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Early Intervention for Youth at High Risk for Bipolar Disorder: A Multisite Randomized Trial of Family-Focused Treatment

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Abstract

Aims—Despite the considerable public health impact of bipolar disorder (BD), no psychosocial interventions have been systematically evaluated in its early stages. We describe the rationale, design, and analytic methods for a 3-site randomized trial of family-focused treatment for youth at high risk for BD (FFT-HR).

Methods—Participants (ages 9 to 17 years) have a diagnosis of unspecified BD or major depressive disorder, current mood symptoms, and at least one first- or second-degree relative with a lifetime history of BD I or II. Participants are randomly assigned to FFT-HR (12 sessions in 4 months of family psychoeducation and skills training) or enhanced care (EC; 6 individual and family sessions over 4 months), with pharmacotherapy provided as needed. A subset of participants undergo pre- and post-treatment fMRI scans while performing face-rating and family problem-solving tasks designed to activate corticolimbic circuitry. Independent evaluators assess participants' status every 4–6 months for up to 4 years.

Results—We hypothesize that FFT-HR will be more effective than EC in reducing the severity of mood symptoms (primary outcome) and the hazard of a first manic episode (secondary) over 4 years. Secondarily, we will explore whether FFT-HR is associated with greater decreases in amygdala activation and increases in dorsolateral, ventrolateral, or anterior medial prefrontal cortex activation from pre- to post-treatment. Clinical characteristics of 133 subjects enrolled at baseline are described.

Conclusions—This study will test a novel intervention to reduce the early symptoms of BD, and identify neural and behavioral mechanisms that may help refine future treatments.

Trial Registration—NCT01483391, registered Nov. 26, 2011 at www.clinicaltrials.gov

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Keywords

Family therapy; prodromal; mania; neuroimaging; expressed emotion

INTRODUCTION

Between 50%–66% of adults with bipolar disorder (BD) report illness onset prior to age 18, and 15%–28% before age 13.[1] The prodromal symptoms of BD can be detected as much as 10 years prior to its full expression. [1,2] Retrospective studies of adults[3,4] and prospective studies of children and adolescents[5] indicate that earlier illness onset and longer delays prior to first treatment are associated with longer and more severe depressive phases, more comorbid disorders, and less time well in adolescence or early adulthood.

Significant controversies exist about the definition, ascertainment, and boundaries of early-onset BD (e.g., [6]). Nonetheless, agreement is substantial that the bipolar spectrum and its antecedent conditions have a significant impact on functionality and quality of life. [3,6,7] Paralleling the recognition of ultra-high risk syndromes in psychosis [8], certain clinical phenotypes have been identified as antecedent to BD in adulthood. A subset of children with bipolar parents - 10.7% in one large-scale study [9] - meet operational criteria for BD, not otherwise specified (BD-NOS in DSM-IV-TR[10], renamed “unspecified BD” in DSM-5[11]), with subthreshold periods or mania or hypomania. BD-NOS youth have levels of mood symptoms, impairment, suicidal ideation, comorbidity and service use that are comparable to or exceed those of youth with BD type I or major depressive disorder. [12,13]

In the 3-site Course and Outcome of Bipolar Youth (COBY) study, 58.5% of children with BD-NOS who also had a family history of mania (“high-risk” youth) progressed to bipolar I or II disorder over 5 years, compared to 35.5% of children with BD-NOS who did not have a family history. [12,14]. Other clinical characteristics of children with a family history of mania - such as severe, recurrent, or prolonged depression, anxiety disorders, and ADHD - have also been linked to an elevated progression to BD I/II. [15, 16, 17–19]

It is reasonable to assert that without early intervention, the social, neurological, and emotional development of youth at high risk for BD may be seriously compromised. Accordingly, well timed interventions during the prodromal period may allow for the normative acquisition of skills such as personal autonomy, academic success, and adaptive peer relationships before the more debilitating syndrome begins. In this study, we hypothesized that a family intervention designed to reduce intrafamilial stress, conflict, and affective arousal by enhancing communication, problem-solving, and emotion regulation skills would decrease a high-risk child’s liability toward persisting symptoms and eventual onset of BD. Several randomized trials indicate that family-focused therapy (FFT) with pharmacotherapy is effective in alleviating symptoms, delaying recurrences, and enhancing functioning in adults and adolescents with BD over 1–2 years. [20–24]. In a two-site treatment development trial, we found that an adaptation of FFT (FFT-high risk version, or FFT-HR) was more effective than an educational control in stabilizing mood symptoms among youth at high risk for BD. [25] Further, an 8-site trial found that a 6-month, 18-session version of FFT was more effective than brief psychoeducation in reducing positive psychosis

symptoms over 6 months among adolescents and young adults at high clinical risk for psychosis. [26]

Primary aims and hypotheses

This 3-site study examines the effects of FFT-HR (given in 12 sessions over 4 months) in stabilizing mood symptoms and reducing the onset of syndromal mania in youth at high risk for BD. Youth and their families are randomly assigned to FFT-HR (12 sessions in 4 months) or Enhanced Care (EC; 6 family and individual sessions over 4 months). In this article, we describe the study's rationale, design, and analytic methods, and describe the demographic and clinical composition of the enrolled sample at baseline. We are testing two central hypotheses:

1. **Severity of affective symptoms (primary outcome)**. FFT-HR will be more effective than EC in reducing the severity of mood (depressive plus manic/hypomanic) symptoms measured at pre-treatment and post-treatment (4 months). The primary outcome is measured from weekly Psychiatric Status Ratings (PSRs) of the Adolescent Longitudinal Interval Follow-up Evaluation, or ALIFE[27] with secondary verification using total scores from the Children's Depression Rating Scale, Revised ([CDRS-R][28] and the Young Mania Rating Scale [YMRS].[29] We hypothesize that FFT-HR will be associated with more durable symptom stabilization than EC, as reflected in a lower severity of mood symptoms and a consistent magnitude of treatment group differences in a 4-year follow-up.
2. **Enhancing long-term course (secondary outcomes)**. Due to its ameliorative effects on acute symptoms, FFT-HR will be superior to EC in delaying onset of a first (hypo)manic or mixed episode (identified from weekly PSR ratings) during a period of up to 4 years.

Secondary aims and hypotheses

A secondary aim is to identify neural factors associated with responses to psychosocial interventions in HR children. Abnormal development and function of the amygdala combined with deficient prefrontal inhibitory control may be at the core of mood dysregulation in BD. [30] A meta-analysis of 29 pediatric studies indicated decreased amygdala volumes, increased amygdala activation, and decreased activation of the ventrolateral and dorsolateral prefrontal cortices (VLPFC and DLPFC) in children with BD compared to typically developing children.[31] Amygdala hyperactivation when rating emotional faces, and aberrant prefrontal activation and connectivity when processing rewards have also been observed in healthy offspring of bipolar parents. [32,33] Thus, dysfunctional patterns of neural processing may predate the onset of mania or other psychiatric symptoms. Some of these patterns may be amenable to reversal through early intervention.

In the present study, we examine the neural correlates of response to psychosocial treatments in high-risk youth using neuroimaging (fMRI) tasks that engage corticolimbic circuits involved in emotion recognition and family problem-solving. Participants are scanned for 1

hr. before they begin FFT-HR or EC and again at the end of these 4-month treatments. The imaging paradigms were chosen to measure neural processes that might shift as a result of FFT, either by a general modulation of emotion-related neural circuitry, or by specific modulation of the circuitry underlying the exact skills taught in FFT.

First, we presented a widely used probe of emotion processing brain circuitry, the facial emotion task, in which subjects are asked to judge the gender of strangers' faces expressing negative and positive emotions. This task has been consistently shown, in our lab as well as others, to activate the amygdala, DLPFC, and VLPFC in healthy children and adults, and to highlight abnormalities in these regions in pediatric mood disorders. [32–36] Moreover, in our pilot randomized trial of FFT-HR, high-risk youth showed reductions in amygdala activity and increases in DLPFC activity while viewing fearful faces (vs. scrambled images) over a 4-month pre - to post-treatment interval, suggesting longitudinal changes in the neural mechanisms associated with emotion perception. [34]

Secondly, we used an in-scanner task that directly probes the problem solving skills that are addressed by FFT. To bring emotion processing into the family context, these same youth are instructed to think about family conflicts that have occurred recently (by their report) and then to think about how they might resolve those conflicts with family members. [37] In both tasks, we hypothesized that (1) participants who receive FFT-HR will show greater reductions in limbic activation and greater increases in dorsolateral (DLPFC), ventrolateral (VLPFC) and anterior medial PFC activation after treatment compared to those who receive EC; (2) decreases in amygdala activation and increases in DLPFC, VLPFC, or anterior medial PFC activation will be associated with symptomatic improvement over the pre/post-treatment interval.

METHODS

Participants

The study design is a single-blind, parallel group RCT with up to 4 years of follow-up (Figure 1). The study is being carried out in three settings: University of California, Los Angeles, School of Medicine; University of Colorado, Boulder; and Stanford University School of Medicine. The study was approved by the medical institutional review boards of each university. Participants are recruited from clinical referrals and online, radio, and print advertisements. After receiving an explanation of the study procedures, participants and their parent(s) give written informed assent/consent to participate. To be eligible, participants must (1) be between 9 and 17 years; (2) meet lifetime DSM-5 criteria for unspecified BD (formerly BD, not otherwise specified) or major depressive disorder (MDD); (3) have at least one first or second-degree relative with a lifetime DSM-5 diagnosis of BD I or II, based on the MINI International Neuropsychiatric Interview; [38] and (4) have current affective symptoms (a prior week YMRS score > 11 or a prior 2-week CDRS-R score > 29). If the lifetime diagnosis is MDD, the child must have had a full major depressive episode in the past 2 years.

To operationalize DSM-5 unspecified BD, we adapted criteria of the Course and Outcome in Bipolar Youth (COBY) study[14] : distinct periods of abnormally elevated, expansive, or

irritable mood plus two (three, if irritable mood only) DSM symptoms of mania that caused a change in functioning, lasted ≥ 4 hours in a day, and occurred for a total of 10 or more days in the child's lifetime. Although the original COBY criteria required only 4 lifetime days with manic symptoms, we used the more stringent cutoff (10 days) to increase the probability of identifying youth with recurrent subthreshold manic symptoms. In a reanalysis of the Pittsburgh COBY data, only 6% of youth with BD-NOS had experienced between 4 and 9 lifetime days of hypomanic/manic symptoms; 94% had experienced 10 days or more. Thus, virtually all (over 90%) of those who met the ≥ 4 day criteria also met the ≥ 10-day criteria, and the rates of long-term conversion to BD I or II would still apply (D. Axelson, personal communication May 22, 2017).

Procedure

Participants' current and lifetime diagnoses are assessed with the "Kiddie" Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KSADS-PL), [39,40] a semistructured interview of the child and at least one parent regarding the child. All sites have MA/PhD level diagnosticians who are trained and reliable in the KSADS-PL rating system. Following training, interrater reliability for KSADS depression and mania scores averaged .74 and .84, respectively, across sites.

The child's biological parents are interviewed directly about their own psychiatric history using the MINI. First- or second-degree relatives who cannot be interviewed directly are diagnosed from secondary information provided by either parent using the Family History Screening Instrument. [41] This instrument yields high specificity (0.83) and sensitivity values (.65) when comparing Family History Screen diagnoses of mood disorders to best estimate diagnoses. [41]

At intake, an expert rater classifies families as high or low in expressed emotion based on parents' responses to the Five-Minute Speech Sample task.[42] Families are classified as high in expressed emotion if a parent makes one or more critical comments toward the offspring or there is evidence of hostility or emotional overinvolvement/overprotectiveness; and low in expressed emotion otherwise.

Pharmacotherapy and Random Assignment to Psychosocial Treatments— Shortly after the K-SADS, the participant receives a full medical evaluation from a study-affiliated psychiatrist. This evaluation is followed by biweekly meetings and then monthly meetings for maintenance pharmacological care (when requested by the parent(s)). Physicians follow a pharmacotherapy algorithm describing medication choices, starting doses, upward titration, dose ranges, and necessary clinical adjustments to optimize care, manage symptoms or control side effects. [43] There is no requirement that the child take psychiatric medications to be in the trial.

Once the medical evaluation has been completed, each site's PI randomly assigns the participant to either FFT-HR or EC (in a 50/50 split) using a computer algorithm that is a modification of Efron's biased coin toss. [44] The algorithm balances the treatment groups within sites on diagnosis (unspecified BD vs. MDD), age (< 13 or ≥ 13 yrs), and initial pharmacotherapy regimen (mood stabilizers or second generation antipsychotics vs. neither).

Psychosocial Treatments—FFT-HR is administered in 12 sessions over 4 mos. (8 weekly, 4 biweekly) by a single therapist. The objectives of FFT-HR (Table 1) are to assist the youth and family members to: (1) recognize early signs of mood episodes; (2) distinguish significant mood dysregulation from healthy emotional reactions; (3) identify stressors that precipitate mood swings; (4) understand the role of medications in maintaining mood stability; (5) develop plans to prevent future mood escalations or deteriorations; and (6) enhance family communication and problem-solving.

In the psychoeducation module, the child and family discuss factors that elicit his or her mood swings (e.g., family arguments, changes in routines) and practice behavioral strategies to modulate one's affective reactions (mood management plan). The communication training sessions aim to reduce criticism, conflict and tension within the household. Skills such as active listening and making positive requests for change – practiced in sessions through role-playing and between sessions through homework assignments - provide parents with strategies to use when the child is behaving aggressively or has become depressed or withdrawn. In problem-solving sessions, families learn to break down large problems (e.g., "we don't get along") into smaller ones ("we need to use lower tones of voice"), generate and evaluate pros/cons of possible solutions, and choose solutions to implement (e.g., alert each other to aggressive voice tones).

The comparison treatment, EC, consists of 3 weekly family sessions in which clinicians summarize the results of the intake assessment, help identify triggers for mood swings, and assist the youth and family in developing a mood management plan. Clinicians then meet with the child individually every month for 3 months to troubleshoot use of the mood plan and to assist with solving daily problems. Following completion of FFT-HR or EC, children continue to see their study-affiliated psychiatrist until at least the end of the first study year.

Fidelity monitoring—Clinicians at UCLA, Colorado and Stanford were trained in both therapy protocols in a 2-day study launch meeting. After the workshops, clinicians read the relevant FFT-HR and EC manuals (available from www.semel.ucla.edu/champ/downloads-clinicians). Once they begin treating study patients, they attend monthly supervisory teleconferences to help ensure consistency with the protocols. Supervisors rate 2–3 audiotaped sessions from each FFT-HR case and one audiotape from each EC case using the Therapist Competence and Adherence Scales, Rev. (TCAS-R).[45] If clinicians fall below established TCAS fidelity thresholds, supervisors provide additional telephone consultation.

Outcome assessments—Independent evaluators who are unaware of treatments assignments interview participants at intake (covering the prior 4 months), every 4 months over the first year, and then every 6 months until 48 months (or last available follow-up). Independent evaluators do not attend clinical staff meetings in which ongoing treatments were discussed. Evaluators who inadvertently learn of a participants' treatment assignment are replaced by a new (blind) interviewer.

At each outcome assessment, the evaluator interviews the child and at least one parent using the A-LIFE and associated PSR ratings. PSRs are assigned to every week of the prior 4–6 month interval using a series of 1 (asymptomatic) to 6 (fully syndromal) scales. The primary

outcome (mood symptom severity) is calculated as a sum of the depression, mania and hypomania PSRs. Just prior to beginning the study, interrater reliabilities for 6-point depression and mania/hypomania PSRs averaged 0.74 (intra-class r) across raters at different sites. At each assessment, independent evaluators also administer the YMRS (mania) and CDRS-R (depression) interviews to the child and one parent regarding the child's mood in the last 1–2 weeks, with summary scores based on a consensus of the two reports.

Neuroimaging at baseline and post-treatment—Subjects at the UCLA and Stanford sites undergo neuroimaging scans at baseline and at 4 months (the length of the psychosocial treatment interval) (at the inception of the study, neuroimaging was not available at the Colorado site). The one-hr. scan session includes two functional MRI (fMRI) scans and a high-resolution T1-weighted anatomical scan. YMRS and CDRS-R ratings are obtained within one week of each scan. FMRI data are collected at UCLA in the Center for Cognitive Neuroscience on a 3.0T Siemens Trio scanner, and at Stanford on a 3T GE Signa scanner. Both sites used an 8 channel head coil and an echoplanar pulse sequence with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 80 degrees; 30 axial slices, 4mm thick, .05 mm skip, field of view = 22 cm, 64x64 matrix, inplane spatial resolution = 3.4275. Scan parameters are optimized for comparability across sites. Participants perform two tasks during the scan.

Emotional faces (Happy Café task): Photographs of fearful, calm, and happy faces taken from the McArthur ('NimStim') stimulus set (macbrain.org/resources.htm) are presented in a block design. Each block contains 8 pictures of the same emotion, and each picture is presented for 3 seconds, with 500 msec ISI. Four blocks of each emotion are presented over the 8 minute 32 second task. Participants view the task by looking directly up into a mirror that reflects the projection screen at the head of the scanner. Participants are instructed to press button '1' if the picture shows a girl, and button '2' for a boy; thus the emotion processing is implicit. No pictures are repeated. Stimuli are presented and responses collected using ePrime software. Based on our pilot study,[34] fearful versus calm faces is our primary contrast for the current study. In secondary analyses, we will examine whether youth with high expressed emotion parents show greater amygdala activation to fearful faces than youth with low-EE parents.

Family Problem-solving: There are no tasks in the fMRI literature that mimic what a patient experiences in FFT. Thus, in addition to the more widely used Happy Cafe task, we designed a task that we believed would be more ecologically valid with respect to interactions that occur in family intervention sessions and would reveal activity in the neural networks associated with emotionally relevant problem-solving, such as might occur in the current family environment. The design of this task is similar to other self-reflective tasks used in the depression literature (e.g. [46]).

Prior to the scan, participants complete a questionnaire listing a number of potential problems that youth can experience in their home life (e.g., conflicts over household rules) or daily routines (e.g., finding lost items). Rather than choosing a fixed list of problems, the investigator identifies 8 family problems and 8 neutral problems that are rated by participants as relevant and emotionally salient to them. These participant-specific problems

are then used as stimuli in the baseline and post-treatment scans. The task alternates between blocks of family problems and blocks of neutral (daily routine) problems (16 total blocks). Participants first view descriptions of each problem and spend time imagining it happening to them (10 sec.). Following a 2–5 second jitter, they press a button when they see a cross displayed on the screen. Then, they are instructed to think about what they might do about the problem (12 sec). The contrasts of interest are activation in anterior medial PFC, DLPFC, amygdala, and ventrolateral PFC when thinking about or solving family-relevant problems vs when thinking about or solving day-to-day problems.

Traveling subjects study: As recommended by the Functional Biomedical Informatics Research Network for multi-site fMRI studies,[47] we conducted a preliminary traveling subjects study to examine inter- and intra-site reliability, utilizing the Emotional Faces task and a finger tapping task and tested in ROIs in motor cortex and fusiform gyrus. Three subjects were scanned on 2 different days at each site. Test-retest consistency was high between sites. Further, the mean cross-site variations in percent signal change were approximately equal to the within-subject variability on the same scanner from separate days, indicating good comparability of fMRI results across sites.

Data analysis plan

Data will be analyzed on an intention-to-treat basis. Our primary analytical tools are mixed effects regression models and survival analyses which handle missing data and censoring, allow for changing degrees of treatment effect over time, and accommodate variable lengths of follow-up. The primary outcome is the stabilization of mood symptoms for up to 4 years. Secondary outcomes include time to conversion to bipolar I or II, psychosocial functioning, and treatment-associated changes in neural activation in regions of interest. In the power calculations, we assumed an attrition rate of 18% by end of follow-up (comparable to the rate in our first early intervention trial[25] and a correlation of .50 between repeated measures within subjects. The sample size (N=150) was chosen to obtain adequate power (> .80) for primary aim 1 using a 2-sided α=.05 and allowing for Bonferroni adjustment for testing of up to 5 symptom measures for the acute treatment and maintenance period contrasts (see Primary Aims, above).

We will fit mixed effects regression models to the primary outcomes (A-LIFE PSRs of mood symptom severity) and secondary outcomes (e.g., CDRS-R and YMRS scores), with main effects for treatment (FFT-HR vs EC), study site, and study visit (0, 4, 8, 12, and every 6 months thereafter), and the interaction of treatment and study visit. Our base models will treat time as a continuous measure with random intercepts and slopes for each subject, allowing a change in slope of outcome scores at the end of the acute treatment period. We expect that differences between treatment groups in mood symptom scores will be lower during maintenance treatment than during the acute (first 4 month) phase. For the weekly PSRs, we will have a sufficient number of timepoints before and after active treatment to identify specific non-linear trends (e.g. quadratic, cyclical) using subject level random effects.

For secondary measures obtained every 4–6 mos, we have 85% power to detect a change from no difference at baseline to a group difference of .50 SDs at the end of acute treatment (assuming α=.05, 150 subjects, and 18% attrition). These medium effect sizes are comparable to those observed in prior FFT studies range 0.49 – 0.56 for depression[20,23] and hypomania scores[25] over 1–2 years. For secondary analyses of moderator effects, we have adequate power (> .80) to detect a medium-sized (Cohen's d = .50) interaction between treatment condition (FFT-HR, EC) and (1) baseline family attributes (e.g., high vs. low expressed emotion attitudes in parents); or (2) the presence/absence of comorbid disorders (e.g., anxiety disorder or substance abuse disorder) on symptomatic or functional outcomes over the course of follow-up.

A secondary outcome is time from randomization to the first prospectively observed manic or mixed episode (hypothesis 2, above). We will use log-rank tests to compare the Kaplan-Meier estimates and confidence intervals of the treatment group survival curves. Proportional hazards models will be used to adjust for potential moderators (e.g., family expressed emotion) and potential confounders (e.g., site, age, sex). With 75 subjects/group, 2 years of follow-up, and 18% attrition, a log-rank test has 80% power to detect a 1.72 hazard ratio indicating a greater probability of a prospectively observed manic episode among patients in EC vs. FFT (α=.05). In two randomized trials of adults with bipolar disorder that examined probability of a mood disorder recurrence over 2 years, we observed hazard ratios of 1.52 – 2.63.[20,21]

FMRI data will be preprocessed and statistically evaluated using FSL[48] and/or SPM12.[49] For each subject we will model fixed effects for the comparisons of interest. Group comparisons will use a random effects model. For association with clinical measures, we will use anatomically defined ROIs based on previous meta-analyses of studies in pediatric-onset BD (amygdala, DLPFC, VLPFC, medial PFC; [31,50]) to extract the mean activation at baseline and follow-up in these clusters for each subject. We will then examine how pre/post changes in anatomically defined ROIs are correlated with changes in symptom measures over 4 months of treatment. Mixed effects models with main effects for group, time of scan and their interaction will be used to assess the effects of the FFT-HR vs. EC on activation in key ROIs and neural circuits. We will include acquisition site as a covariate, and investigate secondarily whether there are treatment group by site/scanner interactions on any of the ROIs. For individual subject-level ROI analyses, we have over 80% power to detect a treatment by time interaction corresponding to a between-group difference of d = .75 at end of acute treatment (using α=.05); or a difference of d=.85 at α=.01 if we allow for correction for multiple comparisons for the multiple ROIs.

Participants in the two study arms will be balanced on medication regimens at time of randomization. We will compare the groups at each follow-up to determine whether any medications are overrepresented in one condition. If needed, we will adjust mixed effect or survival models for medication regimen as a time-varying covariate.[51]

RESULTS

The randomized sample of 133 participants (recruited from June 2012 to September 2016) represents 49.3% of the population assessed for eligibility (N = 270) (Figure 2). The most common reasons for exclusion (n = 79, 57.7%) concerned diagnosis (e.g., met DSM-5 criteria for autism spectrum disorder) or inadequate evidence of BD in any first- or second-degree relative. A total of 51 candidates (18.9%) declined to participate, and 7 (2.6%) were excluded for other reasons.

As indicated in Table 2, the enrolled sample is primarily Caucasian and more often female than male. The ratio of participants with major depressive disorder vs. unspecified BD is approximately 2:1. The mean CDRS-R depression score at baseline is 46.6 ± 14.4; a score of 40 is usually indicative of a major depressive episode.[52] YMRS scores of 12 have been suggested as a cutoff for defining hypomania in adolescents.[53]

DISCUSSION

This article presents the rationale and design for a long-term RCT comparing two psychosocial interventions for youth at high risk for BD. Although this study is primarily powered to examine symptom trajectories, we will examine secondarily whether FFT is associated with a lower rate of conversion to BD I or II compared to EC. The study examines both behavioral and neural targets for psychosocial interventions. High levels of EE in parents and associated behaviors in families provide targets for FFT-HR: reducing the frequency and intensity of negative parent/offspring exchanges and enhancing conflict resolution within families.

We propose that FFT-HR will have greater effects than EC on the child's ability to regulate emotions, as measured by "top-down" corticolimbic activation during fMRI scans. Specifically, when rating the gender of faces expressing negative emotions, or when thinking about or trying to solve a family problem, we expect to see treatment-associated reductions in amygdala activity and increases in DLPFC, VLPFC or anterior medial PFC activity. We will determine whether longitudinal changes in the activation of these neural circuits are correlated with improvements in the severity of the child's mood symptoms.

We acknowledge several limitations of the design. First, despite use of a medication algorithm designed for this population, we cannot fully disentangle the effects of medication management from those of psychosocial interventions. The physicians may adjust medications at follow-up to optimize care and prevent an emerging episode. Further, some of the participants or their parents (about 40% in our prior study[25]) may not opt for medications. The presence/absence of mood stabilizing or antipsychotic agents, plus the number and type of necessary clinical adjustments will be measured throughout the study. The effects of psychosocial treatments will be examined with medication regimens as a time-varying covariate.

Second, although the FFT-HR and EC treatments are both 4 months long, they differ on number of sessions in that interval (12 family vs 6 family plus individual sessions). The EC treatment was designed to reflect usual care for youth at high risk for BD in community care

settings: limited family education and individual support. We have shown previously that in adolescents with bipolar I or II disorder, brief family psychoeducation is associated with equally rapid remission of symptoms compared to FFT. [24] In this study, we will be unable to fully determine whether the effects of FFT-HR are due to its specific content and techniques (e.g., communication training) or to its great number of clinician/patient contact hours. If the results favor FFT-HR, studies that compare FFT-HR with a frequency and duration-matched control that is currently practiced in the community would help to disentangle the effects of specific versus nonspecific factors (e.g., family engagement, therapeutic alliance).

Third, even though the study participants are chosen based on known risk factors (e.g., a family history of mania), we may not know whether participants are progressing toward BD during their tenure in the study; longer-term follow-up of participants will almost certainly be necessary to identify all new onsets of mania in this cohort. Finally, family interventions may operate through alleviating the severity of comorbid psychopathology (e.g., inattention, anxiety or oppositional-defiant behavior) rather than the child's mood disorder. We expect to learn a great deal in this study about the neural and behavioral processes that predate the onset of mania, and whether modifying these processes improves the course of mood symptoms or mitigates risk for the onset of BD or other forms of psychopathology.

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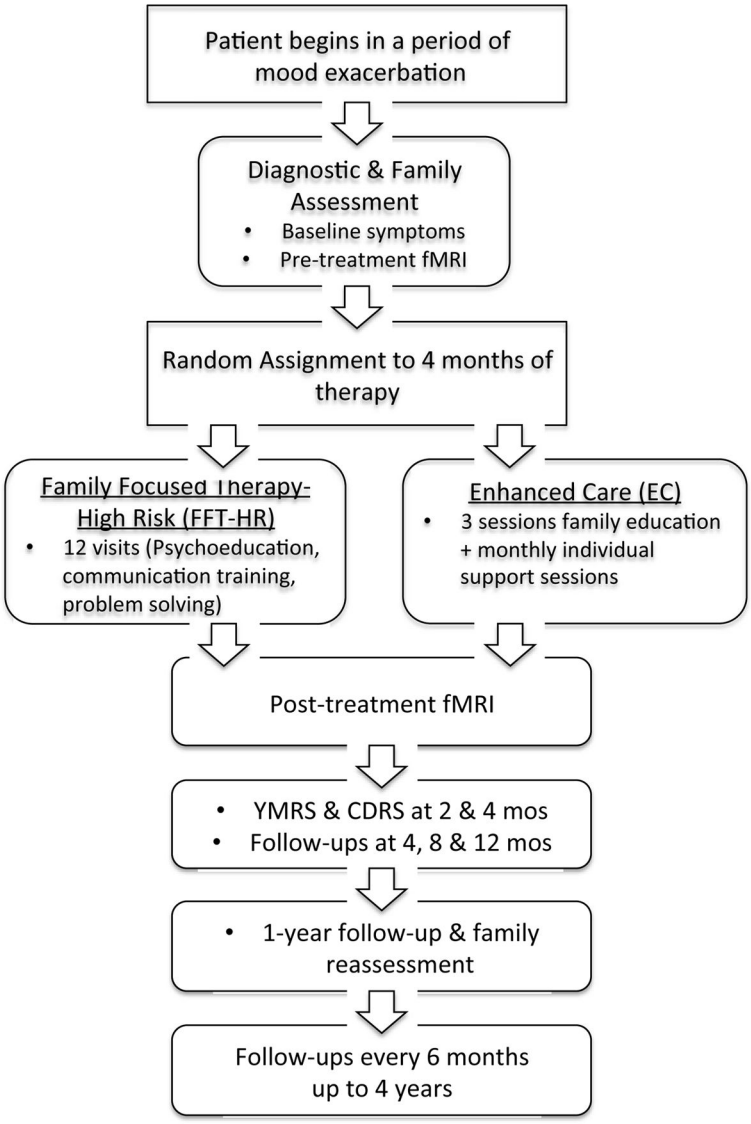

Figure 1.
Study Design.

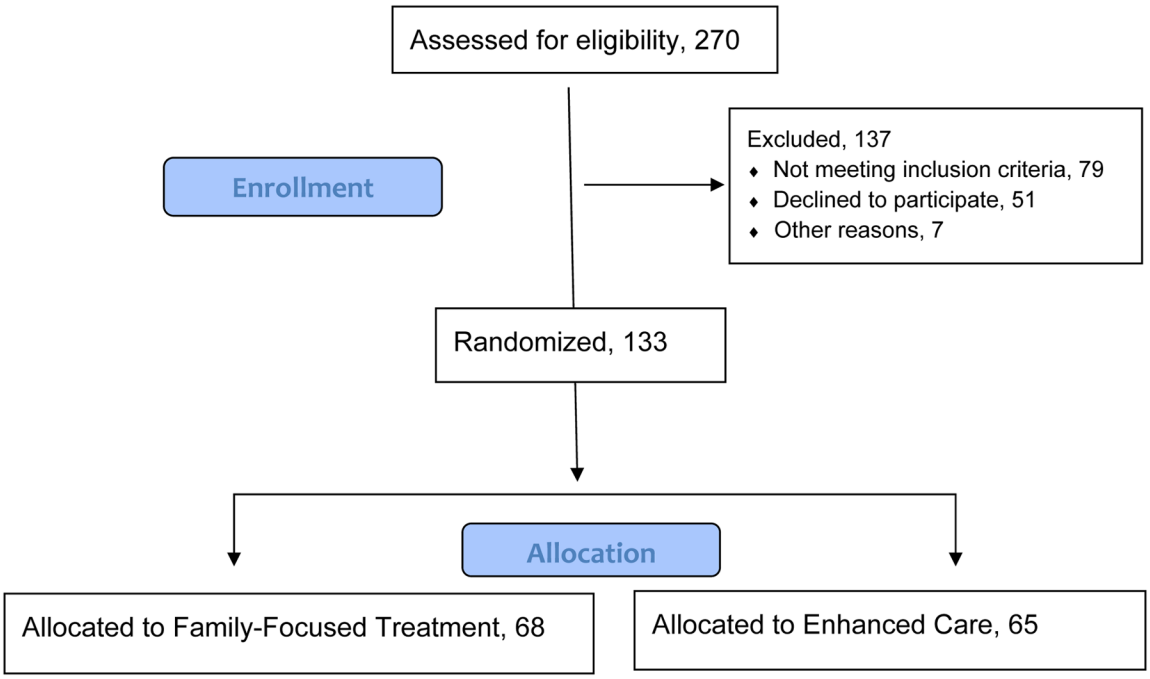

Figure 2.
CONSORT Flow Diagram

TABLE 1

Family-Focused Treatment for Youth at High-Risk for Bipolar Disorder: Session plan

Session #	Frequency	Goals and content
1	weekly	Introduction, treatment overview and expectations, goal-setting
2	weekly	Symptoms of early-onset mood disorders; mood diaries
3	weekly	Vulnerability/stress model of episodes, mood monitoring, role of family, peer and school stressors; role of medications
4	weekly	Develop mood stabilization/management plan
5	weekly	Introduction to communication skills training: expressing positive feelings
6	weekly	Communication skills training: active listening
7	weekly	Communication skills training: requesting changes in another's behavior
8	weekly	Communication skills training: communication clarity and expressing negative feelings about specific behaviors
9	biweekly	Introduction to problem solving; rehearse communication skills
10	biweekly	Problem-solving: examples from daily life
11	biweekly	Problem-solving: examples from daily life
12	biweekly	Review of treatment modules; review mood management plan; assess participants' satisfaction and need for additional care

TABLE 2

Sample composition

Variable	FFT-HR (n=68)	Enhanced Care (n=65)	Total (N = 133)
Age, mean (SD)	13.1 (2.7)	13.1 (2.4)	13.1 (2.6)
Gender, No. female (%)	39 (57.4%)	45 (69.2%)	84 (63.2%)
Race, no. (%) non-white	13 (19.1%)	9 (13.8%)	22 (16.5%)
Ethnicity, no. (%) Hispanic	16 (23.5%)	7 (10.8%)	23 (17.3%)
Young Mania Rating Scale, mean (SD)	12.1 (7.1)	12.2 (7.1)	12.1 (7.0)
Children's Depression Rating Scale, Rev., mean (SD)	45.0 (12.9)	48.3 (15.8)	46.6 (14.4)
Major depressive disorder, no. (%)	43 (63.2%)	40 (61.5%)	83 (62.4%)
Bipolar disorder, not otherwise spec., no. (%)	25 (36.8%)	25 (38.5%)	50 (37.6%)