How to Write a Successful NIH NRSA Grant

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What is an NRSA?

Ruth L. Kirschstein National Research Service Award

- Intended for early research training
- Foster next generation of independent investigators

Dr. Kirschstein

- Key player in the development of polio vaccine
- First woman director of a major institute at the NIH
- Champion of basic biomedical research and training programs
- Mission: provide opportunity to all talented students, especially underrepresented minority students.
NRSA Funding Mechanisms

- F31 Predoctoral NRSA
- F32 Postdoctoral NRSA
NRSA Fellowships and Training Grants (F & T Awards) for Individuals With or Earning a Research Doctorate

- Predoctoral Fellowships (F31)
- MARC COR (T34)
- Institutional Training Grants (T32)
- Postdoctoral Fellowships (F32)
- Senior Fellowships (F33)

Time:
- College
- Graduate School
- Postdoctoral
- Independent Investigator
NRSA Fellowships and Training Grants (F & T Awards) for Individuals With or Earning a Health-Professional Doctorate

- Short-Term Training Grant (T35)
- Institutional Training Grants (T32)
- Postdoctoral Fellowships (F32)
- Senior Fellowships (F33)

Medical School
Residency
Specialty/Sub-Specialty
Independent Investigator
Why write an NRSA proposal?

- Chance to practice skill invaluable to later career
- Opportunity to tailor training towards individual interests
  (e.g. “you want to learn fMRI? Here’s your chance!”)
- Opportunity to get a jump on research ideas early in graduate training
- Nice addition to CV!
Preventing NRSA

1. Generate ideas –
   ◆ Think about what gets you excited
   ◆ Browse Funding Opportunity Announcements (FOA)

2. Narrow ideas –
   ◆ Does it fit with NIH objectives?
   ◆ Is the scope of the project feasible?
   ◆ Goal is to get funded *and* to get the project done!
Strategic Objective 1: Promote Discovery in the Brain and Behavioral Sciences to Fuel Research on the Causes of Mental Disorders  
We will support basic, translational, and clinical research to gain a more complete understanding of the genetic, neurobiological, behavioral, environmental, and experiential factors that contribute to mental disorders.

Strategic Objective 2: Chart Mental Illness Trajectories to Determine When, Where, and How to Intervene  
We will chart the course of mental disorders over the lifespan in order to understand ideal times and methods for intervention to preempt or treat mental disorders, and hasten recovery.
NIMH Funding Objectives

- **Strategic Objective 3**: Develop New and Better Interventions that Incorporate the Diverse Needs and Circumstances of People with Mental Illnesses  
  We will improve existing approaches and devise new ones for the prevention, treatment, and cure of mental illness, allowing those who may suffer from these disorders to live full and productive lives.

- **Strategic Objective 4**: Strengthen the Public Health Impact of NIMH-Supported Research  
  Through research, evaluation, and collaboration, we will further develop the capacity of the Institute to help close the gap between the development of new, research-tested interventions and their widespread use by those most in need.

A word about RDoC….

<table>
<thead>
<tr>
<th>Domain</th>
<th>Units of Analysis</th>
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<td>Systems for Social Processes</td>
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<td>Arousal/Regulatory Systems</td>
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Preparing the Application: Core Sections

1. Specific Aims (1 page)
2. Research Strategy (6 pages)
   (a) Significance
   (b) Innovation
   (c) Approach
   (d) Preliminary Studies
3. Protection of Human Subjects
4. Inclusion of Women/Minorities
5. Targeted/Planned Enrollment
6. Respective Contributions (1 page)
7. Selection of Sponsor and Institution (1 page)
8. Responsible Conduct of Research (1 page)
9. Goals for Fellowship Training and Career (1 page)
10. Activities Planned Under Award (1 page)
11. Doctoral Dissertation and Research Experience (2 pages)
12. Sponsor/Co-Sponsor Information (6 pages)
Follow Instructions Closely!
Specific Aims

**Most important single page of application**

- First impression – hook or lose reviewer?
  - Emotional reaction of reviewer can make or break chances of getting funded!

- Succinctly state aims and hypotheses
  - Summarizes entirety of application
  - State
    1. the problem
    2. how you’re proposal addresses the problem

- Limit to three specific aims

- Revise Review Revise!
B2. SPECIFIC AIMS

The recent NIMH Research Domains Criteria (RDoC) initiative challenges investigators to translate findings from basic science into treatments addressing core processes that span across disorders. Bipolar I disorder (BD-I) is a chronic and debilitating disorder, associated with recurrent manic and depressive episodes, and poor interpersonal, social, and work functioning. This course is further impacted by the presence of comorbid anxiety in BD-I. Compared to BD-I patients without comorbid anxiety, patients with comorbid anxiety have greater BD illness severity, greater functional impairment, and a worse course of illness. Therefore, treating comorbid anxiety in individuals with BD-I has been recognized as one of the biggest unmet needs in the field of bipolar disorder. In response to this need, and in line with the mission of RDoC, the purpose of this proposal is to investigate the feasibility, acceptability, and preliminary efficacy of a transdiagnostic, cognitive-behavioral therapy developed specifically to target common core processes across mood and anxiety disorders [Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP)], for the treatment of patients with BD-I and comorbid anxiety.

Existing treatments thus far do not adequately meet the need to address comorbid anxiety in BD-I. Pharmacotherapy for the treatment of comorbid anxiety in BD faces significant challenges. The two most commonly used classes of medications for the treatment of anxiety disorders are selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines. In BD, these carry the risk of triggering mania (SSRIs) or substance dependence (benzodiazepines). Cognitive-behavioral therapy (CBT), highly effective in the treatment of primary anxiety disorders, may offer a viable treatment alternative. Very few studies of CBT for anxiety in BD-I have been conducted, and those existing studies have been limited to targeting one specific anxiety disorder. Recently, advances in CBT have led to the development of a unified protocol for the combined treatment of anxiety and mood disorders (UP). This protocol targets common underlying cognitive and affective processes that have been found across anxiety and mood disorders. Applying this approach to patients with BD offers the possibility of treating BD and comorbid anxiety using a single psychosocial treatment protocol, and provides a unique opportunity to investigate whether a transdiagnostic approach is also a feasible approach to treating BD. If this is the case, it has the potential to address an important shortcoming in existing treatment as usual (TAU) and provide a much-needed adjunctive therapy for this debilitating, difficult-to-treat disorder.

The specific objective of the proposed study is to conduct a Stage I, Phase I open trial designed to 1) test the feasibility and acceptability of an 18-session, transdiagnostic CBT intervention (UP) developed to target core deficits in cognitive and affective processing across anxiety and mood disorders, as applied to the treatment of BD-I with comorbid anxiety disorders; 2) investigate the preliminary efficacy of the UP as an adjunct to pharmacotherapy treatment-as-usual (TAU) compared to TAU alone, 3) explore whether transdiagnostic treatment of BD-I with comorbid anxiety disorders improves relapse rates over a 6-month follow-up relative to TAU; and 4) investigate whether reduction in symptoms, relapse rates, and changes in functioning are mediated by changes in emotion regulation skills. In addition to these objectives, this project would serve as invaluable for furthering the applicant's training goals to become proficient at designing and implementing randomized controlled clinical trials, and augment the applicant's predoctoral training in clinical neuromaging in support of a career goal to become an independent translational clinical researcher. To that end, the results of this pilot trial will provide crucial initial development and testing data in support of a potential future translational randomized controlled trial.

Primary Aim:

1) Test the feasibility and acceptability of the UP as applied to the treatment of BD-I with comorbid anxiety disorders with regard to recruitment, randomization, retention, administration of the UP, and patient satisfaction with treatment.

Hypothesis 1a: Treatment with the TAU+UP will result in high rates of acceptance for randomization, high rates of retention, and higher ratings of patient satisfaction than TAU.

2) Investigate the efficacy of the TAU+UP in improving symptom and functioning outcomes post-treatment relative to TAU alone in an open trial of BD-I patients with comorbid anxiety disorders.

Hypothesis 1b: TAU+UP will result in significantly greater reductions in symptom measures of anxiety, residual depression, mania and functional impairment over one year compared to TAU.

Exploratory Aims:

1) Investigate the efficacy of TAU+UP in reducing relapse rates over 6 months as compared to TAU.

Hypothesis 2a: TAU+UP will result in reduced relapse rates relative to TAU at one-year post baseline.

2) Explore whether treatment-related changes in residual symptoms and functioning are mediated by changes in emotion regulation.

Hypothesis 2b: Subjects with improvement in emotion regulation skills will show greater advantage of TAU+UP (vs. TAU) with regard to improvement of symptoms and functioning.
Research Strategy

- 6 pages to say everything
- Should directly follow Specific Aims

**A. Significance:** Why should NIH give you money for this proposal? What *unmet public health need* does project address? How does it overlap with NIH priorities?

**B. Innovation:** What makes this project unique? Has this ever been done before, and if so what are you adding?

**C. Approach:** What exactly are you planning to do and why did you choose these methods?
  - Alternate design considerations - anticipate reviewer’s questions
  - Data analysis plan: restate hypotheses from Specific Aims and make sure analysis plan can support

**D. Preliminary studies:** Do you have any evidence you or your mentors know what you’re doing and can pull your proposal off?
  - What came before from you/mentors that led to your current question

- Add graphics
  - Too much text = Bored reviewer = lower score?
mixed anxiety samples. Results from these studies consistently implicate amygdala and vmPFC in extinction learning. Specifically, these studies show amygdala deactivation from early to late extinction phases coupled with increased vmPFC activation (see Fig. 2 above). As part of my predoctoral NRSA, I recently conducted a study examining the neural correlates of mindful awareness and acceptance versus worry in generalized anxiety disorder.

Stimuli for this study were generated through interviews with each patient participant about specific topics of worry. Using a block design, participants viewed their personally-relevant worry statements in the scanner, followed by counterbalanced instructions to 1) worry as usual, 2) don’t think or feel, or 3) observe and accept emotional reactions. Analyses examined patterns of activation early (1-158), mid (6-105) and late (11-158) in the regulation block. Results showed “Acceptance” was associated with increased left dlPFC and amygdala activation relative to worry or suppress early in the regulation block (Fig. 3a), and decreased amygdala and increased vmPFC activation late in the regulation block in regions overlapping with extinction learning studies (Fig. 3b). These results suggest regulating distress through mindful awareness and acceptance engages extinction learning pathways, but this is preceded by engagement of the dlPFC, perhaps reflecting early attentional reorienting. Results of this study raised two important questions: 1) is the mechanism of emotion regulation using mindful awareness through extinction learning, and 2) is extinction learning through mindful awareness facilitated by early cognitive control? The current proposal seeks to explore these questions.

12D. Approach.
12D.1. Participant selection and recruitment. We will recruit 30 male and female patients ages 22-55 (to limit age-related heterogeneity of brain structure and function) seeking treatment through the Massachusetts General Hospital Bipolar Clinic and Research Program (MGH BCRP) and 30 age-matched healthy controls. Patients who endorse clinically significant symptoms of depression, anxiety, and a history of mania as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.), Hamilton Anxiety Rating Scale (HAMA; score 20 or higher), Hamilton Depression Rating Scale (HAM-D-17; score 17 or higher), and Longitudinal Interval Follow-up Evaluation - Range of Impaired Functioning Tool (LIFE-RIFT; score 12 or higher) will be invited to participate. These inclusion criteria will allow for recruitment of a representative sample of patients who typically present at our Clinic for treatment. Healthy participants without a history of psychiatric disorder will be invited to participate. 12D.1.1. Exclusion criteria (1) current symptoms of mania, as determined by a Young Mania Rating Scale (YMRS) score of $\geq 12$ or higher; (2) current or past history of: organic mental disorder; substance abuse within the past 12 months and/or history of substance abuse for > 1 year; past or current substance dependence (including alcohol), schizophrenia, delusional disorder, psychosis not otherwise specified, or non-organic mental medical treatment that would likely interfere with study participation; (3) neurologic disorder, previous ECT, or history of head trauma; (4) Presence of metallic implants that would interfere with safety during fMRI scanning (i.e. heart pacemaker, metal plates, etc.); (5) prior course of mindfulness-based CBT. Additional elaboration on the inclusion/exclusion criteria is provided in the Human Subjects section.

12D.2. Procedure. Following informed consent, eligible participants will complete a brief interview concerning topics the participant worries about in their daily life, to be used as stimuli during the emotion regulation scanning procedure (see Section 12D.2.3, below). In addition, participants will complete the Five Facets Mindfulness Questionnaire (FFMQ) to assess baseline mindfulness levels. All participants will complete a functional magnetic resonance imaging (fMRI) scanning session consisting of: (1) an extinction-learning task; and (2) a mindful awareness emotion regulation task (see Sections 12D.2.2 and 12D.2.3 below). Order of scanning tasks will be randomized across participants. Data from Phase 1 will be analyzed to determine PFC targets for rTMS in Phase 2 (see Section 12D.3.2, below). Phase 2: All participants from Phase 1 will receive (1) one session of EF-rTMS, and (2) sham rTMS session of sham TMS (see Section 12D.2.5, below), in a randomized, crossover design (Fig. 4). Each TMS session will be immediately followed by an fMRI scanning session, during which participants will complete a mindful awareness emotion regulation task. TMS sessions will take place in the scanning bay to enable quick transition to the fMRI task. Active rTMS-fMRI and sham rTMS-fMRI sessions will occur on two separate days, no more than two weeks apart. 12D.2.1. Alternate design considerations: We considered using simultaneous TMS-fMRI for this proposal, following methods pioneered by my advisor, Dr. George. However, rather than providing a "dose" of stimulation as in single-session TMS, simultaneous TMS-fMRI involves single or theta-burst pulses carefully-timed to the
Doctoral Dissertation and Research Experience

- Chance to tell your story, sell yourself!
  - What research experiences have you gained so far?
  - How have these experiences informed your current proposal?
  - Who have your mentors been along the way, and how have they supported you?
  - What roles have your current sponsor(s)/consultants played in your development so far?
  - Where do you hope to take your training/career?

- OK to overlap with other sections (e.g. biosketch, career/training goals) - establish a theme!

- Not OK to simply cut and paste from other sections
Goals for Fellowship Training and Career

- State overarching career goals
  - How has training so far supported goals?
  - What training do you still need?

- State specific training goals for Fellowship
  - Application is for a TRAINING GRANT
  - Need to address how proposal will meet training needs
3. CAREER GOALS AND OBJECTIVES.
My long-term objective is to improve the efficacy and reach of cognitive-behavioral interventions for severe mood and anxiety disorders by developing neuroscience-informed interventions that can be applied transdiagnostically and that can be matched to patients based upon specific neural profiles. Specifically, consistent with the NIMH’s new priorities for clinical trials (e.g., trials that interrogate a specific target and are not constrained by current diagnostic criteria), I wish to 1) use neuroimaging methods to understand mood and anxiety-related pathology at the neural level and identify potential targets of intervention, 2) use this knowledge to develop interventions that serve to specifically modulate identified targets to rehabilitate dysfunction through a combination of advanced neurobehavioral methods (e.g., combined TMS-CBT), and 3) match these interventions to patients through predictive neural profiles.

Figure 1. Progression of Program of Research

Short-term Goals: The proposed K award supports my long-term objectives in important ways.

First, the training the proposed K award will afford me will give me the skills necessary to examine both pathological processes and mechanisms of intervention on the level of neural circuits, allowing me to understand dysfunction and potential intervention on the level of distributed neural networks. This strategy confers a much greater advantage than exploring patterns of regional neural activation in a gross manner as in traditional block designs, as it allows me to identify specific nodes along an interconnected neural network, which in turn allows me to identify specific potential target nodes for intervention. The training in the use of TMS I will receive through this award will give me expertise in a powerful method for modulating identified target nodes within a neural circuit, to see whether this approach can improve the mechanisms of action of behavioral interventions and serve as a viable adjunctive treatment strategy.

Second, the project proposed in this K award is in line with my first stated career objective, to use neuroimaging methods to understand mood and anxiety-related pathology at the neural level and identify potential targets of intervention. Specifically, I seek to clarify the mechanism of action of emotion regulation through mindful awareness in a systematic way using fMRI, by directly comparing patterns of activation during emotion regulation using mindful awareness with those resulting from a well-validated extinction-learning task. This will allow me to identify specific regions to target with TMS, in order to see if TMS is a viable method to enhance neural activation supporting the ameliorative effects of mindfulness. The long-term goal of this proposal is to improve access to this strategy for more severe patients.

Accordingly, through this K award I seek relevant training in the following 2 areas:
1. Advanced fMRI methods. To conduct sophisticated fMRI analyses, I require further training in advanced fMRI design and analysis, particularly time-series and network-level analyses.
2. Training in TMS. In order to be able to use TMS as a research and clinical tool, I require extensive training in TMS methods, use and applications.
Activities Planned Under Award

- Be specific about how plan to achieve training/research goals
- List courses, meetings, didactics, hands-on training
- State sponsors’/advisors’/consultants’ roles in training activities
- Provide a table/timeline
<table>
<thead>
<tr>
<th>Research Activity Related Training Activity</th>
<th>Months (Beginning 05/09)</th>
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<tr>
<td></td>
<td>2</td>
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<tr>
<td>Training in fMRI</td>
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<tr>
<td>Scanner certification</td>
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<td>Scanner assistant</td>
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<td>Linux/Unix training</td>
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<td>SPM training</td>
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<td>Statistical Design/Analysis</td>
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<td>Coursework</td>
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<td>Data Collection</td>
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<td>Pilot subject recruitment</td>
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<td>Pilot data acquisition</td>
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<tr>
<td>Study subject recruitment</td>
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<tr>
<td>Data acquisition</td>
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<td>Acceptance Skills Training</td>
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<td>Skills training delivery</td>
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<td>clinical supervision</td>
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<td>Data entry/Analysis</td>
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<td>Pilot data image processing</td>
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<td>Consultant/mentor mtgs (mthly)</td>
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<tr>
<td>Collaborative team mtgs</td>
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Why did you choose your Sponsor(s)/Consultants?

Can your institution support your proposed research/training plan?

Selection of Sponsor and Institution

Respective Contributions (what is each person’s role)

Sponsor/Co-Sponsor information
Can your selected sponsor support you and your project?

- A. Ongoing Research Support
- B. Sponsor’s previous Fellow’s/Trainees
- C. Training Plan, Environment, Research Facilities
- D. Number of Fellows/Trainees to be Supervised During the Fellowship:
- E. Applicant’s Qualifications and Potential for a Research Career
Ethics-Related Sections

- Protection of Human Subjects:
  - State inclusion/exclusion criteria
  - Plans to minimize risks
  - Plans for remediation in case of adverse events
  - Plans for data storage; protection of participants’ identity

- Inclusion of Women/Minorities; Inclusion of Children
  - Plans to recruit underrepresented populations

- Targeted/Planned Enrollment
  - Follow population % from most recent area census!!

- Responsible Conduct of Research (RCR)
  - Detail Institution’s plan for RCR training
  - Usually combines CITI modules, lectures, and presentations/workshops
  - State how sponsor will add to ethics training (e.g. meetings, didactics)
NIH Grant Cycle

Flow of Application

NIH receives application & assigns ID #

Application assigned to CSR Scientific Review Group

Application’s assignment appears in ERA Commons ~2wks

Summary Statement in ERA Commons ~3-4 wks

Application Peer Reviewed at next SRG Meeting; Assigned Score & %-ile

If score above payline & able to address comments, revise and resubmit

If score in payline, application goes to Council Meeting for funding decisions

If funded, go celebrate and get to work!!
Tracking Your Application

ERA Commons:

https://commons-era.nih.gov/commons/
Some final thoughts...

- Don’t be afraid to think big
- Think about what makes you passionate
- No idea officially stinks until you’ve taken it through to its final conclusion
- Your mentors/colleagues are your greatest resource!!!
  - Don’t be afraid to ask others for advice and guidance – no question is too insignificant!!
  - Get feedback - Ask your mentors to read and re-read your sections
Questions?