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Mediators in the Randomized Trial of Child- and Family-Focused Cognitive-Behavioral Therapy for Pediatric Bipolar Disorder

Heather A. MacPherson*, Sally M. Weinstein, David B. Henry, and Amy E. West

University of Illinois at Chicago, Department of Psychiatry, 1747 West Roosevelt Road, Chicago, IL 60608, USA

Abstract

Mediation analyses can identify mechanisms of change in Cognitive-Behavioral Therapy (CBT). However, few studies have analyzed mediators of CBT for youth internalizing disorders; only one trial evaluated treatment mechanisms for youth with mixed mood diagnoses. This study evaluated mediators in the randomized trial of Child- and Family-Focused CBT (CFF-CBT) versus Treatment As Usual (TAU) for pediatric bipolar disorder (PBD), adjunctive to pharmacotherapy. Sixty-nine children ages 7-13 with PBD were randomly assigned to CFF-CBT or TAU. Primary outcomes (child mood, functioning) and candidate mediators (family functioning, parent/child coping) were assessed at baseline and 4-, 8-, 12- (post-treatment), and 39-weeks (follow-up). Compared with TAU, children receiving CFF-CBT exhibited greater improvement in mania, depression, and global functioning. Several parent and family factors significantly improved in response to CFF-CBT versus TAU, and were associated with the CFF-CBT treatment effect. Specifically, parenting skills and coping, family flexibility, and family positive reframing showed promise as mediators of child mood symptoms and global functioning. Main or mediating effects for youth coping were not significant. CFF-CBT may impact children's mood and functioning by improving parenting skills and coping, family flexibility, and family positive reframing. Findings highlight the importance of parent coping and family functioning in the treatment of PBD.

Keywords

children; bipolar disorder; cognitive-behavioral therapy; family functioning; parent coping; treatment mediators

*Corresponding author. Harvard University, Department of Psychology, 1044 William James Hall, 33 Kirkland Street, Cambridge, MA 02138, USA. macpherson.14@osu.edu (H.A. MacPherson).

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Introduction

Pediatric Bipolar Disorder

There is much controversy surrounding the diagnosis of pediatric bipolar disorder (PBD). According to a recent meta-analysis of epidemiological studies, the mean prevalence of PBD is 1.8% when employing broad definitions (including bipolar I and II disorders, cyclothymia, and other specified/unspecified bipolar and related disorders; Van Meter, Moreira, & Youngstrom, 2011). However, rates are lower when using narrow criteria (1.2% for bipolar I disorder) and higher among older samples (2.7% for PBD in youth > 12 years; Van Meter et al., 2011). Thus, while bipolar disorder is more common in adolescents, it can also onset in prepubertal children, who often initially present with sub-syndromal forms of PBD (cyclothymia and other specified/unspecified bipolar and related disorders), but with comparable symptom severity and functional impairment as youth with bipolar I disorder (Hafeman et al., 2013).

Although the diagnostic criteria for bipolar disorder are the same in children and adults, the clinical presentation varies across the lifespan. The most common symptoms of pediatric mania include increased energy, irritability, and mood lability (Van Meter, Burke, Kowatch, Findling, & Youngstrom, 2016). Compared to adults with bipolar disorder, children and adolescents with PBD spend more time symptomatic with mixed presentations, rapid mood fluctuations, and subthreshold symptoms (Birmaher et al., 2009; Geller, Tillman, Bolhofner, & Zimmerman, 2008), and have greater impairment in functioning and quality of life (Perlis et al., 2009). In addition, youth with PBD often present with: psychotic features and psychiatric comorbidity, especially with attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (Birmaher et al., 2009; Geller et al., 2008; Van Meter et al., 2016); poor psychosocial and family functioning (Keenan-Miller, Peris, Axelson, Kowatch, & Miklowitz, 2012; Kim, Miklowitz, Biuckians, & Mullen, 2007; Nader et al., 2013); and suicidality (Hauser, Gallinger, & Correll, 2013).

Given the considerable morbidity associated with PBD, research has sought to identify efficacious treatments. While pharmacotherapy is often an essential component of the regimen (McClellan et al., 2007; Pavuluri et al., 2004b), psychosocial interventions are also important for teaching families about symptoms and course of PBD and fostering symptom management skills, such as affect regulation, problem solving, and effective communication (Fristad & MacPherson, 2014; Weinstein, West, & Pavuluri, 2013). Currently, approaches that incorporate family-focused psychoeducation and Cognitive-Behavioral Therapy (CBT) have the most empirical support (Fristad & MacPherson, 2014). Efficacy of these psychosocial interventions has been demonstrated in four large, rigorous randomized controlled trials (RCTs): Family-Focused Treatment (FFT) + pharmacotherapy versus brief psychoeducation + pharmacotherapy (Miklowitz et al., 2008; Miklowitz et al., 2013); Multi-Family Psychoeducational Psychotherapy (MF-PEP) + Treatment As Usual (TAU) versus waitlist control (WLC) + TAU (Fristad, Verducci, Walters, & Young, 2009); and Child- and Family-Focused CBT (CFF-CBT) + pharmacotherapy versus enhanced TAU + pharmacotherapy (West et al., 2014). Of these treatments, only MF-PEP and CFF-CBT have been tested exclusively with school-aged children; the original RCT of FFT included

predominantly adolescents (Miklowitz et al., 2008), while the second trial of FFT for youth at high risk for bipolar disorder included both younger children and adolescents (Miklowitz et al., 2013).

Mediators of Cognitive-Behavioral Therapy for Youth Internalizing Disorders

Though RCTs are the gold standard for determining efficacy, moderator and mediator analyses are also important for discerning subgroups for whom treatments may be more or less effective and mechanisms of change, respectively (Kraemer, Wilson, Fairburn, & Agras, 2002). Such factors can offer an empirical basis for matching patients to interventions, identifying treatment targets, and elucidating components associated with outcomes (Weersing & Weisz, 2002). In the adult depression psychotherapy literature, many studies have focused on the temporal relationship between in-session behaviors (e.g., therapist adherence, alliance, and cognitive strategies), reappraisal, and treatment-related symptom change (e.g., Lorenzo-Luaces, German, & DeRubeis, 2015). Indeed, the strongest evidence for mediation occurs when therapeutic procedures lead to changes in mediators, prior to changes in outcomes (Kraemer et al., 2002).

While comparatively less attention has been paid to mechanisms of CBT for youth internalizing disorders (Webb, Auerbach, & DeRubeis, 2012), several potential mediators have been identified. Specifically, CBT for pediatric anxiety may affect change by: reducing children's negative/anxious self-statements; increasing children's perceived control, positive self-statements, and coping strategies; and improving family functioning and strain (Hogendoorn et al., 2014; Kendall et al., 2016; Kendall & Treadwell, 2007; Schleider et al., 2015; Treadwell & Kendall, 1996). Potential mediators of CBT for adolescent depression include: reducing youths' cognitive distortions, automatic negative cognitions, and cognitive avoidance; and improving youths' positive outlook and engagement in pleasant activities (Jacobs et al., 2014; Kaufman, Rhode, Seeley, Clarke, & Stice, 2005; Kolko, Brent, Baugher, Bridge, & Birmaher, 2000; Stice, Rhode, Seeley, & Gau, 2010). Improvements in positive parenting, parental emotional reactions, and maternal depression may also mediate depression reduction in preventive interventions for younger, at-risk children (Compas et al., 2010; DeGarmo, Patterson, & Forgatch, 2004) and CBT for traumatized youth (Holt, Jensen, & Wentsel-Larsen, 2014).

Despite growing research on mechanisms of change in CBT for internalizing disorders, only one trial has evaluated mediators of a psychosocial intervention for youth with PBD or depression. In the RCT of MF-PEP + TAU versus WLC + TAU, improvement in quality of mental health service utilization was mediated by parents' positive beliefs about treatment, and improvement in children's mood symptoms was mediated by quality of services used (Mendenhall, Fristad, & Early, 2009). Thus, MF-PEP helped parents become better mental health consumers and advocates, and access to higher-quality services resulted in children's decreased symptom severity (Fristad et al., 2009). Although not yet studied, it is also expected that improvements in parenting skills and coping, family functioning, and the home environment would facilitate children's symptom improvement, as these deficits are associated with PBD in cross-sectional studies (Keenan-Miller et al., 2012; Nader et al., 2013; Schenkel, West, Harral, Patel, & Pavuluri, 2008), predictive of worse course in

longitudinal analyses (Geller et al., 2008; Kim et al., 2007; Sullivan, Judd, Axelson, & Miklowitz, 2012), and thus directly targeted in Evidence-Based Treatments (EBTs) for PBD (Fristad & MacPherson, 2014; Weinstein et al., 2013).

Child- and Family-Focused Cognitive-Behavioral Therapy for Pediatric Bipolar Disorder

Given limited research on mediators of EBTs for PBD, this study analyzed mechanisms of change in the RCT of CFF-CBT (West et al., 2014). This comprehensive, family-based intervention integrates CBT with psychoeducation and complementary mindfulness and interpersonal/family therapy techniques. The theoretical framework underlying CFF-CBT considers dysfunctions commonly observed in PBD, including: developmental manifestations of PBD (e.g. mixed mood states, rapid mood fluctuations, psychosis, and comorbidity; Birmaher et al., 2009; Geller et al., 2008); affective circuitry brain dysfunction (e.g. poor problem-solving during affective stimulation via hypoactivation of the dorsolateral and ventrolateral prefrontal cortices, hyperactivation of the amygdala, and deficits in the superior temporal and visual cortices; Garrett et al., 2012; Passarotti & Pavuluri, 2011); and impairment in psychosocial and family functioning (Keenan-Miller et al., 2012; Kim et al., 2007; Nader et al., 2013; Schenkel et al., 2008).

Specifically, the 12 acute and 6 maintenance sessions of CFF-CBT teach children, parents, and families coping skills comprising the treatment acronym, “RAINBOW,” including: **R**outine (development of consistent daily routines); **A**ffect Regulation (psychoeducation about emotions; mood monitoring; coping strategies to enhance mood regulation); **I** Can Do It! (improvement in child self-esteem and parent self-efficacy); **N**o Negative Thoughts/Live in the **N**ow (cognitive restructuring and mindfulness to reduce negative thoughts); **B**e a Good Friend/**B**alanced Lifestyle (social skill-building and parent self-care); **O**h How Do We Solve this Problem? (family problem-solving and communication training); and **W**ays to Find Support (enhanced support networks; Pavuluri et al., 2004a; West et al., 2014).

Results from the RCT demonstrated superiority of CFF-CBT versus a dose-matched, enhanced TAU control in terms of treatment attendance and satisfaction, children’s manic and depressive symptoms, and global functioning (West et al., 2014). Moderator analyses indicated that CFF-CBT was most impactful for parents with severe depression and low income, and families with high cohesion (Weinstein, Henry, Katz, Peters, & West, 2015). In addition, children with milder depression and greater self-confidence fared more poorly in TAU. However, mechanisms of change in CFF-CBT have not yet been examined.

Purpose of Current Study

As CFF-CBT targets family functioning, parenting skills and coping, and child coping impaired among youth with PBD, and based on research supporting the role of parent and family functioning in mediating CBT for younger samples with internalizing symptoms and PBD, we hypothesized that: 1) CFF-CBT would improve family functioning, parenting skills and coping, and child coping compared with TAU; and 2) changes in these processes would mediate the CFF-CBT treatment effect, such that CFF-CBT would no longer, or less strongly, predict improvement in children’s mood symptoms and global functioning when family functioning, parenting skills and coping, and child coping were included in models.

Method

Participants

This study analyzed potential mediators in a secondary analysis of the RCT of CFF-CBT versus TAU, which offered empirical support for CFF-CBT [see West et al. (2014) for primary outcomes]. Sixty-nine children and their parents seeking treatment at a specialty pediatric mood disorders clinic in an urban, Midwestern Academic Medical Center were recruited to participate in this study from 2010 to 2013. Sample size was determined via *a priori* power analyses to detect a medium effect on outcomes and potential mediators. Inclusion criteria required children to be between the ages of 7 to 13 and meet *DSM-IV-TR* criteria for a bipolar spectrum disorder with episodic changes in mood (bipolar I, II, or not otherwise specified [NOS]). Bipolar disorder NOS was defined using *DSM-IV-TR* criteria as the presence of depressive and manic symptoms that met symptom severity threshold but not minimal duration criteria, or the presence of recurrent hypomanic episodes without intercurrent depressive symptoms. Children were also required to be stabilized on medication (stable dosages for 4 weeks), which was defined as scores of 20 on the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) and < 80 on the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1984). Children were excluded if they had an IQ < 70; psychosis, substance abuse/dependence, neurological conditions, or other medical problems that complicated psychiatric symptoms, per the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; Geller et al., 2001); and active suicidality requiring hospitalization. Children were also excluded if primary caregivers presented with severely impairing mood symptoms that would limit their involvement in the treatment, though no children were excluded for this reason. Youth with comorbid disorders, including high-functioning autism, were included to ensure a clinically representative sample.

Children were 9.19 years old on average ($SD = 1.61$). A majority were male (58%) and Caucasian (52%) with bipolar disorder NOS (62%). Youth often met criteria for bipolar disorder NOS, as opposed to bipolar I or II disorder, due to insufficient number and/or duration of symptoms. Index episodes for youth with bipolar disorder NOS were most commonly mixed (43%) and unspecified (33%). See Table 1 for baseline demographics, stratified by treatment condition, with no significant differences between groups.

Procedures

Baseline Diagnosis and Randomization—Study procedures were overseen by a University Institutional Review Board. Trained study personnel ($N = 6$), consisting of clinical psychology doctoral students and licensed clinical psychologists, completed informed consent/assent, screening, the WASH-U-KSADS (Geller et al., 2001), and portions of the Kiddie SADS-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) with parents and children. Interviews were reviewed during study meetings to ascertain consensus diagnoses. Children with PBD subsequently completed the baseline assessment and were randomized via Research Randomizer software (Urbaniak & Plous, 2014). Additional evaluations were conducted at 4-, 8-, 12- (post-treatment), and 39-weeks (6-month follow-

up) by blind raters (i.e., clinical psychology graduate students and post-baccalaureate research assistants trained by the treatment developers).

Treatment Conditions—Sixty-nine children and their parents were randomly assigned to CFF-CBT ($n = 34$) via a specialty mood disorders clinic or TAU ($n = 35$) via a general psychiatry clinic, both located within the same outpatient psychiatry program. See West et al. (2014) for details and the Consolidated Standards of Reporting Trials (CONSORT) diagram. Families in both conditions received 12 weekly 60-90 minute sessions and up to 6 monthly booster sessions. The acute phase of CFF-CBT consisted of six family sessions, three parent sessions, and three child sessions (including a family portion for review of session content/homework), while maintenance sessions varied in format depending on families' individualized goals. Though CFF-CBT and TAU sessions were intended to be matched on treatment dosage, more CFF-CBT participants ($n = 30$) completed the core treatment (12 weekly sessions) than TAU ($n = 17$). However, attrition by the 6-month assessment did not differ by condition. In addition to therapy, all participants received medication management via the specialty mood disorders clinic using an evidence-based algorithm (Pavuluri et al., 2004b). Medications were tracked but not manipulated as part of the study.

Twenty-three therapists, consisting of clinical psychology pre- and post-doctoral trainees novice to treatment of PBD, facilitated CFF-CBT following a 3-hour training on the manual. They also received weekly supervision from the treatment developers. Control therapists ($n = 23$) consisted of clinical psychology doctoral students, post-doctoral fellows, psychiatry fellows, and social work interns. They received a 1-hour training on PBD prevalence, symptoms, course, and associated impairments, making this condition “enhanced” compared to typical TAU. Other than efforts to match number of sessions across conditions, TAU sessions were not manipulated in terms of content or structure. Per session audio-recordings coded by trained raters for a random sample of 10 families in each group, therapists demonstrated strong fidelity to CFF-CBT (93%), and there was minimal presence of CFF-CBT concepts in TAU (4%; West et al., 2014).

Measures

All primary child outcomes and candidate mediators were assessed at baseline (pre-treatment), 4-, 8-, 12- (post-treatment), and 39-weeks (6-month follow-up).

Primary Child Outcomes

Mania: The Child Mania Rating Scale (CMRS; Pavuluri, Henry, Devineni, Carbray, & Birmaher, 2006) is a 21-item, parent-report measure of children's manic symptoms. Responses are Likert-style and range from 0 (*never/rarely*) to 3 (*very often*). Total scores range from 0 to 63, with higher scores indicating more severe symptoms. Among children with bipolar disorder, ADHD, and healthy controls, the CMRS demonstrated good internal consistency ($\alpha = .96$), test-retest reliability ($r = .96$), and validity (content, construct, criterion) when compared to clinician-rated scales and when differentiating mania from ADHD and controls (Pavuluri et al., 2006). The CMRS also demonstrated predictive validity as a treatment outcome measure in a randomized medication trial for children with bipolar I

disorder (West, Celio, Henry, & Pavuluri, 2011). In the current study, the CMRS had excellent reliability ($\alpha = .90$).

Depression: The Child Bipolar Depression Rating Scale (CBDRS; Unpublished Data, August, 2003) is a companion measure to the CMRS and contains 22 items completed by parents about children's depressive symptoms. Similar to the CMRS, responses are Likert-style and range from 0 (*never/rarely*) to 3 (*very often*). Total scores range from 0 to 66, with higher scores indicating more severe symptoms. The CBDRS is face valid (i.e., items are consistent with *DSM-IV-TR* diagnostic criteria for a major depressive episode) and in the current study it demonstrated strong reliability ($\alpha = .88$). The CBDRS also had modest construct validity, as it was significantly correlated with the clinician-rated CDRS-R ($r = .32$, $p < .01$; Poznanski et al., 1984) and Clinical Global Impressions Scale for Bipolar Disorder-Severity of Depression ($r = .44$, $p < .01$; Spearing, Post, Leverich, Brandt, & Nolen, 1997).

Global Functioning: The Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) is a clinician-rated measure of children's functioning based on familial, social, academic, and occupational impairment due to psychiatric symptoms. Scores range from 1 to 100, with higher scores indicating better functioning. Inter-rater reliability among child psychiatry fellows rating case studies was adequate ($ICC = .84$), as was test-retest reliability ($ICC = .85$; Shaffer et al., 1983). The CGAS also had good discriminant validity when comparing ratings among children in outpatient versus inpatient settings, and concurrent validity when correlated with other scales (Shaffer et al., 1983). In the current study, the CGAS was completed by blind raters and had good inter-rater reliability ($ICC = .76$).

Candidate Mediators

Family Functioning and Environment: The Family Adaptability and Cohesion Scale (FACES; Olson, 2011) is a 62-item, parent-report measure that assesses family functioning, relationships, attitudes, cohesion, and flexibility. Items use a 5-point Likert-scale. FACES has two balanced subscales (cohesion, flexibility) and four unbalanced subscales that tap high and low levels of cohesion (disengaged, enmeshed) and flexibility (rigid, chaotic). Balanced levels of cohesion and flexibility are associated with healthy family functioning, while unbalanced levels of cohesion and flexibility (very high or very low) are associated with impaired family processes. Subscales are used to create three ratios (cohesion, flexibility, total circumplex), with lower scores representing a more unbalanced system and higher scores indicating greater balance. The formulas are: cohesion ratio = balanced cohesion / (disengaged + enmeshed / 2); flexibility ratio = balanced flexibility / (rigid + chaotic / 2); total circumplex ratio = (balanced cohesion + balanced flexibility) / 2. In a convenience sample of undergraduate students and their families/friends, FACES subscales had good internal consistency ($\alpha = .77$ to $.89$) and high levels of concurrent, construct, and discriminant validity (Olson, 2011). In the current study, the FACES total scale ($\alpha = .79$) and subscales ($\alpha = .55$ to $.83$) had adequate internal consistency.

The Family Crisis Oriented Personal Evaluation Scales (FCOPES; McCubbin, Olson, & Larsen, 1991) is a 39-item, parent questionnaire that measures parents' and families' ability to engage in effective problem solving and cope with hardships. Items use a 5-point Likert-

scale. Five subscales assess coping via: 1) social support; 2) spiritual support; 3) acceptance and positive reframing of problems; 4) acquiring/accepting help; and 5) passive appraisal. Scores for the total scale and subscales are calculated by summing item responses. In a nationally representative sample, the FCOPES had adequate internal consistency and test-retest reliability for the overall scale ($\alpha = .77$ to $.86$; $r = .81$) and subscales ($\alpha = .63$ to $.83$, $r = .61$ to $.95$), and good factorial and concurrent validity (McCubbin et al., 1991). In the current study, the FCOPES total scale ($\alpha = .84$) and subscales ($\alpha = .58$ to $.78$) had adequate internal consistency.

Parenting Skills and Coping: The Therapy Outcome Parents Scale (TOPS; West et al., 2009) is a 20-item, parent-report measure that assesses parents' feelings and perceptions regarding their child's bipolar disorder, including their knowledge about PBD and efficacy in coping with it. Sample items include: "I am able to identify my child's mood – and have words to describe them" and "I am able to avoid my own angry outbursts when responding to my child's negative behaviors." Items use a 5-point Likert-scale and total scores range from 20 to 100, with higher scores indicating greater knowledge, parenting capabilities, and coping skills. The TOPS had high internal consistency ($\alpha = .86$ to $.90$) and predictive validity as a treatment outcome measure in an open trial of group CFF-CBT for children with PBD and their parents (West et al., 2009). In the current study, the TOPS demonstrated good internal consistency ($\alpha = .83$).

Child Coping: The Youth Coping Index (YCI; McCubbin, Thompson, & Elver, 1996) is a 31-item, child-report measure that assesses youths' ability to enact effective coping strategies. Items use a 5-point Likert-scale. Three subscales assess personal development, problem solving, and stress management/communication. Scores for the total scale and subscales are calculated by summing item responses. Among youth in residential care, the YCI total scale had good internal consistency ($\alpha = .86$), test-retest reliability ($r = .43$), and predictive validity (McCubbin et al., 1996). In the current study, the YCI demonstrated good internal consistency ($\alpha = .82$).

Data Analysis

The test of joint significance was used to evaluate mediation (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). This test requires that the path from the independent variable (CFF-CBT versus TAU) to the mediator (family/parent/child factors; α Path) and the path from the mediator to the outcome (child mood symptoms/functioning; β Path) are significant, controlling for the independent variable. In addition, change in mediator must be independent of change in outcome, and the path from the independent variable to the outcome (primary analyses in RCTs; τ Path) should show reduced- or non-significance when the mediator is included (τ' Path; see Figure 1). In final models, mediation may occur via a significant main effect of change in mediator on change in outcome, or a significant interaction between intervention and change in mediator on change in outcome (Kraemer et al., 2002; MacKinnon et al., 2002).

Two-level mixed-effects regression (growth curve) models (MRMs) were used with the intent-to-treat (ITT) sample. MRMs account for change over time in a nested dataset, model

repeated measures with subject- and group-specific regression coefficients, and allow for missing data via full maximum likelihood estimation (Singer & Willett, 2003). Given the secondary nature of analyses, significance was set at $p < .05$.

A step-up model building strategy evaluated each outcome and candidate mediator separately. CFF-CBT was coded 1 and Time was centered at 12 weeks (post-treatment). The Treatment Effect indicated post-treatment group differences in intercept, the Time Effect revealed overall trajectory of outcomes, and the Treatment*Time Effect evaluated group differences in slope through follow-up. Random intercept and slope effects were modeled via unstructured covariance matrices, and a quadratic time function was included if significant. Model fit was assessed via Akaike's Information Criterion, Schwarz's Bayesian Criterion, -2 Log Likelihood, and the Deviance Statistic. Effect sizes were calculated via Cohen's d .

Significant candidate mediators were then grand-mean-centered and added to primary outcome MRMs. A step-up model building strategy evaluated each mediator parameter (and its impact on outcomes) sequentially, in the following order: main effect of mediator at post-treatment (Mediator Effect intercept); change in mediator through follow-up (Mediator*Time slope); post-treatment group differences in mediator (Mediator*Treatment intercept); and group differences in change in mediator through follow-up (Mediator*Time*Treatment slope). Mediator effects were retained when significant in MRMs.

Results

Descriptive Statistics

Table 2 reports descriptive statistics for candidate mediators at baseline and across treatment. Per independent-samples t -tests, children in the CFF-CBT group initially had lower manic symptoms (CMRS; $t(66) = -2.90, p = .005$), family cohesion (FACES Cohesion Ratio; $t(65) = -2.01, p = .048$), and family passive appraisal (FCOPES Passive Appraisal Subscale; $t(66) = -2.04, p = .045$), compared with TAU. Thus, baseline levels of these constructs were included in subsequent models as covariates, with the time term excluding baseline, to control for group differences. Table 3 displays Pearson correlations for all putative mediators. All family, parent, and child factors were moderately correlated with one another, suggesting that these were related but distinct constructs. As expected, the highest correlations were found for subscales and total scores of the same measure.

Effect of CFF-CBT on Primary Outcomes (τ Path)

As originally demonstrated in West et al. (2014), final MRMs showed significant improvement in outcomes for CFF-CBT versus TAU (see Table 4). At post-treatment, children receiving CFF-CBT experienced significant reduction in mania (CMRS; Treatment intercept $F(48.69) = 7.90, p = .007, d = 0.69$) and depression (CBDRS; Treatment intercept $F(66.82) = 4.92, p = .030, d = 0.54$) compared with TAU. Treatment*Time slope effects indicated greater improvement in global functioning (CGAS; $F(190.78) = 4.26, p = .040, d = 0.51$) and depression (CBDRS; $F(161.56) = 3.82, p = .052, d = 0.48$) through 6-month follow-up for children who received CFF-CBT versus TAU.

Effect of CFF-CBT on Candidate Mediators (α Path)

In final MRMs, three candidate mediators showed greater change across treatment in response to CFF-CBT versus TAU (see Table 5). Compared to TAU, CFF-CBT families reported significantly higher parenting skills and coping (TOPS; Treatment*Time slope $F(165.91) = 5.74, p = .018, d = 0.59$), flexibility (FACES Flexibility Ratio; Treatment*Time slope $F(33.06) = 4.72, p = .037, d = 0.53$), and positive reframing (FCOPES Reframe Scale; Treatment*Time slope $F(172.22) = 4.19, p = .042, d = 0.50$). Family cohesion also significantly improved over time for all participants (FACES Cohesion Ratio; Time slope $F(109.98) = 6.20, p = .014, d = 0.61$), though there were not significant differences in intercept or slope by treatment group.

Mediation of CFF-CBT on Primary Outcomes (β Path and τ' Path)

According to final mediation MRMs, there was a significant main effect for parenting skills and coping on mania (TOPS intercept $F(109.09) = 6.46, p = .012, d = 0.62$), and a significant interactive effect of parenting skills and coping with treatment on global functioning (TOPS*Treatment intercept $F(169.21) = 4.33, p = .039, d = 0.51$). With the addition of parenting skills and coping, the Treatment intercept effect remained significant for mania but the Treatment*Time slope effect was no longer significant for global functioning (see Figures 2-3 and Table A.1, in the appendix).

There was a significant interactive effect for family flexibility with time and treatment on global functioning (FACES Flexibility Ratio*Time*Treatment slope $F(188.56) = 3.96, p = .048, d = 0.49$). With the addition of family flexibility, the Treatment*Time slope effect was no longer significant (see Figure 3, Table A.2). When significant mediators for global functioning were added simultaneously, both family flexibility (FACES Flexibility Ratio*Time*Treatment slope $F(185.59) = 3.91, p = .049, d = 0.48$) and parenting skills and coping (TOPS*Treatment intercept $F(178.83) = 5.13, p = .025, d = 0.55$) remained significant, while the Treatment*Time slope effect was no longer significant (see Figure 3).

Finally, there was a significant main effect for family positive reframing and its interaction with treatment on depression (FCOPES Reframe Scale intercept $F(216.86) = 4.70, p = .031, d = 0.53$; FCOPES Reframe Scale*Treatment intercept $F(207.22) = 11.10, p = .001, d = 0.81$). With the addition of family positive reframing, the Treatment intercept effect remained significant and the Treatment*Time slope effect remained trend significant (see Figure 4, Table A.3).

Given differences in attrition between treatment conditions, post-hoc analyses examined all models with attrition included as a covariate. Results remained the same when controlling for attrition.

Discussion

This study marks the second investigation of mediators of a psychosocial treatment for youth with PBD. As hypothesized, several parent and family factors significantly improved in response to CFF-CBT versus TAU, and were associated with the CFF-CBT treatment effect. Specifically, parenting skills and coping, family flexibility, and family positive reframing

showed promise as mediators of child mood symptoms and functioning. Main or mediating effects for youth coping were not significant. Results are discussed within the context of prior mediation findings, study limitations, and clinical implications.

Parenting Skills and Coping

As hypothesized, parenting skills and coping significantly improved as a result of CFF-CBT and may mediate the treatment effect on children's manic symptoms and global functioning. Results are in line with those reported in the RCT of MF-PEP, the only other study to evaluate mechanisms of change in psychosocial intervention for youth with PBD or depression, which found that parent factors (i.e., positive beliefs about treatment, quality of services used), as opposed to child processes, mediated improvement in youths' mood severity (Mendenhall et al., 2009).

While children learn symptom management strategies in CFF-CBT, the intervention largely seeks to regulate children's mood by improving parenting skills, coping, and the family environment (Pavuluri et al., 2004a; West et al., 2014). This is because impairing mood symptoms (Birmaher et al., 2009; Geller et al., 2008) and affective circuitry brain dysfunction (Garrett et al., 2012; Passarotti & Pavuluri, 2011) likely make it challenging for youth with PBD to learn and use strategies during a mood episode. Also, impairments in parenting abilities and family functioning (Keenan-Miller et al., 2012; Nader et al., 2013; Schenkel, 2008) and their association with worse course (Geller et al., 2008; Kim et al., 2007; Sullivan et al., 2012) suggest that by directly targeting these familial deficits and promoting a safe and supportive environment, children's mood may stabilize to where they could enact coping skills independently.

CFF-CBT includes parenting skills that are congruent with other child EBTs, but with unique emphases on symptoms and impairments specific to PBD. For example, CFF-CBT teaches caregivers about structure and routine for stabilizing the home and children's mood, as opposed to solely youth-directed coping. CFF-CBT also encourages use of family coping plans during episodes of extreme dysregulation, which involve strategies for maintaining the child's safety, disengaging from the situation, and delaying delivery of consequences until the child has calmed, to prevent mood escalation. In addition, CFF-CBT emphasizes parental self-care and social support, given the stress associated with caring for a child with PBD (Schenkel et al., 2008). Thus, empowering and supporting the family may enhance child outcomes.

In final mediation models, improvement in parenting skills and coping occurred prior to increased global functioning and concurrently with reduced mania. Indeed, parenting techniques may be challenging to implement within the context of severe mania and thus potentially less impactful initially. Also, parents may require practice with skills before they influence family processes. Thus, while effective parenting strategies and coping may explain improvements in mania, the reverse may also be true. Similar sequence of child improvements mediating parent factors has been found in prior treatment outcome trials (Compas et al., 2010; DeGarmo et al., 2004; Silverman, Kurtines, Jaccard, & Pina, 2009).

Importantly, models suggest that parenting skills and coping may be a stronger mediator of global functioning and a partial mediator of mania. Biologically-driven manic symptoms likely require pharmacological intervention in addition to psychotherapy, as recommended in practice parameters for PBD (McClellan et al., 2007; Pavuluri et al., 2004b). In contrast, functioning in familial, social, and academic/occupational domains may be more amenable to psychosocial treatment alone. Nevertheless, parent coping and capabilities appear important for facilitating improvement in both mania and global functioning among youth with PBD.

Family Flexibility

Family flexibility also significantly improved as a result of CFF-CBT and may mediate the treatment effect on children's functioning. In this study, family flexibility represented a balanced way of responding amidst extremes of rigidity and chaos. A mediating effect was not apparent for cohesion, despite documented deficits in this construct among families impacted by PBD (Keenan-Miller et al., 2012; Nader et al., 2013). Rather, both groups demonstrated improvement in cohesion over time. Thus, both structured EBTs and general psychotherapy may be effective for enhancing cohesion. However, focus on family flexibility appeared unique to CFF-CBT, and may have facilitated improvement in children's functioning.

Indeed, youth with PBD have deficits in cognitive flexibility, or the ability to adapt to changing environments (McClure et al., 2005). Clinically, this could translate to inflexible response patterns to emotional stimuli, especially during mood episodes. Family members can model flexibility in coping for youth with PBD, which may offer support for symptom reduction. For example, in response to child dysregulation, the family can respond flexibly by offering solutions, suggesting coping skills, or disengaging. Family flexibility may then improve youths' ability to adapt to stressors and enhance functioning. Imaging work with adolescents who received a similar family-focused EBT for PBD demonstrated increased activation of the dorsolateral prefrontal cortex (Garrett et al., 2015), which has been implicated in cognitive flexibility impairment in PBD (Nelson et al., 2007); thus, improvement in this neuropsychological deficit may be possible with therapy. In the present study, when family flexibility and parenting capabilities were entered simultaneously, both remained significant in the final, combined mediation model. Therefore, both constructs may be important for enhancing global functioning among youth with PBD.

Family Positive Reframing

Finally, family positive reframing significantly improved as a result of CFF-CBT and may partially mediate the treatment effect on children's depression. Reframing represented families' ability to accept difficult situations, think positively, and redefine problems to make them manageable. Main or mediating effects for other family coping strategies (social and spiritual support, mobilizing help, passive appraisal) were not significant. Mindfulness and reframing are emphasized in CFF-CBT, whereas aforementioned methods reflect general coping skills, which may have been equivalent across groups. Thus, depression outcomes were potentially driven by focus on cognitive skills, rather than nonspecific support-seeking.

According to treatment outcome trials for pediatric internalizing disorders, CBT may affect change by reducing youths' negative thinking via cognitive restructuring (Hogendoorn et al., 2014; Jacobs et al., 2014; Kaufman et al., 2005; Kendall & Treadwell, 2007; Kolko et al., 2000; Stice et al., 2010; Treadwell & Kendall, 1996). The younger age of children in the current study, coupled with severe mood symptoms and affective neural dysfunction commonly observed among youth with PBD, likely rendered it difficult for children to implement cognitive skills. However, families' ability to think adaptively and realistically about problems may have enhanced their ability to implement strategies, potentially promoting children's improved depression. Prior research has similarly shown that improvements in caregiver factors, such as parenting skills, emotional reactions, and mood, are important for reducing younger children's depressive symptoms (Compas et al., 2010; DeGarmo et al., 2004; Holt et al., 2014; Schleider et al., 2015).

Results from the current study suggest that family positive reframing may be a partial mediator of depression; thus, biologically-driven depressive symptoms in PBD likely require supplementary interventions, such as pharmacotherapy, to maximize outcomes (McClellan et al., 2007; Pavuluri et al., 2004b). In addition, mechanisms of change in CFF-CBT may be complex and transactional. For instance, the focus on engagement and psychoeducation in early sessions could have instilled hope for families and facilitated an initial decrease in mood, subsequently allowing for more effective use of CBT skills by parents and compounded positive changes for parents and children. Nevertheless, parent and family factors appear important in the treatment of PBD and associated with the CFF-CBT intervention response

Limitations

Strengths of this study included the use of randomization, a dose-matched psychotherapy control, and a diverse, clinically representative sample; and examination of family, parent, and child factors potentially involved in treatment-related symptom change in PBD. However, findings should be interpreted within the context of limitations. First, the modest sample coupled with heterogeneity in demographics precluded evaluation of mediating processes based on these subgroups. While potential mediators were identified, the sample size may have lacked power to detect additional mechanisms of change. Despite randomization, baseline differences in children's manic symptoms and family factors emerged between conditions, suggesting that the two groups were not entirely equivalent. Controlling for these differences also reduced power. In addition, equal distribution of bipolar diagnoses was not observed. A majority of children had bipolar disorder NOS, which is expected given the age of the sample, though these youth had comparable symptom severity and functional impairment as youth with bipolar I disorder (Hafeman et al., 2013).

Other limitations concern methodology. Variables were assessed concurrently at all time points. However, evidence for mediation is strongest when changes in mediators precede changes in outcomes (Kraemer et al., 2002). As some analyses demonstrated concurrent change in mediators and outcomes, the temporal ordering of effects cannot be certain, and transactional processes may be involved in treatment-related symptom changes in CFF-CBT. Additionally, all possible mediators were not assessed. For example, unmeasured child

factors may have enhanced improvements in symptoms and parent/family factors. Measurement of mediators was also limited to self-report questionnaires on family functioning, parenting skills and coping, and child coping. Only one measure was completed by children about their coping, with moderate test-retest reliability. Observational or semi-structured assessment may have offered more sensitive information, as would examination of specific parenting behaviors. In addition, the CBDRS demonstrated only modest correlations with clinician-rated measures. Also, child mood was evaluated via parent questionnaires because research suggests that parent report is most useful in assessing symptoms of PBD (Youngstrom et al., 2004), though semi-structured interviews are the gold-standard.

Finally, several limitations involve missing data. Differential treatment completion in CFF-CBT versus TAU and attrition over follow-up may have limited the power to detect group differences, though controlling for attrition in analyses did not change findings. Relatedly, as information regarding use of other interventions following the study was not gathered, the long-term impact of CFF-CBT is not certain. Lastly, while fidelity ratings indicated that treatment elements between CFF-CBT and TAU did not overlap, specific session content and structure in TAU was not available.

Future Directions

Future research should address limitations to offer more definitive conclusions about mediators of CFF-CBT. Use of a larger sample may offer less likelihood for pretreatment differences, comparison of mediating effects across demographic groups, and more power to detect additional mediators. Sequential measurement of mediators and outcomes over a longer follow-up with higher retention may provide clarity regarding the relationship between mediators and outcomes and the long-term impact of CFF-CBT. Relatedly, examination of the relation between therapist adherence and changes in family processes and child outcomes may shed light on therapeutic procedures linked to improvement. In addition, more sensitive, multi-informant measurement of a broad range of possible mediators, specific parenting behaviors, neural correlates, and clinical outcomes may identify other mechanisms. If research continues to implicate parent/family factors as mediators of CFF-CBT, future iterations of the treatment should incorporate these components more heavily. Finally, assessment of TAU sessions would offer valuable information regarding general clinical care provided to youth with PBD.

Clinical Implications

Findings support the efficacy of CFF-CBT for PBD, and suggest that parenting skills and coping, family flexibility, and family positive reframing should be emphasized in treatment. Specifically, parenting skills (e.g., emotion/trigger identification, routine development, safety monitoring) and coping (e.g., distraction, self-care, social support) may be important for improving children's mania and global functioning, family flexible responding may enhance functioning, and family positive reframing of problems may ameliorate depression. Moreover, treatment-related changes may involve transactional relationships between child symptoms/functioning and parent/family factors, rather than purely linear processes. Importantly, these findings are consistent with moderator results, which demonstrated

superiority of CFF-CBT versus TAU for children whose parents had higher baseline depressive symptoms and lower income, and for families with higher cohesion (Weinstein et al., 2015). Collectively, our research highlights the importance of parent and family functioning in the treatment of PBD and the CFF-CBT treatment effect. Future work should further examine the complex mechanisms underlying intervention response in PBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, Keller M. Fouryear longitudinal course of children and adolescents with bipolar spectrum disorders: The Course and Outcome of Bipolar Youth (COBY) study. *American Journal of Psychiatry*. 2009; 166(7):795–804. [PubMed: 19448190]
- Compas BE, Champion JE, Forehand R, Cole DA, Reeslund KL, Fear J, Roberts L. Coping and parenting: Mediators if 12-month outcomes of a family group cognitive-behavioral preventive intervention with families of depressed parents. *Journal of Consulting and Clinical Psychology*. 2010; 78(5):623–634. [PubMed: 20873898]
- DeGarmo DS, Patterson GR, Forgatch MS. How do outcomes in a specified parent training intervention maintain or wane over time? *Prevention Science*. 2004; 5(2):73–89. [PubMed: 15134313]
- Fristad MA, MacPherson HA. Evidence-based psychosocial treatments for child and adolescent bipolar spectrum disorders. *Journal of Clinical Child and Adolescent Psychology*. 2014; 43(3):339–355. [PubMed: 23927375]
- Fristad MA, Verducci JS, Walters K, Young ME. Impact of multifamily psychoeducational psychotherapy in treating children aged 8 to 12 years with mood disorders. *Archives of General Psychiatry*. 2009; 66(9):1013–1020. [PubMed: 19736358]
- Garrett AS, Miklowitz DJ, Howe ME, Singh MK, Acquaye TK, Hawkey CG, Chang KD. Changes in brain activation following psychotherapy for youth with mood dysregulation at familial risk for bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2015; 56:215–220. [PubMed: 25283342]
- Garrett AS, Reiss AL, Howe ME, Kelley RG, Singh MK, Chang KD. Abnormal amygdala and prefrontal cortex activation to facial expressions in pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012; 51(8):821–831. [PubMed: 22840553]
- Geller B, Tillman R, Bolhofner K, Zimmerman B. Child bipolar I disorder: Prospective continuity with adult bipolar I disorder; Characteristics of second and third episodes; Predictors of 8-year outcome. *Archives of General Psychiatry*. 2008; 65(10):1125–1133. [PubMed: 18838629]
- Geller B, Zimmerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, Soutullo C. Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001; 40(4):450–455. [PubMed: 11314571]
- Hafeman D, Axelson D, Demeter C, Findling RL, Fristad MA, Kowatch RA, Birmaher B. Phenomenology of bipolar disorder not otherwise specified in youth: A comparison of clinical

characteristics across the spectrum of manic symptoms. *Bipolar Disorders*. 2013; 15(3):240–252. [PubMed: 23521542]

Hauser M, Galling B, Correll CU. Suicidal ideation and suicide attempts in children and adolescents with bipolar disorder: A systematic review of prevalence and incidence rates, correlates, and targeted interventions. *Bipolar Disorders*. 2013; 15(5):507–523. [PubMed: 23829436]

Hogendoorn SM, Prins PJM, Boer F, Vervoort L, Wolters LH, Moorlag H, de Haan E. Mediators of cognitive behavioral therapy for anxiety-disordered children and adolescents: Cognition, perceived control, and coping. *Journal of Clinical Child and Adolescent Psychology*. 2014; 43(3):486–500. [PubMed: 23795885]

Holt T, Jensen TK, Wentzel-Larsen T. The change and the mediating role of parental emotional reactions and depression in the treatment of traumatized youth: Results from a randomized controlled study. *Child and Adolescent Psychiatry and Mental Health*. 2014; 8:11. [PubMed: 24712976]

Jacobs RH, Becker SJ, Curry JF, Silva SG, Ginsburg GS, Henry DB, Reinecke MA. Increasing positive outlook partially mediates the effect of empirically supported treatments on depression symptoms among adolescents. *Journal of Cognitive Psychotherapy*. 2014; 28(1):3–19. [PubMed: 24944436]

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Ryan N. Schedule of Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (KSADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36(37):980–988. [PubMed: 9204677]

Kaufman NK, Rohde P, Seeley JR, Clarke GN, Stice E. Potential mediators of cognitive-behavioral therapy for adolescents with comorbid major depression and conduct disorder. *Journal of Consulting and Clinical Psychology*. 2005; 73(1):38–46. [PubMed: 15709830]

Keenan-Miller D, Peris T, Axelson D, Kowatch RA, Miklowitz DJ. Family functioning, social impairment, and symptoms among adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012; 51(10):1085–1094. [PubMed: 23021483]

Kendall PC, Cummings CM, Villabø MA, Narayanan MK, Treadwell K, Birmaher B, Albano AM. Mediators of change in the Child/Adolescent Anxiety Multimodal Treatment Study. *Journal of Consulting and Clinical Psychology*. 2016; 84(1):1–14. [PubMed: 26460572]

Kendall PC, Treadwell KRH. The role of self-statements as a mediator in treatment for youth with anxiety disorders. *Journal of Consulting and Clinical Psychology*. 2007; 75(3):380–389. [PubMed: 17563155]

Kim EY, Miklowitz DJ, Biuckians A, Mullen K. Life stress and the course of early-onset bipolar disorder. *Journal of Affective Disorders*. 2007; 99(1-3):37–44. [PubMed: 17084905]

Kolko DJ, Brent DA, Baugher M, Bridge J, Birmaher B. Cognitive and family therapies for adolescent depression: Treatment specificity, mediation, and moderation. *Journal of Consulting and Clinical Psychology*. 2000; 68(4):603–614. [PubMed: 10965636]

Kraemer HC, Wilson T, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*. 2002; 59(10):877–883. [PubMed: 12365874]

Lorenzo-Luaces L, German RE, DeRubeis RJ. It's complicated: The relation between cognitive change procedures, cognitive change, and symptom change in cognitive therapy for depression. *Clinical Psychology Review*. 2015; 41:3–15. [PubMed: 25595660]

MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*. 2002; 7(1):83–104. [PubMed: 11928892]

McClellan J, Kowatch R, Findling RL, Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2007; 46(1):107–125. [PubMed: 17195735]

McClure EB, Treland JE, Snow J, Schmajuk M, Dickstein DP, Towbin KE, Leibenluft E. Deficits in social cognition and response flexibility in pediatric bipolar disorder. *American Journal of Psychiatry*. 2005; 162(9):1644–1651. [PubMed: 16135623]

- McCubbin, HI.; Olson, DH.; Larsen, AS. F-COPES: Family crisis oriented personal evaluation scales. In: McCubbin, HI.; Thompson AI, AI., editors. Family assessment inventories for research and practice. 2nd. University of Wisconsin-Madison; Madison, WI: 1991. p. 203-218.
- McCubbin, HI.; Thompson, AI.; Elver, KM. Youth coping index (YCI). In , , & (Eds.). In: McCubbin, HI.; Thompson, AI.; McCubbin, MA., editors. Family assessment: Resiliency, coping and adaptation—Inventories for research and practice. University of Wisconsin-Madison; Madison, WI: 1996. p. 585-612.
- Mendenhall AN, Fristad MA, Early TJ. Factors influencing service utilization and mood symptom severity in children with mood disorders: Effects of multifamily psychoeducation groups (MFPGs). *Journal of Consulting and Clinical Psychology*. 2009; 77(3):463–473. [PubMed: 19485588]
- Miklowitz DJ, Axelson DA, Birmaher B, George EL, Taylor DO, Schneck CD, Brent DA. Family-Focused Treatment for adolescents with bipolar disorder: Results of a 2-year randomized trial. *Archives of General Psychiatry*. 2008; 65(9):1053–1061. [PubMed: 18762591]
- Miklowitz DJ, Schneck CD, Singh MK, Taylor DO, George EL, Cosgrove VE, Chang KD. Early intervention for symptomatic youth at risk for bipolar disorder: A randomized trial of Family-Focused Therapy. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013; 52(2):121–131. [PubMed: 23357439]
- Nader EG, Kleinman A, Gomes BC, Bruscagin C, dos Santos B, Nicoletti M, Caetano SC. Negative expressed emotion best discriminates families with bipolar disorder children. *Journal of Affective Disorders*. 2013; 148(2-3):418–423. [PubMed: 23218896]
- Nelson EE, Vinton DT, Berghorst L, Towbin KE, Hommer RE, Dickstein DP, Leibenluft E. Brain systems underlying response flexibility in healthy and bipolar adolescents: An event-related fMRI study. *Bipolar Disorders*. 2007; 9(8):810–819. [PubMed: 18076530]
- Olson D. FACES IV and the circumplex model: Validation study. *Journal of Marital and Family Therapy*. 2011; 37(1):64–80. [PubMed: 21198689]
- Passarotti AM, Pavuluri MN. Brain functional domains inform therapeutic interventions in attention-deficit/hyperactivity disorder and pediatric bipolar disorder. *Expert Review of Neurotherapeutics*. 2011; 11(6):897–914. [PubMed: 21651336]
- Pavuluri MN, Graczyk PA, Henry DB, Carbray JA, Heidenreich J, Miklowitz DJ. Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: Development and preliminary results. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004a; 43(5):528–537. [PubMed: 15100559]
- Pavuluri MN, Henry DB, Devineni B, Carbray JA, Birmaher B. Child Mania Rating Scale: Development, reliability, and validity. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45(5):550–560. [PubMed: 16601399]
- Pavuluri MN, Henry DB, Devineni B, Carbray JA, Naylor MW, Janicak PG. A pharmacotherapy algorithm for stabilization and maintenance of pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004b; 43(7):859–867. [PubMed: 15213587]
- Perlis RH, Dennehy EB, Miklowitz DJ, Delbello MP, Ostacher M, Calabrese JR, Sachs G. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: Results from the STEP-BD study. *Bipolar Disorders*. 2009; 11(4):391–400. [PubMed: 19500092]
- Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. *Journal of the American Academy of Child Psychiatry*. 1984; 23(2):191–197. [PubMed: 6715741]
- Schenkel LS, West AE, Harral EM, Patel NB, Pavuluri MN. Parent-child interactions in pediatric bipolar disorder. *Journal of Clinical Psychology*. 2008; 64(4):422–437. [PubMed: 18357574]
- Schleider JL, Ginsburg GS, Keeton CP, Weisz JR, Birmaher B, Kendall PC, Walkup JT. Parental psychopathology and treatment outcome for anxious youth: Roles of family functioning and caregiver strain. *Journal of Consulting and Clinical Psychology*. 2015; 83(1):213–224. [PubMed: 25222799]
- Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S. A Children's Global Assessment Scale (CGAS). *Archives of General Psychiatry*. 1983; 40(11):1228–1231. [PubMed: 6639293]

- Silverman WK, Kurtines WM, Jaccard J, Pina AA. Directionality of change in youth anxiety treatment involving parents: An initial examination. *Journal of Consulting and Clinical Psychology*. 2009; 77(3):474–485. [PubMed: 19485589]
- Singer, JD.; Willett, JB. *Applied longitudinal data analysis*. Oxford University Press, Inc.; New York, NY: 2003.
- Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): The CGI-BP. *Psychiatry Research*. 1997; 73:159–171. [PubMed: 9481807]
- Stice E, Rohde P, Seeley JR, Gau JM. Testing mediators of intervention effects in randomized controlled trials: An evaluation of three depression prevention programs. *Journal of Consulting and Clinical Psychology*. 2010; 78(2):273–280. [PubMed: 20350038]
- Sullivan AE, Judd CM, Axelson DA, Miklowitz DJ. Family functioning and the course of adolescent bipolar disorder. *Behavior Therapy*. 2012; 43(4):837–847. [PubMed: 23046785]
- Treadwell KRH, Kendall PC. Self-talk in youth with anxiety disorders: States of mind, content specificity, and treatment outcome. *Journal of Consulting and Clinical Psychology*. 1996; 64(5): 941–950. [PubMed: 8916623]
- Urbaniak, GC.; Plous, S. *Research Randomizer (Version 3.0)* [Computer software]. 2014. Retrieved on September 24, 2014, from <http://www.randomizer.org/>
- Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA. Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania. *Bipolar Disorders*. 2016; 18(1): 19–32. [PubMed: 26748678]
- Van Meter AR, Moreira AL, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *Journal of Clinical Psychiatry*. 2011; 72(9):1250–1256. [PubMed: 21672501]
- Webb CA, Auerbach RP, DeRubeis RJ. Processes of change in CBT of adolescent depression: Review and recommendations. *Journal of Clinical Child and Adolescent Psychology*. 2012; 41(5):654–665. [PubMed: 22867130]
- Weersing VR, Weisz JR. Mechanisms of action in youth psychotherapy. *Journal of Child Psychology and Psychiatry*. 2002; 43(1):3–29. [PubMed: 11848335]
- Weinstein SM, Henry DB, Katz AC, Peters AT, West AE. Treatment moderators of child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2015; 54(2):116–125. [PubMed: 25617252]
- Weinstein SM, West AE, Pavuluri M. Psychosocial intervention for pediatric bipolar disorder: Current and future directions. *Expert Review of Neurotherapeutics*. 2013; 13(7):843–850. [PubMed: 23898854]
- West AE, Celio CI, Henry DB, Pavuluri MN. Child Mania Rating Scale-Parent Version: A valid measure of symptom change due to pharmacotherapy. *Journal of Affective Disorders*. 2011; 128(1-2):112–119.
- West AE, Jacobs RH, Westerholm R, Lee A, Carbray J, Heidenreich J, Pavuluri MN. Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: Pilot study of group treatment format. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*. 2009; 18(3):239–246. [PubMed: 19718425]
- West AE, Weinstein SM, Peters AT, Katz AC, Henry DB, Cruz RA, Pavuluri MN. Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: A randomized clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2014; 53(11):1168–1178. [PubMed: 25440307]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity, and sensitivity. *British Journal of Psychiatry*. 1978; 133:429–435. [PubMed: 728692]
- Youngstrom EA, Findling RL, Calabrese JR, Gracious BL, Demeter C, Bedoya DD, Price M. Comparing the diagnostic accuracy of six potential screening instruments for bipolar disorder in youths aged 5 to 17 years. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004; 43(7):847–858. [PubMed: 15213586]

Highlights

- CFF-CBT improved children's manic and depressive symptoms and global functioning.
- CFF-CBT improved parent coping, family flexibility, and family positive reframing.
- Parent coping and family functioning showed promise as mediators of CFF-CBT.
- CFF-CBT may improve child outcomes via enhanced parent coping and family functioning.

Figure 1.

Conceptual model of treatment effects on outcomes in primary randomized controlled trial analyses (a) and in secondary analyses including mediators (b). CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; TAU = Treatment As Usual; α = impact of CFF-CBT on candidate mediators; β = impact of candidate mediators on child mood/functioning outcomes; τ = impact of CFF-CBT on child mood/functioning outcomes without inclusion of mediators; τ' = impact of CFF-CBT on child mood/functioning outcomes with inclusion of mediators.

Figure 2.

Final mixed-effects regression mediation model for children's manic symptoms. CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; CMRS = Child Mania Rating Scale; TOPS = Therapy Outcome Parents Scale; α = impact of CFF-CBT on TOPS; β = impact of TOPS on CMRS; τ = impact of CFF-CBT on CMRS without inclusion of TOPS; τ' = impact of CFF-CBT on CMRS with inclusion of TOPS. Regarding effects: Treatment = post-treatment group differences in intercept; Treatment*Time = group differences in slope though follow-up; TOPS Main Effect = overall Parenting Skills & Coping at post-treatment (intercept); CMRS Main Effect = baseline mania scores covaried, given pre-treatment group differences in mania.

* $p < .05$; ** $p < .01$; *** $p < .001$.

Figure 3.

Final mixed-effects regression mediation model for children's global functioning. CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; CGAS = Children's Global Assessment Scale; TOPS = Therapy Outcome Parents Scale; FACES = Family Adaptability and Cohesion Scale; α = impact of CFF-CBT on TOPS and FACES Flexibility Ratio; β = impact of TOPS and FACES Flexibility Ratio on CGAS; τ = impact of CFF-CBT on CGAS without inclusion of TOPS and FACES Flexibility Ratio; τ' = impact of CFF-CBT on CGAS with inclusion of TOPS and FACES Flexibility Ratio. Regarding effects: Treatment = post-treatment group differences in intercept; Treatment*Time = group differences in slope through follow-up; TOPS Main Effect = overall Parenting Skills & Coping at post-treatment (intercept); TOPS*Treatment = post-treatment group differences in Parenting Skills & Coping (intercept); FACES Flexibility Ratio Main Effect = overall Family Flexibility at post-treatment (intercept); FACES Flexibility Ratio*Time*Treatment = group differences in change in Family Flexibility through follow-up (slope).

* $p < .05$.

Figure 4.

Final mixed-effects regression mediation model for children's depressive symptoms. CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; CBDRS = Child Bipolar Depression Rating Scale; FCOPES = Family Crisis Oriented Personal Evaluation Scales; α = impact of CFF-CBT on FCOPES Reframe Scale; β = impact of FCOPES Reframe Scale on CBDRS; τ = impact of CFF-CBT on CBDRS without inclusion of FCOPES Reframe Scale; τ' = impact of CFF-CBT on CBDRS with inclusion of FCOPES Reframe Scale. Regarding effects: Treatment = post-treatment group differences in intercept; Treatment*Time = group differences in slope though follow-up; FCOPES Reframe Scale Main Effect = overall Family Positive Reframing at post-treatment (intercept); FCOPES Reframe Scale*Treatment = post-treatment group differences in Family Positive Reframing (intercept).

$\sim p < .10$; $* p < .05$; $** p < .01$.

Table 1

Baseline Demographic and Descriptive Statistics

Variable	CFF-CBT (<i>n</i> = 34) <i>M</i> (<i>SD</i>) or <i>n</i> (%)	TAU (<i>n</i> = 35) <i>M</i> (<i>SD</i>) or <i>n</i> (%)
Age, <i>M</i> (<i>SD</i>)	9.26 (1.93)	9.11 (1.25)
Sex, <i>Male</i>	18 (53)	22 (63)
Ethnicity		
Caucasian	18 (53)	18 (52)
African American	11 (32)	10 (29)
Hispanic	4 (12)	3 (8)
American Indian or Alaskan Native	0 (0)	3 (8)
Native American or Pacific Islander	0 (0)	1 (3)
Other	1 (3)	0 (0)
Family Income, < \$50,000/year	12 (43)	12 (39)
Living Situation, <i>single-parent home</i>	12 (38)	13 (39)
Bipolar Disorder Diagnosis		
Bipolar I Disorder	8 (24)	14 (40)
Bipolar II Disorder	2 (6)	2 (6)
Bipolar Disorder Not Otherwise Specified	24 (70)	19 (54)
Comorbidity		
Attention-Deficit/Hyperactivity Disorder	22 (65)	31 (89)
Oppositional Defiant Disorder	20 (61)	22 (63)
Any Anxiety Disorder	13 (39)	8 (27)
Conduct Disorder	3 (9)	3 (9)

Note. CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; TAU = Treatment As Usual.

Table 2

Descriptive Statistics for Primary Child Mood and Functioning Outcomes and Candidate Family, Parent, and Child Mediators

Measure	Baseline		Post-Treatment (12 weeks)		Follow-Up (39 weeks)	
	CFF-CBT (<i>n</i> = 34) <i>M</i> (<i>SD</i>)	TAU (<i>n</i> = 35) <i>M</i> (<i>SD</i>)	CFF-CBT (<i>n</i> = 30) <i>M</i> (<i>SD</i>)	TAU (<i>n</i> = 17) <i>M</i> (<i>SD</i>)	CFF-CBT (<i>n</i> = 16) <i>M</i> (<i>SD</i>)	TAU (<i>n</i> = 13) <i>M</i> (<i>SD</i>)
Primary Child Outcomes						
Mania (CMRS)	19.82 (8.59)	26.82 (11.18)	13.94 (9.01)	29.91 (11.39)	11.03 (6.59)	23.18 (14.06)
Depression (CBDRS)	17.92 (9.72)	20.59 (10.59)	12.76 (7.06)	19.17 (11.92)	12.60 (7.04)	18.31 (11.28)
Functioning (CGAS)	50.50 (5.87)	48.74 (4.86)	62.64 (12.20)	58.94 (10.43)	65.80 (11.30)	56.25 (9.95)
Candidate Family Mediators (FACES)						
Cohesion Ratio	2.03 (0.72)	2.41 (0.84)	2.50 (1.04)	2.72 (1.07)	2.51 (1.19)	2.47 (1.13)
Flexibility Ratio	1.44 (0.35)	1.57 (0.54)	1.54 (0.35)	1.68 (0.49)	1.69 (0.43)	1.55 (0.45)
Total Circumplex Ratio	1.73 (0.47)	1.99 (0.65)	2.02 (0.65)	2.20 (0.75)	2.10 (0.74)	2.01 (0.77)
Candidate Family Mediators (FCOPES)						
Social Support	27.22 (6.74)	28.29 (6.57)	27.32 (7.29)	26.44 (7.62)	28.40 (4.48)	27.86 (8.44)
Spiritual Support	12.90 (4.88)	13.88 (4.26)	12.46 (5.52)	14.13 (3.16)	13.53 (5.22)	14.18 (5.06)
Positive Reframing	27.78 (4.95)	28.65 (5.45)	29.21 (3.55)	30.69 (4.96)	30.47 (4.63)	28.00 (6.00)
Mobilizing Help	15.10 (3.33)	15.62 (3.48)	15.04 (3.03)	14.75 (3.57)	15.07 (2.58)	15.15 (4.30)
Passive Appraisal	15.00 (3.74)	16.63 (2.75)	15.88 (2.52)	16.19 (3.02)	15.73 (2.79)	15.27 (2.76)
Overall Family Coping	98.01 (12.96)	103.06 (14.24)	99.95 (14.11)	102.19 (14.36)	103.20 (8.78)	100.41 (18.68)
Candidate Parent Mediator (TOPS)						
Parenting Skills & Coping	69.48 (10.49)	71.89 (11.75)	80.29 (7.30)	78.37 (12.76)	79.47 (7.39)	78.00 (13.80)
Candidate Child Mediator (YCI)						
Overall Youth Coping	92.79 (17.19)	100.11 (16.80)	96.91 (17.27)	107.00 (17.44)	95.50 (17.67)	101.02 (15.37)

Note. CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; TAU = Treatment As Usual; CMRS = Child Mania Rating Scale; CBDRS = Child Bipolar Depression Rating Scale; CGAS = Children's Global Assessment Scale; FACES = Family Adaptability and Cohesion Scale; FCOPES = Family Crisis Oriented Personal Evaluation Scales; TOPS = Therapy Outcome Parents Scale; YCI = Youth Coping Index. The CMRS, CBDRS, FACES, FCOPES, and TOPS were completed by parents. The CGAS was completed by blind raters. The YCI was completed by children.

Table 3

Pearson Correlations between Candidate Family, Parent, and Child Mediators

	1	2	3	4	5	6	7	8	9	10	11
1. Cohesion Ratio (FACES)	–										
2. Flexibility Ratio (FACES)	.68***	–									
3. Total Circumplex Ratio (FACES)	.96***	.86***	–								
4. Social Support (FCOPES)	.26*	.11	.23~	–							
5. Spiritual Support (FCOPES)	.22~	.26*	.25*	.27*	–						
6. Positive Reframing (FCOPES)	.36**	.46***	.43***	.45***	.31**	–					
7. Mobilizing Help (FCOPES)	.09	.11	.11	.43***	.22~	.04	–				
8. Passive Appraisal (FCOPES)	.31**	.11	.26~	–.12	–.16	–.10	–.03	–			
9. Overall Family Coping (FCOPES)	.43***	.36**	.44***	.82***	.60***	.68***	.54***	.10	–		
10. Parenting Skills & Coping (TOPS)	.22~	.32**	.27*	.32**	.02	.23~	.31*	.06	.35**	–	
11. Overall Youth Coping (YCI)	–.07	.13	.00	–.03	.28*	.05	.11	–.05	.11	–.02	–

Note. FACES = Family Adaptability and Cohesion Scale; FCOPES = Family Crisis Oriented Personal Evaluation Scales; TOPS = Therapy Outcome Parents Scale; YCI = Youth Coping Index.

~ $p < .10$;

* $p < .05$;

** $p < .01$;

*** $p < .001$.

Table 4

Final Mixed-Effects Regression Models Examining Impact of CFF-CBT on Primary Child Mood and Functioning Outcomes

Effect	Mania (CMRS)		Depression (CBDRS)		Functioning (CGAS)	
	β (SE)	<i>d</i>	β (SE)	<i>d</i>	β (SE)	<i>d</i>
Intercept	7.24 (2.46) **	—	18.38 (1.61) ***	—	60.32 (1.66) ***	—
Time	−0.06 (0.06)	0.25	−0.10 (0.06)	0.39	0.50 (0.10) ***	1.20
Treatment	−4.56 (1.62) **	0.69	−4.57 (2.06) *	0.54	2.76 (1.85)	0.37
Treatment × Time	−0.08 (0.08)	0.24	−0.12 (0.06) ~	0.48	0.21 (0.10) *	0.51
Quadratic	—	—	0.01 (0.00) **	—	−0.03 (0.00) ***	—
Baseline CMRS	0.65 (0.08) ***	—	—	—	—	—

Note. CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; CMRS = Child Mania Rating Scale; CBDRS = Child Bipolar Depression Rating Scale; CGAS = Children's Global Assessment Scale. Regarding effects: Time = overall trajectory of outcomes; Treatment = post-treatment group differences in intercept; Treatment × Time = group differences in slope though follow-up; Baseline CMRS = baseline mania scores covaried, given pre-treatment group differences in mania. Effect sizes were calculated via Cohen's *d*.

~ $p < .10$;

* $p < .05$;

** $p < .01$;

*** $p < .001$.

Table 5

Final Mixed-Effects Regression Models Examining Impact of CFF-CBT on Candidate Family, Parent, and Child Mediators

Effect	Cohesion Ratio (FACES)		Flexibility Ratio (FACES)		Total Circumplex Ratio (FACES)		Social Support (FCOPES)	
	β (SE)	<i>d</i>	β (SE)	<i>d</i>	β (SE)	<i>d</i>	β (SE)	<i>d</i>
Intercept	0.67 (0.28) *	—	1.56 (0.07) ***	—	2.00 (0.10) ***	—	27.83 (1.01) ***	—
Time	0.03 (0.01) *	0.61	−0.00 (0.00)	0.17	0.00 (0.00)	0.02	0.00 (0.04)	0.01
Treatment	0.06 (0.16)	0.08	−0.10 (0.09)	0.26	−0.19 (0.14)	0.35	−0.19 (1.40)	0.03
Treatment × Time	0.01 (0.01)	0.19	0.01 (0.00) *	0.53	0.01 (0.00)~	0.42	0.02 (0.06)	0.10
Quadratic	−0.00 (0.00) *	—	—	—	—	—	—	—
Baseline Cohesion	0.80 (0.10) ***	—	—	—	—	—	—	—
Effect	Spiritual Support (FCOPES)		Positive Reframing (FCOPES)		Mobilizing Help (FCOPES)		Passive Appraisal (FCOPES)	
	β (SE)	<i>d</i>	β (SE)	<i>d</i>	β (SE)	<i>d</i>	β (SE)	<i>d</i>
Intercept	13.99 (0.76) ***	—	29.18 (0.73) ***	—	15.47 (0.48) ***	—	8.47 (1.24) ***	—
Time	0.01 (0.02)	0.18	−0.03 (0.03)	0.22	−0.01 (0.02)	0.09	−0.01 (0.02)	0.10
Treatment	−1.26 (1.07)	0.29	−0.62 (1.00)	0.15	−0.41 (0.66)	0.15	0.12 (0.46)	0.06
Treatment × Time	0.00 (0.03)	0.03	0.09 (0.04) *	0.50	0.00 (0.03)	0	0.03 (0.03)	0.25
Baseline Appraisal	—	—	—	—	—	—	0.45 (0.07) ***	—
Effect	Overall Family Coping (FCOPES)		Parenting Skills & Coping (TOPS)		Overall Youth Coping (YCI)			
	β (SE)	<i>d</i>	β (SE)	<i>d</i>	β (SE)	<i>d</i>		
Intercept	102.64 (2.12) ***	—	79.05 (1.71) ***	—	105.52 (2.89) ***	—		
Time	−0.04 (0.08)	0.12	0.37 (0.07) ***	1.30	0.22 (0.15)	0.38		
Treatment	−3.46 (2.94)	0.29	0.18 (2.17)	0.02	−5.84 (3.49)~	0.41		
Treatment × Time	0.15 (0.11)	0.36	0.16 (0.07) *	0.59	−0.01 (0.14)	0.02		
Quadratic	—	—	−0.02 (0.00) ***	—	−0.02 (0.01) *	—		

Note. CFF-CBT = Child- and Family-Focused Cognitive-Behavioral Therapy; FACES = Family Adaptability and Cohesion Scale; FCOPES = Family Crisis Oriented Personal Evaluation Scales; TOPS = Therapy Outcome Parents Scale; YCI = Youth Coping Index. Regarding effects: Time = overall trajectory of outcomes; Treatment = post-treatment group differences in intercept; Treatment × Time = group differences in slope though follow-up; Baseline Cohesion = baseline FACES Cohesion Ratio covaried, given pre-treatment group differences in family cohesion; Baseline Appraisal = baseline FCOPES Passive Appraisal scores covaried, given pre-treatment group differences in passive appraisal. Effect sizes were calculated via Cohen's *d*.

~ $p < .10$;

* $p < .05$;

** $p < .01$;

*** $p < .001$.