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An Open Pilot Study of Training Hostile Interpretation Bias to Treat Disruptive Mood Dysregulation Disorder

Joel Stoddard, M.D.[1], Banafsheh Sharif-Askary, B.S.[1], Elizabeth A. Harkins, B.A.[1], Heather R. Frank, B.A.[1], Melissa A. Brotman, Ph.D.[1], Ian S. Penton-Voak, Ph.D.[2], Keren Maoz, M.A.[3], Yair Bar-Haim, Ph.D.[3,4], Marcus Munafò, Ph.D.[2,5], Daniel S. Pine, M.D.[6], Ellen Leibenluft, M.D.[1]

[1]Section on Bipolar Spectrum Disorders, Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

[2]School of Experimental Psychology, University of Bristol, Bristol, UK

[3]School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel

[4]Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

[5]MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK; UK Centre for Tobacco and Alcohol Studies, University of Bristol, Bristol, UK

[6]Section on Development and Affective Neuroscience, Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland.

Corresponding author: Joel Stoddard, 9000 Rockville Pike MSC-2670, Building 15K Bethesda, MD 20892-2670; Tel.: (301) 594-9197; Fax: (301) 402-6100; Email: joel.stoddard@nih.gov

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Keywords: disruptive mood dysregulation disorder, irritable mood, interpretation bias

Abstract

Objectives

Irritability in Disruptive Mood Dysregulation Disorder (DMDD) may be associated with a biased tendency to judge ambiguous facial expressions as angry. We conducted three experiments to explore this bias as a treatment target. We tested: 1) whether youths with DMDD express this bias; 2) whether judgment of ambiguous faces can be altered in healthy youths by training; and 3) whether such training in youth with DMDD is associated with reduced irritability and associated changes in brain function.

Methods

Participants in all experiments made happy vs. angry judgments of faces that varied along a happy-to-angry continuum. These judgments were used to quantify a "balance point," the facial expression at which a participant's judgment switches from predominantly happy to predominantly angry. We first compared balance point in youth with DMDD (*n*=63) vs. healthy youths (*n*=26). We then conducted a double-blind, randomized controlled trial of active versus sham balance-point training in 19 healthy youths. Finally, we piloted open, active balance-point training in 14 youths with DMDD, with 10 completing an implicit fMRI face-emotion processing task.

Results

Relative to healthy youths, DMDD youths manifest a shifted balance point, expressed as a tendency to classify ambiguous faces as angry rather than happy. In both healthy and DMDD youths, active training is associated with a shift in balance point towards more happy judgments. In DMDD, evidence suggests that active training may be associated with decreased irritability and changes in activation in the lateral orbitofrontal cortex.

Conclusion

These results set the stage for further research on computer-based treatment targeting interpretation bias of angry faces in DMDD. Such treatment may decrease irritability and alter neural responses to subtle expressions of happiness and anger.

Introduction

Severe, chronic irritability in youths is a major public health issue. It is associated with significant current impairment (Deveney et al. 2015) as well as risk for future anxiety and depression (Brotman et al., 2006; Copeland et al. 2014; Savage et al. 2015; Stringaris et al. 2009; Stringaris et al. 2014), suicidality (Pickles et al. 2010), and socioeconomic under-attainment (Copeland et al. 2014; A. Stringaris and Goodman 2009). Nonetheless, few effective treatments exist. The biased tendency to interpret ambiguous social cues as hostile, a so-called "hostile interpretation bias" (HIB[1]), may provide a treatment target for irritable youths (Leibenluft and Stoddard 2013). The current set of studies lays the groundwork for further research evaluating this possibility in Disruptive Mood Dysregulation Disorder (DMDD), a DSM-5 (American Psychiatric Association 2013) disorder whose hallmark symptom is chronic, severe irritability.

Three factors inform this work. First, as elaborated below, prior research suggests that youths with conduct problems respond to a computer-based treatment targeting a form of HIB (Penton-Voak et al. 2013). Second, as also detailed below, youth with chronic irritability have deficits labeling face emotions. Finally, chronic, severe irritability in youths shares concurrent, longitudinal, and genetic associations to depression and anxiety (Brotman et al. 2006; Copeland et al. 2014; Leibenluft 2011;

[1] Here, we use the atheoretical term 'hostile interpretation bias (HIB)' to refer to the specific behavior of making happy-angry judgments of rapidly presented faces. This is distinct from the more specific term 'hostile attribution bias,' which refers to biased assessments of the motivations of individuals depicted in social scenarios and is associated with social information processing theory and reactive aggression (Wilkowski and Robinson 2010; Crick and Dodge 1994). A large body of work has related a hostile attribution bias to aggression in youths. The magnitude of such a hostile attribution bias increases in association with increases in the severity of aggression (Orobio de Castro 2002).

Savage et al. 2015; Stringaris et al. 2009; Stringaris et al. 2014) for which interpretation biases of ambiguous cues are established targets for cognitive bias modification training (Hallion and Ruscio 2011; MacLeod and Mathews 2012).

HIB has been associated with irritability-related phenomenon such as dispositions toward anger (Wilkowski and Robinson 2010) and verbally or physically aggressive reactions (Crick and Dodge 1996; Orobio de Castro et al. 2002). Targeting HIB, Penton-Voak and colleagues (2013) conducted two randomized controlled trials of sham vs. active computer-based training to shift participants' judgments of ambiguous facial expressions from "angry" to "happy." Active training was associated with decreased anger in healthy young adults and aggression in youths with conduct problems, measured by blinded self and youth-program staff ratings.

Irritable youth with Severe Mood Dysregulation (SMD; Leibenluft et al. 2003), a syndrome that was defined for research purposes and formed the basis for DMDD, tend to rate themselves as more afraid of neutral faces than do youth without psychopathology (Brotman et al. 2010). SMD youth also exhibit perturbed neural and attentional responses to face emotions signifying threat (Brotman et al. 2010; Hommer et al. 2013). However, other studies report generalized labeling deficits across emotions in SMD youth, without specific hostile interpretation biases (Guyer et al. 2007; Rich et al. 2008). Thus, although the data are somewhat mixed, prior work suggests HIB may be present in DMDD, raising the question of whether training to reduce this bias might decrease impairing irritability.

To provide preliminary evidence on the potential utility of interpretation bias training in DMDD, we report on an open trial of such training. As context, we first demonstrate the presence of HIB in youth with DMDD, as measured by happy/angry judgments of ambiguous facial affect (Experiment 1). Next, we show that active, but not sham, training shifts emotional judgments of ambiguous faces in healthy youth (Experiment 2). In Experiment 3A, we conduct an open trial of interpretation bias training in DMDD youths. Concurrently, we explore putative neural mechanisms for this open trial by testing post vs. pre-training responses to subtle emotional expressions in key components of the threat monitoring system, i.e. the orbitofrontal cortex (OFC) and amygdala (Experiment 3B).

Methods

Methods common to all experiments

The study was approved by the NIMH Institutional Review Board. Written informed consent was obtained from parents and assent from children. Families were paid for participation. All experiments accrued convenience samples. Inclusion criteria and assessment techniques are detailed in the supplement. All non-neuroimaging analyses were conducted in R (R Core Team 2014).

Experiment 1: Interpretation bias in DMDD vs. healthy volunteer (HV) youths

Participants with a lifetime diagnosis of DMDD (*n*=70; ages 8-18 years) and HV youths (*n*=27; ages 8-18 years) attempted to complete the interpretation bias task (IBT), with *n*=63 DMDD and *n*=26 HV youths providing acceptable data (see below for quality assurance; participant characteristics Table 1). Lifetime rather than current DMDD was the inclusion criteria because the goal of Experiment 1 is to identify a stable trait cognitive marker for DMDD.

Parent- and self-report forms assessed irritability (Affective Reactivity Index; ARI; Stringaris et al. 2012), anxiety (Screen for Child Anxiety Related Disorders; SCARED; Birmaher et al. 1999), anger (State Trait Anger Expression Inventory, Second Edition, Child Adolescent; STAXI-2 C/A; Brunner and Spielberger 2009), and depression (Children's Depression Inventory; CDI; Kovacs 1992).

The IBT developed by co-authors KM and YB used happy and angry face-emotion pictures (stimuli from Tottenham et al. 2009). For each identity, 15 “morphs” were created that were equally-spaced on a continuum from happy to angry. Each trial consisted of a fixation cross (800-1200ms), image presentation (200ms), visual noise mask (200ms), and a response screen with a question mark. The response screen remained until the participant made a forced-choice response of ‘angry’ or ‘happy’. Each morph was presented 3 times for a total of 180 trials.

To assure engagement with the task, participants who failed to correctly identify at least 70% of the four overtly angry and happy facial expressions were excluded (1 HV and 7 DMDD youths; see supplement for determination of this threshold).

The response variable was judgment (happy or angry), and the independent variables were group (DMDD or HV) and morph (1 through 15). Using morph as a continuous variable, we tested between-group differences in the point at which judgments switch from predominantly happy to predominantly angry (i.e., the balance point) by fitting a four-parameter logistic curve to group-level data (see supplement).

This approach was consistent with that of Pollak and Kistler (2002), who suggested using a four-parameter logistic curve to model two-choice judgments of face-emotions which are morphed between two emotional extremes. We used R package *drc* which was designed to test group differences in logistic curve fits (Ritz and Streibig 2005). In this analysis, balance point is operationalized as the inflection point of the logistic curve, and is the point on the happy-to-angry morph continuum where judgments switch from predominantly happy to angry, adjusted for the maximum probability of either judgment. A lower balance point indicates a hostile interpretation bias, defined as a switch to angry judgments earlier on the continuum of happy-to-angry morphs.

In other analyses within the DMDD group, we correlated balance point with level of irritability (ARI), trait anger (STAXI-2 C/A, T-scores relative to a gender and age norm), state anger (STAXI-2 C/A, T scores relative to a gender and age norm), anxiety disorder symptoms (SCARED), and depressive symptoms (CDI). Participants or their caregivers who completed these measures within 2 days of doing the IBT task were included in these analyses (*n'*s=41-48). To estimate individuals' balance points for this within-DMDD group analyses, we defined individual-level balance points as the inflection point of logistic curves fit to individual-level data.

Experiment 2: Active v. sham interpretation bias training in HV youths

Twenty HV youths were randomly allocated to active (*n*=8) and sham (*n*=12) interpretation bias training. One sham participant dropped out after allocation due to misunderstanding participation instructions. Youths in the active or sham arm did not differ by age [mean (*SD*) active = 13.8 (1.7) years, sham =14.7 (2.8) years; *p*=0.38], gender [% female active=63%, sham=82%, *p*=0.60], or IQ [mean (*SD*) active = 112 (11.4), sham =106 (5.1); *p*=0.20].

We used the training IBT (tIBT) procedure developed by co-authors IPV and MM (Figure 1; Penton-Voak et al. 2013). Because they were designed for separate studies, the task in Experiment 1 (IBT) and the training tasks in Experiments 2 and 3 (tIBT) have minor differences in timing and differ in stimuli. They are reported here because they are closely related in that they target interpretive bias. Unlike the IBT, the tIBT used one face-identity of a prototypical male, derived from composite images of 20 male individuals from the Karolinska Directed Emotional Faces (Lundqvist et al. 1998). As in the IBT, 15 morphs on a continuum of happy to angry were generated. The tIBT included a sham and an active version. In both versions, each training session consists of an assessment block, followed by six training blocks, and ends with another assessment block.

All trials consist of a fixation cross (1500-2500ms), image presentation (150ms), visual noise mask (250ms), and a response screen with a question mark. The response screen remained until the participant made a response of ‘angry’ or ‘happy’. In the assessment block, each morph was presented 3 times in random order. Data from the assessment block were used to estimate the balance point for each individual (Penton-Voak et al. 2012). Balance point was estimated as the proportion of happy responses to total responses multiplied by 15. Thus, in this instance, balance point is estimated from the proportion of happy responses over all morphs as in Penton-Voak et al. (2013), rather than using the more precise logistic curves used in Experiment 1. The simplified, proportion-based calculation of balance point could be performed in real time during a training session by custom software written by us in Tcl (www.tcl.tk). In addition, less precision could be tolerated in Experiments 2 and 3 because training effects on balance point are large (Penton-Voak et al. 2012; Penton-Voak et al. 2013). Of note, balance point estimates by logistic curve fits or proportions are highly correlated (*r*=0.78); their relationship is described further in supplemental information.

In the training blocks, timing and stimulus presentation were the same as in the assessment block, but feedback was provided after each response. Active training is designed to shift the balance point (measured at the beginning of each training session, during that session's pre-training assessment block) towards happy judgments of ambiguous faces. Participants receive positive feedback for rating as happy (and negative feedback for rating as angry) two ambiguous morphs. These two ambiguous morphs were those that, during the pre-training assessment block of each training session, were nearest the balance point and had been rated as angry by the participant. Similarly, sham training provides feedback based on the balance point measured at the beginning of each session during the pre-training assessment block. In the case of sham training, the feedback is designed to reinforce, rather than shift, the current balance point. Both conditions present each morph twice in random order during each training block. There are 6 training blocks consisting of 180 total trials. Both the active and sham versions of tIBT ended with a second assessment block. All participants completed four sessions of once daily training, with any missed sessions made-up with another day of training. Participants trained using their own computer or a laptop loaned to them. Participants completed the first and last training sessions at the NIMH and the middle two training sessions at home. Day 1 was defined as the first day of training.

One and two weeks after the final session (Days 10 and 17), a participant's balance point was assessed with a single assessment block.

The outcome measure was change in balance point as calculated based on the post-training assessment block from the final training session, relative to the pre-training assessment block from the first training session. As noted above, this is estimated from the proportion of happy responses over all morphs as in Penton-Voak et al. (2013), rather than the more precise logistic curves. We used a linear mixed-effects (LME) model with no imputation of missing data to test the effect on balance point of the factors Group (active or sham) and Session (pre-training, post-training, 1 and 2 weeks post-training).

Experiment 3A: Interpretation bias training in youths with DMDD

To be included in Experiment 3 (the open clinical trial), youth had to have 1) a lifetime diagnosis of DMDD, and 2) at the time of enrollment into the trial, clinically significant DMDD symptoms, operationalized as a score of 3 or more on the Clinical Global Impressions Scale-Severity (CGI-S; Guy 1976) for the preceding month. Fourteen youth enrolled in the trial (Table 2). The CGI scales are clinician-rated measures of the severity (CGI-S) or improvement (CGI-I) of a specific disorder. In this instance, the CGI scales integrate clinical impressions of the severity of DMDD, whose hallmark symptom is irritability.

At the start of the trial, two CGI-S measurements were obtained. One was for the month prior to training; this measurement was used to determine severity of DMDD for inclusion. The other CGI-S covered the week prior to the start of the trial and served as a baseline for CGI-I ratings throughout the trial. The 8-point version of the CGI-I (Klein et al. 1992) was used as a primary outcome measure of DMDD-related clinical improvement. CGI-I ratings compare the severity of symptoms during the week being rated to the severity of symptoms during the baseline week. The CGI scales are commonly used in psychiatric clinical trials where they have established utility and reliability (Berk et al. 2008). Ratings were performed by master's- or doctoral-level clinicians. Raters conducted simultaneous, independent CGI ratings of DMDD in youths participating in several studies and met weekly to discuss the ratings to achieve consensus. No formal reliability measures were obtained for clinician CGI ratings.

Participants had no changes in their outpatient treatment regimens (medications or psychosocial treatments) for at least two weeks prior to training and throughout their participation. Training comprised four sessions of the active tIBT task from Experiment 2. Participants received standardized ratings by clinicians at baseline, post-training on Day 6, and one week after training on Day 10. The time intervals covered by these three ratings were the month and the week prior to training, the week of training, and the week post-training. In addition, participants and their caregivers completed the ARI immediately prior to training (Day 1), post-training (Day 6), and one and two weeks (Days 10 and 17) post-training.

The outcome measures were balance point, calculated as in Experiment 2, DMDD-related clinical improvement (Clinical Global Impressions Scale- Improvement; CGI-I; Guy 1976), and irritability (parent and self-report ARI, analyzed separately). We used an LME model to test any change in the repeating measures, with no imputation of missing data, participant as a random factor, and Session as a fixed factor. As CGI-I scores reflect a change, we used one-sample two-tailed t tests of CGI-I scores centered on 5, a score corresponding to no clinical change. Exploratory Spearman's correlations were conducted between change in balance point after training and the CGI-I and ARI measures.

Experiment 3B: Amygdala and OFC responses to subtle affect after interpretation bias training in DMDD

During each of two fMRI scanning sessions, 10 of the 14 participants from Experiment 3A completed a task adapted from Kim et al. (2012) before and after training (see supplement). Briefly, participants labelled the gender of 10 actors' (Ekman and Friesen 1976) happy, angry, and fearful face-emotion pictures. Expressions at intensities of 50%, 100% and 150% were created by morphing with neutral. Face stimuli were presented in random order for 2s followed by a fixation cross for a jittered time of mean 1.4s, range 0.5-6s. Trials were divided into 3 blocks with a total of 30 trials for each of the emotion by intensity conditions and 90 neutral face-emotion trials. BOLD signal response was modelled during 2s of face-emotion presentation. See supplement for image acquisition and processing.

Regions of interest were each of the amygdalae and lateral OFC (extracted from the DKD_Desai_MPM atlas packaged with AFNI neuroimaging processing software (Cox 1996; Desikan et al. 2006). For each participant, neural activity within each region was estimated by computing the mean percent BOLD signal change of all voxels in its volume. Because we were interested in neural responses to subtle emotional expressions, we extracted the contrast of neural activity to 50% emotional intensity relative to fixation for each of the three face-emotions. We used an LME model to test the change in post-training v. pre-training neural response to emotion (fearful, happy, and angry), with participant as a random factor.

Results

Experiment 1: Interpretation bias in DMDD vs. HV youths

Accuracy of labelling the two morphs on the extremes of the happy-angry continuum did not differ between groups (mean (*SD*) accuracy HV=88.8 (6.8)%, DMDD=89.9 (7.6)%; $t(52.1)=0.66$, $p=0.51$). Relative to HV, DMDD required less angry affect in morphs to switch their judgments from predominantly happy to predominantly angry (*b*(*SE*) balance point HV=7.56 (0.10); DMDD=7.27 (0.07); $t(87)=2.39$, $p=0.017$; $d=0.51$; a ‘medium’ effect; Cohen 1992). When we analyzed each of the four face-identities presented in the IBT separately, the difference appeared to be driven by an angry judgment bias in DMDD to one male face-identity ($p<0.001$), but not to the three others (*p*’s >0.1) (Figure 2).

Within the DMDD group, individual balance point estimates did not differ by gender ($t(52.7)=0.59$, $p=0.56$) or age ($r=0.16$, $p=0.20$). Exploratory correlations did not detect associations between balance point and any self or parent measures or irritability, anxiety, depression, or anger.

Experiment 2: Active v. sham interpretation bias training in HV youths

The two groups did not differ in pre-training balance point (*b(SE)* active group=7.0 (0.77) v. sham group=7.03 (1.03); $t(17)=0.01$, $p=0.99$). The balance point of

HV youths in the sham condition did not change, with the balance point remaining reliably consistent across all four training sessions (*ICC*(2,1)=0.76, *F*(10,30)=15, *p*<0.001) (Figure 3). However, in the active group only, the balance point increased (i.e., shifted away from an angry judgment bias) after four sessions of daily active training, (*b(SE)*=2.9 (0.67) morphs, *t*(46)=4.4, *p*<0.001). This increase was maintained at both 1 and 2 weeks after training, *b*(*SE*)=2.5(0.79) and 2.2(0.67) morphs, respectively, *p*'s<0.003. Active and sham balance points differed at each post-training interval (*p*'s<0.005) (Figure 3).

Experiment 3A: Interpretation bias training in youths with DMDD

In 14 youths with DMDD, the pre-training balance point was *b(SE)* =7.37(0.47) morphs. After four sessions of daily training, balance point increased (away from an angry judgment bias) by *b(SE)*=2.25(0.41) morphs. This increase was maintained 1 and 2 weeks after training, *b*(*SE*)=2.16(0.41) and 2.54(0.41) morphs, respectively, *p*'s<0.001 (Figure 4).

Clinician-rated CGI-I scores covering the immediate post-training to the pre-training period were in the 'slightly improved' range (mean(*SD*)=4.4(1.1), *t*(13)=2.2, *p*=0.044, *d*=0.59). Scores comparing 1-week post-training to immediate post-training were in the 'improved' range (mean(*SD*)=3.5(1.3), *t*(13)=4.4, *p*<0.001, *d*=1.17). Training was associated with reductions in parent-reported irritability with a pre-training parent ARI rating of *b(SE)*=7.50(0.81) points that decreased immediately after training by *b(SE)*=-1.57(0.64) points, *p*=0.017. These reductions in parent ARI ratings persisted 1 and 2 weeks after training, *b(SE)*=-1.50(0.64) and -2.41(0.65) points, respectively, *p*’s≤0.023. Training was not associated with changes in self-reported irritability on the ARI (p=0.484).

Exploratory correlations may indicate the degree to which learning more benign interpretations is associated with clinical improvement. With Spearman’s rank correlations, we measured associations between differences in post- vs. pre-training balance point, and change in irritability by (1) parent and child reports (post- minus pre-training ARI) and (2) clinician rating (post-training CGI-I). We did not detect significant associations between changes in balance point and CGI-I ($r_s(12)=-0.49$, $p=0.079$) or change in self-report ARI ($r_s(12)=-0.52$, $p=0.056$) or parent-report ARI ($r_s(12)=-0.24$, $p=0.417$). However, the correlation coefficients suggest a medium-sized association between the degree of balance point shift and clinical improvement ($r \geq 0.3$; Cohen 1992). (Figure 5).

Experiment 3B: Changes in Amygdala and OFC responses to subtle affect after interpretation bias training in DMDD

After training, neural activation to subtle (i.e., 50%) expressions of happiness increased relative to subtle expressions of anger in right lateral OFC, $b(SE)=0.19(0.08)$, $p=0.021$, and left lateral OFC, $b(SE)=0.21(0.08)$, $p=0.009$, with a trend in the left amygdala $b(SE)=0.15(0.08)$, $p=0.072$ (Figure 6).

Discussion

Three experiments lay the groundwork for a controlled trial of interpretation-bias training treatment in irritable youths. Experiment 1 shows evidence of biased rating of face emotion in youths with DMDD. Experiments 2 and 3 show that daily computer-based training can shift such ratings toward happy judgments and away from angry judgments, and that this shift persists for two weeks without further training. Finally, Experiment 3, in youth with DMDD, suggested that four sessions of daily open interpretation bias training was associated with reduced irritability and possibly altered brain function in lateral OFC and amygdala in response to subtle expressions of happiness relative to anger.

We expected to find an interpretation bias towards angry judgments of ambiguous facial affect in DMDD based on earlier work in SMD (Brotman et al. 2010; Hommer et al. 2013) and the foundational work of Dodge (Crick and Dodge 1994; Wilkowski and Robinson 2008). Of note, we found a clear interpretation bias to only one male face-identity in the IBT task. While our data do not allow us to draw any conclusions as to why this may have occurred, this finding highlights the importance of future research on the possible effect of non-emotional facial features on interpretations of hostility (Marsh et al. 2005).

We found a training effect in HV and DMDD youths, consistent with prior work in healthy adults and in adolescents with conduct problems (Penton-Voak et al. 2013). Such training could reduce irritability by altering interpretative biases that promote anger-based reactions, a possibility supported by our preliminary fMRI results suggesting that tIBT may alter circuits mediating responses to ambiguous social threat cues (Brotman et al. 2010; Hooker et al. 2006; Thomas et al. 2012; Thomas et al. 2013). However, more work is needed to establish a brain-based mechanism mediating interpretation bias training and its possible effects on irritability. These results are also consistent with two meta-analyses of trainings targeting a variety of disorder-specific negative interpretation biases. These studies have shown small effects on clinical depression and anxiety (Hallion and Ruscoe 2011; Cristea et al. 2015). Another type of training, attention bias modification, also has also shown small to moderate effects on depression and anxiety symptoms (Hakamata et al. 2010; Linetzky et al. 2015).

As an early investigation of interpretation bias in pathologic irritability, this study has limitations. We have not developed a nonlinear model to assess the influence of potential confounds, such as gender and anxiety, as covariates. The results of Experiment 1 may not be directly comparable to the results in Experiments 2 and 3, because Experiment 1 used a different task and analytic method than Experiments 2 and 3. Results may be confounded by high psychiatric comorbidity in DMDD. In the open trial, we cannot distinguish between the effects of expectancy, observer bias, social desirability, regression to the mean, or interpretation bias training on irritability and irritability-related clinical improvement. Additionally, the sample size of both the pilot clinical trial and the fMRI study was quite small. A randomized controlled trial of tIBT in a larger sample of DMDD, with pre- and post-trial fMRI, is needed to confirm these results and provide more data regarding potential mechanisms.

Conclusions

We provide preliminary evidence that youths with DMDD exhibit a hostile interpretation bias, as measured by a bias towards judging ambiguous facial expressions as angry, which is likely moderated by a participant’s reaction to non-emotional facial features. A small, open, pilot trial of training towards benign interpretations of ambiguous facial expressions suggests that such training may be associated with reduced irritability and decreased clinical impairment due to DMDD, and possibly with alterations in relevant brain circuitry.

Clinical Significance

Few evidence based treatments exist for pathologic irritability. We provide preliminary evidence that a novel, computer-based treatment targeting interpretation bias warrants further testing as a novel intervention designed to decrease irritability in youths with DMDD.

Disclosures

MRM and IPV are co-directors of Jericoe Ltd, which produces software for the assessment and modification of emotion recognition. All other authors have no conflicts of interest or outside financial support to report.

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Table 1: Experiment 1 Participant characteristics.

	HV[a] ***n*=26**	**DMDD[a]** ***n*=63**	**Test Statistic**	***p***
Gender **% female**	53.8	41.3	χ^2=0.72	0.40
Age (years) **Mean (SD)**	13.9 (2.5)	13.4 (2.8)	*t*(53.6)=0.79	0.43
IQ **Mean (SD)**	112.1 (9.6)	109.8 (13.4)	*t*(53.4)=0.85	0.40
KSADS Diagnoses, Lifetime ***n*** **(%)**				
Any Anxiety[b]		42 (67%)		
ADHD		55 (87%)		
ODD/CD[c]		46 (73%)		
MDD		20 (32%)		

a. HV=healthy volunteer; DMDD=disruptive mood dysregulation disorder.

b. Any anxiety disorder includes generalized anxiety disorder, social phobia, or separation anxiety disorder.

c. ODD/CD diagnoses are for comparing to the prior literature. In DSM 5, a diagnosis of DMDD precludes a diagnosis of ODD.

Table 2: Experiment 3 Participant characteristics.

	DMDD[a] ***n*=14**
Gender **F:M**	8:6
Age (years) **Mean (*SD*)**	14.1 (2.4)
IQ **Mean (*SD*)**	114.5 (13.7)
KSADS Diagnoses, Lifetime ***n* (%)**	
Any Anxiety[b]	10 (71%)
ADHD	10 (71%)
ODD/CD[c]	14 (100%)
MDD	2 (14%)
Pre-training measures **Mean (*SD*)**	
CGI-S[d]	3.9 (0.7)
Parent-report ARI[e]	7.5 (2.8)
Self-report ARI	4.2 (3.1)

a. DMDD=disruptive mood dysregulation disorder.

b. Any anxiety disorder includes generalized anxiety disorder, social phobia, or separation anxiety disorder.

c. ODD/CD diagnoses are for comparing to the prior literature. In DSM 5, a diagnosis of DMDD precludes a diagnosis of ODD.

d. CGI-S=clinical global impressions, severity due to irritability, 3, 4, and 5 represents mild, moderate and marked illness, respectively. A score of 3 was the minimum score required for open trial inclusion.

e. ARI = affective reactivity index, a 12 point scale from 0=no irritability to 12=extreme irritability. Irritability in mental disorders characterized by severe, chronic irritability is often reported about 4-5 by self-report and 5-8 by a parent report (Stringaris et al., 2012).

Figure 1. The procedure for a single training session. Training is designed to shift interpretation of ambiguous morphs bias towards happy judgments. There are two types of blocks: assessment blocks determine balance point and training blocks shift balance point towards more happy judgments. Seven of 15 morphs are displayed here. Subjects see them in random order but here, for presentation purposes, they are shown along a continuum of happy to angry. The balance point (i.e., the morph at which judgments switch from predominantly happy to predominantly angry) is measured during assessment blocks. During active training, feedback is given after each response. The feedback threshold is the baseline balance point, measured during the first assessment block, shifted two morphs towards the angry end of the continuum. In sham training, the feedback threshold is the same as the baseline balance point.

Figure 2. Relative to HV youths (*n*=26), DMDD youths (*n*=63) have a bias toward judging ambiguous morphs as angry for the male face in the upper right panel ($p<0.001$). Mean proportions of angry responses are plotted against facial morphs, ordered from happy to angry. For each group, solid lines represent the fitted four-parameter logistic curves. A DMDD bias towards judging ambiguous morphs as angry is indicated by a leftward shift of the red curve relative to the black curve. Note that judgments differ by face-identity. Ethnicity descriptions and pictures of each actor can be found at http://www.macbrain.org (Tottenham et al., 2009). Probability values are of balance point difference between the curves.

Figure 3. Interaction plot of active (*n*=8) vs. sham (*n*=11) double blind, randomized controlled trial of training in HV youth. Asterisks represent $p<0.01$ from the linear mixed-effects model parameter estimate t-tests between the two groups at the sessions indicated. Error bars=standard error.

Figure 4. DMDD youths (*n*=14) responded to four daily sessions of training towards happy judgments of ambiguous faces, reflected by increasing balance points, decreased parent-report irritability (ARI), and clinical improvement (mean CGI-I scores less than 5). For balance point and parent-report ARI, asterisks indicate p-values for post-training assessment vs. initial parameter estimates. For CGI-I, asterisks indicate p-values of a t-tests vs. a score of 5, which indicates no improvement. *=p<0.05, **=p<0.01, error bars = standard error.

Figure 5. An increased bias towards happy judgments after training may be associated with reduced irritability and irritability-related clinical improvement in 14 youths with DMDD. Blue trend lines are from outlier resistant “robust regression,” using re-weighted least squares regression. The red line at a score of ‘5’ in the CGI-I corresponds to no clinical improvement, values less than five indicate improvement and values greater than 5 indicate clinical worsening. Insets contain Spearman’s correlation coefficients and uncorrected *p*-values.

Figure 6. Interpretation bias training is associated with increased neural activity in response to subtle expressions of happiness, relative to anger, in bilateral OFC and left amygdala. The brain image shows the four ROI's (lateral orbital frontal cortices and amygdalae) that were examined. Bar charts indicate mean % BOLD signal change to each 50% emotion-neutral facial morph, relative to a fixation cross, measured before (solid bars) and after (striped bars) four sessions of daily training. Asterisks represent *p*-values for the pre vs. post, angry vs. happy contrast parameter estimates. ł=$p<0.1$, *=$p<0.05$, **=$p<0.01$.