



LIBR

Laureate Institute for Brain Research



THE UNIVERSITY *of*
TULSA

K Club, Week 3

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Today's Topics



- ▶ Forms
- ▶ Research Strategy
- ▶ Significance
- ▶ Innovation
- ▶ Approach
- ▶ Action Items

Forms

- ▶ Each FOA tells you what set of forms to use for your K application
- ▶ Often it is SF424 (R&R) forms/instructions
- ▶ Later on in the course we will go through these forms and from time to time we may mention SF424



Required Application Instructions

It is critical that applicants follow the Career Development (K) Instructions in the [SF424 \(R&R\) Application Guide](#), except where instructed to do otherwise (in this FOA or in a Notice from the [NIH Guide for Grants and Contracts](#)). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in [Section IV](#). When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

K Application Sections

Research

- **Specific Aims** (1 page)
- **Research Strategy** (6 pages: **Significance, Innovation, Approach**)
- **Training in Responsible Conduct of Research** (1 page)
- **Project Summary / Abstract** (30 lines of text)
- **Project Narrative** (3 sentences)
- **Protection of Human Subjects from Research Risk**
- **Inclusion of Women and Minorities**
- **Inclusion of Individuals Across the Lifespan**
- **Inclusion Enrollment Report**
- **Budget + Budget Justification**
- **Bibliography + References Cited**

Career

- **Candidate Information and Goals for Career Development** (6 pages: **Candidate Background, Career Goals/Objectives, Career Development/Training Plan**)
- **Plans and Statements of Mentor and Co-Mentors** (6 pages)
- **NIH Biosketches** for you, Mentor, Co-Mentors (max 5 pages each)
- **Three Letters of Reference**
- **Letters of Support from Collaborators, Contributors and Consultants** (6 pages max)
- **Cover Letter**

Setting

- **Facilities and Other Resources**
- **Equipment**
- **Environment and Institutional Commitment to Candidate**
- **Resource Sharing Plan**



Research Strategy
(6 pages max)

Unlike **Specific Aims**, citations are required in this section

Significance

Expand on **Specific Aims**

Innovation

Explain the novelty of your theory, approach and/or methods

Approach

Explain study design, methods, and statistical analyses to accomplish each of your **Specific Aims**

Significance

(~1.5 pages max)



- ▶ Explain the problem and why it is horrible (take from **Specific Aims**)
- ▶ Describe the “knowns” and “unknowns” in the literature (take from **Specific Aims** and add a few more details if you need to)
- ▶ Clearly say what ***the gap(s) are in the literature*** that your project will address
- ▶ Mention preliminary data that you are basing your central hypothesis on, and where data are from (your lab, or the literature)
- ▶ State your overall study design, your central hypothesis and your **Specific Aims**
- ▶ Positive Impact #1: Explain how the project will improve at least one of the following:
 - ▶ Scientific knowledge
 - ▶ Technical capability
 - ▶ Clinical practice
- ▶ Positive Impact #2: Describe how the field will be changed if your **Specific Aims** are achieved (e.g., concepts, methods, technologies, treatments, services, and/or preventative interventions)

Significance

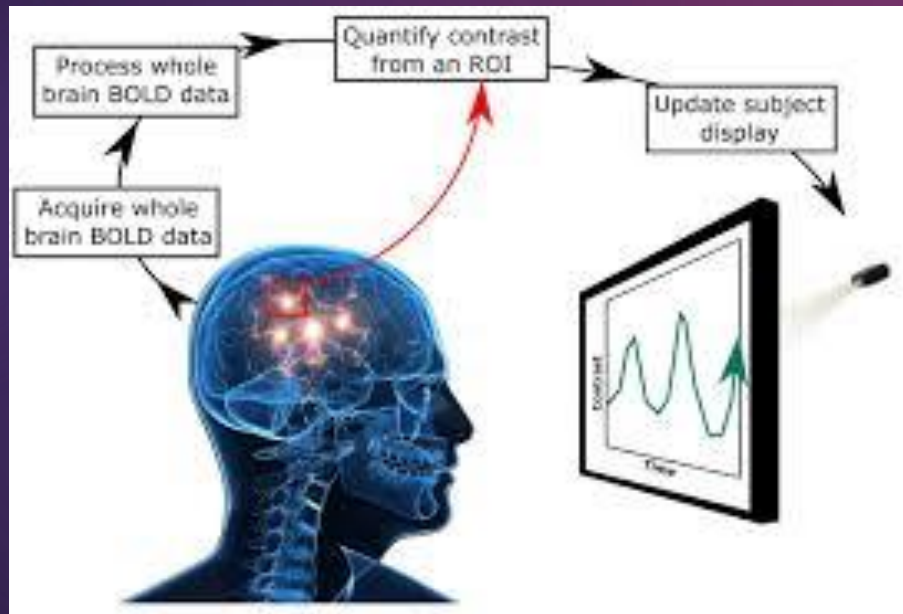
- ▶ You have most of this info in your **Specific Aims** already!!!! 😊
- ▶ Think of this section as an Introduction to a manuscript
- ▶ Make sure to include citations to support all of your statements! They will go in a **Bibliography & References Cited** section
- ▶ Make sure to cover the gaps in the literature that address both the K99 and R00 phases of your study!
- ▶ Here you can include an **OVERVIEW** of your study (groups, conditions, anything relevant to testing your **Specific Aims**)
- ▶ However, study **DETAILS** go in the **Approach** section



Significance (Example)

Grant Title:

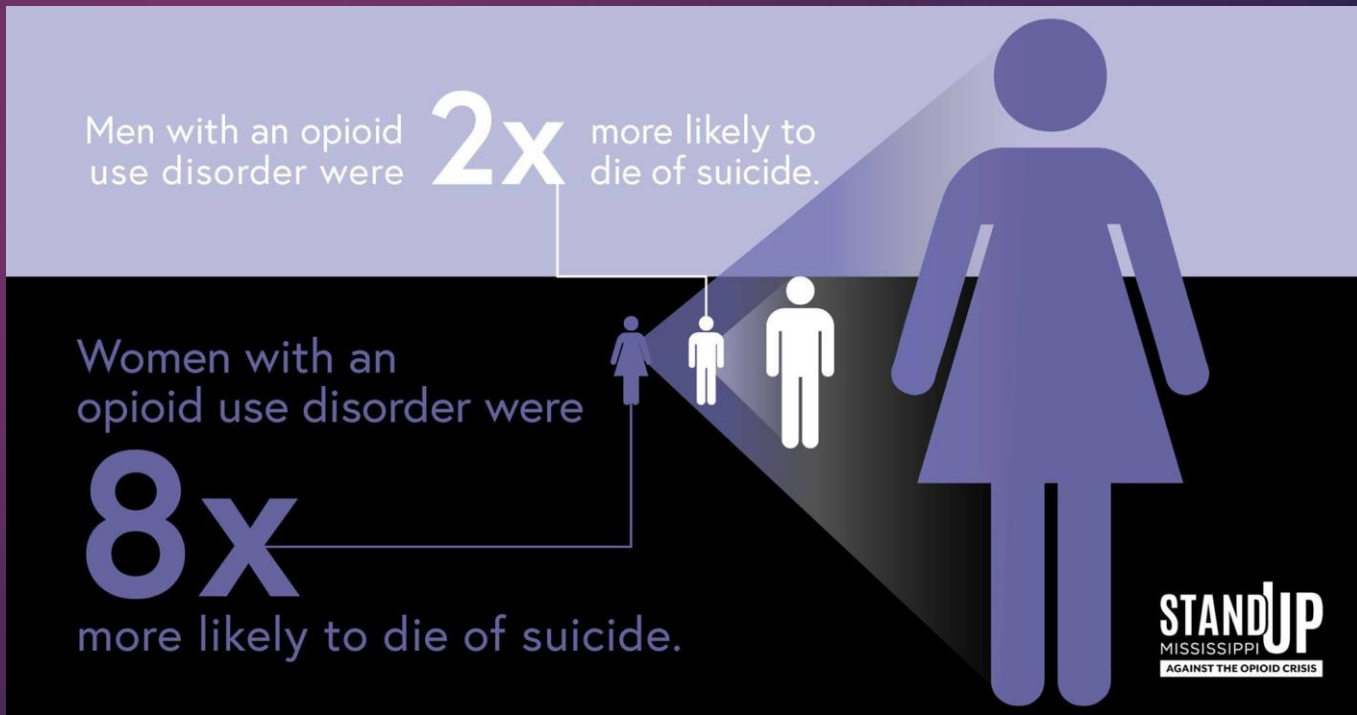
“Real-time fMRI neurofeedback to reduce suicidal ideation in opioid use disorder:
Treatment outcomes as a function of biological sex”



Step 1. Define the problem and why it is horrible

Opioid use disorder (OUD) is a chronic, relapsing condition, associated with a \$75 million public health burden, attributable to a 350% increase in deaths over the past two decades.

Up to 30% of OUD overdoses are intentional suicide attempts and suicide risk is over 6 times the national average (8 times for women versus 2 times for men) [citations].



Step 2. Explain the Knowns and Unknowns (covering K99/R00 research aims)

Known #1:

Although research suggests that opioid medication management (Methadone, Suboxone, Naltrexone) can be effective to manage OUD symptoms [citation], over 50% of individuals with OUD still relapse within three months despite this medication [citations].

Known #2:

Real-time fMRI neurofeedback targeting increased activity in the ventromedial prefrontal cortex (vmPFC) and greater focus on positive goal-directed activities has been successful in reducing suicidal thoughts and plans in women (but not men) with major depressive disorder (MDD) [citations].

Known #3:

Multiple studies demonstrate that (1) over 50% of men and women with OUD meet criteria for comorbid MDD [citations]; (2) > 40% of users report that suicidal thoughts drive their drug use [citations]; and (3) OUD show lower fMRI signal in vmPFC than controls during emotional processing tasks [citations].

Step 3. Gap in Literature

A crucial gap in the literature is the lack of effective interventions to reduce relapse and deaths in people struggling with OUD, particularly those contemplating suicide.

The present study addresses this gap by testing the utility of vmPFC real-time fMRI neurofeedback in reducing suicidality and relapse for treatment-seeking men and women with comorbid OUD and MDD.

Step 4. Preliminary Data

We conducted a pilot study testing the real-time vmPFC fMRI neurofeedback positive affect protocol developed by [citation] that had previously shown success in female MDD patients.

Our preliminary data show that ten women (5 comorbid OUD+MDD, 5 controls) completed the active neurofeedback condition and were successfully able to increase vmPFC activity as well as engage in positive goal-setting [show a figure or a table and stats if you can].

Step 5. Overall Study Design + Central Hypothesis

The present study follows up our preliminary data by: (1) comparing OUD+MDD and controls (men and women) on the degree of vmPFC upregulation during active versus sham neurofeedback conditions; and (2) determining whether successful vmPFC upregulation predicts lower suicidal ideation and lower drug craving in OUD: post-scan, 1 week, 4 weeks, and 12 weeks later.

Our central hypothesis is that active vmPFC upregulation and greater positive goal-setting will decrease suicidal ideation and drug craving in OUD+MDD, and that this relationship will be stronger in women than men.

Step 6. Specific Aims

The K99 phase focuses on cross-sectional real-time fMRI data collection and analysis of OUD+MDD versus control groups, while the R00 phase focuses on the analysis of longitudinal relationships between brain activity, suicidality, and relapse within OUD+MDD.


The specific aim for the K99 phase of this project is to identify whether degree of vmPFC upregulation differs as a function of group (OUD+MDD, controls), sex, and condition (active versus sham).

The specific aim for the R00 phase of this project is to identify whether degree of vmPFC upregulation at baseline, biological sex, and their interaction decreases future suicidality, drug craving, and relapse within three months in OUD+MDD.



Step 7 (Positive Impact #1). Explain how the project will improve at least one of the following: Scientific knowledge, Technical capability, Clinical practice

This project will enhance scientific knowledge and clinical practice by determining whether vmPFC neurofeedback treatment for MDD can be successfully extended to OUD+MDD populations that presently suffer from a lack of viable long-term treatment options.




Step 8 (Positive Impact #2). Describe how the field will be changed if your Specific Aims are achieved (e.g., concepts, methods, technologies, treatments, services, and/or preventative interventions)

If vmPFC neurofeedback is indeed successful in reducing suicidal ideation and opioid craving/use in women with OUD+MDD, this neurofeedback protocol can be disseminated to clinics/hospitals worldwide to reduce suffering and early mortality in female opioid users.

For Positive Impact #1 and #2

- ▶ You can also explain how your study addresses **SPECIFIC** Strategic Goals of the Institute where you are submitting your grant
- ▶ NIMH: https://www.nimh.nih.gov/about/strategic-planning-reports/2020_nimh_strategic_plan_508_160162.pdf
- ▶ NIDA: <https://www.drugabuse.gov/about-nida/strategic-plan/directors-message>
- ▶ NIA: <https://www.nia.nih.gov/research/blog/2020/06/nias-strategic-directions-priorities-continued-progress>



Step 9. Briefly describe your training (career) goals for the K99 and R00 phases of the award.

With respect to training goals, the K99 phase of this award will provide me with the mentorship and skills to obtain an Assistant Professor position, while the R00 phase of this award will support the development of my own research lab and pilot data for an R-level grant application, promoting my career as an independent investigator.

Hold the Reviewer's Hand

- ▶ Make it as EASY for the Reviewer as possible to find the information they are judging you on and check off a box
- ▶ Use BOLD font for SIGNIFICANCE sentences related to:
 - ▶ “gaps in literature”
 - ▶ “the central hypothesis”
 - ▶ “Specific aims for the K99 phase are”
 - ▶ “Specific aims for the R00 phase are”



Research Strategy
(6 pages max)

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Significance

Expand on **Specific Aims**

Innovation

Explain the novelty of your theory, approach and/or methods

Approach

Explain study design, methods, and statistical analyses to accomplish each of your **Specific Aims**

Innovation (1 paragraph)

- ▶ Explain how your application challenges **current research or clinical practice** paradigms
- ▶ Describe:
 - ▶ Any **novel theoretical concepts, approaches or methodologies**
 - ▶ Any **novel instrumentation or interventions** to be developed or used
 - ▶ Any **advantage** over existing methodologies, instrumentation, or interventions
- ▶ You can include results from preliminary studies in this section or the **Significance/Approach** sections to show study feasibility
- ▶ MAKE SURE TO COVER **BOTH** K99 and R00 phases of your project!!!

Innovation (1 paragraph)

- ▶ Make sure that you say ****WHY**** something is novel/innovative
- ▶ How is it BETTER than whatever is traditionally done in the field?



▶ Examples

- ▶ *Machine Learning* → WHY is it better than traditional statistics?
- ▶ *Real-time fMRI neurofeedback* → WHY is it better than regular fMRI recording and/or EEG feedback?
- ▶ *Giving people immune challenge* → WHY is it better than just measuring their blood at rest?
- ▶ *EEG-fMRI integration* → WHY is it better than either method alone?
- ▶ *Exosomes* → WHY are they better than peripheral blood markers?
- ▶ *Dyadic fMRI Tasks* → WHY better than solo fMRI tasks?
- ▶ *EEG microstates* → WHY better than traditional EEG frequency analyses?

Innovation (1 paragraph)

- ▶ BE as CLEAR as possible in explaining the advantages of your novel approach
- ▶ Assume that the Reviewer knows NOTHING about your methods/statistics/intervention or the literature where it came from
- ▶ A NIH Reviewer who is an expert on heart rate variability in adolescent depression may know VERY LITTLE about
 - ▶ Inflammatory cytokines
 - ▶ Machine learning
 - ▶ EEG / fMRI



Innovation Example #1

- ▶ The recovery process is fundamental to our biological understanding of the dynamics of opioid use disorder (OUD).
- ▶ The goal for any intervention is to alter this dynamic, thereby reducing or eliminating the probability of relapse.
- ▶ This proposal is innovative because it will:
 - ▶ (1) use rigorously characterized clinical, brain and behavioral outcome measures to create a large OUD early recovery dataset;
 - ▶ (2) use a comprehensive neuroscience-based approach probing interoception and aversive salience processes previously implicated in addiction in the K99 phase;
 - ▶ (3) focus on a drug use population of highest national concern (opioids);
 - ▶ (4) use a prospective longitudinal follow-up design and sequential assessments combined with sophisticated statistical approaches to chart recovery trajectories in the R00 phase;
 - ▶ (5) quantify dysfunction across units of analysis (symptoms, behavior, and neuroimaging) to develop predictive and sensitive typologies of recovery.

This hypothesis-driven approach will enable us to determine major contributors to relapse, including but not limited to impairments in interoception, reward/punishment sensitivity, pain, and negative affectivity.

Innovation Example #2

- ▶ The proposed study is innovative because it provides:
 - ▶ (A) A novel conceptual approach examining multilevel assessments of emotion in binge eating disorder (BED);
 - ▶ (B) Development and testing of a novel probe of emotional awareness in the fMRI environment in the K99 phase; and
 - ▶ (C) It is the first neuroimaging study to examine the interaction of meal anticipation with emotion in BED during the R00 phase.

Innovation Example #3

- ▶ The proposed research is innovative because we use an easy and non-invasive tool of blood sample collection to study information from the brain towards diagnostic and therapeutic intervention.
- ▶ Specific micro-RNA (miRNA) exosomes derived from the brain may provide a mechanistic view of inflammatory subtypes of anxiety disorders.
- ▶ To date, only one study has investigated whole exosomal miRNA cargo alterations in mental disorders in humans.
- ▶ No studies have investigated the role of miRNAs from brain-derived exosomes specifically as a function of anxiety disorders.
- ▶ Because exosomes can cross the blood-brain barrier, we are able to capture brain-derived exosomes from a peripheral blood source.
- ▶ Using Next-Generation Sequencing, a technology that can sequence millions of small fragments of DNA in parallel, we will be able to find aberrant miRNA profiles from brain-derived exosomes in two inflammatory subtypes of generalized anxiety disorder (GAD); some of these targets may be useful for development of drugs to treat GAD and other anxiety disorders.

Research Strategy
(6 pages max)

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Significance

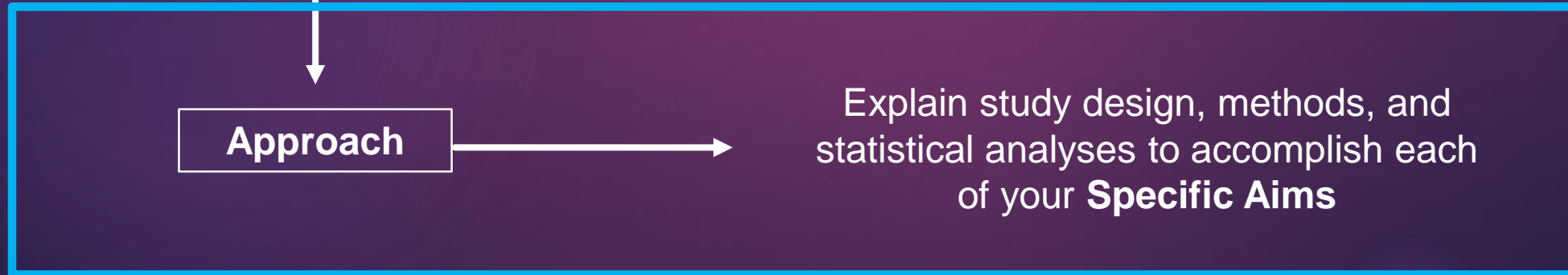
Expand on **Specific Aims**

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Approach

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Action Items

- ▶ Revise your Specific Aims based on **Primary Mentor** and **Program Officer** feedback
- ▶ Write drafts of your **Significance and Innovation sections** and get feedback from your **Primary Mentor**

