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Effects of family intervention on psychosocial functioning and mood symptoms of youth at high risk for bipolar disorder

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Abstract

Objectives: Family-focused therapy (FFT) is associated with reduced rates of mood episodes among youth at high risk for bipolar disorder (BD). In a randomized trial of FFT compared to a psychoeducational-only treatment (enhanced care, EC), we sought to determine if changes in psychosocial functioning mediate mood improvements among high-risk youth.

Method: 119 youths with active mood symptoms and a family history of BD were randomized to either 4 months of FFT or EC. Participants were rated on mood symptom severity and provided self-ratings of psychosocial functioning across domains of social-emotional, family, and school functioning. Repeated measures mixed modeling and bootstrapped mediational analyses determined the effects of treatment conditions and psychosocial functioning on mood improvements immediately post-treatment and over 2 years of follow-up.

Results: Youths in FFT reported greater improvements in family functioning over 24 months compared to those in EC, $F(5,76.8) = 3.1$, $p < 0.05$. Improvements in family functioning partially mediated participants' improvements in depressive symptoms, $B = -0.22$, $p < 0.01$; 95% CI: −0.55, −0.02. The effects of FFT versus EC on family functioning were stronger among youth

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with comorbid anxiety and externalizing disorders than among youth without these comorbid disorders.

Conclusions: The findings suggest a temporal link between changes in youths' perceptions of family functioning and improvements in depressive symptoms among high-risk youth in FFT. Family conflict and cohesion are important treatment targets for youth who present with early signs of BD. Future studies should examine whether changes in observational measures of family interaction precede improvements in mood among high-risk youth.

Keywords

family-focused therapy; family functioning; depression; pediatric

BACKGROUND

Bipolar disorder (BD) typically presents in subclinical high-risk stages years before youths reach full threshold for bipolar I or II illness (Perlis et al., 2004; Shaw et al., 2005). High risk youth are usually identified by recurrent and brief period of elevation and activation in childhood or early adolescence that fall short of DSM-5 criteria (American Psychiatric Association, 2013) for (hypo)mania, but represent clear departures from baseline moods and functioning. Youths with depression, anxiety, mood instability, and subthreshold manic symptoms who have a parent with early-onset BD have a 49% chance of converting to full threshold BD in 8 years compared with 6.8% of youth without these symptom and family features (Hafeman et al., 2016). High risk youth are comparable to youth with BD I or II in clinical characteristics (e.g., comorbidities, depression severity) and degree of functional impairment despite having shorter or less severe elevated phases (Axelson et al., 2006; Hafeman et al., 2013; Weintraub, Schneck, Walshaw, Chang, Singh, et al., 2020).

Years prior to the development of full BD, youth at risk for BD display impairments in psychosocial functioning across multiple domains, including family, social-emotional, and school functioning (Birmaher et al., 2009; Goldstein et al., 2006; Keenan-Miller & Miklowitz, 2011). Family and social difficulties are related to greater symptomatic severity in high risk youth (Weinstock & Miller, 2008; Weintraub, Schneck, Walshaw, Chang, Sullivan, et al., 2020). At a granular level, family relationships characterized by severe conflict, criticism, and poor problem-solving are prognostically associated with relapse likelihood, recovery time, and psychosocial impairment among adults and adolescents with BD (Keenan-Miller et al., 2012; Miklowitz et al., 1988; Rosenfarb et al., 2001; Schudlich et al., 2021; Sullivan et al., 2012) as well as youth at high-risk for BD (Shalev et al., 2019).

Significant efforts have been undertaken to identify and treat children and adolescents at high risk for BD (Birmaher et al., 2018; Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Forgey-Borlik, et al., 2020). Family-focused therapy for high-risk youth is a semistructured treatment that provides psychoeducation about the nature of mood episodes, individual and family coping strategies to manage mood swings, and training for the youth and family members in communication and problem-solving skills. For adolescents and adults with BD I or II, FFT combined with pharmacotherapy has been found to be more effective than supportive care and pharmacotherapy in hastening episode recovery

and reducing rates of recurrence over 1-2 years (Miklowitz et al., 2008; Miklowitz et al., 2003; Miklowitz et al., 2007; Miklowitz et al., 2014; Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Borlik, et al., 2020; Rea et al., 2003). In youth at high risk for BD, FFT is associated with reductions in symptom severity and longer intervals prior to new mood episodes compared to standard psychoeducation over 1-4 years (Miklowitz et al., 2013; Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Forgey-Borlik, et al., 2020).

FFT is proposed to reduce mood symptoms through improving family functioning, which is achieved through communication and problem-solving skills training (Miklowitz & Chung, 2016). Compared to psychoeducation-only conditions (FFT's most common comparator), the addition of communication and problem-solving skills is hypothesized to lead to reductions in family conflict and improvements in family cohesion (emotional connection between family members) and adaptability (ability to change under conditions of stress). In studies of adults with bipolar disorder and adolescents/young adults with psychosis risk syndromes, FFT was associated with greater improvements in observer-rated family interactional behavior compared to brief family psychoeducation (O'Brien et al., 2014; Simoneau et al., 1999). FFT was also associated with greater improvements in family cohesion and quality of life compared to brief psychoeducation among adolescents with BD I and II (O'Donnell et al., 2017; O'Donnell et al., 2020). In adults and adolescents with BD I and II, treatment-related improvements in family functioning were correlated with improvements in depressive and manic symptoms over 1-2 years (Simoneau et al., 1999; Sullivan et al., 2012).

Comorbid psychiatric disorders, most notably anxiety and attention deficit hyperactivity disorder (ADHD), are associated with more severe mood symptoms and poorer courses of illness among youth with or at high risk for BD (Cummings & Fristad, 2012; DelBello et al., 2007; Weintraub, Schneck, Walshaw, Chang, Sullivan, et al., 2020). These conditions are also consistent predictors of psychosocial impairment in youth, including increased family conflict and peer difficulties (Ahmad et al., 2020; Hinshaw, 2018; Schleider & Weisz, 2017; Weinstock & Miller, 2010). FFT was associated with greater mood improvements among youth with BD I or II who had comorbid anxiety disorders and ADHD than among youth with BD who did not have these comorbid disorders (Weintraub et al., 2019). Compared to psychoeducation alone, the provision of communication and problem-solving skills training in FFT may enable youth with comorbid conditions to learn social skills that generalize outside of the family setting, which may in turn be associated with improvements in mood symptoms.

Prior studies of FFT and other psychological interventions for BD have not clarified the mediational pathways between treatment and mood improvement, or the subpopulations of youth who respond best to specific approaches. First, we do not know whether changes in family functioning (i.e., decreases in family conflict) *precede* improvements in mood symptoms, an important consideration in selecting targets for early intervention. Second, the effects of FFT on social-emotional or school functioning has received little examination. It is possible that acquisition of more effective communication and problem-solving skills carry over to relationships outside as well as inside the family. Third, it is unclear whether comorbid presentations moderate the effects of FFT on the course of high-risk presentations.

This study examined whether enhancing psychosocial functioning through early family intervention is associated with decreases in symptom severity over 2 years among youth at high risk for BD. We examined the effects of two randomly assigned family treatments (FFT and a standardized psychoeducational treatment, Enhanced Care, or EC) on self-reported psychosocial functioning (i.e., family, social-emotional, and school) during the post-treatment period (4-8 months post-randomization) as well as over a sustained period (24 months after randomization) among youth at high risk for BD. We hypothesized that (a) FFT would have greater effects than EC on psychosocial functioning in both intervals; and (b) the greater association between FFT and improvements in youths' mood states over these intervals would be mediated by greater improvements in psychosocial functioning. Additionally, we expected that FFT would have greater effects on psychosocial functioning for youth with comorbid anxiety or externalizing disorders compared to EC.

METHOD

Participants

This study was reviewed and continuously approved by the institutional review boards at the UCLA Semel Institute, Stanford University School of Medicine, and the University of Colorado (Boulder and Anschutz Medical Campus). Participants were high-risk youth and their parents recruited for a randomized clinical trial (ClinicalTrials.gov Identifier: NCT00943085). Eligible youth participants had the following characteristics: (1) aged 9 years, 0 months to 17 years, 11 months; (2) meets lifetime DSM-IV (American Psychiatric Association, 2000) and later, DSM-5 criteria for other specified BD or major depressive disorder (American Psychiatric Association, 2013), (3) had at least moderate levels of current mood symptoms (i.e., scored more than 11 on the Young Mania Rating Scale (YMRS; Young et al., 1978) over the prior week or more than 29 on the Child Depression Rating Scale, Revised (CDRS; Poznanski & Mokros, 1996) over the prior two weeks), and (4) had at least one first- or second-degree relative who met lifetime criteria for BD I or II.

Psychiatric diagnoses were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS), Present and Lifetime Version (Chambers et al., 1985; Kaufman et al., 2013), administered to the youth and at least one parent about the youth's current (previous month) and lifetime behavior. Diagnoses were based on a consensus rating of information obtained from both reports. Interrater reliability (based on intraclass correlations) for KSADS Depression and Mania Rating Scales were 0.74 and 0.84, respectively, across study sites. Study assessors administered the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) to first- or second-degree relative(s) who reported having lifetime bipolar I or II disorder or were reported by other relatives to have these diagnoses. When relatives could not be interviewed directly, we administered the Family History Screening Interview (Weissman et al., 2000) to a parent regarding the relative's history.

Study assessors first learned the assessment instruments. Then, they rated sample videotapes with trainer feedback, followed by ratings of a set of standardized videotapes. Interrater reliability was calculated among 28 raters at the three study sites, each of whom rated a minimum of 3 standardized tapes. More details regarding study procedures can be found

elsewhere (Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Forgey-Borlik, et al., 2020).

Allocation to Treatment Conditions

Once a youth and family were deemed study-eligible, they were randomly assigned to FFT or EC based on a computerized dynamic allocation procedure (Begg & Iglewicz, 1980) that balanced treatment groups within sites on youths' diagnosis (unspecified BD or MDD), age (> 13 or ≤ 18 years), and medications at study entry (mood stabilizers/antipsychotics vs. neither). FFT consisted of 12 sessions (8 weekly, 4 biweekly) over the 4 months following randomization, and included the youth, parents, and whenever possible, siblings. The treatment consisted of three modules: psychoeducation about mood disorders (notably, the development of a mood management and family coping plan), communication enhancement training, and problem-solving skills training. The 4-month EC treatment consisted of 3 weekly family psychoeducation sessions followed by 3 monthly individual psychoeducation sessions focused on implementing a mood management plan [see Miklowitz et al. (2020)].

Clinicians were trained to deliver both psychosocial treatments and supervised monthly by experts throughout the study. Therapist Competence and Adherence Scale ratings (Weisman et al., 1998) indicated consistently high levels of fidelity to both protocols (Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Forgey-Borlik, et al., 2020). When pharmacological care was clinically indicated or requested by a family, study psychiatrists met with the child biweekly and then monthly during the study. Psychiatric medications were prescribed or adjusted using a decision tree designed for this high-risk population (Schneck et al., 2017).

Study Measures

Independent evaluators who were unaware of treatment assignments conducted baseline symptom assessments and follow-up assessments every 4 months in year 1 and every 6 months for up to 4 years. Youths' reports of degree of impairment in psychosocial functioning were gathered at each study assessment via the Social Adjustment Scale – Self Report: Short Form (SAS; Gameroff et al., 2012). SAS items are rated on 5 and 6-point Likert scales, with higher scores indicative of poorer functioning over the prior 2 weeks. The SAS has multiple subscales, including school (e.g., "Have you been able to keep up with your classwork in the last two weeks?" and "Have you found your schoolwork interesting?"), social-emotional (e.g., "Have you felt lonely and wished for more friends?") and family functioning (e.g., "Have you had arguments with your parents?" and "Have you been able to talk about your feelings and problems with your parents?"). The Cronbach's alphas for the SAS subscales were acceptable (α's=0.71-0.75).

Independent evaluators who were unaware of treatment assignments separately interviewed the youth and at least one parent every 4-6 months and rated the youth's symptoms during each week of the preceding interval, using Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE) Psychiatric Status Ratings (PSRs; Keller et al., 1987). PSR Depression scores range from 1-6, with a score of <2 indicating minimal (if any) depressive symptoms, scores of 3 to 4 indicating subsyndromal symptoms, and scores of >5 indicating syndromal

symptoms that would ordinarily meet DSM-5 criteria for a major depressive episode. Due to a limited range of mania symptom severity scores in this sample, the mania and hypomania Psychiatric Status Rating subscales were combined into one 8-point (hypo)mania scale, where 1-2 indicates no hypo(manic) symptoms, 3-5 indicates subsyndromal hypomanic symptoms, 6 indicates full hypomania, and 7-8 indicates varying levels of fully syndromal mania. Weekly PSR scores were averaged across each 4- or 6-month interval between assessments to derive mean depression and (hypo)mania scores for each follow-up visit. Across independent evaluators at different sites, interrater reliabilities (intraclass *r*s) for PSRs ranged from 0.88 to 0.99 for agreement on number of weeks with subthreshold or threshold depression and (hypo)mania scores. Cross-site agreement was 0.90 for depression and 0.99 for (hypo)mania.

Statistical Analyses

Treatment Effect on Psychosocial Functioning.—Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS 22). Repeated measures mixed-effect regression models were used to examine main and interactive effects of treatment (FFT vs. EC) and study visit (0, 4, 8, 12, 18 and 24 months) on SAS subscales ratings. Due to significant participant attrition in years 3 (82% attrition) and 4 (91% attrition) that interfered with convergence of the model, we limited the analyses to the first 2 years of post-randomization follow-up. Subject-level random intercepts were included to account for within-subject correlations induced by repeated measurements. The effect of treatment group (FFT or EC) was entered as the between-subject factor. Time (study visit) was treated categorically to allow for group differences in higher-order non-linear trajectories throughout the 24-month period. Estimates of psychosocial functioning over time as a function of treatment group were determined with fixed time and time × group interaction effects, with Satterthwaite approximation for denominator degrees of freedom. Treatment site and initial mood diagnosis (MDD vs. unspecified BD) were covaried in each model.

We computed repeated measure mixed regression models to determine the concurrent relation between each functional domain (school, social-emotional, family) and mood symptom severity (mean Psychiatric Status Ratings for depression and (hypo)mania) during matched intervals over the 24-month period. Treatment site and mood diagnosis (MDD vs. unspecified BD) were covaried in each model.

Mediation Analyses.—Mediational hypotheses regarding treatment, psychosocial functioning and post-treatment symptoms were examined in R 4.0.3 using the mediate function from the *psych* package (Revelle, 2017). SAS subscales that were significantly affected by treatment assignment were examined as mediators of the relation between treatment assignment and post-treatment (8-month) mood symptoms. This analysis was conceptualized as the effect of treatment on SAS scores from baseline to the interval following treatment termination (i.e., the 4-month assessment). Changes in SAS scores from baseline to 4 months were then examined as mediators of treatment group on depressive scores at the 8-month assessment. Baseline SAS and depression scores as well as depression scores at 4 months were used as covariates in this model.

Next, we extended the 8-month mediation design above to examine whether the indirect effects of treatment group on mood outcomes (through changes in youths' perceptions of functioning) increased in magnitude from baseline across two years of follow-up. These analyses used longitudinal "moderated mediation" models with 1000 bootstrap iterations, using the R 4.0.3 *lme4* (Bates et al., 2007) and *boot* (Canty, 2002) packages. To model the moderated mediation effect, SAS scores at time *t* were regressed on treatment group interacted with time and then used to predict depression scores at time *t+1* using mixed linear regression, fitting random intercepts and slopes within-subject. The bootstrapped standard errors of the estimates and percentile intervals of the indirect effects were estimated to test the time-varying indirect effects of treatment group on PSR mood scores via the mediator, lagged SAS scores.

Psychiatric Comorbidities as Moderators of Treatment Effect.—Repeated measures mixed-effect regression models were examined in SPSS-22 to examine the interactive effects of treatment (FFT vs. EC), study visit (0, 4, 8, 12, 18 and 24 months), and baseline psychiatric comorbidities on SAS subscales ratings. In order to examine large enough subgroups of youth with/without comorbidities within each treatment condition, we classified youths as present vs. absent for any anxiety disorder (i.e., generalized anxiety, social anxiety, panic, separation, or specific phobic disorders) and, separately, for externalizing disorders (i.e., attention deficit/hyperactivity disorder (ADHD), conduct disorder, or oppositional defiant disorder). Subject-level random intercepts were included to account for within-subject correlations induced by repeated measurements. The effect of treatment group was entered as the between-subject factor. Study visit and psychiatric comorbidity (analyzed in separate models for each comorbidity class) were entered as categorical variables. Treatment site and initial mood diagnosis (MDD vs. unspecified BD) were covaried in each model. When observing significant main effects or interactions, we conducted post-hoc least square comparisons to determine the locus of effects.

RESULTS

Sample Characteristics

A total of 127 participants were randomly assigned to treatment conditions (61 to FFT and 66 to EC). Data on psychosocial functioning at baseline were available for 119 of these youth (93.7%), with data on 93 youth at the 4-month, 75 at the 8-month, 69 at the 12-month, 58 at the 18-month, and 37 at the 24-month intervals. The majority of youth were female (65.5%) with an average age of 13.2 (SD = 2.6), and predominantly middle class (Hollingshead SES=3.9, SD = 0.8). Of the 119 youth, 70 met DSM-5 criteria for major depressive disorder (MDD) and 49 for other specified BD. Participants completed the treatment an average of 18.1 weeks (SD = 4.1) following randomization. There were no differences between treatment conditions in average completion time ($F(1,111) = 0.36$, $p = 0.55$). Additional demographic and clinical characteristics are presented in Table 1. Full descriptions of the sample and recruitment strategies are available in Miklowitz et al. (2020).

Treatment Effect on Psychosocial Functioning

The effects of treatment condition, study visit, and their interaction (controlling for baseline diagnosis and study site) were examined for each of the youth-rated SAS subscales (i.e., family, social-emotional, and school functioning) over 24-months. Scores on the SAS Family subscale improved over time across both conditions, $F(5,76.9) = 5.95$, $p < 0.001$. There was a significant treatment by time interaction indicating that youth in the FFT condition reported greater improvement in family functioning compared to those in the EC condition, $F(5,76.8) = 3.1$, $p < 0.05$ (see Figure 1). Follow-up analyses indicated that FFT was associated with statistically significant improvements in family functioning compared to EC at 4-months, $F(1,114.3) = 4.58$, $p < 0.05$, as well as at the 18 and 24-month intervals, $F(1,83.9) = 7.95$, $p < 0.01$; $F(1,47.6) = 4.65$, $p < 0.05$, respectively. The treatment effect remained significant when controlling for concurrent depression and (hypo)mania PSR scores at each of the corresponding study visits.

Youth in both treatment conditions reported improved social-emotional functioning over the 24-month period, $F(5,73.1) = 4.2$, $p < 0.01$, with no difference between treatment groups ($F(5,73.2) = 0.6$, $p = 0.72$. Youth in both conditions also improved in their self-reported school functioning over 24-months, $F(5,92.7) = 4.3$, $p < 0.001$, independent of treatment groups, $F(5,93.1) = 0.4$, $p = 0.81$. There was a significant positive association between each SAS functional domain and PSR depression symptoms over time, indicating that functioning improved as depressive symptoms improved (school: $b = 0.11$, $SE = 0.01$, $p < 0.01$; social-emotional: $b = 0.05$, $SE = 0.01$, $p < 0.01$; family: $b = 0.10$, $SE = 0.01$, $p < 0.01$). Functioning scores were not associated with PSR (hypo)manic symptoms across the study visits, possibly indicating the more limited range of mania symptoms in the sample.

Mediational Effects of Psychosocial Functioning at Post-Treatment

There was no direct effect of treatment group on changes in depression PSR scores from baseline to 4 or 8 months. As seen in the preliminary treatment analysis, there was a significant treatment effect on youth-reported SAS-family subscale scores such that youth in the FFT condition reported greater improvement in family functioning compared to those in EC condition over 4 months, $B = -1.82$, $p < 0.01$; 95% CI: −3.11, −0.53. Additionally, SAS-Family scores at 4 months were associated with depression scores at 8 months, $B = 0.12$, $p < 0.01$; 95% CI: 0.06, 0.18. The mean bootstrapped indirect effect of treatment on 8-month depression via family functioning at 4 months was significant, $B = -0.22$, $p < 0.01$; 95% CI: −0.55, −0.02, indicating partial mediation of treatment effects on depression scores via changes in self-reported family functioning. There was no direct or indirect effect of treatment on (hypo)mania symptoms. The path diagram for the relationships between treatment, SAS family scores and PSR depression symptoms over 8 months is shown in Figure 2.

Mediational Effects of Psychosocial Functioning over 24 Months

The bootstrap moderated mediation results shown below indicate that the indirect effect of treatment condition on PSR depressive symptoms via lagged SAS-family scores significantly increased in magnitude over 24 months. The indirect mediation effect becomes significant at approximately the 8-month mark in follow-up and grows in magnitude from

that point onward throughout the remainder of the 2-year period. The strength of the indirect effects of treatment on depression via SAS Family scores and the 95% bootstrapped confidence intervals of the treatment effects are shown in Figure 3. Treatment condition was unrelated to stabilization of (hypo)mania symptoms over 24 months, and there was no relationship between SAS family scores and (hypo)mania symptoms.

Comorbid Disorders as Moderators of Treatment Effect

Next, we examined the separate effects of baseline psychiatric comorbidities (anxiety and externalizing disorders) and treatment condition on youth-rated psychosocial functioning subscales over 24 months. There was a significant three-way interaction between treatment, study visit, and comorbid anxiety disorders on SAS family functioning scores $F(5, 71.1) = 2.49$, $p < 0.05$. Post hoc analyses indicated that youth with comorbid anxiety disorders had greater improvements in family functioning scores in FFT compared to EC, at the 8, 18, and 24-month assessment intervals, $F(1,117.9) = 4.11$, $p < 0.05$; $F(1,84.2) = 4.58$, $p =< 0.04$; $F(1,42.0) = 6.28$, $p < 0.02$, respectively. Youth without comorbid anxiety did not differ in family functioning scores across treatment groups, except at the 8-month follow-up, where youth without anxiety reported poorer family functioning in FFT compared to EC, $F(1,115.9) = 4.97$, $p < 0.03$). There were no significant interactions between treatment, time and comorbid anxiety for school or social-emotional functioning.

There was a significant three-way interaction between treatment, study visit, and comorbid externalizing disorders, $F(5, 76.0) = 3.73$, $p < 0.01$) on SAS Family scores over 24 months. Post-hoc comparisons indicated that youth with comorbid externalizing conditions who received FFT had greater improvements in youth-rated family functioning at 18 and 24-months compared to those in EC (18-month: $F(1,77.1) = 10.26$, $p < 0.01$; 24-month: $F(1,49.8) = 8.16$, $p < 0.01$; Figure 5). There were no significant interactions between treatment, time and comorbid externalizing conditions for school or social-emotional functioning.

As exploratory analyses, the externalizing comorbidity variable was broken down into two sub-categories – comorbid ADHD and comorbid conduct disorder (CD) and/or oppositional defiant disorder (ODD). The three-way interactions with treatment, time, and comorbid ADHD and CD/ODD remained significant for both of these comorbid sub-categories, $F(5, 73.01) = 2.66$, $p < 0.05$; $F(5, 75.22) = 2.77$, $p < 0.02$, respectively.

DISCUSSION

In a randomized clinical trial we examined whether enhancing psychosocial functioning (i.e., family, social-emotional, and school functioning) through family intervention is associated with decreases in symptom severity over 2 years among youth at clinical and familial risk for BD. Whereas both FFT and EC were associated with improved functioning across all domains, youth randomly assigned to FFT reported better family functioning (e.g., fewer arguments, better communication) compared to youth assigned to EC. Family functioning was significantly improved by the end of the active treatment period of FFT (~16 weeks) whereas treatment-associated improvements in depressive symptoms were observed at the next study assessment (8 months). Moreover, changes in family functioning

preceded improvements in depression during each lagged study interval over 2 years. These findings may inform the expectations of providers and parents of high-risk youth, in terms of when and by what mechanisms one should expect symptomatic improvement.

Family functioning is the primary target by which FFT is hypothesized to have effects on mood symptoms in bipolar spectrum populations (Miklowitz & Chung, 2016). While FFT has previously been linked with improved verbal and nonverbal communication between patients and caregiving relatives (O'Brien et al., 2014; Simoneau et al., 1999), this is the first study to establish a temporal link between changes in family functioning and changes in patients' mood symptoms. In randomized trials of family psychoeducation for patients with schizophrenia, improvements in depression and anxiety symptoms are mediated by improvements in family cohesion (Brown & Weisman de Mamani, 2018). Negative and critical parent/offspring communication patterns have consistently been linked to increased symptoms and a greater likelihood of relapse among individuals with bipolar disorder (Keenan-Miller et al., 2012; Miklowitz et al., 1991; Rosenfarb et al., 2001) and schizophrenia (Rosenfarb et al., 1995). Youth at high risk for BD appear to be especially sensitive to criticisms from parents (Schudlich et al., 2021).

Although FFT was associated with delays in occurrences of depressive episodes in this sample, there was no evidence that it delayed the new onset of manic episodes (Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Forgey-Borlik, et al., 2020). In the present study, we were unable to establish a link between child-reported family functioning and improvements in mania or hypomania symptoms. Mania symptoms may be affected by other risk processes associated with BD, including life events involving goal attainment (Johnson et al., 2008) and sleep/wake cycle disruption (Alloy et al., 2017; Goldstein et al., 2018; Sylvia et al., 2009) that were not evaluated in this analysis.

The effects of FFT (compared to EC) were associated with greater improvements in self-ratings of family functioning among youth with anxiety and externalizing disorders. Of note, the benefits for youth with comorbid conditions was seen most at the 18- and 24-month study intervals, indicating that the effects of FFT for these youth continued for at least 20 months beyond treatment termination. In comparison, youth with comorbid conditions in EC reported the same level of family functioning at 24 months as they reported at baseline. The greater effect of FFT for youth with comorbid disorders replicates our previous findings in adolescents with syndromal BD I and II, in which youth with comorbid ADHD had greater mood improvements in FFT compared to their counterparts who received brief psychoeducation (Weintraub et al., 2019). Possibly, structured communication and problem-solving skill training may assist parents and youth in better focusing their interchanges and balancing critical or argumentative statements with praise or acknowledgement, which may reduce household tension among youth with mood disturbance, anxiety, and attentional impairments.

Youth in both treatment conditions showed improvement in school and social-emotional functioning. Although these improvements may simply be the result of time and corresponding mood improvements, both treatment conditions included family psychoeducation for coping with mood disorders. The nonspecific effects of family

psychoeducation (e.g., developing a mood management plan) may promote improvements school and social-emotional functioning as well as family functioning. In order to more clearly elucidate the active ingredients of the FFT's approach, future research should investigate whether individual mastery of the successive FFT modules (psychoeducation, communication, and problem-solving) is associated with change in family functioning and symptom trajectories, perhaps using treatment dismantling designs.

This study had several limitations. First, the functioning outcomes were measured via self-report from youths as opposed to direct observations of family or individual functioning. It is unclear whether parent- or clinician-reports of youths' functioning would yield these same results. Second, about 60% of the high-risk youth in this trial received pharmacotherapy as well as psychosocial treatment, although medication regimens did not differ across the randomly assigned treatment conditions (Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Forgey-Borlik, et al., 2020). Nonetheless, we cannot rule out the possibility that certain medication strategies (e.g., certain mood stabilizers or adjunctive antipsychotics, psychostimulants, or anxiolytics) had an impact on the youths' perceptions of psychosocial functioning. Third, we did not measure changes in expressed emotion, a measure of parental criticism, hostility, and/or emotional overinvolvement toward the offspring; or parents' attributions about the causes of youths' negative or aversive behaviors (e.g., Hooley, 2007). Improvements in youths' functioning may results from changes in parental attitudes, attitudes, or direct communication behaviors. Finally, we did not assess for skill development/mastery over the course of the treatment. Measuring the degree to which effective communication or problem-solving skills are integrated into the family's day-to-day functioning would be a more definitive test of the mediational hypotheses of this study.

Together with the primary outcomes from this RCT (Miklowitz, Schneck, Walshaw, Singh, Sullivan, Suddath, Forgey-Borlik, et al., 2020), we conclude that FFT leads to reductions in depressive mood severity in high-risk youth, in part through the avenue of improving youths' perceptions of family functioning. It remains unclear what components of FFT are associated with changes in the youths' perceptions of the family, whether these effects would be observed for other measures of family functioning, or whether these same findings would hold true among other psychiatric populations.

Appendix

The primary outcomes of the randomized controlled trial from which the data are drawn for this current manuscript were published in *JAMA Psychiatry* in 2020 (Miklowitz et al.). The primary outcomes presented in *JAMA Psychiatry* involve the effect of the RCT on mood outcomes. This current manuscript examines mediators and moderators of the treatment effects, including family functioning and psychiatric comorbidities.

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Public Health Significance:

This study found that family-focused therapy leads to reductions in depressive symptoms via improvements in family functioning among youth who are at high risk for bipolar disorder. These findings highlight the importance of intervening on the immediate family unit in order to improve mood symptoms among these youth.

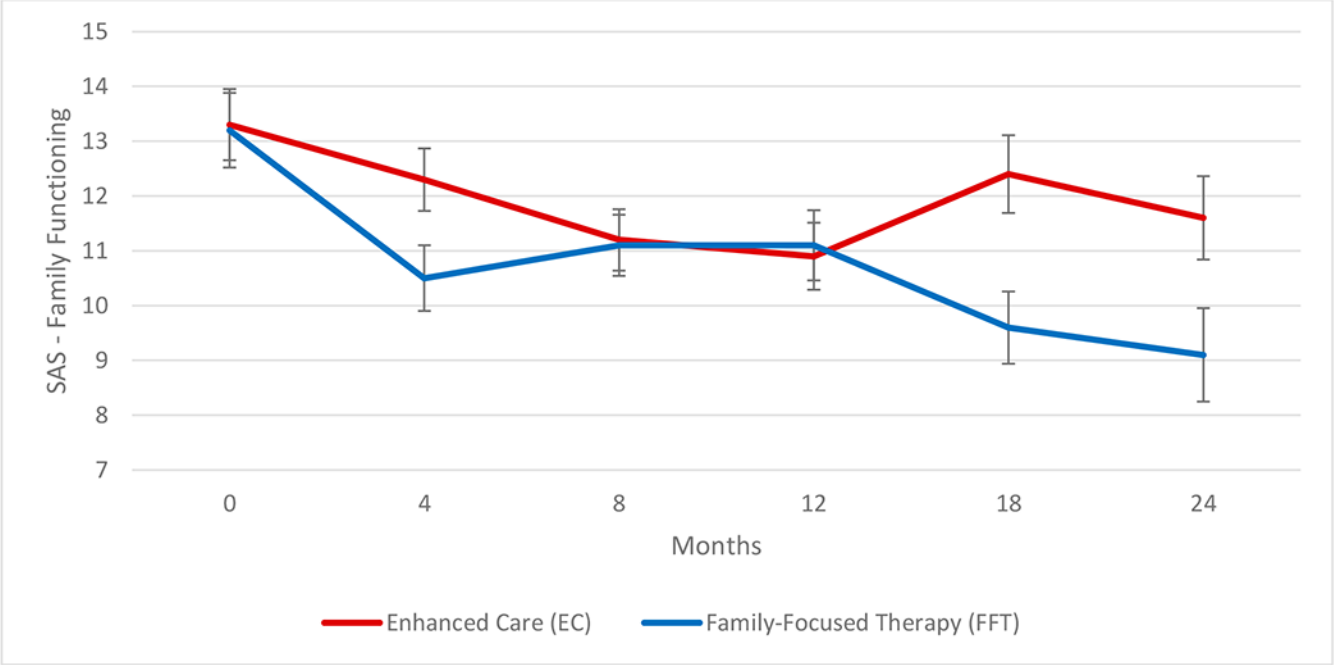

Figure 1.
The effect of Family-Focused Therapy (FFT) versus Enhanced Care (EC) on youth-rated family functioning over 2 years. Error bars represent standard error of the mean.

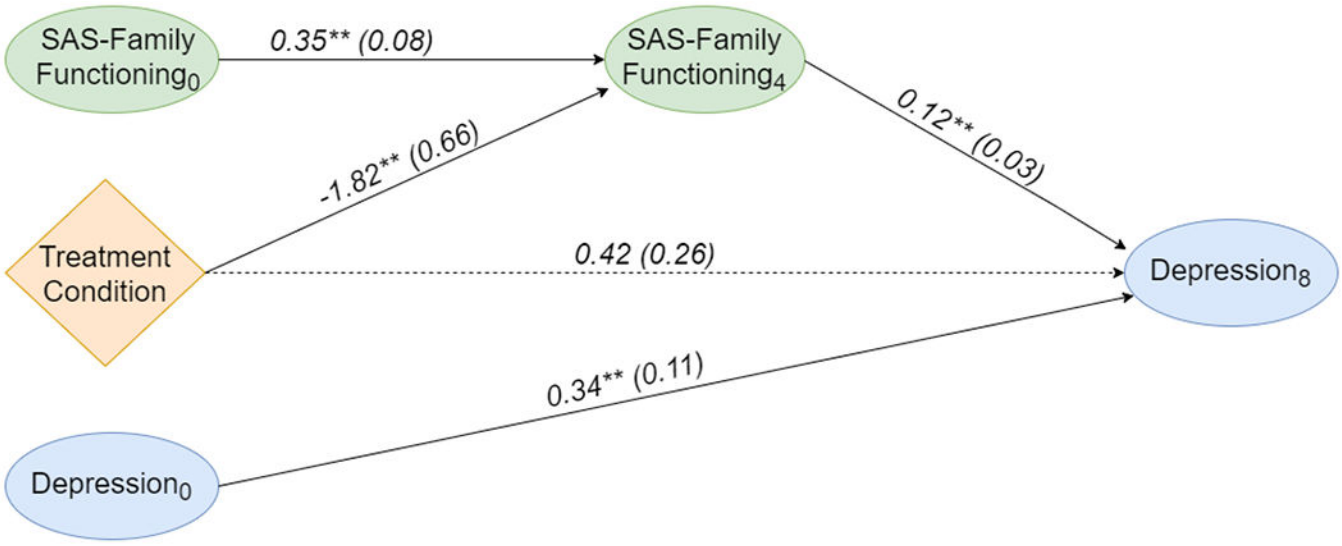

Figure 2.

Mediational effect family functioning at 4-months on treatment condition and 8-month depressive symptoms. Note: Values in parentheses represent the standard errors for the corresponding unstandardized beta weights. ** = $p < 0.01$.

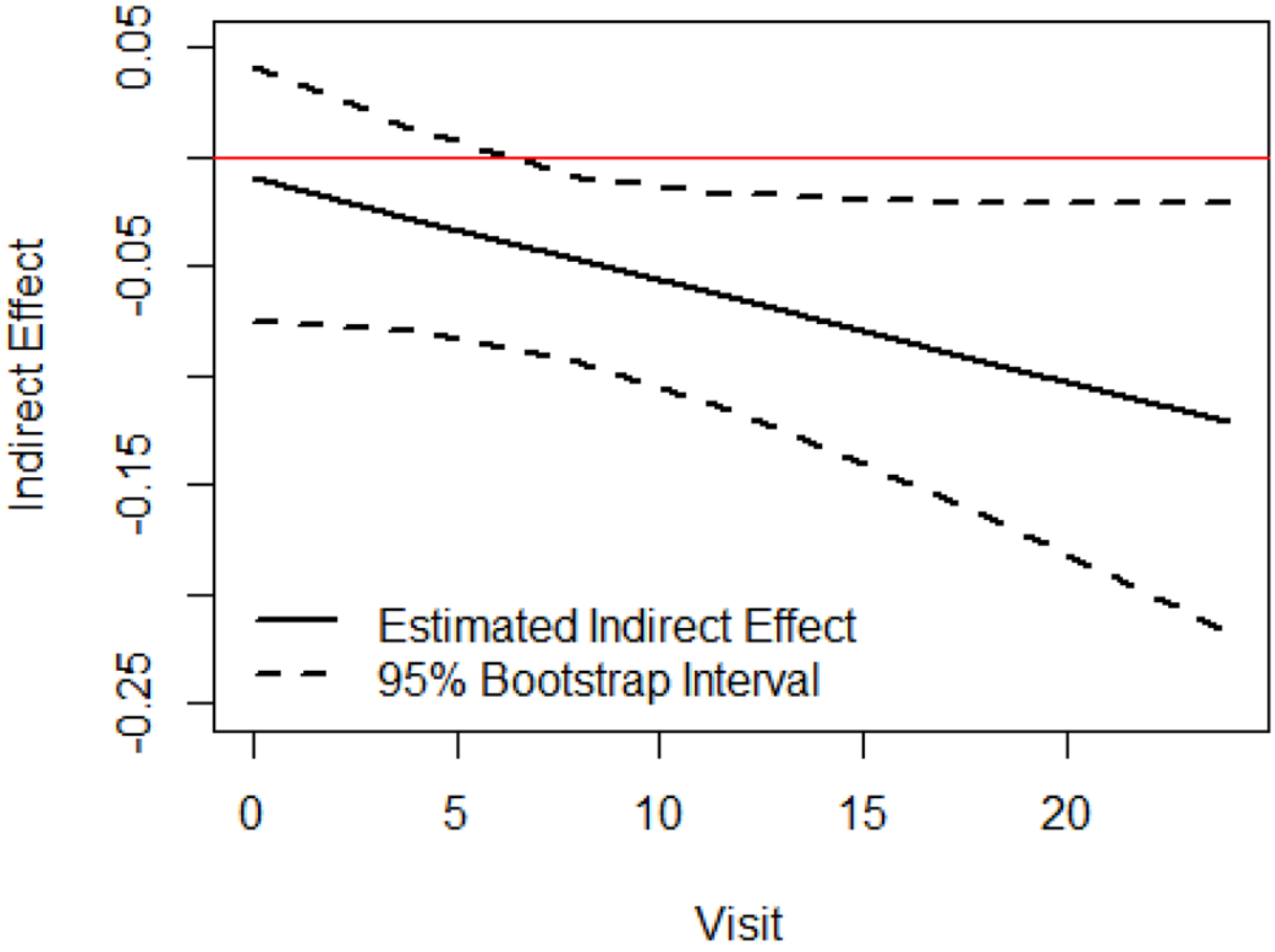

Figure 3.

Plotted Bootstrap Indirect Effect of Treatment on Depressive Symptoms Mediated by Family Functioning over 24 months. The negatively sloped line above shows that the estimated indirect effect of treatment on depressive symptoms via improvements in family functioning increased in magnitude over time. This indicates that improvements in family functioning in the family-focused therapy (FFT) group compared to the enhanced care (EC) group grew over time, which in turn were associated with reductions in future depressive symptoms. The 95% bootstrap percentile confidence interval indicates that this indirect effect becomes significant around the 8-month mark of follow-up, where the full interval is shown to be less than the red line at zero.

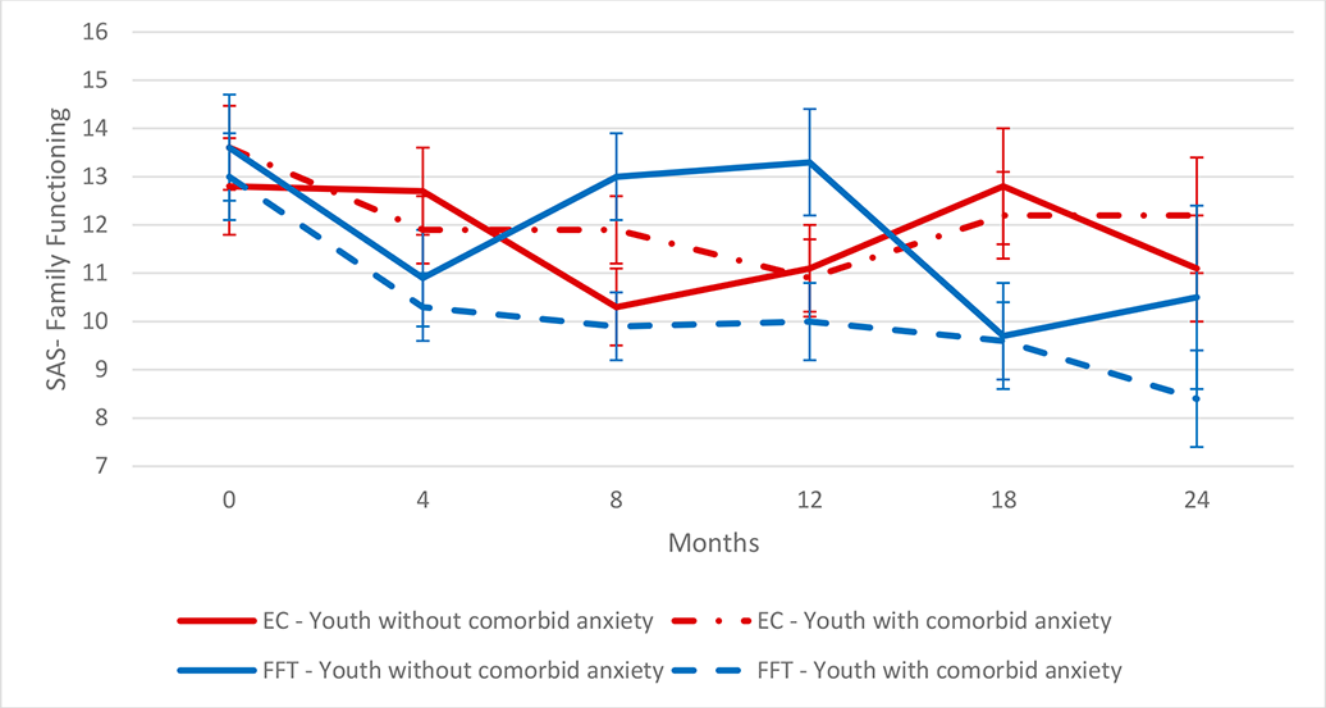

Figure 4.

Effect of treatment on youth perceptions of family functioning moderated by comorbid anxiety disorders. Youth with comorbid anxiety in FFT showed greater improvements in family functioning compared to those in EC at the 4, 8, 18, and 24-month intervals. Error bars represent standard error of the mean.

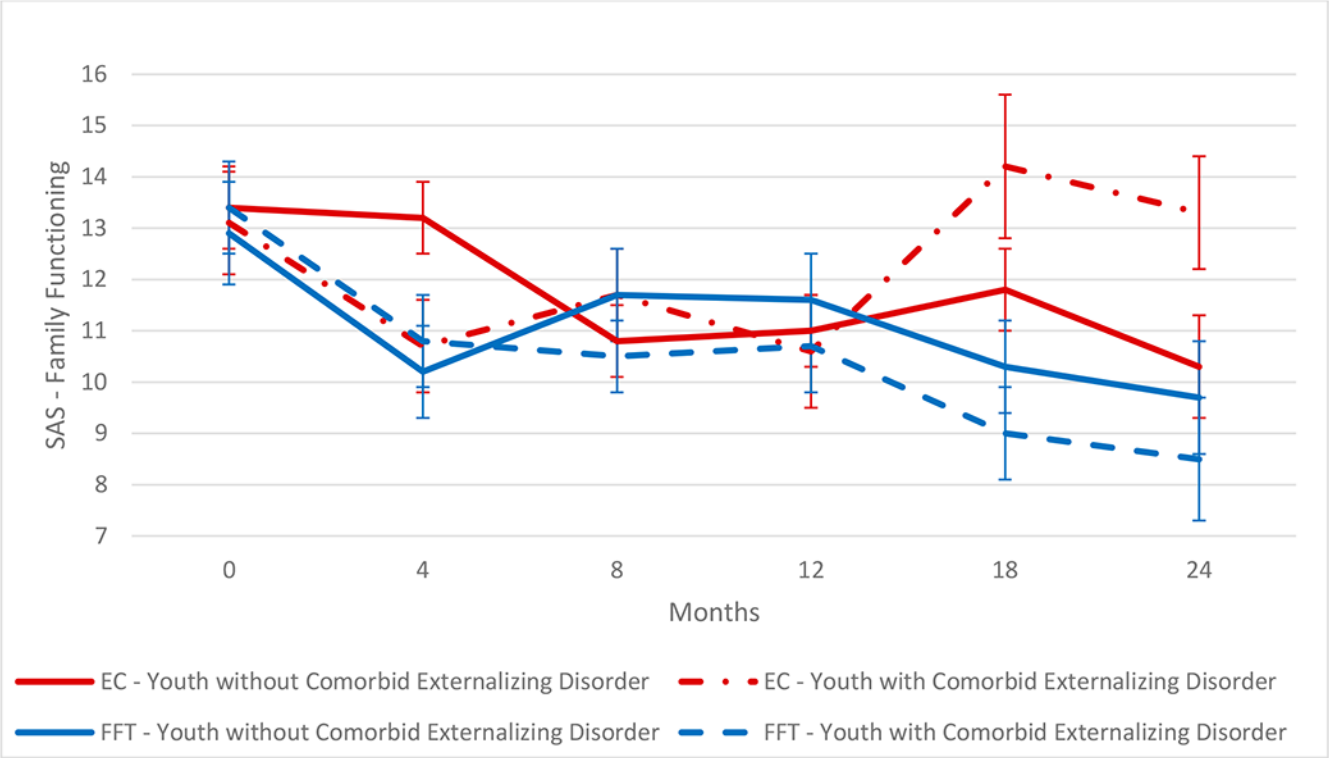

Figure 5.

Effect of treatment on youth perceptions of family functioning moderated by comorbid externalizing disorders. Youth with comorbid ADHD in FFT showed greater improvements compared to those in EC at the 4, 18, and 24-month intervals. Error bars represent standard error of the mean.

Table 1.

Demographic and baseline clinical characteristics of 119 youth at high risk for bipolar disorder

Demographics	
	Mean (SD)
Age (years)	13.2 (2.6)
Socioeconomic status (Hollingshead-Redlich)	3.9 (0.8)
	n (%)
Female	78 (65.5)
Nonwhite race	22 (18.5)
Hispanic ethnicity	21 (17.6)
Clinical Characteristics	
	Mean (SD)
SR Depression	3.7 (1.0)
PSR Hypo(Mania)	1.6 (0.7)
SAS School	13.6 (4.8)
SAS Social-Emotional	21.2 (6.5)
SAS Family	13.4 (4.6)
	n (%)
Primary diagnosis	
Major depressive disorder	70 (58.8)
Unspecified Bipolar disorder	49 (41.2)
Comorbid anxiety disorder	75 (63.0)
Comorbid ADHD	42 (35.3)
Comorbid Conduct/Oppositional Defiant Disorder	29 (24.4)
Psychopharmacology	
None	57 (47.9)
Lithium	1 (0.8)
Antipsychotic	25 (22.3)
Anticonvulsant	16 (13.4)
Antidepressant	40 (33.6)
Anxiolytic	3 (2.5)
Psychostimulant or other ADHD agent	21 (17.6)
Family history of bipolar disorder	
Youths with first-degree relative	100 (84.0)
Youths with second-degree relative	19 (16.0)

PSR = Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE) Psychiatric Status Ratings, which can range from 1 (absent) to 6 (severe) for depression, or 1 to 8 (syndromal) for (hypo)mania; SAS = Social Adjustment Scale.