TAU) and a time factor (pre vs post). These analyses were performed within SPSS (Version 25, IBM Corp., Armonk, NY, USA). All statistical analysis except for the treatment group by time ANOVA of the pre-registered primary outcome (MOAS) are considered exploratory. Utilizing R studio version 4.12 and the WebPower package, a posteriori power analysis was performed to evaluate the trial's capability to detect between-group treatment effects with a power of 80 % for the primary outcome, demonstrating that the trial has the power to detect large between-group effect sizes (f = 0.6).

2.4.2. *Analysis of learning of self-regulation*

ROI activity for the up- and no-regulation condition was quantified as condition-related activity minus baseline activity (up-regulation-fixation and no regulation-fixation), averaged across the individual target ROI for each participant. Linear mixed models (LMM) were fitted in R (Version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) using the lme4 package with ROI activity as a dependent variable to compare learning effects between and within the NF subgroups. Fixed within-subject factors were run (simple, video, and transfer reflecting the type of feedback) and condition (up-regulation and no-regulation). Time (sessions) was included as a continuous predictor. NF-training subgroup (AMG vs INS) was included as a random between-subject factor. The model further included interaction terms between sessions and subgroup, sessions and run, sessions

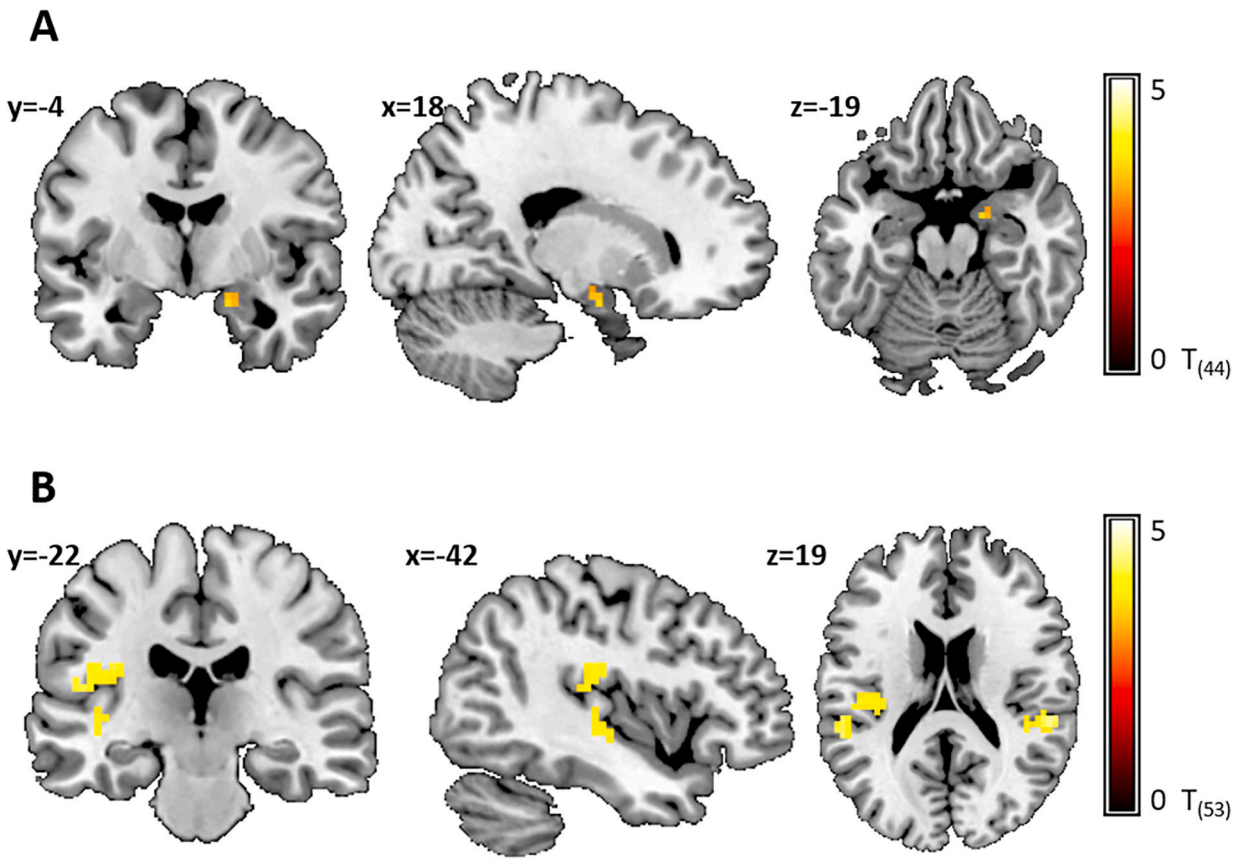

Fig. 5. Increase of neural activity in the up-regulation vs. no regulation condition over time within the NF groups. A: Linear increase over time in the video condition in right AMG-activity in the AMG-NF group. B: Linear increase over time in the transfer condition in in bilateral INS-activity in the INS-NF group.

and condition, subgroup and condition, subgroup and run, as well as 3-way interactions between subgroup, session and run and subgroup, session and condition. Finally, a random effect of subject on the intercept was included. Significant interactions were followed-up by either an exploratory simple slope analysis or pairwise comparisons using estimated marginal means. To explore non-linear learning effects, a separate model was constructed with linear and quadratic terms for time, as well as the previously described interactions with quadratic time. Model fits were compared using likelihood ratio test. To explore differences in regulation between specific training sessions, another model was constructed where session was included as a fixed within-subject factor and significant effects were followed up using exploratory pairwise comparisons based on EMM.

2.4.3. FMRI subject- and group-level analyses

During subject-level analysis, general linear models were assessed separately for each training session (up to 10 per subject) and for each NF-run (simple feedback, video feedback and transfer). Each model included the experimental conditions (up-regulation, no-regulation, fixation cross and reinforcement delivery) plus six realignment parameters as covariates of no interest, to account for residual motion-related variance. Low-frequency signal drift was removed using a high-pass filter (cut-off 128 s) and autoregressive correction for serial correlations (AR1) was applied. Contrast images for the comparison of up-regulation vs no-regulation were generated and subjected to second-level analysis.

To test for effects of learning on the subgroup level as a linear increase of this differential neural activity in the target regions (AMG or INS), multiple regression models were calculated across the participants in the two NF-training subgroups (AMG-NF/INS-NF) for each NF-run separately. All models included time as a covariate of interest, coded with increasing distinct values from 1 to 10 (subsuming all available participant data at each number of training session). Age, sex, IQ, pubertal development and medication status were included as covariates of no interest. To account for the different target regions and drop-out during training, completion and training ROI were also included as dichotomous covariates of no interest in the analyses across the NF subgroups. Missing sessions were replaced by the last-observation-carried-forward (LOCF) method, which is a common approach of imputing missing data in longitudinal studies (Woolley et al., 2009). In this analysis, if a person stopped NF-training before completing full number of sessions, fMRI data of their last observed training session was used for all subsequent observation points. The NF target regions AMG and INS were defined as ROIs, thresholded at a familywise error corrected (FWE < 0.05) level.

2.4.4. Association between NF performance, ROI activity change, and clinical outcomes

To test for associations between NF performance, ROI activity change, and clinical outcomes, nonparametric spearman's rank-order correlation was used. Thus, correlational analyses with all clinical outcomes (MOAS, CBCL-CD and CBCL-ODD, ICU and RPQ) were performed for first, the slope of individual target-ROI regulation over time and, second, the absolute difference in target ROI-activity between the last and the first session. These analyses were performed within SPSS (Version 25, IBM Corp., Armonk, NY, USA). Exploratory analysis relating localizer baseline activity in the target and control ROIs (by NF subgroup) to symptoms are reported in the supplementary material.

3. Results

From the 27 randomized patients, 25 patients started treatment. In

the TAU group, two patients dropped out before treatment (one started medication, one was relocated to psychiatric ward) and one patient terminated study participation after the first session and could not be reassessed. In the NF group, one patient rejected rtfMRI-measurement at the first NF-training. Finally, 21 patients participated in both pre- and post-treatment assessment (11 in the NF group, 10 in the TAU group). However, two patients in the TAU group and three patients in the NF group discontinued treatment early (TAU: one after two sessions, one after four sessions; NF: two after five sessions, and one after six sessions). Groups were matched with regard to sex and IQ and symptoms at baseline, except for the CBCL ODD T score ($p = .016$), in which the rtfMRI neurofeedback group presented a higher score.

3.1. Clinical outcome

In the analysis of treatment effects on clinical outcome, no significant effects of time for the primary clinical outcome (MOAS) were observed ($F(1,19) = 3.53$, $p = .075$, partial $\eta^2 = 0.157$). Exploratory analyses of secondary clinical outcomes revealed significant main effects of time for the parent-rated CBCL-ODD ($F(1,19) = 8.62$, $p = .008$, partial $\eta^2 = 0.312$) but not for the CBCL-CD ($F(1,19) = 2.91$, $p = .104$, partial $\eta^2 = 0.133$) indicated some reduced symptom severity after treatment across both treatment groups (NF and TAU). Interactions between time and treatment type were not significant. No clinical improvement was observed in parent-rated ADHD symptoms and CU traits (parent and self-rating). Additionally, the interaction between time and treatment type was significant in the reactive aggression domain, as measured by the RPQ self-rating ($F(1,15) = 9.15$, $p = .009$, partial $\eta^2 = 0.379$). Post-hoc comparison revealed a significant improvement in the TAU group (mean difference = −2.90 (1.22), $p = .031$) and a marginally significant aggravation in the NF group (mean difference = 2.85 (1.46), $p = .069$). No effects were observed for proactive aggression. Additional exploratory repeated measure ANOVA analyses, comparing the clinical outcome between the NF subgroups (INS-NF vs AMG-NF), interactions between NF subgroup and time were not significant for CBCL-CD ($F(1,9) = 0.29$, $p = .600$), CBCL-ODD ($F(1,9) = 1.55$, $p = .244$) and RPQ reactive aggression ($F(1,5) = 0.90$, $p = .386$). For a summary of symptom change effects see Fig. 3 and Table 2.

Table 2
Clinical outcome.

		Pre treatment			Post treatment		
		M	SD	N	M	SD	N
NF	CBCL-ODD	8.18	1.33	11	6.36	2.54	11
	CBCL-CD	11.45	6.14	11	8.82	7.85	11
	CBCL-ADHD	9.09	3.36	11	8.27	3.32	11
	MOAS	7.36	7.27	11	6.09	8.13	11
	ICU	37.55	10.92	11	39.82	5.85	11
	RPQ reactive	9.14	5.05	7	12.00	5.72	7
	RPQ proactive	2.86	3.13	7	3.00	2.58	7
TAU	CBCL-ODD	7.00	1.25	10	5.80	2.53	10
	CBCL-CD	13.3	5.20	10	11.20	6.30	10
	CBCL-ADHD	8.60	2.17	10	7.20	3.77	10
	MOAS	7.40	5.62	10	4.00	4.00	10
	ICU	35.22	6.64	9	34.56	7.10	9
	RPQ reactive	10.90	4.07	10	8.00	6.07	10
	RPQ proactive	6.00	5.14	10	4.50	5.10	10

Clinical outcomes for the NF and TAU groups. NF: real-time fMRI NF group. TAU: treatment as usual group. CBCL-ODD: oppositional defiant disorder subscale of the child behavior checklist. CBCL-CD: conduct disorder subscale of the child behavior checklist. MOAS: modified overt aggression scale. RPQ reactive: reactive subscale of the reactive-proactive aggression questionnaire. RPQ proactive: proactive subscale of the reactive-proactive aggression questionnaire. M: mean. SD: standard deviation.

3.2. Learning of self-regulation per target region (exploratory)

In the LMM a significant main effect of time indicated a linear increase of ROI activity over time across all subgroups, runs and conditions ($t(114.68) = 3.65$, $p < .001$, see Fig. 4 A and E), and a significant main effect of condition indicated higher overall activity in the up-regulation condition ($M = 0.44$, $SD = 3.19$) compared to the no-regulation condition ($M = -0.53$, $SD = 4.70$, $t(624.60) = 2.06$, $p = .040$, see Fig. 4 B and D). Further, the interaction of time and subgroup ($t(107.71) = -2.59$, $p = .011$) was significant. Post-hoc simple slope analysis revealed a significant increase of ROI activity over time in the AMG-NF subgroup ($p < .001$) but not in the INS-NF subgroup ($p = .093$, see Fig. 4 C and E). No further main effects or interactions of run could be observed. Furthermore, we repeated the analysis without one participant (355) whose data exhibited higher variability and outlier-like behavior, which strengthened our main outcomes (Main effect of time $t(46.84) = 4.932$, $p < .001$ and interaction time x subgroup $t(42.88) = -3.710$, $p < .001$).

The additional model exploring quadratic learning effects yielded a significant main effect of time indicating a quadratic increase of ROI activity over time across all subgroups, runs and conditions ($t(318.59) = 1.99$, $p = .047$, see Fig. 4), and a significant main effect of condition indicated higher overall activity in the up-regulation condition ($M = 0.44$, $SD = 3.19$) compared to the no-regulation condition ($M = -0.53$, $SD = 4.70$, $t(626.30) = 3.55$, $p < .001$). Further, the interaction of quadratic time and subgroup ($t(679.82) = -2.62$, $p = .010$) was significant, indicating quadratic terms differed between groups (see Fig. 4). Finally, a significant interaction between condition and subgroup emerged ($t(626.30) = 2.82$, $p = .005$) with significant differences between up- and no-regulation in the amygdala group ($p < .001$) but not in the insula group ($p = .99$). Comparison of the two models yielded no significant differences (AIC(linear): 3055.0, AIC(quadratic):3055.2, $p = .185$).

The model exploring differences in regulation between specific training sessions revealed a significant effect of session ($F(9,36.82) = 2.27$, $p = .039$), with post-hoc pairwise comparisons showing higher overall ROI activity during session 9 ($EMM = 0.86$, $SE = 0.51$) compared to the second ($EMM = -0.64$, $SE = 0.31$, $p = .034$), third ($EMM = -0.47$, $SE = 0.35$, $p = .046$), and fifth ($EMM = -0.52$, $SE = 0.30$, $p = .035$) session. Similarly ROI activity was higher during the last (tenth, $EMM = 0.60$, $SE = 0.43$) compared to the second session ($EMM = -0.64$, $SE = 0.31$, $p = .044$). Further, the significant effect of condition showed higher ROI activity during up- ($EMM = 0.60$, $SE = 0.16$) compared to no-regulation trials ($EMM = -0.50$, $SE = 0.16$, $F(1,611.49) = 33.99$, $p < .001$) as described in the previous models. A significant effect of NF subgroup ($F(1,105.98) = 14.48$, $p < .001$) emerged with higher ROI activation in the AMG ($EMM = 0.42$, $SE = 0.18$) compared to the INS NF subgroup ($EMM = -0.32$, $SE = 0.15$). The interaction of session and condition ($F(9,611.49) = 2.50$, $p = .008$) was significant with post-hoc pairwise comparisons showing higher ROI activation in up- compared to no-regulation for the first ($p = .018$), seventh ($p < .001$) and eighth ($p < .001$) session. Within the up-regulation condition, significant differences in ROI activation emerged with higher values for session 7 compared to sessions 2 ($p = .004$), 3 ($p = .009$), 4 ($p = .013$), and 5 ($p = .006$), for session 8 compared to sessions 1 ($p = .048$), 2 ($p = .002$), 3 ($p = .004$), 4 ($p = .005$) and 5 ($p = .002$), and for session 10 compared to session 2 ($p = .047$). Within the no-regulation condition, no significant difference between training sessions emerged. Post-hoc exploration of the significant interaction of condition and NF subgroup ($F(1,611.49) = 34.27$, $p < .001$) showed significant differences between up- and no-regulation in the AMG-NF subgroup ($p < .001$) but not in the INS-NF subgroup ($p = .653$). Finally, the interaction of session, condition and NF subgroup was significant ($F(9,611.49) = 2.33$, $p = .014$), and post-hoc pairwise comparisons revealed that the effects were mainly driven by the AMG-NF subgroup and the up-regulation condition: Significantly higher target ROI activation was observed in the AMG-NF group for the

up-regulation condition in session 7 compared to sessions 2 ($p = .001$) and 3 ($p < .001$), session 8 compared to sessions 1 ($p = .026$), 2 ($p < .001$), 3 ($p < .001$), 4 ($p < .001$), 5 ($p < .001$) and 6 ($p = .015$), in session 9 compared to sessions 2 ($p = .041$), 3 ($p = .012$) and 4 ($p = .033$) and in session 10 compared to session 3 ($p = .028$). In contrast, in the INS-NF subgroup, no differences between sessions emerged. Additionally, in the AMG-NF subgroup, significantly higher ROI activation was observed for the up-regulation condition compared to the no-regulation condition during sessions 1 ($p < .001$), 6 ($p = .016$), 7 ($p < .001$) and 8 ($p < .001$), while on no day up- and no-regulation differed in the INS-NF group. For further details on the three-way interaction, please refer to supplementary table S2 and Fig. 4D.

3.3. Learning of self-regulation by run and NF subgroup (exploratory)

Separate multiple regression models across all participants in each NF subgroup examined increases of target region activity as a correlate of self-regulation learning.

Simple feedback: No specific linear increase in AMG- or INS-activity could be detected.

Video feedback: A linear increase over time of the right AMG-activity was observed in the AMG-NF subgroup (ROI-analysis: 11 voxel, MNI: 18, −4, −19; $T = 3.54$, $p_{FWE} = 0.009$ (Fig. 5A)). No increase in INS-activity could be observed in the INS-NF subgroup.

Transfer feedback: A linear increase over time of bilateral INS-activity in the INS-NF subgroup in five distinct clusters (ROI-analysis: 18 voxel, MNI: 54, −34, 20; $T = 4.50$, $p_{FWE} = 0.020$; 11 voxel, MNI: −54, −40, 20; $T = 4.27$, $p_{FWE} = 0.026$; 52 voxel, MNI: −48, −25, 14; T = 4.27, $p_{FWE} = 0.008$; 11 voxel, MNI: −39, −25, 2; $T = 3.01$, $p_{FWE} = 0.026$; 7 voxel, MNI: 45, −16, 17; $T = 3.91$, $p_{FWE} = 0.031$ (Fig. 5B)). No increase in AMG-activity was observed in the AMG-NF subgroup. For whole brain analysis for each subgroup by run see supplementary material.

3.4. Association between NF performance, ROI activity change, and clinical outcomes (exploratory)

Regarding the association between individual NF performance and clinical outcomes, we found no significant association between the slopes of the individual learning curves and clinical improvement. However, correlating the absolute differences of specific ROI activity between the first and last day of training with clinical outcomes, we found a significant correlation with CBCL-ODD for the simple feedback run ($r_s = 0.602$, $p = .038$). No significant correlations could be observed in the primary outcome (MOAS), the CBCL-CD or for subtype-specific measures ICU and RPQ. Individual learning trajectories are shown in supplementary figs. S1 and S2. A qualitative summary of the cognitive self-regulation strategies can also be found in the supplemental material.

4. Discussion

In this exploratory RCT, feasibility and efficacy of individualized rtfMRI-NF in adolescents with DBD and elevated CU traits were investigated for the first time, using rtfMRI-NF as a tool for learning self-regulation of emotion processing regions.

No clinical improvement was observed for the primary outcome (MOAS), which may be related to the fact that the MOAS is a relatively brief measure, intended to capture transient aspects of aggressive behavior over the course of one week prior to each assessment. However, NF and TAU showed comparable and partly significant clinical improvement on DBD-related behavioral scales. Thus, the results can be tentatively interpreted as non-inferiority of the rtfMRI-NF treatment compared to TAU. Within the NF group, clinical improvement was not specific to either target ROI. This indicates comparable efficacy for both target ROIs and generally suggests individualized target ROI selection may be a valid approach for rtfMRI-NF in DBD. The significant main effect of condition, with increased ROI activity during up vs. no-regulation condition, further suggests that NF regulation worked across both subgroups, and the significant main effect of time indicates increasing ROI activity over time in the desired direction. However, as the interaction between time and condition remained non-significant, this ROI activity increase across time seems to be similar for up-and no-regulation, suggesting no linear or quadratic increase or decrease of the ability to differentiate between up- and no-regulation across time. Importantly, the interaction of time and NF subgroup further suggests differences in linear and quadratic learning slopes between the AMG-NF and INS-NF subgroups. Irrespective of run or condition, the AMG-NF group showed steeper slopes than the INS-NF group. Thus, the significant increase of ROI activity over time was mainly driven by the AMG-NF group. The main effect of run and interaction between time and run was not significant, suggesting similar regulation abilities across simple, video and transfer run.

Visual inspection of the learning curve of the AMG-NF subgroup (Fig. 4D), showed a steep brief increase in ROI activity after the sixth session, a maximum of ROI activity during the eighth session and a subsequent decrease until the final session. The exploratory comparisons between training sessions further showed significant differences in the AMG-NF subgroup for the up-regulation condition between most of the earlier (sessions 1 to 5) compared to most of the later sessions (sessions 7 to 9), as well as successful regulation (as characterized by significant differences between up- and no-regulation) only in the AMG-NF subgroup for sessions 1, 6, 7 and 8. The increase of ROI activity after the sixth session is similar to Alegria et al. (2017) where, however, no substantial decrease in ROI activity was observed for later sessions. Since NF-studies in adult healthy and clinical populations with fewer number of sessions (from 1 up to 5) already show significant effects of training even after one session (Paret et al., 2018; Posse et al., 2003; Sitaram et al., 2014; Veit et al., 2012) a learning effect around the seventh session may be viewed as comparatively late. However, little is known about rtfMRI-NF in adolescents to date, and one of the few available studies with participants in a comparable age range showed a similar onset of learning (Alegria et al., 2017). A later onset of learning of self-regulation (around the sixth session) in adolescents in comparison to adults might for instance be attributable to delayed maturation of prefrontal emotion-regulation related areas during adolescence (Nelson and Guyer, 2011). Another explanation for a comparatively late onset of the learning of self-regulation might be functional re-organization of connectivity between the amygdala and the prefrontal cortex, with potentially reduced efficiency for regulation in these regions during adolescence (Gee et al., 2013).

When analyzing each run separately for each NF subgroup using a multiple regression model, we were able to show a linear increase of differentiation between no- and up-regulation over time in the video run in the AMG-NF subgroup in the right AMG and, in the INS-NF subgroup, a linear increase over time in the transfer run could be detected in bilateral INS. Results between the LMM and the multiple regression approach may differ, since the LMM is restricted to mean target ROI values while the multiple regression approach in SPM assesses effects on the voxel level. However, concerning the AMG-NF subgroup, congruent results of the LMM and multiple regression models are indicating successful and partly linear learning of AMG-upregulation in this subgroup. Whereas for the INS-NF subgroup potential learning of INS-upregulation was only indicated for the transfer run. Together, our data suggest that the self-regulation of emotional processing regions might be more promising when receiving feedback from the AMG (as compared to the INS).

Individual learning slopes were not associated with clinical outcome. However, clinical (CBCL-ODD) and regulation improvement from first to last session were correlated, irrespective of the target ROI, for the simple feedback run. In summary, this suggests that overall increase of ROI activity but not the location of the target ROI affect clinical improvement. This might partly be attributable to additional unspecific effects of the experimental setting (highly technical, large fMRI machine, etc.) but

also motivational and emotional components from taking part in a study and feeling cared of by a professional, as such positive interaction is often missed by patients with these disorders.

The tentative differences in learning of self-regulation between AMG-NF and INS-NF may be also partially explained by the anatomical structures and functional connections of the respective target regions used in this study and the resulting ROI sizes (large INS ROI vs. smaller AMG ROI). The AMG is a relatively small and marked out structure and has strong functional connections to prefrontal areas (Murray and Wise, 2010), which may ease the addressing of the AMG via cognitive emotion regulation, which is moderated by prefrontal areas (Morawetz et al., 2017). In contrast, the insula is a relatively large and complex structure and is considered as a multi-modal functional network hub that is widely connected across the brain (Dionisio et al., 2019), which might complicate addressing this structure via cognitive regulation strategies. Further, potential learning effects within subregions of the INS (for example only in the anterior part) may have been underestimated in our LMM (but not our SPM) analyses due to averaging brain activity across the entire ROI.

To verify a specific relation between successful AMG (or INS) self-regulation and improvement in clinical behavioral domains, further investigations with larger treatment groups and possibly additional control conditions such as including a sham feedback run or a more technology-based behavioral therapy would be needed. However, considering the technical, financial and human effort of both treatments, conducting rtfMRI-NF training requires much more resources. Thus, although technical feasibility of rtfMRI-NF in adolescents´ diagnosed with DBD has been demonstrated, it still is a very complex and costly setting. The results of our exploratory study suggest clinical improvement and neither superiority nor inferiority compared to an active treatment option, but further studies are needed to confirm efficacy and clarify underlying mechanisms and cost effectiveness.

The strengths of this study include the innovative, non-pharmacological and individualized treatment of adolescents with particularly severe DBD including elevated CU traits, and the comparison to an active behavioral control treatment (TAU) in an RCT. However, there are also limitations worth noting. First, our small sample allowed only detection of large differential treatment effects for the preregistered primary outcome. For the exploratory analyses each NF subgroup contained even fewer adolescents (6 each) and therefore statistics regarding these NF subgroups remain extremely tentative. This study must thus be considered a proof-of-concept. Second, both groups had different numbers of sessions, which were however delivered within a matched 10 weeks period. For some cases with reduce compliance we had to extend this periods also up to 20 weeks. Third, parents or caregivers were not blinded to the intervention, which may well have impacted our findings.

Further, in our analysis we applied the LOCF method, which is a common technique to substitute missing values in longitudinal data, but is less conservative than imputing missing values with e.g. the baseline or worst observed data-point. However, trajectories of gradual improvement might also be underestimated with more conservative methods. Additionally, the trial durations for regulation of 40s might have encouraged continuous up-regulation in each trial, but trial durations are still comparable to other rtfMRI NF trials (see Emmert et al., 2016) and to the trial duration of 50s in the study of Alegria et al. (2017).

Regarding adverse effects of NF, a marginal aggravation in reactive aggression was observed in the NF group, whereas a significant improvement was observed in the TAU group. However, this finding has to be interpreted with caution because the effect was only marginal, limited to one aggression measure, and not compared to an inactive control group.

5. Conclusion

To conclude, we show feasibility of amygdala rtfMRI NF training in adolescents with DBD. While we demonstrate clinical improvement comparable to TAU in all NF subgroups, linear and quadratic learning effects on the training ROI level were shown exclusively for AMG-NF but irrespective of condition or run. Differentiation between up- and no-regulation increased in the right amygdala in the AMG-NF group during the video feedback run and in the bilateral insula for the INS-NF group during the transfer run. As clinical efficacy is not sufficiently validated for any NF-approach, and financial resources and technical advances limit the application of rtfMRI-NF, individually tailored child- and/or parent-centered behavioral interventions following evidence-based guidelines (AWMF, 2016; NICE, 2017) will currently remain the most cost-efficient and evidence-based first-line-therapy of DBD.

CRediT authorship contribution statement

Boris Böttinger and Pascal-M. Aggensteiner: Recruitment, trainings, testing, formal analysis; methodology; validation; visualization; writing – original draft; writing – review and editing. **Stefan Heinz:** Investigation; treatment; review and editing. **Sarah Hohmann and Nathalie Holz:** Design; writing – original draft; writing – review and editing. **Matthias Ruf:** Methodology; review and editing. **Jeffrey Glennon:** funding acquisition, writing – review and editing. **Daniel Brandeis, Tobias Banaschewski:** Conceptualization; funding acquisition; methodology; project administration; resources; supervision; writing – review and editing. **Sarah Baumeister:** Conceptualization; methodology; project administration; resources; supervision; writing – original draft; writing – review and editing.

Declaration of competing interest

D. Brandeis served as an unpaid scientific consultant for an EU-funded neurofeedback trial. T. Banaschewski served in an advisory or consultancy role for eye level, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Janssen, Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.10.036.

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