Welcome to the SBSM Science and Research Webinar

Title: Searching for 10: Grant Writing Strategies, Tactics, & Techniques

We will be joined by

Our Presenter: Daniel J. Buysse, MD

UPMC Professor of Sleep Medicine
Professor of Psychiatry, Clinical and Translational Science
University of Pittsburgh School of Medicine

Our Discussant: Natasha Williams, EdD, MSW, MPH

Department of Population Health Center for Healthful Behavior Change
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Searching for 10: Grant Writing Strategies, Tactics, and Methods

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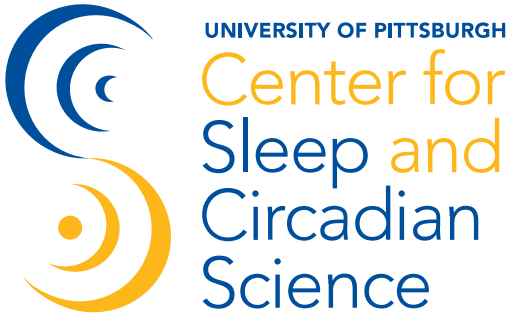
Society of Behavioral Sleep Medicine

Science and Research Webinar

February 11, 2020



Conflict of Interest Disclosures

	The presenter does not have any potential conflicts of interest to disclose
X	The presenter wishes to disclose the following potential conflicts of interest:

Type of Potential Conflict	**Details of Potential Conflict**
Grant/Research Support	Weight Watchers International
Consultant	Bayer, BeHealth Solutions, Cereve/Ebb Therapeutics, Emmi Solutions, Pear Therapeutics, Weight Watchers International
Speakers' Bureaus	None
Financial support	None
Licensing fees	Pittsburgh Sleep Quality Index (PSQI), Daytime Insomnia Symptoms Scale (DISS), Insomnia Symptoms Questionnaire (ISQ), Consensus Sleep Diary (CSD), SATED and RU_SATED Scales
Educational products	CME Institute, American Academy of Physician Assistants, Eisai

	The material presented in this lecture has no relationship with any of these potential conflicts
X	This talk presents material that is related to one or more of these potential conflicts, and references are provided throughout this lecture as support.

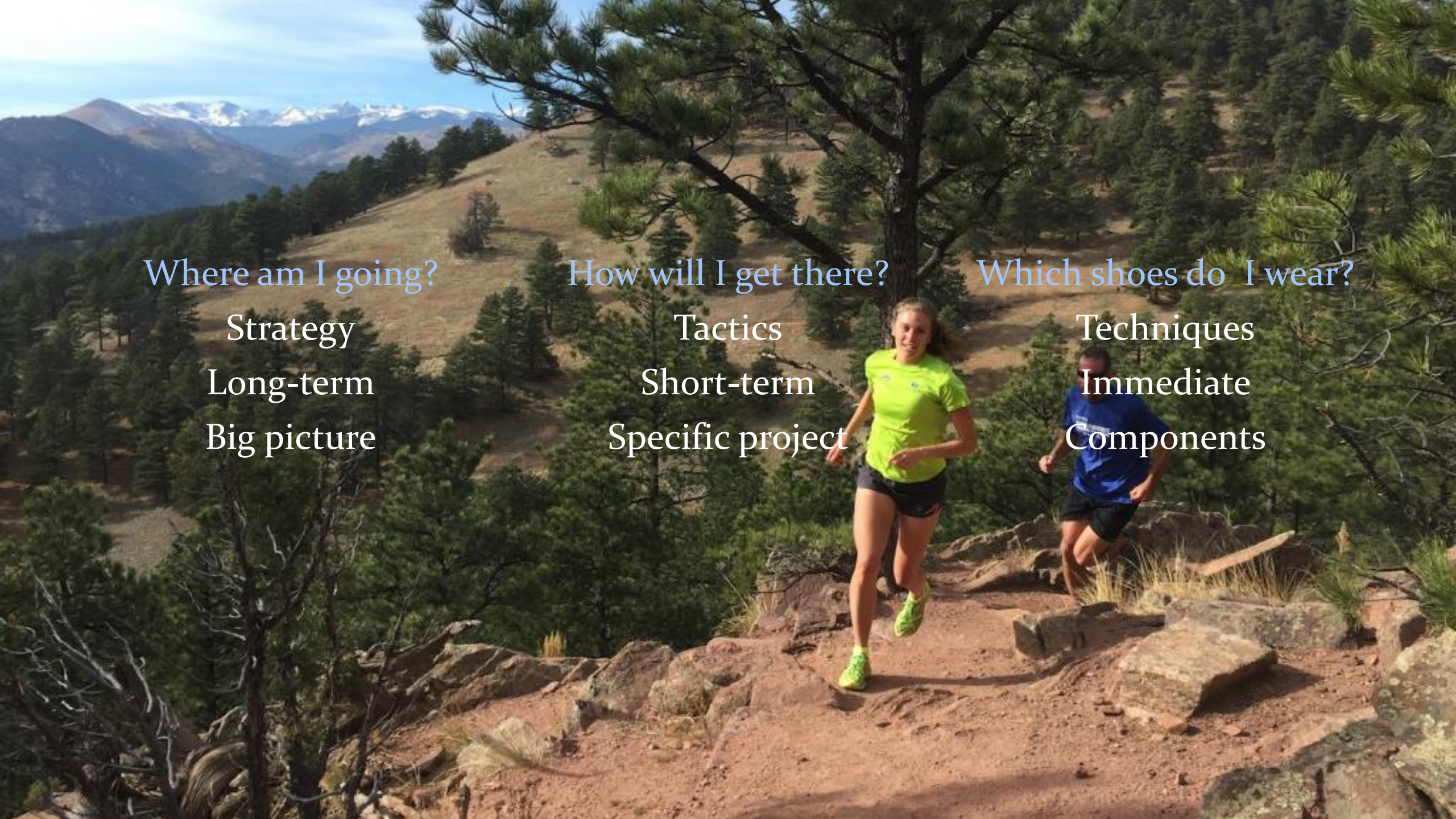
Objectives

At the end of this session, participants will be able to:

- Plan long-term strategies for grant writing
- Use short-term tactics for writing specific grants
- Implement effective techniques for grant writing

3 Questions

Where am I going?
How will I get there?
Which shoes do I wear?


Where am I going?
Strategy
Long-term
Big picture
How will I get there?
Tactics
Short-term
Specific project
Which shoes do I wear?
Techniques
Immediate
Components


SALOMON
MAMMUT
BROOKS
CASCADIA

RPG/X01/R01/R03/R21/R33/R34 Review

If you cannot access the hyperlinks below,
visit http://grants.nih.gov/grants/peer/critiques/rpg_D.htm.

Application #:

Principal Investigator(s):

OVERALL IMPACT

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact.

Overall Impact *Write a paragraph summarizing the factors that informed your Overall Impact score.*

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance

Strengths

-

Weaknesses

-

2. Investigator(s)

Strengths

-

Weaknesses

-

3. Innovation

Strengths

-

Weaknesses

-

4. Approach

Strengths

-

Weaknesses

-

5. Environment

Strengths

-

Weaknesses

-

ADDITIONAL REVIEW CRITERIA

As applicable for the project proposed, reviewers will consider the following additional items in the determination of scientific and technical merit, but will not give separate scores for these items.

— Responses for Protections for Human Subjects, Vertebrate Animals, and Biohazards **are required from reviewers for all applications**.

— A response for Inclusion of Women, Minorities and Children **is required from reviewers** for applications proposing Human Subjects Research.

Protections for Human Subjects

Click Here to Select

Comments (Required Unless Not Applicable):

-

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Click Here to Select

Comments (Required Unless Not Applicable):

-

Inclusion of Women, Minorities and Children **Applicable Only for Human Subjects research and not IRB Exemption #4.**

- Sex/Gender: Click Here to Select
- Race/Ethnicity: Click Here to Select
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Click Here to Select
- Inclusion/Exclusion of Children under 18: Click Here to Select

Comments (Required Unless Not Applicable):

-

Vertebrate Animals

Is the proposed research involving vertebrate animals scientifically appropriate, including the justifications for animal usage and protections for research animals described in the Vertebrate Animals section (and method of euthanasia described in the Cover Page Supplement or PHS Supplemental Form, if applicable)?

Click Here to Select

Comments (Required Unless Not Applicable):

-

Biohazards

Click Here to Select

Comments (Required Unless Not Applicable):

-

Resubmission

Comments (if applicable):

-

Renewal

Comments (if applicable):

-

Revision

Comments (if applicable):

-

ADDITIONAL REVIEW CONSIDERATIONS

As applicable for the project proposed, reviewers will address each of the following items, but will not give scores for these items and should not consider them in providing an overall impact/priority score.

Applications from Foreign Organizations

Click Here to Select

Comments (Required Unless Not Applicable):

-

Select Agents

Click Here to Select

Comments (Required if Unacceptable):

-

Resource Sharing Plans

Click Here to Select

Comments (Required if Unacceptable):

-

Authentication of Key Biological and/or Chemical Resources

Click Here to Select

Comments (Required if Unacceptable):

-

Budget and Period of Support

Click Here to Select

Recommended budget modifications or possible overlap identified:

-

ADDITIONAL COMMENTS TO APPLICANT

Reviewers may provide guidance to the applicant or recommend against resubmission without fundamental revision.

Additional Comments to Applicant (Optional)

-

Understand the review criteria

- Overall Impact
  - "Likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the five core review criteria"
  - Synthesis/integration of the five core review criteria that are scored individually *and* the additional review criteria which are not scored individually
  - NOT the simple average of the scored review criteria
  - An application does not need to be strong in all categories to deserve a high impact/priority score

Understand the review criteria

- Significance
  - Does the project address an important problem or critical barrier to progress in the field?
  - If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
  - How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
  - Evaluate the rigor of the existing science in the area

Understand the review criteria

- Other scored criteria: R series
  - Investigators
  - Innovation
  - Approach
  - Environment
- Other scored criteria: K series
  - Candidate
  - Career Development Plan/ Career Goals and Objectives
  - Research Plan
  - Mentors, Co-Mentors, Consultants, Collaborators
  - Environmental & Institutional Commitment
  - Training in Responsible Conduct of Research

Enhancing Reproducibility in NIH Applications: Resource Chart

NIH Grants Policy Website: http://grants.nih.gov/reproducibility/index.htm

NIH Website: https://www.nih.gov/research-training/rigor-reproducibility

4 AREAS OF FOCUS	WHAT DOES IT MEAN?	WHERE SHOULD IT BE INCLUDED IN THE APPLICATION?
Rigor of the Prior Research	A careful assessment of the **rigor of the prior research** that serves as the key support for a proposed project will help applicants identify any weaknesses or gaps in the line of research. Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project. Describe plans to address weaknesses in the rigor of the prior research that serves as the key support for the proposed project *See related FAQs, blog post	**Research Strategy** ➢ Significance ➢ Approach
Scientific Rigor (Design)	**Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Emphasize how the experimental design and methods proposed will achieve robust and unbiased results. *See related FAQs, blog post, examples from pilots	**Research Strategy** ➢ Approach
Biological Variables	**Biological variables**, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response. Explain how relevant biological variables, such as the ones noted above, are factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data or other relevant considerations must be provided for applications proposing to study only one sex. *See related FAQs, blog posts, article	**Research Strategy** ➢ Approach
Authentication	**Key biological and/or chemical resources** include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. These resources may or may not have been generated with NIH funds and: • may differ from laboratory to laboratory or over time; • may have qualities and/or qualifications that could influence the research data; • are integral to the proposed research. The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research. Note: Do not include authentication data in your plan. *See related FAQs, blog post, examples	**Other Research Plan Section** ➢ Include as an attachment ➢ Do not include in the Research Strategy.

****This chart is based on general instructions for research grant applications submitted for January 25, 2019 due dates and beyond. It should only be used as a guide. For all applications, please read the applicable Funding Opportunity Announcement (FOA) & Application Guide for specific instructions.**

Overall impact scoring

Overall Impact:
The likelihood for a project to exert a sustained, powerful influence on research field(s) involved

Overall Impact	High	Medium	Low
Score	1 2 3	4 5 6	7 8 9

Evaluating Overall Impact:
Consider the 5 criteria: significance, investigator, innovation, approach, environment (weighted based on reviewer's judgment) and other score influences, e.g. human subjects, animal welfare, inclusion plans, and biohazards

e.g. Applications are addressing a problem of high importance/interest in the field. May have some or no weaknesses.

e.g. Applications may be addressing a problem of high importance in the field, but weaknesses in the criteria bring down the overall impact to medium.

e.g. Applications may be addressing a problem of moderate importance in the field, with some or no weaknesses

e.g. Applications may be addressing a problem of moderate/high importance in the field, but weaknesses in the criteria bring down the overall impact to low.

e.g. Applications may be addressing a problem of low or no importance in the field, with some or no weaknesses.

5 is a good medium-impact application, and the entire scale (1-9) should always be considered.

Understand the review criteria

- Additional (non-scored) criteria
  - Protection for human subjects
  - Inclusion of women, minorities, and children
  - Resubmission
- Additional review considerations
  - Budget and period of support
  - Additional comments to applicant

Is it worth doing?

- Overall impact
- Significance
- Innovation

Can they do it?

- Investigators
- Approach
- Environment

Toni Scarpa, Former Director of the Center for Scientific Review (CSR)

Structuring your application: Approximate page lengths

Section	K award	R01	R03, R21
Specific Aims	1	1	1
Candidate information	5-6		
Candidate's background	1-1.5		
Career Goals and Objectives	0.5-1		
Career Development/Training Act.	2-3		
Research Plan	6-7	12	6
Significance	1.5	2-3	1-1.5
Innovation	<0.5	0.5	<0.5
Preliminary studies	0.5-1	1-2	0.5
Approach (Methods portion)	2-3	6-7	2-3
Statistics, power	0.5-1	1-2	0.5-1
Timeline, expected results, problems, alternatives, future directions	0.5	0.5-1	0.5

Specific Aims

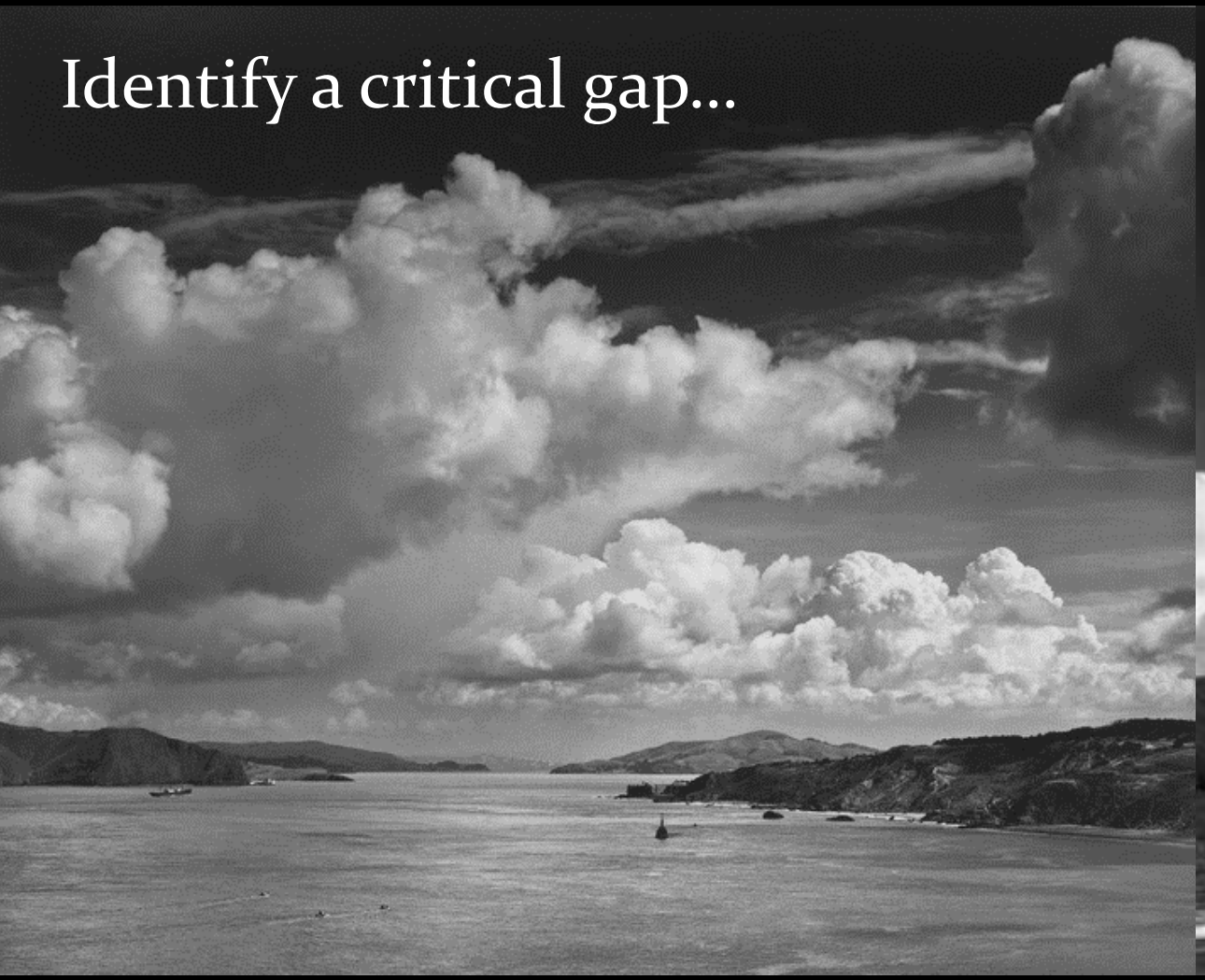

“Shopping around”
your application

Sharpen your questions,
methods, outcomes

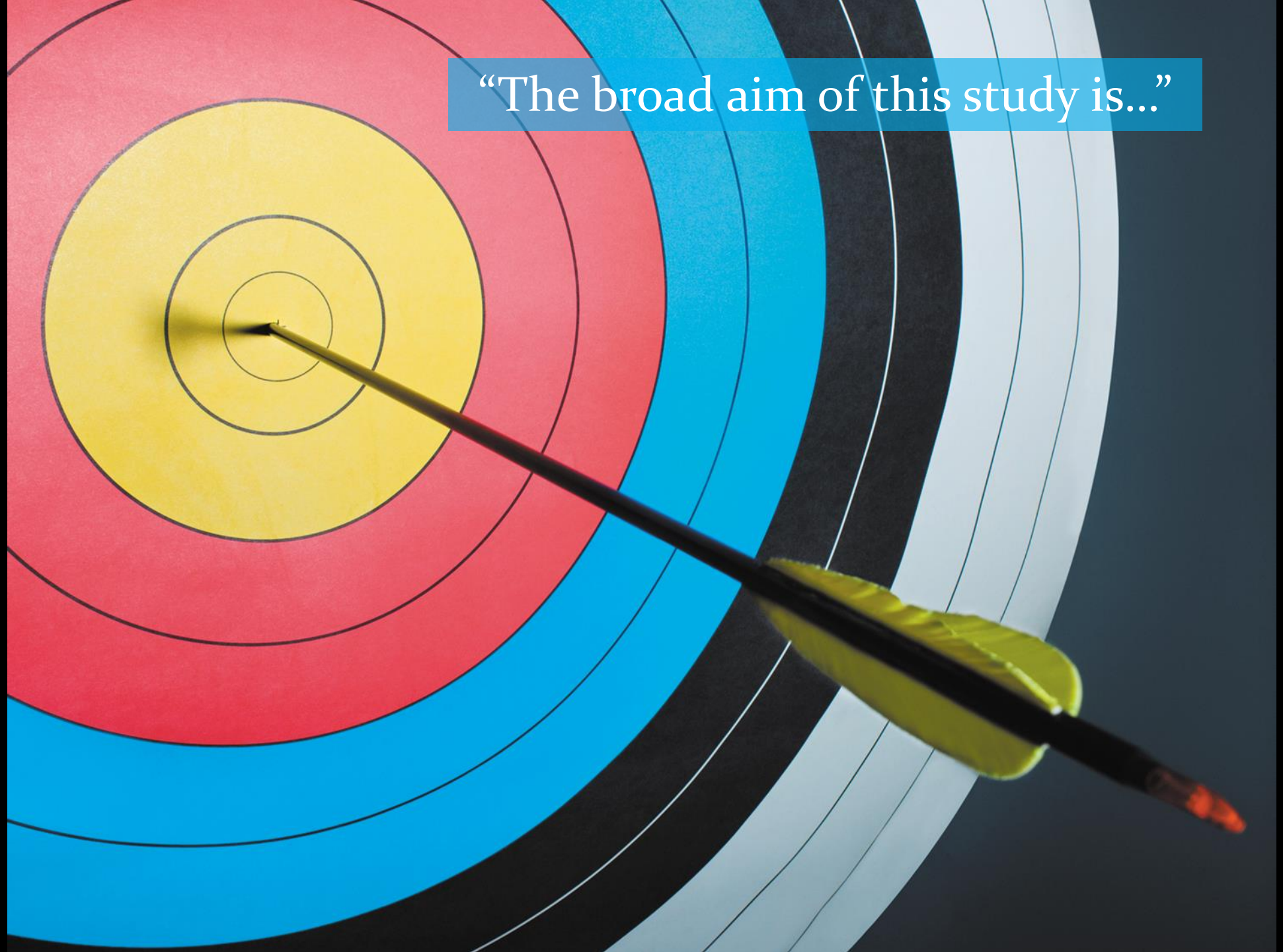
Your application in miniature


Make a
good first
impression


Wide angle
Public health significance

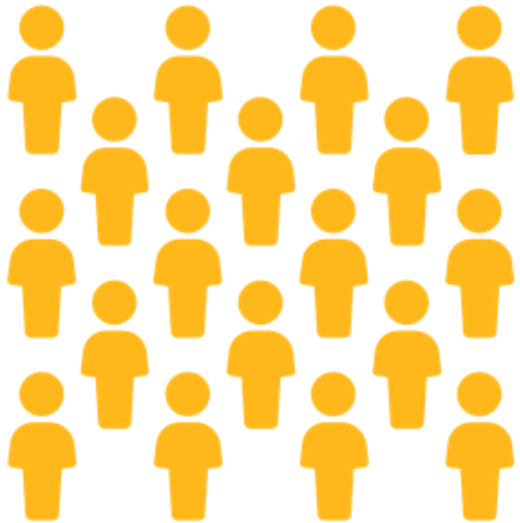

Identify a critical gap…

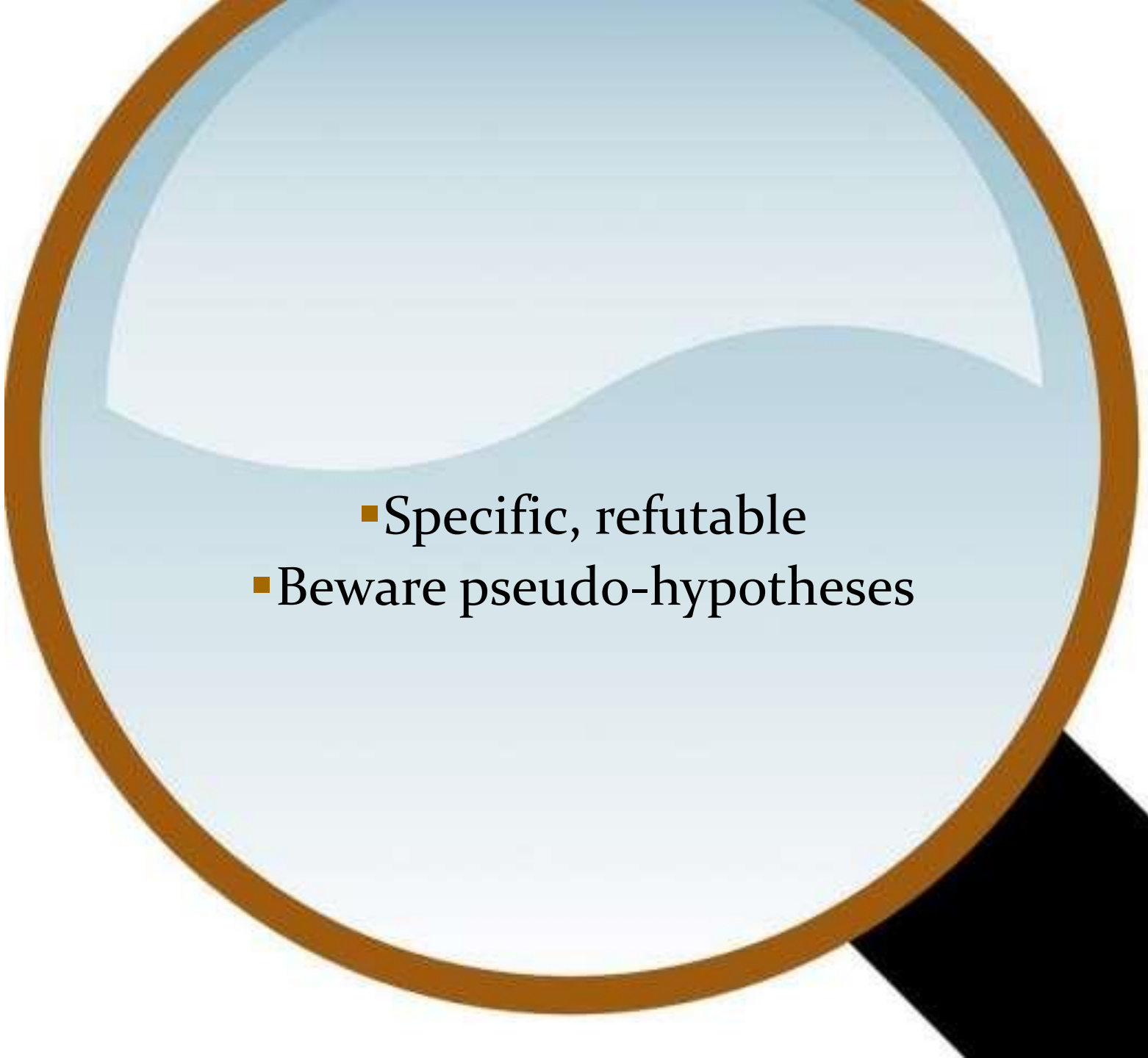

…that you plan to fill.


“The broad aim of this study is…”


PROBLEM
SOLUTION
"In order to address this critical problem we plan to…"

Key methods and outcomes





- Specific, refutable
- Beware pseudo-hypotheses

Aim 1: To ***compare***…

Aim 2: To ***determine***…

Aim 3: To ***examine***…

Exploratory aims: Pros and cons


Impact
Innovation
Future directions

Statement of the problem

Our solution

Description of study, outcomes

Specific Aims

Exploratory Aims

Impact

SPECIFIC AIMS

Insomnia is a prevalent health problem associated with adverse cardiovascular, metabolic, and mental health outcomes. Plausible pathophysiological mechanisms for insomnia have been described, and efficacious cognitive-behavioral and pharmacologic treatments exist. However, our preliminary data demonstrate that neither health consequences, nor pathophysiology, nor treatment response are evenly distributed among individuals with insomnia. Rather, we have identified a particular phenotype, insomnia with short sleep duration (ISS), that is associated with increased risk for adverse health outcomes, greater physiological hyperarousal as indicated by hypothalamic-pituitary-adrenal (HPA) axis activation, and worse response to Cognitive-Behavioral Treatment for Insomnia (CBT-I). The proposed study represents the next logical extension of our previous observations: **To determine whether patients with ISS and insomnia with normal sleep duration (INS) demonstrate a differential response to two common insomnia treatments, CBT-I and trazodone.**

CBT-I is recommended as first-line treatment for insomnia, and trazodone is a widely-prescribed medication for insomnia. In addition to being widely-used and well-tolerated, our preliminary data demonstrate differential efficacy of CBT-I and trazodone in ISS and INS, which may in turn result from different effects on HPA axis function: trazodone, but not CBT-I, results in downregulation of HPA axis function as indicated by evening cortisol measurements. Because of the association between ISS and hypertension, we also plan to measure the impact of interventions on home blood pressure (HBP), the recommended standard for measuring BP. We will recruit participants who meet current AHA guidelines for hypertension (HTN; >120/80 mm Hg), and measure changes in HBP as a function of insomnia phenotype and treatment assignment.

We propose a 3-site, 2-arm, stratified randomized clinical efficacy trial in a total of 330 adults (≥18 yo) to compare the effects of CBT-I vs. trazodone in individuals with ISS (n = 165) or INS (n = 165) and HTN. Investigators at the 3 study sites have a long history of collaboration and successful completion of NIH-funded mechanistic and clinical trial studies. Our **primary study outcome measure** will be the total score on the Insomnia Severity Index (ISI), the gold-standard self-report measure of insomnia symptoms, at 8 weeks. **Secondary outcomes** will include polysomnographic (PSG) and actigraphy measures of sleep duration, and HBP measurements. In exploratory analyses, we will test whether changes in evening cortisol values mediate treatment effects, and whether treatments affect other key patient-reported outcomes. Outcomes will be assessed at 8 weeks and 6 months following the start of treatment. The main analytic strategy consists of analysis of covariance and linear mixed models for repeated measures to compare the two interventions and their interaction with insomnia phenotype, while controlling for stratification variables (site, age, sex, previous treatment exposure). We estimate having 90% power to detect an interaction for ISI among the 4 cells, assuming a type I error rate of 0.05, a two-sided alternative hypothesis, a within-cell standard deviation in ISI of 5, and a drop-out rate of 20%.

Specific Aim 1: To examine the effect of CBT-I and trazodone on **insomnia symptoms** (primary outcome) and **sleep duration** (secondary outcome) among individuals with ISS and INS, defined by PSG sleep duration. **Hypothesis 1a:** We will observe an interaction between insomnia phenotype and treatment, such that individuals with INS will have lower ISI scores following CBT-I treatment, and individuals with ISS will have lower ISI scores following trazodone treatment. **Hypothesis 1b:** We will observe an interaction between insomnia phenotype and treatment, such that individuals with ISS treated with trazodone will have a larger increase in PSG sleep duration following treatment compared to other groups.

Specific Aim 2: To examine the effect of CBT-I and trazodone on **home BP** among individuals with ISS and INS. **Hypothesis 2:** We will observe an interaction between insomnia phenotype and treatment, such that individuals with ISS will demonstrate greater BP reduction with trazodone than CBT-I, and individuals with INS will demonstrate no differential treatment effect.

Specific Aim 3 (Exploratory Mechanistic): To examine whether treatment effects on HBP and PSG sleep duration are mediated by changes in HPA axis, as indexed by evening salivary cortisol levels.

Specific Aim 4 (Exploratory Hypothesis-Generating): To examine the effects of CBT-I and trazodone treatment on other preclinical cardiovascular markers and key patient-reported outcomes, including pro-inflammatory cytokines, health-related quality of life, sleepiness, and mood.

Demonstration of differential treatment response would aid the goals of precision medicine, which directs therapy not only on the basis of genetics, but also on the basis of clinical phenotypes and physiology, as is the case with insomnia. If our hypotheses are supported, we will further validate two common phenotypes of insomnia defined by objective sleep duration, thereby improving treatment outcomes and potentially reducing adverse health consequences associated with insomnia and its treatments.

Significance

- Use simple, declarative sentences for subsection headings
  - Gives high-level outline
  - Leads the reviewer along
- Should inevitably lead to the critical remaining question…
- ..which just so happens to be the one you are going to address!
- Then address impact

Numbered, bolded paragraph heads

Scientific premise

Model

Our plan

SIGNIFICANCE

1. Insomnia is a common problem with important health consequences. Insomnia is defined by sleep problems (difficulty falling asleep, staying asleep, or poor quality sleep) that result in impaired function, last for at least 3 months, and occur despite adequate sleep opportunities/circumstances[1,2]. Over 33% of adults experience occasional symptoms, and 10-22% have chronic insomnia[3-8]. Although its significance is often minimized[9,10], chronic insomnia has important health consequences including fatigue, depression and increased suicide risk, impaired social/vocational functioning and reduced quality of life.[4,11-25] Insomnia is commonly comorbid with, and exacerbates, other medical and psychiatric disorders[26]. Moreover, insomnia contributes to increased health care utilization and costs, totaling over $285M for prescription sleeping pills and $90B in total direct treatment-related costs annually in the US[27,28]. **Insomnia has also been identified as a novel risk factor for cardiometabolic morbidity and mortality, conferring a 3- to 5-fold increased odds of hypertension, diabetes or all-cause mortality**[29]. Insomnia is not just an inconvenience, but is a serious condition that poses significant health risks.

2. Efficacious treatments are available. Recent systematic reviews and clinical practice guidelines support the efficacy of cognitive-behavioral treatment for insomnia (CBT-I) and various hypnotic medications[30-34]. CBT-I is recommended as first-line treatment, with insomnia remission rates of ~50-60% and significant symptom reduction in ~75-80%[35-39]. Hypnotic medications, primarily benzodiazepine receptor agonists, also significantly reduce insomnia symptoms, but with somewhat lower remission rates of ~30-40%[40]. Whereas CBT-I is generally well-tolerated, hypnotic medications are associated with a range of potential adverse effects, ranging from sedation and motor vehicle accidents to increased risk for dementia and mortality[41]. As a result of these concerns, non-FDA-approved medications are commonly used to treat insomnia. Low-dose trazodone, in particular, is the second most widely-prescribed medication for insomnia[42]. Although large randomized clinical trials (RCT) have not been conducted, small studies show that trazodone improves insomnia symptoms with few side effects[43-45]. However, the general efficacy of available insomnia treatments is tempered by the fact that we know very little about which treatment works best for which patient. **Identifying insomnia phenotypes that differ consistently on biological characteristics and treatment responses would help to maximize CBT-I treatment resources and minimize exposure to adverse medication effects.**

3. Traditional Clinical Measures Do Not Identify Meaningful Phenotypes. Various classification sysems have proposed insomnia subtypes on the basis of clinical features such as sleep onset/maintenance, psychophysiological or paradoxical insomnia.[2,11,46-51] However, these subtypes have poor reliability and validity[52-56] and they have not shown utility for guiding insomnia treatment decisions. Likewise, patient characteristics such as sex, marital status, education, and occupation are generally not associated with CBT-I outcomes[51]. Although medical/psychiatric comorbidities are associated with smaller treatment effects[57-60], this information is not particularly useful for treatment selection because insomnia treatments are standard and not specific to the presenting comorbidity. Small laboratory studies have suggested subgroups of insomnia on the basis of features such as quantitative EEG characteristics[61-64]. But these studies have not been replicated and as such cannot be used for treatment selection. **In short, we still lack an objective measure or biomarker that discriminates insomnia phenotypes with distinctive pathophysiology, morbidity risks and putative treatment needs.**

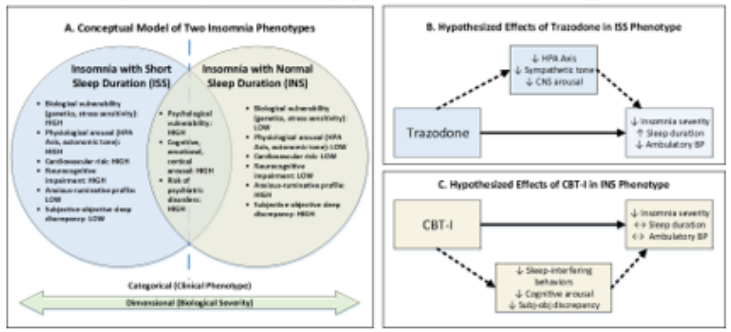
4. Insomnia with Short Sleep Duration: A Novel Phenotype with Increased Health Risks. In 2009, Vgontzas and colleagues demonstrated that **insomnia with short sleep duration (ISS), defined as <6 hours of total sleep time (TST) by polysomnography (PSG), is a distinct insomnia phenotype** associated with higher risk for hypertension.[65] About 50-60% of individuals with insomnia have short sleep duration,[65] and only 16% of individuals with short sleep duration have insomnia.[66] Despite sleep duration being a continuous variable, the 6 hour threshold value has been consistently identified across multiple studies as predictive of adverse health outcomes[29,65,67-72]. Moreover, we have shown that the ISS phenotype is stable over short and long time intervals, up to 10 years (see Preliminary Studies below). We have subsequently demonstrated that the ISS phenotype is associated with increased risk of hypertension[65,73], diabetes[67], cognitive impairment,[68] incident depression,[74] and persistence of sleep disturbance[75,76] relative to insomnia with normal sleep duration (INS). We have also found increased mortality risk among men with ISS.[69] These findings from the PSU group are supported by an increasing number of studies from other investigators and cohorts, that show differences between ISS and INS phenotypes in cardiometabolic and neurocognitive morbidity and mortality risk.[71,73,75,77-81] These studies indicate that the combination of insomnia plus short sleep duration has larger effects on health outcomes than either insomnia or short sleep duration alone. Thus, **ISS is a meaningful insomnia phenotype in terms of health risks.**

5. The ISS Phenotype is Associated with Distinct Physiology. Studies investigating the pathophysiology of insomnia may help to understand **why** the ISS phenotype is associated with a range of morbidities and mortality. Insomnia has long been considered a disorder of "hyperarousal." Compared to good sleepers, individuals with insomnia —particularly those with short sleep duration— have physiologic hyperarousal, as reflected by hypothalamic-pituitary-adrenal (HPA) axis activation, increased heart rate, 24-hour whole-body metabolic rate, impaired heart rate variability (HRV), and increased catecholamine secretion.[82-91] Specifically, we found that 24-h cortisol levels, norepinephrine, and catecholamine metabolites correlate with PSG indices of sleep efficiency[92,93], and that adrenocorticotropic hormone and cortisol levels among individuals with insomnia were most elevated in the evening and during the first half of the night.[93] Cortisol levels for insomnia patients with normal sleep duration did not differ from levels in good sleepers. **Thus, HPA axis activation distinguishes insomnia phenotypes with differing levels of PSG sleep disturbance[28,83], and physiologic hyperarousal in insomnia predicts cardiometabolic risk.**

6. The ISS Phenotype May be Associated with Differential Treatment Response. As noted above, there are currently no evidence-based guidelines for matching particular treatments to particular patient phenotypes. Rather, the choice of CBT-I or medications for insomnia relies on the personal preferences of clinicians and patients. **Our findings regarding the ISS phenotype provide the basis for a more guided approach to treatment.** Because ISS is associated with HPA axis activation, medications that down-regulate the HPA axis may represent the optimal therapy for this insomnia phenotype. Low-dose sedative antidepressants such as trazodone or doxepin have such effects, which may help to explain their widespread use for insomnia (even without FDA approval, in the case of trazodone). For example, low-dose doxepin improves sleep and normalizes plasma cortisol secretion in individuals with insomnia[94]. Our pilot data (Preliminary Studies) show that trazodone increases TST and lowers cortisol in individuals with the ISS phenotype. Moreover, we[95] and others[96,97] have shown that individuals with the ISS phenotype have blunted treatment response to CBT-I relative to those with INS (Preliminary Studies). **The ISS phenotype confers increased health risks, has a distinct physiology, and may be associated with differential responses to the most common insomnia treatments.**

7. Scientific Premise. Our previous findings led us to develop the conceptual model depicted in Figure 1A. **Our scientific premise is based on this model.** We propose that individuals with ISS represent a severe insomnia phenotype characterized by increased activation of the HPA axis and autonomic systems; elevated risks for medical morbidity and mortality; and a distinct treatment profile with reduced response to CBT-I and increased response to trazodone (the latter associated with reduced HPA axis activation; Figure 1B). In contrast, individuals with INS represent a less severe insomnia phenotype with less physiological hyperarousal, less risk for significant medical sequelae, robust response to CBT-I treatment, and less response to trazodone (Figure 1C).

Figure 1: Conceptual Models Underlying Clinical Trial in Two Insomnia Phenotypes



8. Where do we go from here? Our scientific premise also points to the next logical step: **An adequately-powered randomized clinical trial to compare the effects of CBT-I and trazodone among individuals with the ISS and INS phenotypes.** Outcomes should include insomnia symptoms, as the key patient-reported outcome, and sleep duration as the key objective outcome; home blood pressure (HBP), as an important health outcome; and cortisol profiles, to evaluate a plausible physiological mechanism for treatment effects. **This is precisely the study that we propose in this application.**

Innovation

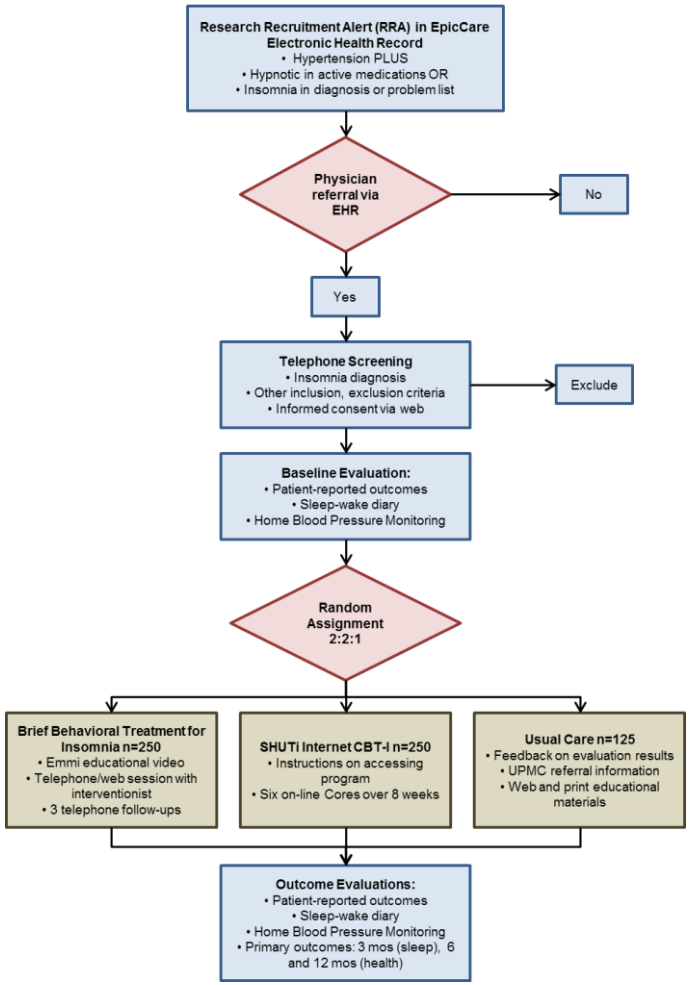
- Innovation ≠ Significance (at least, not necessarily)
- A novel problem/solution is not necessarily important
- The solution to a significant problem may not be novel
- Innovation often resides in the combination of approaches, or the application of accepted approaches to a new problem

Innovation: The Goldilocks Effect

Approach

- Start out with a one-paragraph overview to orient reviewer
- Include a study diagram/flow chart if possible
  - # of Ss at various stages
  - Time dimension
  - Major stages/ procedures
- Participant recruitment, inclusion/ exclusion criteria (major)
- Research procedures
- Specific tools, methods

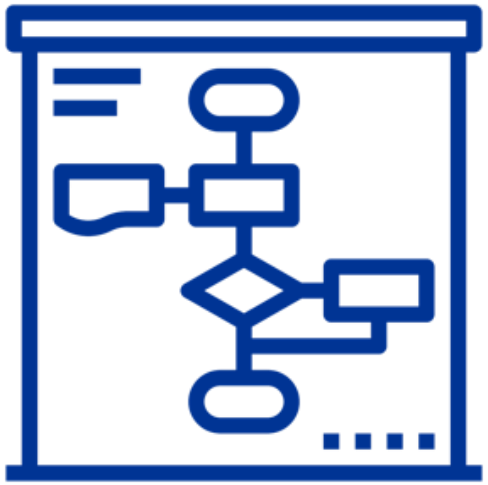
FIGURE 4: Study Flow Diagram



Approach

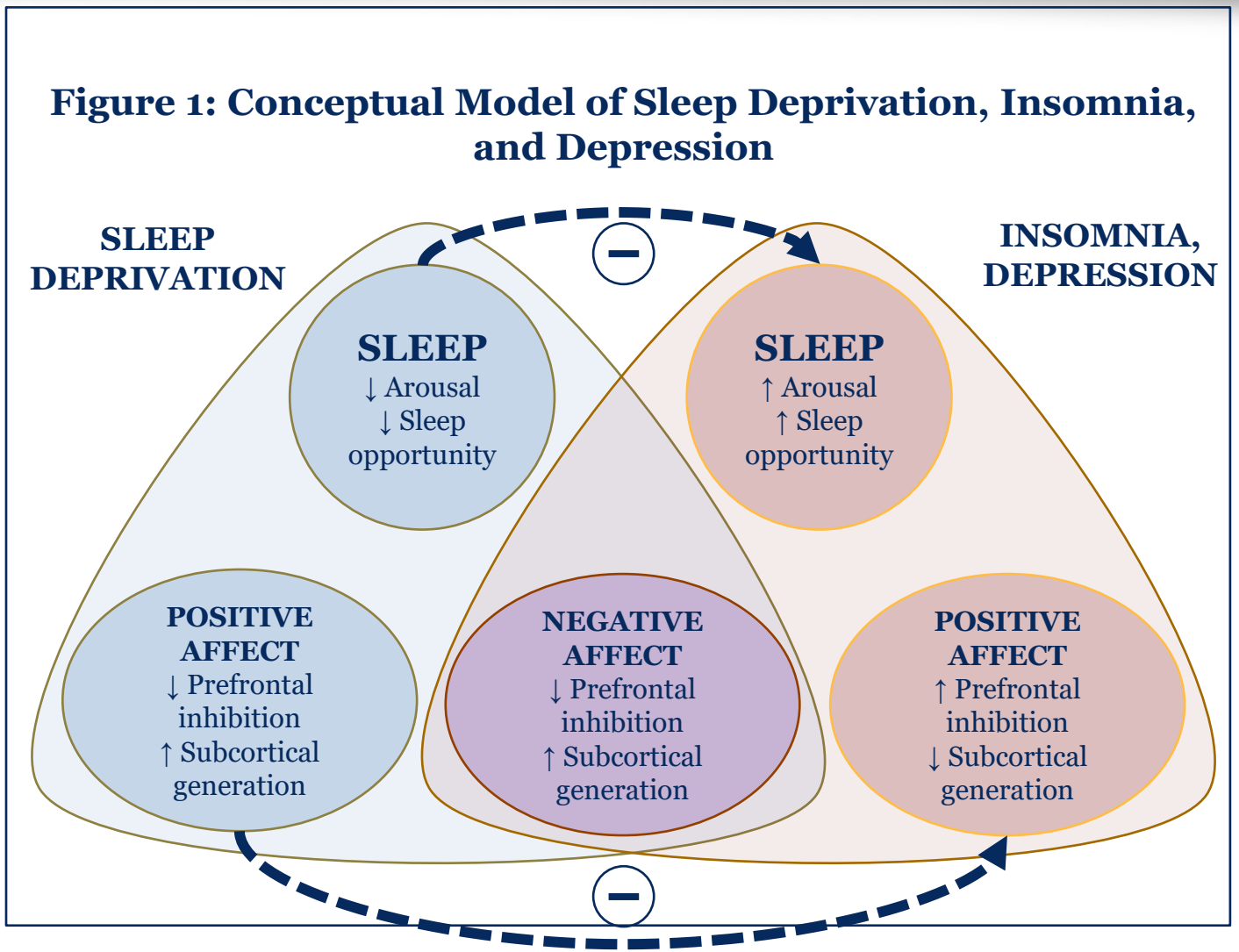
Conceptual model

Procedures, flow



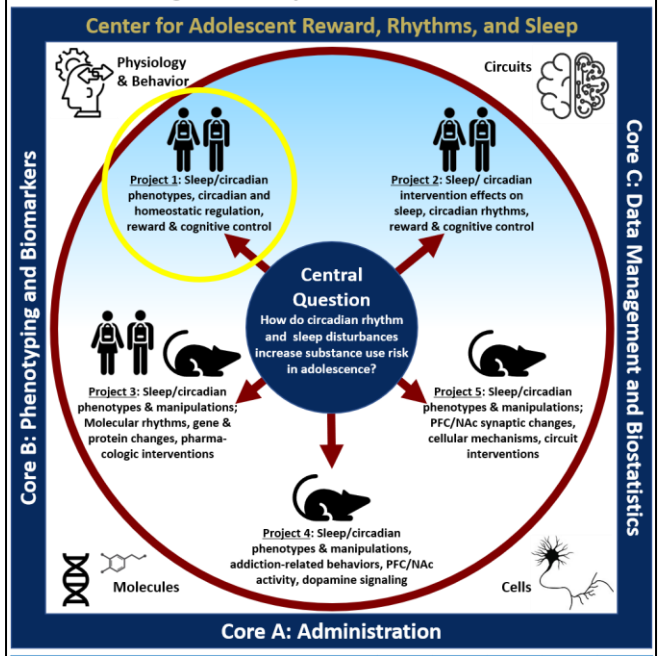
Assessments

Conceptual model diagram



Interesting figures and tables

Figure 1.3: Project-Core Interactions



Technique/ Level of Analysis	P1	P2	P3	P4	P5
Molecules			•	•	•
Cells			•		•
Circuits	•	•		•	•
Physiology/Behavior	•	•		•	•
Manipulations/ Interventions		•	•	•	•
Core A: Administration	•	•	•	•	•
Core B: Phenotyping & Biobanking	•	•	•	•	•
Core C: Data management & Biostatistics	•	•	•	•	•

Table 1.2. Reward, Cognitive Control, and Substance Use Measures, Methods, and Outcomes

Domain	Measure Types		Description, key features and methods	Primary outcomes of interest
Reward: sensitivity & motivation	Behavior	Reward Anti-Saccade task[158-160]	Indexes behavioral inhibition via eye-tracking (ability to refrain from making a rapid eye movement [saccade] toward the stimulus when it appears [i.e., inhibitory response] and instead make a voluntary saccade to the opposite location in space [anti-saccade]) on trials with and without monetary incentives. Completed every 2 h during the CR/SD.	• Response errors (saccades toward a cue) during incentivized minus neutral trials
	fMRI	Monetary Incentive Delay Task (MID)[166]	fMRI tasks indexing anticipation and receipt of monetary gains and losses. MID is fast event related with varying magnitude rewards and losses. CGRT is slow-event-related with high magnitude rewards only. Both sensitive to sleep/circadian factors.	• Activation of BOLD circuitry • Functional Connectivity (gPPI) • Effective Connectivity (See Table 1.3 for specific contrasts) • Post-scan VAS ratings of responses to wins and losses
		Card Guessing Reward Task (CGRT)		
		Best Friend Task[5]	fMRI task indexing personal social reward. See text.	
	SR	VAS[150]	VAS of mood completed every 2 h during the CR/SD.	• Global affect (positive affect)
Cognitive control	Beh.	Reward Anti-Saccade task	Indexes behavioral inhibition via eye-tracking (ability to inhibit pre-potent saccade response).	• Errors on non-rewarded trials • Secondary outcome: saccade latency
	fMRI	Stop Signal Task[177]	Behavioral inhibition fMRI task used to index cognitive control; also used in ABCD	• See Table 1.3
Substance use	Objective/SR	Time-Line Follow-Back (TLFB)[157]	Collected every 6 months: days of use in past 6 months of most commonly used substances in teens (cannabis, alcohol, and nicotine-tobacco & vaping).	• Age when regular use occurs
		Urine Drug Screen & Breathalyzer	Administered at screening & lab visits	• Drug/alcohol intoxication

Approach

- Statistical methods
  - Include data management
  - Recap study aims/hypotheses
  - Clearly indicate specific outcome measures for each construct
  - Specify statistical procedures
  - Sex as a biological variable
- Power analyses
  - Based on preliminary data*
  - Based on published data
  - Maximum difference/change/effect possible with proposed # of Ss (best if combined with above)

*Consider Kraemer HC et al. *Arch Gen Psychiatry.* 2006;63(5):484-489

Approach

- Timeline (Gantt chart)
- Anticipated results, problems
- Design considerations
- Future directions

STUDY TIMELINE

Study Phase/ Task	Year 01				Year 02				Year 03				Year 04				Year 05			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
UH2																				
Finalize UPMC, primary care agreements	■	■																		
Finalize EpicCare RRA and reports	■	■																		
Primary care education sessions		■	■																	
Finalize Emmi programs, interventions		■	■																	
Test BBTI and SHUTi in 20 participants			■	■																
UH3																				
Participant recruitment					■	■	■	■	■	■	■	■	■	■						
2, 6, 12-month follow-ups						■	■	■	■	■	■	■	■	■	■	■	■	■		
Data analysis, manuscript preparation																			■	■

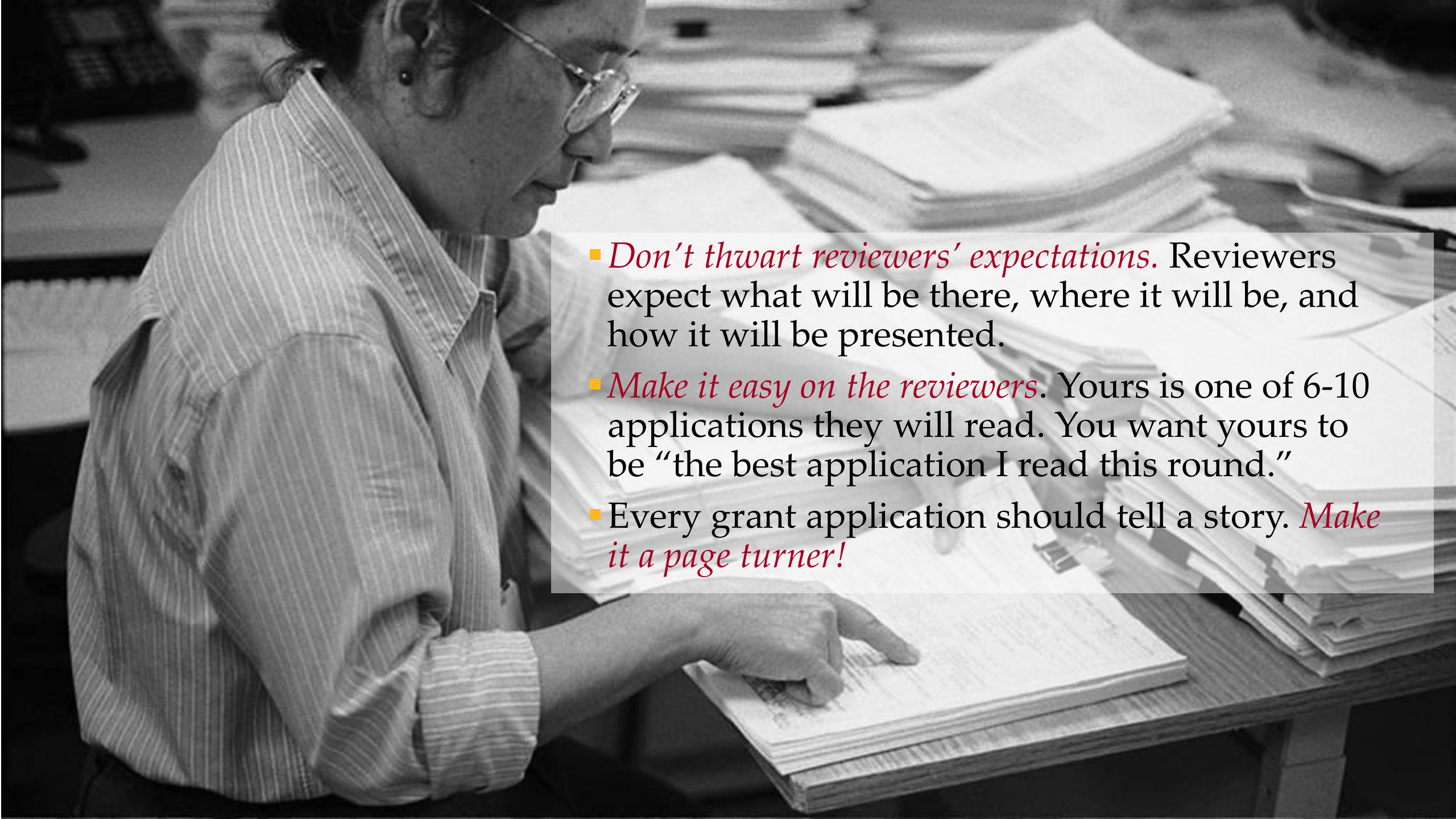
Revise

Revise

Revise

Get feedback.

Lots of
feedback.



- *Don't thwart reviewers' expectations.* Reviewers expect what will be there, where it will be, and how it will be presented.
- *Make it easy on the reviewers*. Yours is one of 6-10 applications they will read. You want yours to be "the best application I read this round."
- Every grant application should tell a story. *Make it a page turner!*

Words of wisdom: Formatting

- Leave some white space on the page
  - Reviewers appreciate it
  - The space is more important than the additional text.
- Use figures and tables
  - Make them look professional
  - Make them legible
- Check and re-check for inconsistencies
- Ask someone to proofread it

Which would you rather read?

A

7. Screening and diagnostic evaluation. Following informed consent, we will use the assessments in Table 2 to evaluate inclusion and exclusion criteria for psychiatric, sleep, and medical disorders. A consensus conference will be conducted to review all information and establish final diagnoses. Insomnia diagnostic and assessment procedures are consistent with published recommendations for insomnia research.[94]

Table 2. Eligibility and Diagnostic Measures and Procedures

Measure Type	*Specific Measure*	*Variables of Interest (Criterion addressed)*
Clinician-Administered Instruments	Structured Clinical Interview for DSM-IV (SCID; ~1 hour)[157]	Exclusionary past or present mood, anxiety disorders, substance use disorders (Psychiatric eligibility)
	Structured Clinical Interview for Sleep Disorders (SCI-SLED; 30 minutes): Locally-developed interview to evaluate specific sleep disorders	Symptoms of exclusionary sleep disorders (Sleep eligibility). Presence of DSM-IV and ICSD-2 general insomnia symptoms and daytime impairments (Sleep eligibility).
Self Report Instruments	*Survey of Sleep (20 minutes): Locally developed questionnaire to evaluate sleep habits and problems.	Sleep history to assist diagnostic evaluation (Sleep eligibility)
	Pittsburgh Sleep Diary (5 minutes for completion of morning and evening sections)[156]	Sleep latency, Wake After Sleep Onset (WASO), Sleep Efficiency (assist diagnostic evaluation)
Medical Evaluation	*Medical History (10 minutes): Locally-developed questionnaire for major medical conditions	Medical conditions (Medical stability and eligibility)
	*Medication List (5 minutes)	Prescribed and OTC medications (Medical stability and eligibility)
	Physical Exam (1 hour)	Vital signs: height, weight, body mass index, blood pressure and heart rate (Medical stability and eligibility)
	Blood work (10 minutes)	Complete blood count, electrolytes, glucose, BUN, creatinine, T4, T3 uptake, FTI, AST, ALT, fasting glucose levels (Medical stability)
Sleep apnea screening	ApneaLink Plus (Portable home screening device includes nasal pressure, chest/abdominal movement, oximetry).	Apnea-hypopnea index AHI; (Exclude moderate-severe apnea, AHI>10)

* These measures will be sent to participants by mail prior to the consent visit in order to lessen the length of the initial visit (consent and clinical assessments), and to gather preliminary eligibility information.

8. Self-report and clinical measures (Table 3). We will collect self-report and interviewer-administered assessments to fully characterize CI and GSC samples, to measure CBT-I effects, and to correlate with functional imaging results. These instruments were chosen to evaluate the symptom domains most relevant to emotion and insomnia. Assessments will be conducted prospectively in participants' home environments (mood and sleep diary, actigraphy) or the research clinic (retrospective assessments, interviewer-administered measures). Assessments at home and in the clinic will utilize smartphones or computers to provide easily-accessed, reliable, time-stamped data that are entered directly to our data base. *Assessments will be completed at baseline (T1) and after 10 weeks (T2) in both CI and GSC.*

Table 3a: Retrospective Rating Scales: Completed in Clinic

Domain	*Instrument and Reference*	*Content area*	*Format*
Global sleep and insomnia questionnaires	Pittsburgh Sleep Quality Index (PSQI)[158]	General sleep quality	18 questions; Self-report
	Insomnia Severity Index[159]	Sleep and daytime symptoms of insomnia	7 items; Self-report
	Composite Scale of Morningness[140]	Trait morningness-eveningness	13 items; Self-report
Self-report emotion and arousal questionnaires	Inventory of Depressive Symptomatology (IDS-C, IDS-SR)[141]	Depression symptoms	30 items; Interviewer and self-report versions will be used
	State-Trait Anxiety Inventory (Trait)[142]	Anxiety symptoms	20 items; Self-report
	Pre-Sleep Arousal Scale[143]	Bedtime somatic/ cognitive arousal	16 items; Self-report
	Hyperarousal Scale[144]	Tendency to experience arousal	26 items; Self-report
Daytime sleepiness and fatigue questionnaires	Epworth Sleepiness Scale[145]	Sleepiness in common activities	8 items; Self-report
	Multidimensional Fatigue Inventory-20[146]	Dimensions of fatigue	20 items; Self-report
General function:	Medical Outcomes Survey SF-36[147]	Health-related functioning	36 items; Self-report
	PROMIS health battery[148- 149] (www.assessmentcenter.net)	11 item banks assessing a range of health-related functions	Adaptive testing averaging 60-70 items; Self-report
Table 3b: Prospective sleep and symptom ratings: Completed at home			
Sleep	Pittsburgh Sleep Diary[156]	Sleep timing and daytime activity	12 items at night, 18 items in morning; Self-report
Affect	Positive Affect Negative Affect Scale	Affect and arousal symptoms	20 items; Self-report
	Daytime Insomnia Symptom Scale[55]	Affect and arousal symptoms	20 items; Self-report

9. Objective sleep methods: Actigraphy and Polysomnography (PSG). (a) ***Rationale:*** Actigraphy and PSG data will be used to characterize CI-GSC differences, to verify CBT-I effects on sleep, and to examine relationships with neural circuitry. Actigraphy provides an objective, longitudinal measure of rest-activity patterns that correlate with objective sleep-wake measures from PSG.[150-152] PSG is considered the gold standard physiological measure of sleep, and is collected in the controlled laboratory environment. ***(b) Actigraphy methods:*** We will use Actiwatch 2 devices and Actiware v5.59 software set at the medium threshold to derive outcome variables such as wake after sleep onset (WASO), total sleep time, and sleep efficiency (SE). Participants will wear actigraphs concurrently with sleep diary completion, and will use the event marker to indicate bedtime and waketime. All actigraphy records will be manually edited to delete times when the device

B

inhomogeneity interactions. Realigned images are then co-registered with each participant's anatomical image, normalized with the anatomical gray matter parameters to the standard Montreal Neurological Institute template, and spatially smoothed with a Gaussian kernel of 6-mm full-width at half-maximum (FWHM).

11. PET methods. ***(a) General PET methods.***[165] PET studies will be conducted on a Siemens/CTI ECAT HR+ PET scanner in 3D mode. The scanner acquires 63 transaxial planes (2.4-mm thick) and has a final reconstructed in-plane resolution of approximately 6 mm FWHM. Data will be acquired as participants lie in the scanner with eyes closed, positioned in the scanner parallel to the canthomeatal line with the cerebellum in the central 7 cm of the axial field of view. This assures the most uniform 3D sensitivity of the tomography[166] and allow visualization of structures from the brainstem through the cortex. A 30 minute emission scan (six summed sequential 5-minute scans) will be performed at T=60 minutes following radioligand injection. A 10-15-minute windowed transmission scan will be obtained immediately after the emission scan to allow quantitative correction of attenuation. ***(b) FDG PET studies.*** A subset of CI will have two PET studies—during morning wakefulness 2-4 hours following sleep offset, and during early NREM sleep—at each of two time points, baseline and post-CBT-I (4 scans per participant). These scanning times are designed to capture a period of high alertness in the morning, after sleep inertia has dissipated, and a period of deep NREM sleep; are consistent with previous data collected in our laboratory; and will permit us to use data from archival GSC controls, thereby reducing expenses for this grant. *Except for time of day, procedures for the two PET studies are identical.* Intravenous catheters will be placed in each arm: One for injection of the radioligand, the other to sample glucose and radioactivity for semi-quantitative modeling of the metabolic rate of deoxyglucose (MRDglc).[167] For the *waking PSG PET study*, participants will lie supine with eyes closed and no specific mental task, while continuously monitored with PSG to ensure wakefulness. After 20 minutes, an intravenous bolus of 5 mCi [^{18}F]-FDG will be injected. The participant will lie quietly with EEG-monitored wakefulness for a 20-minute uptake period, then be transported to the PET Center for scanning. Six 1-ml venous samples will be drawn for radioactivity from 45-90 minutes following injection, and plasma glucose will be assayed from the first and last samples. For the *NREM PSG PET study*, the 5 mCi FDG injection will occur 20 minutes after sleep onset, defined as the first minute of ten consecutive minutes of N2 or N3 sleep. After sleeping for an additional 20 minutes during the FDG uptake period, the participant will be transported to the PET Center for scanning. *Across all groups and types of scans in the current grant period, 88.7% of PET scans yielded usable data.* ***(c) Automated PET data processing.*** PET data processing , ROI generation, and calculation of MRDglc will be conducted by the PET Data Analyst, supervised by Julie Price, Ph.D. BrainSuite software will be used to eliminate non-brain tissue from the MR. Standard alignment and co-registration will be performed using automated algorithms for PET to PET alignment and PET to MR cross modality registration. The six centered, co-registered emission scans will be summed and registered to the subject's cropped MR study for use in MR-based ROI generation. For exploratory SPM analyses, the cropped MR image will be registered to a lab standard MR template image to permit between subject comparisons in a common brain space. Equations translating the MR template image into Talairach space have previously been formulated.[168] The translation parameters used to transform the subject's high resolution MR into Talairach space will be used to translate the summed PET image into Talairach space. Data will be reviewed to ensure adequate registration (error <1 pixel). PET images will be smoothed and adjusted for changes in global PET counts prior to analysis. ***(d) Regions of interest (ROI).*** ROIs will be defined from the Anatomical Automatic Labeling (AAL) atlas.[127] We have also used an automated ROI analysis using a fully deformable model for atlas-based segmentation of structural MR images.[169] ***(e) Metabolic rate of deoxyglucose (MRDglc).*** A modification of the simplified kinetic method (SKM)[167] will be used as an indirect measure of absolute glucose metabolism, based on the six venous samples. After whole brain and regional ROIs are determined from MR images, ROIs will be applied to the co-registered PET image data set to obtain C_{PET} values for 63 PET image planes. The modified SKM method will be applied on a plane-by-plane and whole brain basis. We will define relative MRDglc for each ROI as ROI MRDglc/whole brain MRDglc (with lumped constant=1.0). For whole-brain normalization of regional MRDglc, segmentation will be applied to the structural MR data to create a brain tissue mask for PET data. We routinely use this approach to obtain reliable, reproducible estimates of whole brain MRDglc.

13. CBT-I methods. ***(a) Rationale:*** CBT-I is being used as a non-pharmacologic intervention probe to test study hypotheses regarding neural circuitry in CI. This is NOT a controlled efficacy trial. Although we have developed an even more targeted behavioral intervention for insomnia,[57] CBT-I remains the best-validated and most standard non-pharmacologic intervention. ***(b) Methods:*** The CBT-I treatment manual and materials (Appendix) are adapted from those being used in our ongoing NIA-funded Program Project (AG020677) and are derived from published CBT-I protocols.[46-48] CBT-I will be delivered in 8 individual in-person sessions over 10 weeks (to allow for scheduling conflicts), each lasting 45-50 minutes. Participants will maintain a sleep diary

C

Specific Aim 2: Relationship between RRGM, self-reported sleep quality, and affect. **(a)** We used SPM-8 to examine correlations between scores on the Pittsburgh Sleep Quality Index (PSQI) and RRGM in 76 participants (n=33 GSC, n=43 CI) (Figure 3). PSQI scores range from 0-21; higher scores = worse sleep quality. PSQI scores correlated positively with RRGM in a single cluster of >15,000 voxels (p<.001 corrected, peak voxel t=3.88) including precuneus, thalamus, and medial cortex. PSQI scores correlated negatively with RRGM in a single cluster of >12,000 voxels (p<.001 corrected, peak voxel t=4.12) that included subgenual ACC and OFC. Because PSQI scores were essentially non-overlapping in PI and GSC groups, we found very similar results on a direct comparison of RRGM during NREM sleep in CI vs. GSC (data not shown). *These results suggest that worse sleep quality and insomnia are associated with altered metabolic activity in key components of DMN, emotion regulatory, and sleep-wake circuits.* **(b)** We examined the relationships between diurnal variation in positive affect (PA), diurnal variation in RRGM, and chronotype in CI (n=27). We found robust circadian variation in PA, with delayed and smaller amplitude rhythms in CI with evening chronotype vs. CI with morning chronotype.[132] In addition, diurnal variation in RRGM differed among chronotypes: Compared to morning-types, evening-types showed smaller a.m.-p.m. *increases* in RRGM in a cluster within the right putamen (peak voxel t=3.80, p < 0.001). Evening-types showed smaller a.m.-p.m. *decreases* in RRGM in the medial prefrontal cortex, (BA8; peak voxel t = 3.36, p = 0.001). *Thus, different diurnal patterns of PA are accompanied by different diurnal patterns of RRGM in brain regions known to regulate reward and PA.*

Figure 3: Correlations between RRGM during NREM sleep and PSQI Scores

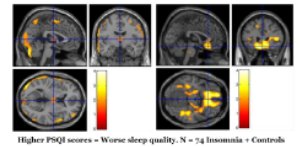
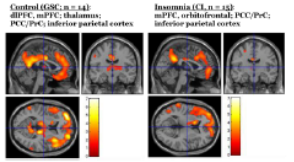


Figure 4: Baseline NREM sleep > Post-restriction NREM sleep RRGM

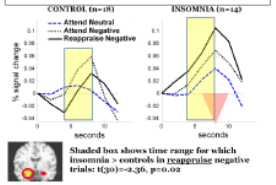


Specific Aim 3: Effects of sleep restriction (Figure 4). We examined the effects of one night of sleep restriction (to 2 hours) on RRGM, hypothesizing that this homeostatic sleep challenge may "correct" some of the RRGM alterations in CI. GSC (n=14) showed a robust response to sleep restriction, with reduced RRGM during NREM sleep in 2 large clusters (p<.001 corrected, peak voxel t=7.43) including mPFC, dlPFC, thalamus, and inferior parietal cortex. CI (n=15) had a smaller extent of RRGM decreases during NREM sleep following sleep restriction, with 2 large clusters (p<.001 and p=.012 corrected, peak voxel t=6.64). Similar to GSC, CI showed reductions of RRGM in mPFC, dlPFC, Pcc/PrC, and inferior parietal cortex. Unlike GSC, CI did not show reduced RRGM in thalamus. Thus, sleep restriction was associated with reductions in PCC/PrC (which showed reduced sleep-related reductions in RRGM for CI vs. controls, and (+) correlation with PSQI at baseline), as well as orbitofrontal cortex (which showed (–) correlation with PSQI at baseline). *The effects of sleep restriction on RRGM during NREM sleep suggest potential mechanisms for the therapeutic effects of CBT-I, i.e., reductions in RRGM in cortical and subcortical regions associated with emotion regulation, DMN, and sleep-wake regulation.*

2. Preliminary data relevant to new study aims.

(a) fMRI studies of emotion regulation in CI (Specific Aim 1). We have begun to collect fMRI studies examining the neural circuitry of emotion regulation in CI. Using the same event-related voluntary emotion regulation task proposed below, participants viewed pictures under three conditions: passive viewing of neutrally-valenced pictures; passive viewing of negatively-valenced pictures; and cognitively reappraising one's response to negatively-valenced pictures. Both CI (n=14) and GSC (n=18) showed increased amygdala activation when viewing negative vs. neutral affective stimuli (Figure 5). In controls, the reappraisal condition was associated with reduced amygdala activation, consistent with prior studies (e.g.,[133]). In CI, however, reappraisal was associated with increased amygdala activation, a pattern similar to that observed in healthy young adults undergoing experimental sleep

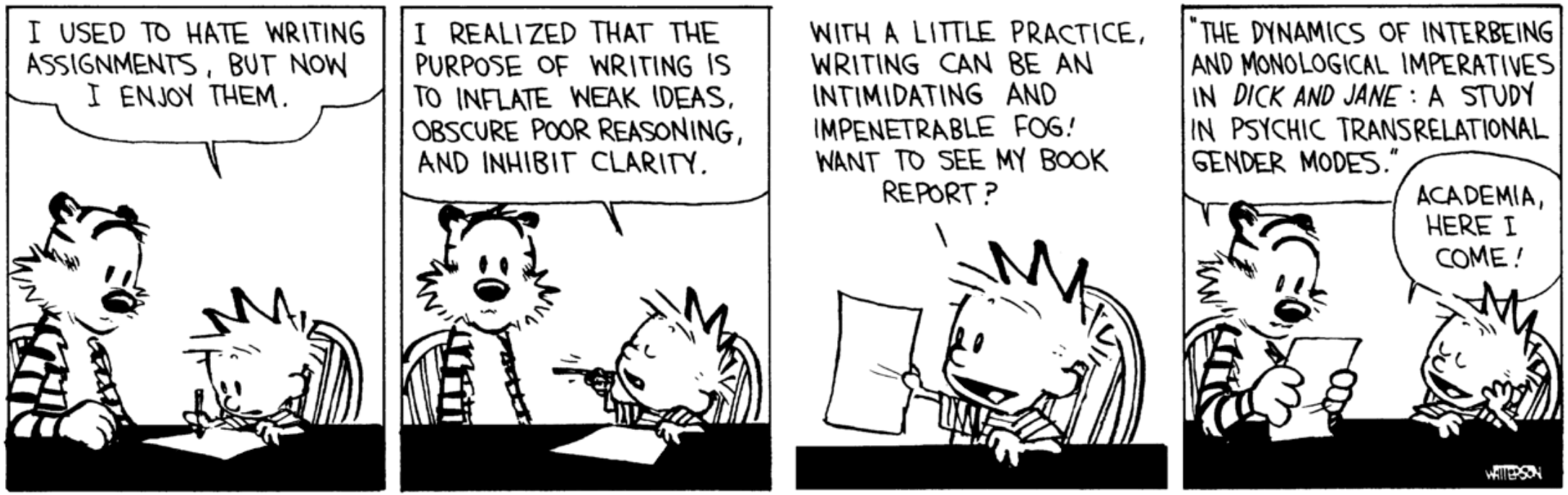
Figure 5: Amygdala reactivity during voluntary emotion regulation in insomnia



Other resources

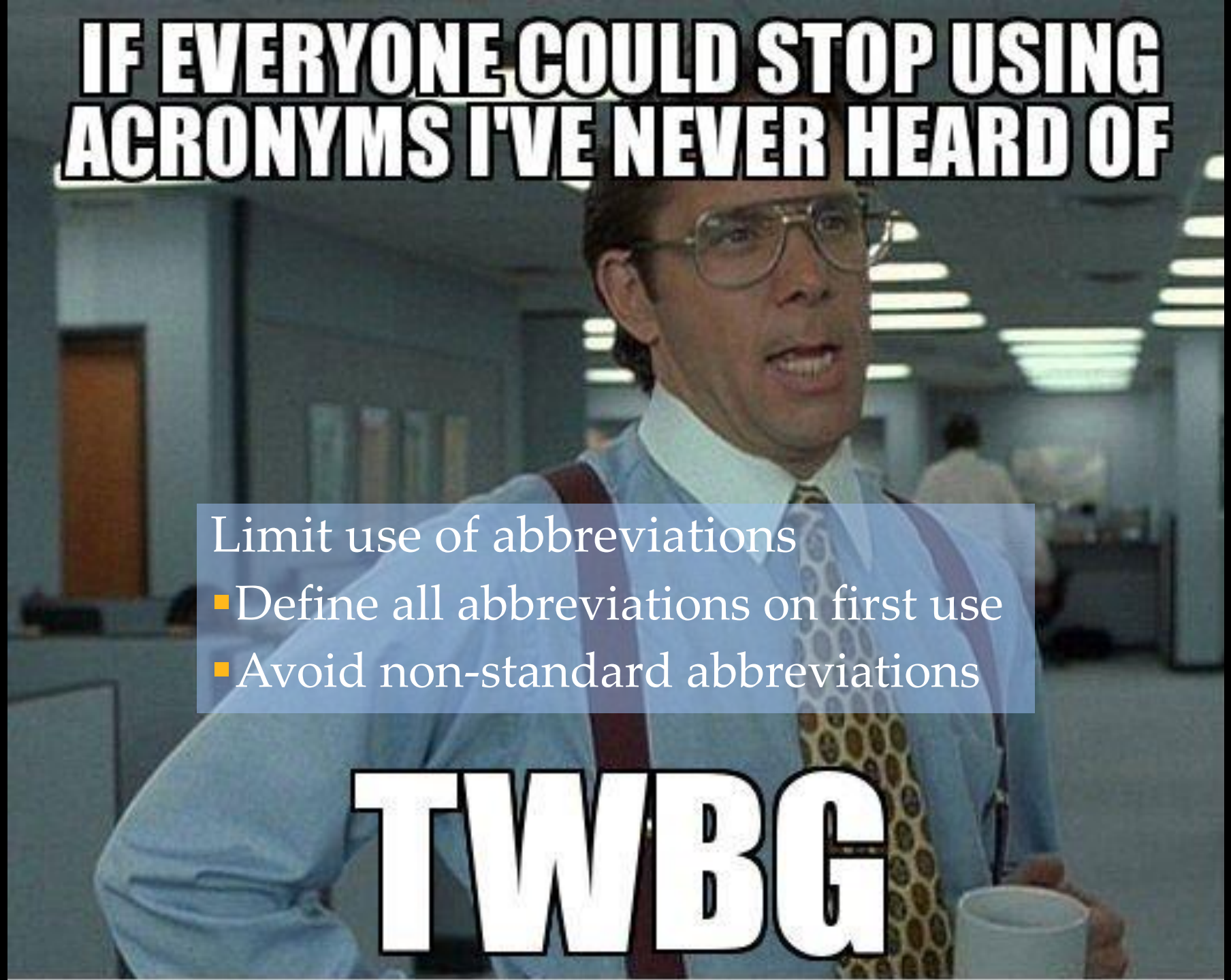
- At your institution: CTSI, school, departmental workshops
- NIH workshops and website
- Professional grant writing workshops, books
- Your senior and near peers

Words of wisdom: Writing



Words of wisdom: Writing

- Use an outline
- Tell a story
- Summarize your application in one sentence.
- Strategic repetition
- The ~~passive voice should not be used~~.
  - Do not use the passive voice
- ~~It is important to~~ limit use of the verb "to be."
- ~~It is important to~~ eliminate dead phrases.
  - ~~"Research has shown that…"~~
  - ~~"Further research is needed to…~~."

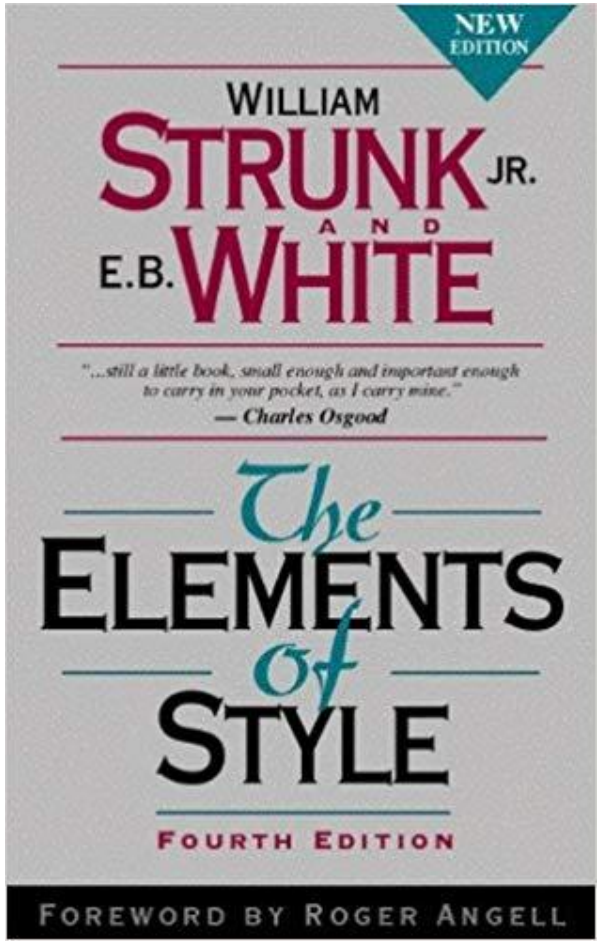


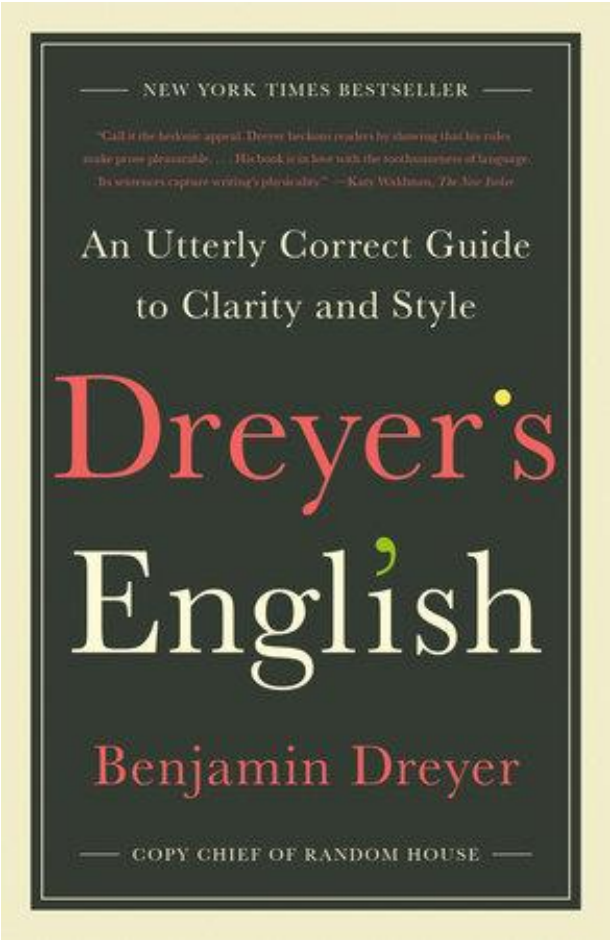
Limit use of abbreviations

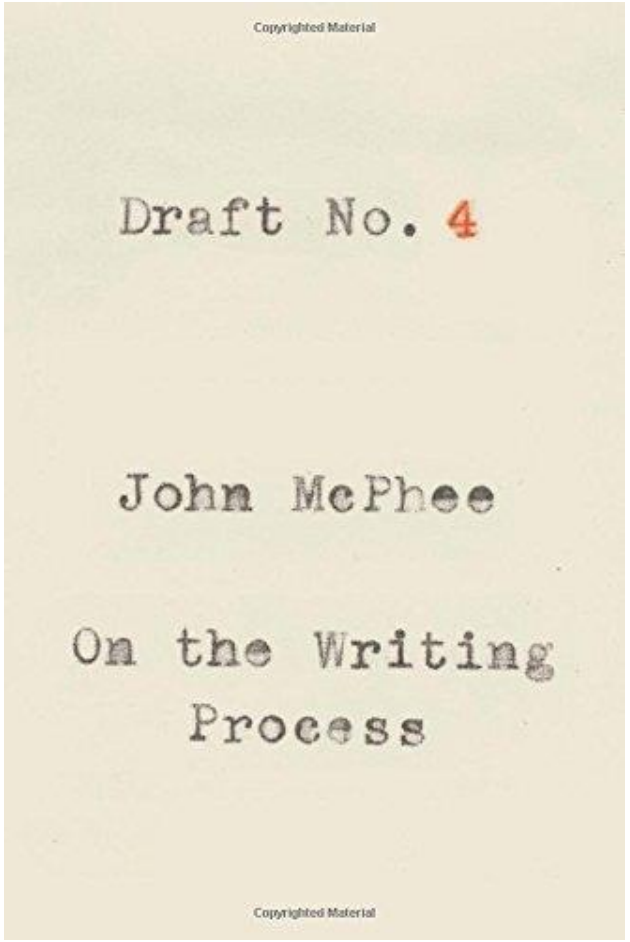
- Define all abbreviations on first use
- Avoid non-standard abbreviations

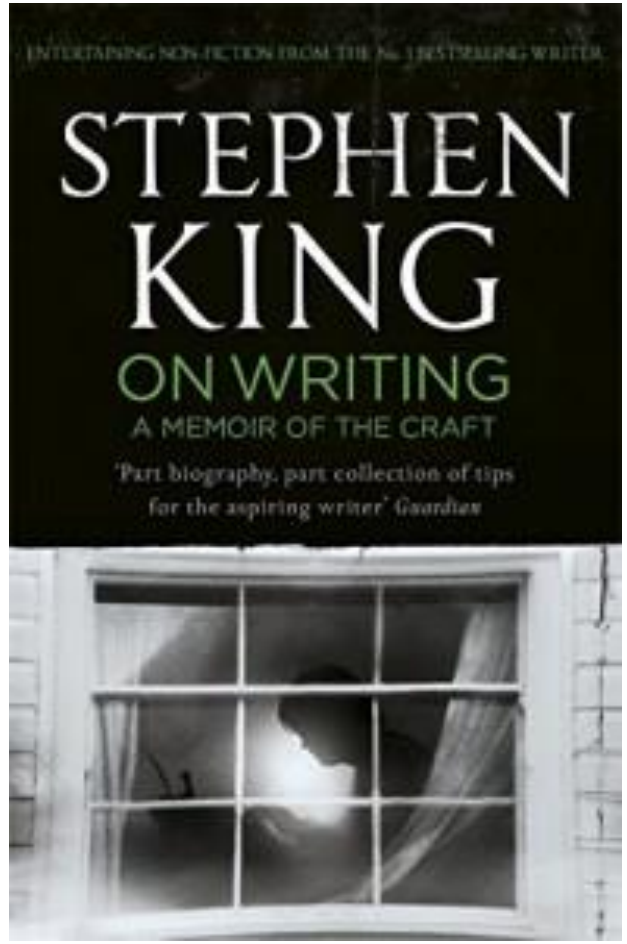
"I'm a fiction writer in the grant-proposal genre."

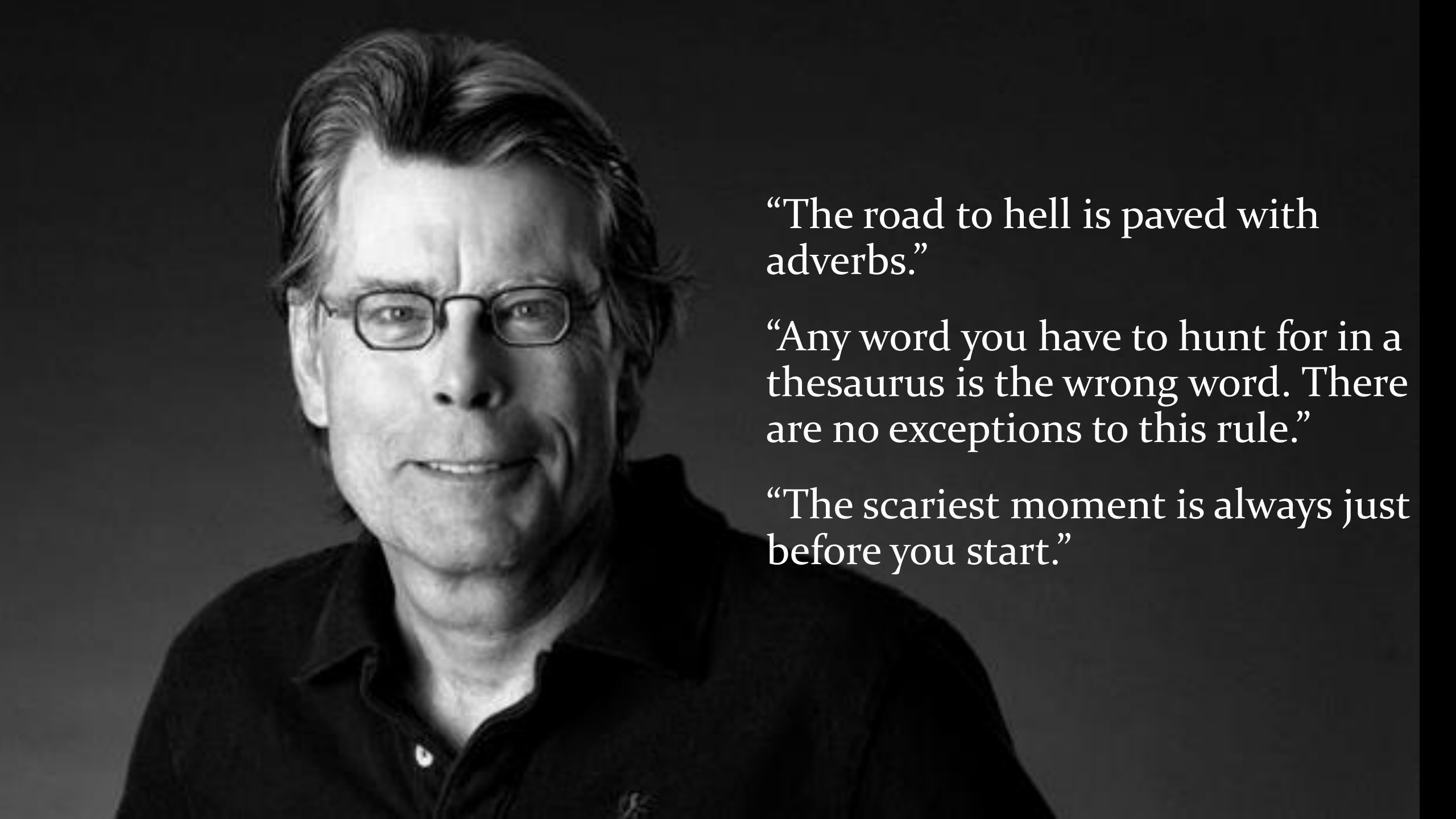
Read to write well





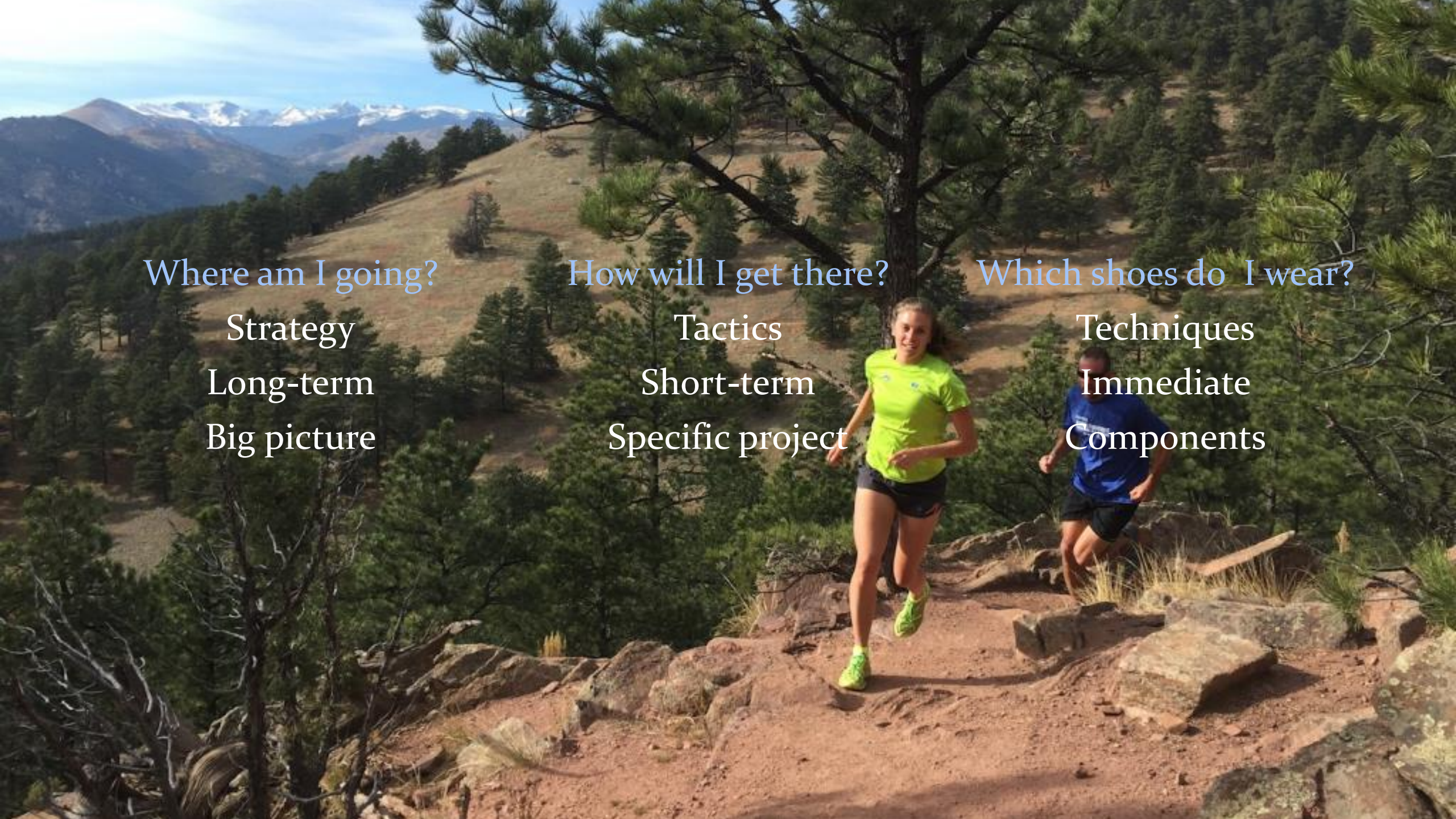





“The road to hell is paved with adverbs.”
“Any word you have to hunt for in a thesaurus is the wrong word. There are no exceptions to this rule.”
“The scariest moment is always just before you start.”

“Perfection is achieved, not when there is nothing left to add, but when there is nothing left to take away.”

-Antoine De Saint-Exupéry


Where am I going?
Strategy
Long-term
Big picture
How will I get there?
Tactics
Short-term
Specific project
Which shoes do I wear?
Techniques
Immediate
Components

Thank you for participating in the SBSM Science and Advisory Committee Webinar

Join us for future scheduled events:

Science and Research Webinar:
MARCH 4, 2020
12:00 PM EASTERN TIME

TOPIC: Searching for 10: Grant Writing Strategies, Tactics & Techniques Part 2

SPEAKER : Daniel J. Buysse, MD
UPMC Professor of Sleep Medicine
Professor of Psychiatry and
Clinical and Translational Science

DISCUSSANT : Natasha Williams, EdD, MPH, MSW
Department of Population Health
Center for Healthful Behavior Change
NYU Grossman School of Medicine

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November 5-8, 2020
Nashville, TN at Opryland