In the room where it happens: How grants are reviewed and mock study section workshop

Robert McCullumsmith, MD, PhD, FACNP

Table of contents

Mccullumsmith, Robert

From: Scott, Brian (NIH/CSR) [E] <brianscott@mail.nih.gov>
Sent: Monday, December 2, 2019 3:14 PM
To: aa324@columbia.edu; wadeb@mail.med.upenn.edu; stephanie_j_crowley@rush.edu; bchristian@wisc.edu; Erica.Duncan@va.gov; hanlon@musc.edu; dkareken@iu.edu; mkocak1@uthsc.edu; Andrew.Krystal@ucsf.edu; MAITRA@IASTATE.EDU; Mccullumsmith, Robert; evan.morris@yale.edu; enwulia@howard.edu; gnpandey@uic.edu; prasadkm@upmc.edu; cr2163@stanford.edu; carol.tamminga@utsouthwestern.edu; EWEERTS@JHMI.EDU
Subject: [EXTERNAL] NPAS review meeting, Feb 6-7: RSVP

Dear NPAS reviewers,

I hope you found some time to unplug over the Thanksgiving weekend. As you stare down the pile of manuscripts that you promised yourself would be submitted in 2019, I ask that you also look ahead to the first NPAS meeting of 2020, which will be in Washington DC on Feb 6-7 (Thursday/Friday). If you have not confirmed yet, please let me know if you'll be available to review, and let me know of any special circumstances (participating by phone, unavailable for part of the meeting, etc.).

We already have almost 100 applications this round, so please plan for a full 2-day meeting. I'll send detailed travel and hotel information with your assignments, but at this point I just need a head count.

Thank you, and I look forward to working with you again,

--Brian

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CSR Reviewer Training and Guidance
Integrity matters. Say something! For concerns or questions about possible violations of peer review integrity, please contact your Scientific Review Officer, or the CSR Review Integrity Officer at csrrio@mail.nih.gov, or the NIH Review Policy Officer at reviewpolicyofficer@mail.nih.gov. See the NIH Guide Notice on integrity in review.

Situation: Grant Reviews

Proposed reviewer may not be on the study section if :

- The reviewer is named on the application in a major professional role
- The reviewer is a member of an NIH Advisory Council
- The reviewer (or close family member) would receive a direct financial benefit if the application is funded

Proposed reviewer may be on the study section but may not review certain applications and must leave the room when:

- The PI or others on the application with a major role are from the reviewer's institution or institutional component (e.g., department)
- Within in the past three years, the reviewer has been a collaborator or has had any other professional relationship (e.g., served as a mentor) with any person on the application who has a major role
- The application includes a letter of support or reference letter from the reviewer
- The reviewer serves as a member of the advisory board for the project under review
- The reviewer has an indirect financial interest from the applicant institution or PD/PI of over $10,000 in honoraria, stocks, and fees during the course of the last year or during the project period

Proposed reviewer may be on the study section and may review specific applications without a waiver if: (not considered COIs)

- An application originates from an institution where the reviewer has collaborators, but the reviewer's collaborators are not listed on the application
- The reviewer has an indirect financial interest of less than $10,000
- The reviewer freely donates reagents or other materials to the proposed project, and these reagents or materials would also be available to other researchers
- The reviewer, as well as a person with a major role on the proposed project, contributes data, reagents, specimens, etc., to the same repository or database
- The reviewer is a member of a research network that involves a person with a major role on the proposed project
- The reviewer is a co-author of a non-research publication (e.g., review, commentary) or a mega-multi-authored publication with a person with a major role on the proposed project.

Note: A Federal employee serving as an NIH peer reviewer is responsible for obtaining any clearance required by his employing institute, agency, or office.

NIH Center for Scientific Review

ACTION ITEMS FOR NPAS REVIEWERS

Subject: NPAS Review meeting, February 6-7, Embassy Suites Chevy Chase Pavilion, Washington DC

Thank you for being part of the NPAS study section! The table below tells you what you need to do and when.

The other attached PDF (**Review _Information_NPAS)** has guidelines and instructions for reviewing. Read it before you start to review the applications.

What?	When?	Comments
Make sure you can get to the applications you are going to review. Check again for conflicts of interest with your assignments or other applications.	Now	Go to Commons Internet Assisted Review (IAR) through https://commons.era.nih.gov/commons Your assignment list could still be a bit fluid and depending on unforeseen conflicts, I might have to make a few minor changes within the next few days.
Sign the electronic Confidentiality Agreement Sign the Conflict of Interest forms.	Now	The links are in Commons IAR.
Arrange your airline or train travel through **World Travel Service.** www.nihreviewers.com 1-800-638-8500 (8 AM – 7 PM Eastern Time, Mon-Fri) Corporate ID: NIH Meeting code: NPAS	Now	You **MUST** use the NIH Travel Agency, World Travel Service, so your airline or train costs are billed directly to NIH. • Meeting starts: Thursday, February 6, at 8:00 am sharp • Meeting ends: Friday, February 7, 5:00 pm (approx.) • **You are expected to stay for the entire meeting.** Therefore, do not plan a plane or train departure on Friday earlier than 7-8 PM. NIH has already booked a hotel room for you for Wednesday and Thursday nights (See below.) If you must depart Saturday, contact me to stay over Friday night as well.
Review and post your critiques and scores **Reminder: Applications and reviews are confidential.** Do not leave applications or reviews where other people could see them.	**By Friday, January 31, midnight**	Post your reviews in Commons IAR. I must have your reviews by Friday, January 31 • Don't impinge on other reviewers' time to read your critiques and adequately prepare for the meeting. • I need time to identify any potential problem with the reviews. • You need time to read others' critiques. • You see other critiques only if you have submitted yours. • The meeting agenda depends on the preliminary overall impact scores.

Come to the review meeting ready to discuss the applications.	February 6-7, 2020	At the Embassy Suites Chevy Chase, Room TBD

Where are we staying and meeting?
The meeting will be at the:

Embassy Suites by Hilton Chevy Chase Pavilion
4300 Military Road NW, Washington, District of Columbia, 20015

This hotel is directly on top of the Friendship Heights stop on the Metro Red Line (you can actually get from the train to the hotel without stepping outside). Take the Yellow Line from Washington (Reagan) National Airport and change trains at Gallery Place/Chinatown; take the Red Line in the direction of Shady Grove. Amtrak's Union Station is also on the Red Line.

NIH has already reserved a room for you for Wednesday and Thursday nights. You do not need to confirm your reservation with the hotel. NIH is paying directly for the room and taxes. The hotel will ask for a credit card at check in just to handle incidentals.

How many applications do we have?

- We have 99 applications in this round – this will be a FULL 2-day meeting.
- Plan your departure no earlier than 7:00 pm on Friday.
- Hotel rooms will be available for reviewers who need to stay an extra night: feel free to extend your reservation through Saturday if you cannot make it home by 8 pm, your local time.

How do I receive reimbursement and honoraria?
You must be registered in the "**Secure Payee Registration System**" (SPRS) through your NIH Commons account. Follow these Instructions to register, Flat Reimbursement Rates are described here.

Are other events planned?
I will organize a **group dinner on Thursday night** (location TBD). Relax and get to know your fellow reviewers. Please plan to join us.

If you have questions
Contact me with *any* questions or concerns.

Thank you for your time, effort, and participation. I realize this is a big commitment on your part and appreciate your help.

Thank you!

--Brian

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DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health

NIH Center for Scientific Review

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REVIEWER INFORMATION & GUIDELINES MEMO

To: Neural Basis of Psychopathology, Addictions and Sleep Disorders Study Section Reviewers

Re: NPAS Review meeting, Feb 6-7, Embassy Suites Chevy Chase Pavilion, Washington DC

Posting date: Friday, January 31, midnight
Meeting starts: Thursday, February 6, at 8:00 am EST
Meeting ends: Friday, February 7, 5:00 pm

Dear All,

Thank you very much for contributing your time and effort to peer review at NIH.
It is very important that you read this memo prior to conducting your review because it includes important and new information about the review procedures and the scoring of the applications.

Also, please remember NIH's ongoing initiative on enhancing reproducibility of research through Rigor and Transparency. (See below, as well as https://grants.nih.gov/policy/reproducibility/guidance.htm)

I also invite you to consult CSR's Reviewer Orientation Site
This site provides a very comprehensive overview of the CSR review process from pre- to post-meeting and it will be very useful to both new and experienced reviewers.
I also invite you to review the information materials I have posted under NPAS's "Meeting Materials" at IAR.

CONFIDENTIALITY

- It is extremely important and it is legally incumbent upon you to adhere to the rules of confidentiality.
- All discussion related to the scientific merit of an application must be confined to the actual meeting room, and what occurs during the review is strictly confidential. Everyone in the room must feel free to openly discuss the strengths and weaknesses of an application without concern that any of that discussion might filter back to the applicant through any avenue other than the summary statement.
- Please refrain from discussing applications amongst yourselves prior to the review and/or outside the meeting room. Also, you should have no discussion with any applicant, or any NIH program official, regarding any aspect of the study section meeting before, during or after the review. If you are approached by anyone seeking information about the review of an application at the meeting, refer them to me and, furthermore, to protect yourself, notify me of your conversation.
- All applications, related materials are privileged information and may not be made available to anyone other than the review group or the NIH program staff present at the meeting. Should you

wish to seek input from a colleague about some detail or concept related to your review of an application and it would require showing them the application, please contact me first.
- Violation of NIH confidentiality and conflict of interest rules could lead to administrative actions. For details see NOT-OD-18-115.

YOUR REVIEW ASSIGNMENT

- The average workload this round is ~ 9-10 applications.
- Please check one more time for any conflict of interest you may have with any applications in the meeting **especially the ones you are assigned to** and notify me immediately. Conflicts include ongoing collaborations. You are also in conflict if you have collaborated or published with an applicant within the past 3 years.
- It is critical that you contact me if you feel that I have assigned you with an application that is significantly outside your area(s) of expertise. I will make other arrangements, or I will recruit a mail reviewer to supplement your review. Please do not wait until the day of the meeting to let me know your concerns.

REVIEWER TYPES

- NPAS will use up to 4 types of Reviewers: Reviewer 1, 2, 3 and in some instance mail reviewers.
- **Reviewer 1** and **Reviewer 2** write a full-length written critique, provide individual criterion scores, and a preliminary overall impact score. Rev 1 is the primary reviewer and will start the discussion.
- **Reviewer 3** provides no less than a full-length overall impact section (see above), as well as a preliminary overall impact score AND scores for individual criteria. Providing a few evaluative statements for each core review criterion is always encouraged.
- **Mail reviewer** writes full length written critiques and provides individual and overall impact scores.

- The **Overall Impact section** must be in the form of a paragraph summarizing the factors that informed your overall impact score. There **is NO NEED to summarize the proposed research**. This section should only focus on providing evaluative statements about the **scientific merit** of the proposed work, its **premise** (i.e., rigor of the prior research) and **rigor** and its **potential impact** to the field, rather than merely restating the aims and summarizing the experimental approaches and/or methods. The goal of this section is to help Program at NIH Institutes and applicants to better understand why the research may or may not have the potential to successfully impact the field.

SCORING SCALE

- A 1-9 scoring scale, whole number only (1 being the best and 9 being the worst) to individually score the five core review criteria and assign an overall impact/priority score that weights the individual criterion scores.
- **A medium-impact, good R01 application is a 5**. Try starting with the assumption that every application is a 5 before you read it, then adjusting up or down based on its criterion strengths or weaknesses to come up with a preliminary overall impact score. There is no need to give equal weight to each criterion.
- For low-impact R01 applications, use the 7-9 range, not the 4-6 range. This allows you the flexibility to use the 4-6 range for good applications with medium impact.

- Do not use R21s or R03s to balance the distribution of scores. They have absolutely no impact on our study section's percentiles.

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)

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

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

- When you feel uncertain (2 or 3?), try giving the worse score initially – you can revert to the better score if necessary depending on the discussion.
- Note that it's the ranking/percentile that matter, not the absolute score. Percentiles are calculated after the meeting based **only** R01 priority scores over 3 review cycles of NPAS (this meeting and the previous two rounds).
- NPAS needs to make a distinction between many high-quality applications and using the entire 1-9 scoring scale is an absolute requirement. The greater the score spread, the clearer your decision, and that of NPAS, will be to the Institutes.
- Inflating the scores will NOT translate into increasing the number of applications in the fundable range. Instead, it will compress the scoring system and limit NPAS's present and future ability to discriminate the scientific merit of the applications.

WRITTEN CRITIQUES – TEMPLATE-BASED FORMAT

- It is critical that you only use the critique templates linked to the applications in IAR
- Do not use an earlier version of this template, change its format, or change its security settings.
- **Write directly into the critique template** to provide direct and concise, yet substantive evaluative statements for the overall impact and on the strengths and weaknesses of each the core review criteria.
- Do avoid long and descriptive narratives that summarize the content of the application.

- Do use a direct style rather than using question marks: a question mark often means that something is not clear to you, so it is best to state it as such.
- Do remember to address the Human Subjects and Vertebrate animal sections when applicable, as well as non-scorable issues such as the budget, Authentication plan, sharing plan, foreign applications, etc.

ELECTRONIC REVIEW

- Your assignment is posted on your eRA Commons IAR account.
- All the PDFs of the applications are available and downloadable from IAR by selecting "List of all Applications" link and by clicking on the application number.
- NPAS's zApps package is currently being assembled by eRA Commons. CSR zApps is an electronic solution to deliver applications and review information and guidelines as a single zip file. I will email you the password-protected instructions to access the zApps package in a few days.
- Supplemental material submitted by the applicants may be found under "Additions for Review" and may be considered at your discretion.
- ⚠ It is critical that you upload your critiques and scores by Friday, January 31, so please do not create your own alternate, later deadline that would impinge on other reviewers' time to adequately prepare for the meeting.
- Respecting the deadline provides everyone with enough time to look at as many posted critiques as possible and it will allow me to identify any potential problem with the reviews, and set up the order of review. It is imperative that everyone has sufficient time before the meeting to look through the written critiques posted for their assigned applications as well as the applications in the same scoring neighborhood.

PRELIMINARY OVERALL IMPACT/PRIORITY SCORES

- Focus your evaluation on whether the research proposed is worth doing rather than how an application proposes to do the research. Your evaluation should thus put less emphasis on methodological details and approaches and more on the scientific premises on which the research strategy is based and on the potential scientific impact and significance of the work.
- However, the scientific merit of an application cannot rely solely on the potential significance/impact of the proposed studies, or on the investigator, no matter how stellar he or she could be. Obviously, a significant flaw and/or the lack of scientific rigor in the approach would dramatically reduce the impact and the potential for success.
- What is the difference between overall impact and significance:
    - NIH guideline states that significance is whether *"the project addresses 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... be improved? How will successful completion of the aims change the concepts, methods, technologies... that drive this field?*
    - The overall impact of an application *"the likelihood for the proposed research to exert a sustained and powerful influence on the research field involved"*. Impact is thus linked to feasibility/success and even though less emphasis on methodological details is encouraged, one should not disregard a flaw in the approach.
- The overall impact score is not an average of the individual criteria scores – you may weight them as you see fit. However, **the overall impact score cannot be better than the Significance** – effectively, the overall impact is the significance score weighted by the probability of success.

NIH's ongoing initiative about RIGOR, REPRODUCIBILITY, AND REVIEW

The topic of rigor and reproducibility in the context of peer review at NIH is not new. The focus on scientific premise and rigor has always been at the forefront when evaluating the scientific merit of applications submitted to the study section. This being said, NIH is renewing its commitment to enhancing reproducibility of research through rigor and transparency by updating its guidelines instructions and review language for research grants.

These are ***not*** additional review criteria but are review updates focusing on the following four areas:

- The scientific premise forming the basis of the proposed research, now re-phrased as the "rigor of the prior research".
- Rigorous experimental design for robust and unbiased results
- Consideration of relevant biological variables, such as sex, for studies for studies involving human subjects or vertebrate animals
- Authentication of key biological and/or chemical resources (***this a non-scorable issue***)

I strongly encourage you to consult the Guidance for Reviewers on Rigor and Transparency.

A few comments about translational studies versus basic research

- NIH is *not* just interested in supporting applications with translational/therapeutic potential rather than basic research with broad applicability/relevance.
- NPAS generally reviews human, clinical translational research. However, basic research may be reviewed in NPAS if we have the required expertise. Therefore, unless it is a clear stated goal of an application, moderate or even limited relevance to human disease or limited translational potential of an otherwise highly significant topic/question for a given field does not necessarily diminish overall impact.

PRIORITY SCORES AND ORDER OF REVIEW AT THE MEETING

- We have **99 ~~problems~~ applications** this round, which will be clustered into groups:
  - 38 R01s
  - 9 New Investigators/Early Stage Investigators R01s (NI/ESI status applies only to R01 applicants, NOT R21s or R03s)
  - 29 R21s
  - 4 R03s
  - 4 R61/33 phased research awards (a NIDA-specific PAR)
  - 15 K Awards:
    - 5 K01 Mentored Research Scientist Career Development Award
    - 2 K08 Mentored Clinical Scientist Research Career Development Award
    - 6 K23 Mentored Patient-Oriented Research Career Development Award
    - 1 K25 Mentored Quantitative Research Career Development Award
    - 1 K24 Midcareer Investigator Award in Patient-Oriented Research
- We will discuss only applications with the greatest scientific merit (i.e. with a reasonable chance of being considered for support by the Institutes). It is generally accepted that these applications belong to the stronger half. Thus, we will aim at discussing approximately 45-50% of the applications in each group.
- Remember that preliminary overall impact scores are just that: **preliminary**. I do expect that the overall impact scores of many of the discussed applications will change during the meeting using the full 9-point score range, or at the very least or at the very least the 1-7 range. Discussed applications

will be ranked by percentiles that are calculated after the meeting using R01 ranking (NOT R21s or R03s) over 3 review cycles of NPAS. Most importantly, scores are really used to generate a ranking. Percentiles are a function of rank and the absolute score does not factor into the percentile calculation. Thus, **inflating the scores will NOT translate into increasing the number of applications in the fundable range.** Instead, it will compress NPAS's score distribution and limit NPAS's present and future ability to discriminate the scientific merit of the applications.

- When we have discussed approximately the top 45-50% of each cluster, our Chair or I will ask if anyone wishes to discuss any of the remaining lower-half applications. As usual, any eligible reviewer can request an application to be discussed.

DISCUSSION PROCEDURE

- Please come prepared to speak about the strengths and weaknesses of an application in terms of the specific review criteria and overall impact to the field, and present a numerical score. Again, it is important to keep the focus of the discussion on whether/why the research proposed is worth doing, and what would be its likelihood to impact to the field, rather than how an application proposes to do the research.

Reviewer 1:

- Introduce the application. Briefly summarize the purpose and hypothesis of the application in a few sentences. State the overall impact upfront. Be concise. You may summarize the approach in one or two sentences. Please don't spend time with extensive descriptives *unless* it informs your score.
- You can then move **stepwise** through the criteria with specific comments on the strengths and weaknesses of **each** of the core criteria.
- You may briefly summarize the approach, but again, keep the focus of your presentation on whether/why the research proposed is worth doing, on the scientific premises on which the research strategy is based, and on the potential scientific impact and significance of the work.
- Basically, the panel needs to know if anybody in that field would care (impact) if the project was successful.

Reviewer 2:

- Offer complementary points on each of the 5 core review criteria and emphasize issues that inform the score.
- Minimize redundancy

Reviewer 3:

- Offer additional non-redundant comments that emphasize issues that inform the score.

The application is open for general discussion:

- Try for consensus but also identifying areas of difference. Reaching a consensus is obviously not a requirement.
- Do not forget to address Vertebrate animals and Human Subjects during the discussion and before voting.
- The Chair will briefly summarize the discussion and ask the assigned reviewers to state their final overall impact scores.

VOTING ON FINAL OVERALL SCORE

- We will use IAR for electronic voting as well as a hard copy scoring sheet for back-up.
- Anyone can vote outside the scoring range recommended by the assigned reviewers. You just need to raise your hand and/or speak out so that I know this is your intention. You may be asked to briefly state your reason for doing so if it is not already obvious to the rest of the panel.

- Additional review considerations discussed *after* scoring include the plan for authentication of key biological and/or chemical resource, sharing plan, budget, overlap, etc.

REVISITING THE CONTENT OF YOUR CRITIQUES

- There will be an **Edit phase** at IAR if you need to modify or polish your written critiques after the meeting. This is especially important if the discussion has changed your opinion on a particular aspect of an application you were assigned to.
- I cannot stress enough the importance of providing the NIH Institutes and the investigators meaningful and substantive comments, **with the individual criterion scores reflecting the text.** For instance, one would typically expect to see at least one weakness stated for any criterion score of 4 and above.
- The Edit phase will begin right after the meeting is adjourned and will stay open until **Tuesday, February 11, at 9:00 AM.**

Thank you!

--Brian

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CSR Reviewer Training and Guidance
Integrity matters. Say something! For concerns or questions about possible violations of peer review integrity, please contact your Scientific Review Officer, or the CSR Review Integrity Officer at csrrio@mail.nih.gov, or the NIH Review Policy Officer at reviewpolicyofficer@mail.nih.gov. See the NIH Guide Notice on integrity in review.

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

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 Plans is required from reviewers for applications proposing Human Subjects Research, except those designated Exemption 4.

Study Timeline (Specific to applications designated clinical trial on the electronic cover sheet)

Strengths

-

Weaknesses

-

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 Plans **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 Based on Age: 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:

-

SUMMARY STATEMENT

(Privileged Communication)

Release Date: 03/04/2019
Revised Date:

PROGRAM CONTACT:
VICTORIA Arango
301-443-3187
victoria.arango@nih.gov

Application Number: 1 R01 MH121102-01
Formerly: 1R01NS113550-01

Principal Investigators (Listed Alphabetically):

MCCULLUMSMITH, ROBERT E
ROWLAND, LAURA M (Contact)
WEN, ZHEXING

Applicant Organization: UNIVERSITY OF MARYLAND BALTIMORE

Review Group: ZRG1 BDCN-J (02)
Center for Scientific Review Special Emphasis Panel
Member Conflict: Addictions, Depression, Bipolar Disorder and Schizophrenia

Meeting Date: 02/27/2019
Council: MAY 2019
Requested Start: 07/01/2019

RFA/PA: PA18-484
PCC: A3-NSS

Project Title: Translational assessment of brain bioenergetic function in schizophrenia

SRG Action: ++
Next Steps: Visit https://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Project Year	Direct Costs Requested
1	493,315
2	493,319
3	495,862
4	498,442
5	499,061
TOTAL	2,479,999

++NOTE TO APPLICANT: Members of the Scientific Review Group (SRG) were asked to identify those applications with the highest scientific merit, generally the top half. Written comments, criterion scores, and preliminary impact scores were submitted by the assigned reviewers prior to the SRG meeting. At the meeting, the more meritorious applications were discussed and given final impact scores; by concurrence of the full SRG, the remaining applications, including this application, were not discussed or scored. The reviewers' comments (largely unedited by NIH staff) and criterion scores for this application are provided below. Because applications deemed by the SRG to have the highest scientific merit generally are considered for funding first, it is highly unlikely that an application with an ND recommendation will be funded. Each applicant should read the written critiques carefully and, if there are questions about the review or future options for the project, discuss them with the Program Contact listed above.

1R01MH121102-01 ROWLAND, LAURA

DESCRIPTION (provided by applicant): Schizophrenia is a devastating illness with no cure, affecting about 1% of the population worldwide, costing billions of dollars annually. The scientific premise for this proposal is based on accumulating imaging, postmortem, animal model, genetic, and bioinformatics data converging on alterations in the production of bioenergetic molecules in limbic brain regions in this illness. We previously reported abnormally high levels of lactate in living patients with schizophrenia that were strongly associated with poor everyday functioning. This finding complements our induced pluripotent stem cell (iPSC) and postmortem work showing higher lactate levels in schizophrenia in iPSC-derived cortical neurons and postmortem anterior cingulate cortex in subjects with schizophrenia. Based on this evidence, we hypothesize that diminished everyday functioning in schizophrenia is due to impaired bioenergetic metabolism in limbic circuits with increased pathological generation or utilization of lactate in schizophrenia. Specifically, we posit that there is increased production and release of lactate from astrocytes, coupled with increased uptake and utilization of lactate, in lieu of glucose uptake and oxidative phosphorylation, to produce ATP in support of neuronal plasticity in limbic circuits. This new R01 project uses complementary, but distinct approaches, to examine abnormalities of bioenergetic function in schizophrenia. For SA1, we will use magnetic resonance spectroscopy (MRS) to quantify lactate levels in limbic region and comprehensively characterize patients using neuroimaging, clinical, cognitive, functioning, and metabolic assessments. For Aim 2, brain organoids will be generated from iPSCs made from blood obtained in SA1 to assess lactate production and utilization challenges. We will further delineate the functional consequences of lactate production on cellular energy metabolism and neuronal development/function at molecular and cellular levels in 3-D cerebral organoids. In Aim 3, we will use a bioinformatics approach to identify lactate-associated targets for cell-subtype specific studies of biochemical/lactate changes in postmortem brain. Taken together, our aims will comprehensively assess perturbations of lactate and lactate associated pathways across clinical, tissue culture, and postmortem substrates in schizophrenia. By developing a more sophisticated understanding of the pathophysiology of schizophrenia, this project will help identify targets in bioenergetic pathways for development of treatment interventions for this debilitating illness.

PUBLIC HEALTH RELEVANCE: This project will investigate brain bioenergetic alterations in schizophrenia using a translational approach that includes brain imaging, cognition, functioning, and clinical assessments in living patients, bioenergetics studies in cultured brain organoids, and biochemical confirmation studies in postmortem brain accompanied with bioinformatics. This project will help identify treatment targets in bioenergetic pathways that may improve quality of life in those with this devastating illness.

CRITIQUE 1

Significance: 3
Investigator(s): 1
Innovation: 2
Approach: 4
Environment: 1

Overall Impact: The proposed study aims to understand the bioenergetic function in schizophrenia and its impact on neuronal development and function. The central hypothesis is that diminished everyday functioning in schizophrenia is due to impaired bioenergetic metabolism in limbic circuits with increased pathological generation or utilization of lactate in schizophrenia. To examine the consequences of abnormalities in lactate related processes in SZ, an extensive and translational assessment of pathological changes in lactate and lactate-associated biological pathways in limbic cells and circuits in schizophrenia is proposed. The PIs propose to use brain imaging and clinical and NP testing in living patients, bioenergetics studies in cultured 3-D human brain organoids, and biochemical

confirmation studies in postmortem brain. The application has several strong points which include the focus on lactate processes and their relationship to abnormal neurochemistry in SZ, the use of in vivo MRS assessment of three brain regions, all implicated in the pathology of SZ coupled with in depth testing of bioenergetic functions in brain organoids cultivated from the same subject group that received MRS assessments and biochemical confirmations in postmortem tissue. At the same time, the application has some weak points. The two major issues are the lack of carefully articulated theoretical model or framework which would accommodate statements and predictions made in the study, and overpromising what this study can accomplish. For example, the PIs make a strong statement that limbic bioenergetic abnormalities are responsible for reduced everyday level of function in SZ and cognitive abnormalities without elucidating why they think this might be the case. While ACC figures prominently in both models of SZ and in reports of cognitive abnormalities related to ACC, it does so as a member of brain circuits involved in specific abnormalities in SZ and not so much as a limbic structure per se. In addition, there is very little explanation why thalamus was chosen as a subcortical limbic structure to examine, other than for the fact that it is subcortical. In fact, recent theories and accounts of SZ dysfunction put a spotlight on thalamus as an important contributor to SZ abnormality. Finally, the visual cortex has been implicated in several cognitive abnormalities in SZ and it is not clear why the PIs think that lactate abnormalities will not be observed in that brain region. There is little in the line of identifying treatment targets in bioenergetic pathways. It is suggested that a more focused and better defined investigation would improve the overall impact of the proposed study.

1. Significance:

Strengths.

- Identifying lactate as an important possible contribution to SZ abnormalities at a cellular level with consequences at the phenomenological levels including clinical/cognitive and functional outcomes in SZ.
- Testing the processes of metabolic dysfunction at a cellular level using genetically identical cellular structures to construct brain organoids

Weaknesses

- The major premise of the study is that there are lactate perturbations in ACC SZ which the PIs plan to identify with several different approaches. These perturbations are predicted to result in adverse clinical, cognitive and functional outcomes in SZ. However, the presentation of the arguments in support of this premise is rather chaotic. We are informed about two different types of theories regarding bioenergetic mechanisms: 1. Systemically derived glucose taken up by neurons and metabolized by oxidative phosphorylation and 2. The involvement of astrocytes in the production of lactate with lactate then moving from astrocytes to fulfill bioenergetic needs of neurons. It is not clear how the current investigation will contribute to the resolution of these two theories and if it does not, what is the point of this argument in the Introduction to significance section.
- We are informed about the metabolic deficits in DLPF and in STG, as well as about deficits found by the PI in the ACC. Again, it is not clear how these disparate pieces of evidence fit into the overall hypothesis of abnormal lactate metabolism in the limbic structures, one of which is ACC.
- On the other hand, there is no mention of the thalamus and its possible role/function in the model of limbic metabolic abnormalities in SZ which, presumably, translate into abnormalities across several brain regions in SZ, as per literature, and result in clinical/cognitive and functional abnormalities.
- While I agree with the idea that metabolic dysfunction in SZ may be both 'direct' and 'indirect' I do not see how this concept advances an argument about abnormal lactate processes driving SZ abnormalities.

- I am not suggesting that lactate abnormalities in SZ are not important; or that this approach is not novel or even legitimate as a research question. In fact, I think that is a very interesting line of inquiry. However, what I am suggesting is that the rationale for this type of study will have to be better articulated and a clear line drawn between cellular lactate associated processes and system level abnormalities which in turn result in functional/clinical/cognitive outcomes in SZ.

2. Investigator(s):

Strengths

- The investigators with their respective fields of expertise are well equipped to carry out the planned investigation.

Weaknesses

- None noted

3. Innovation:

Strengths:

- The emphasis on lactate and metabolic processes as core abnormality in SZ is novel
- IPSCs derived from SZ with high limbic values in new
- Proposed studies are technically innovative including 3-D models of brain organoids
- Laser microdissection and enzyme assays is an innovative approach

Weaknesses:

- Lack of integration of information gathered at different analyses levels both conceptually and statistically

4. Approach:

Strengths

- Strong preliminary data for two aims of the study, including generation and testing of the hIPSCs properties aligned with the goals of the study
- Careful characterization of participants in terms of their metabolic profiles.
- Strong neuroimaging methods
- Strong methodology for creating and testing hIPSCs organoids

Weaknesses

- There exist clear descriptions of how several measures related to lactate perturbations will be quantified based on cerebral organoids; these include mitochondrial respiration, membrane potential, motility, morphology and mitochondria distribution at synapses. However, how these measures will be compared between groups is not clear.
- Likewise, while power analyses for post mortem brain analyses are provided, statistical analyses aimed at group comparisons are lacking.
- Furthermore, the system level (MRS) and cellular level analyses are not integrated – understanding the limits of what comparisons are possible, relating MRS derived ACC lactate levels with some of the cellular measures would help understand which cellular levels factors drive system level lactate measures.
- Similarly, no cognitive/functional/and clinical measures are attempted to be related to cellular level mechanisms. While a great deal of information will be generated in terms of characterizing

cellular mechanisms it is not clear this information informs our understanding of clinical and functional manifestations of the disease.

- The PI proposed to select top 15 ACC lactate levels SZ and match these subjects on age and sex to 15 HC as the source of genetic materials for iPSCs. I am wondering if this is an optimal strategy. I think that matching both groups, in addition to age and sex, on their ACC lactate levels is important. Furthermore, it might be worthwhile to select for example 10 highest and 10 lowest ACC levels individuals in both groups and compare them on all relevant measures to get a better sense of how different levels of lactate in both groups are associated with all measures of interest for lactate.

5. Environment:

Strengths

- Excellent environment for the proposed studies.

Weaknesses

- None noted

Study Timeline:

Strengths

- Not applicable

Weaknesses

Protections for Human Subjects:

- Acceptable Risks and/or Adequate Protections
- Risks are acceptable and adequate protections are in place.

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

- Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

Vertebrate Animals:

- Not Applicable (No Vertebrate Animals)

Biohazards:

- Not Applicable (No Biohazards)

Applications from Foreign Organizations:

- Not Applicable (No Foreign Organizations)

Select Agents:

- Not Applicable (No Select Agents)

Resource Sharing Plans:

- Acceptable

Authentication of Key Biological and/or Chemical Resources:

- Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 3
Investigator(s): 1
Innovation: 2
Approach: 6
Environment: 1

Overall Impact: The project proposes to investigate a novel increased lactate bioenergetics pathway in live humans with and without schizophrenia using MRS, in pluripotent stem cell derived brain organoids, and in post-mortem brain. This appears to be an interesting idea, but the projects are not really well conceptually integrated, to the reader the link to phenomenology is not clear, and there are other moderate weaknesses that dampen overall enthusiasm.

1. Significance:

Strengths

- Bioenergetics and mitochondrial dysfunction and oxidative stress have become important new leads to understanding the circuit dysfunctions that may underlie some of the abnormalities in schizophrenia.

Weaknesses

- A comprehensive integrated explanation of the cell to circuit to system to behavior is lacking, and other pathways under investigation in bioenergetics are not really discussed. It's not really clear how this work will translate to real world treatment, given the lack of clarity between cell-type specific abnormalities vs regional deficits.

2. Investigator(s):

Strengths

- Very good solid team.

Weaknesses

- None noted

3. Innovation:

Strengths

- Methods used are excellent, and this translational approach uses live human imaging, dead human tissues, and derives iPSCs to examine a specific neurobiological pathway.

Weaknesses

- None noted.

4. Approach:

Strengths

- Solid translatable approach to the finding of elevated lactate in Sz limbic structures.

Weaknesses

- The link between bioenergetics and diminished everyday functioning is too great a leap. A more detailed systems-level neurobiological model needs to mediate that relationship. Oxidative stress? Circuit dysfunction? Need more details in the mechanisms at cell circuit and system levels. This really needs a comprehensive translatable model that goes from increased lactate to social function by linking cells, circuits, systems, and behavior.
- Why is lactate higher in cingulate and thalamus but not occipital cortex? This should be a brain-wide phenomenon. This point is confused between S1 and S2 and S3. Is it a cell-type specific deficit, and brain-wide deficit, a regional deficit? The studies mix what is predicted. Certainly a forebrain organelle implies it is brain-wide, but the use of visual cortex as a cortical control region implies some sort of regional specificity. This really clouds the cohesiveness of the project and the solidity of the model.
- Although it was the former gold standard, the UPSA is horribly outdated. No one writes checks or uses a rotary phone anymore or calls 411 for Information. The UPSA in some sense tests historical knowledge/semantic memory. A better measure of everyday social functioning is needed.
- Is urine an equally good source for iPSCs as blood? It would be less invasive. Just a point to consider. Other groups use urine.
- Bioenergetic coupling is not defined.
- There is a lack of discussion of fast-spiking interneurons, burst interneurons, and pyramidal cells. Bioenergetic deficits may be selective to fast-spiking PV cells. That is, cell-type specific but not necessarily regionally specific.
- Lack of discussion of the circuit cascade (local pyramidal - various interneurons circuitry), such as Beherns work.
- Why are there 3 blood draws necessitating extra visits? How much blood do you need? If the purpose is to screen for various things as stated (e.g., diabetes) then the recruitment Table needs to be adjusted for rule-outs. You'll need more than 24 per year.
- Recruiting 24/year over 5 years does not allow for "catching up" as stated in the recruiting section.
- Sex as a biological variable states if there is a sex effect, you will do another study later. But you need some sort of regression methodology to account for the effects in this data. That's the important issue.

- No study listed potential pitfalls and alternative strategies
- There are no pilot data in the molecular studies showing any lactate effect related to Sz. It is not clear that showing delectability of LH in SA3 is sufficient.

5. Environment:

Strengths

- Excellent.

Weaknesses

- None noted.

Protections for Human Subjects:

- Acceptable Risks and/or Adequate Protections
- Standard procedures with appropriate protections in place

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

- Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically
- Inclusive and justified

Vertebrate Animals:

- Not Applicable (No Vertebrate Animals)

Biohazards:

- Not Applicable (No Biohazards)

Applications from Foreign Organizations:

- Not Applicable (No Foreign Organizations)

Select Agents:

- Not Applicable (No Select Agents)

Resource Sharing Plans:

- Acceptable
- Plans in place

Authentication of Key Biological and/or Chemical Resources:

- Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

Recommended budget modifications or possible overlap identified:

- Fine for multisite project

CRITIQUE 3

Significance: 2
Investigator(s): 3
Innovation: 1
Approach: 6
Environment: 3

Overall Impact: This is a fascinating proposal from a team of investigators who are extraordinarily well suited for their roles. The topic is innovative, with potential for high impact. Enthusiasm for the overall concept is thus very high, but there are major concerns, particularly with Aim 2, that reduce enthusiasm for the current proposal. Among those concerns are the use for preliminary data of the mitochondrial-associated DISC1 mutant subjects with SZ for justification of the current proposal that uses non-genetically defined subjects (despite the high enthusiasm for defining SZ subjects based on high lactate levels), and the organoid system that at day 84 will model very early cortical development that metabolically is likely to have fairly little in common with the adult cortex elevated lactate that forms the foundation for the proposal.

1. Significance:

Strengths

- This is a highly innovative proposal from a team of well position investigators to study the hypothesis that schizophrenia might be caused by metabolic compromise

Weaknesses

2. Investigator(s):

Strengths

- The three PIs have the necessary experience to conduct these studies and the contact PI has the experience and focus on schizophrenia to lead conceptualization.

Weaknesses

- Running experimental studies across three widely separated locations is not an ideal situation.

3. Innovation:

Strengths

- It is highly innovative to attempt to relate subject MRI data related to metabolics to those subjects' stem cell derived neural tissue metabolics.

- There is also tremendous enthusiasm for the theme of this proposal, given the tendency for pathways to be recapitulated across development and tissue, as approaches to reduction of metabolic compromise perhaps hold more therapeutic promise than do efforts to identify medication-targetable biology with the specificity for disrupted circuits and processes necessary to be practical.

Weaknesses

4. Approach:

Strengths

- Variability and statistical power issues notwithstanding, there is enthusiasm for attempting to relate imaging and blood studies on individual patients with IPSC-model results from the same patients/controls. That include the choice of patients for IPSC derivation from those with the highest "lactate" levels based on MRI.

Weaknesses

- Cerebral organoids model the first half of gestation, and are thus not a relevant model for the lactate in the adult cerebral cortex
- In addition, protocols for generation of astrocytes are well established, so what is the rationale for studying organoids in which differentiation is measurably less mature than culture of ipsc derived neurons and astrocytes, in which the astrocytes derive from SZ patients—thus fitting with the lactate shuttle hypothesis? Of note, contrary to what is mentioned on page 114, such cultures are neither 'monolayer" or "2d", as they make carpets, multiple cell bodies thick. Organoids have tremendous advantages for studying proliferation and perhaps migration in initial cerebral cortex development, but their advantages for studying activity-related processes remain to be established. What is the rationale for studying day 84 organoids, that might be similar to 14-16 week human fetuses in which proliferation and early migration are the main processes? On that note, preliminary data that mito enrichment at synapses can be demonstrated at organoid day 84 would be very reassuring.
- The brief mention that cell cultures are an alternative, without mentioning how the cell composition would be determined, is not an adequate alternative for the focus on organoids that are not adequately justified.
- What is the rationale for evaluating proliferation and excitatory neuron migration, that may be mostly glycolytic, in the context of the grant rationale on elevated lactate in adult with SZ?
- What is the rationale for focusing on thalamus/AC/occipital cortex?
- The lactate data from cultured neurons is excellent and intriguing, but since DISC1 is not an accepted "risk" gene for schizophrenia per se, and especially since Disc1 is a mitochondria-functioning protein (among other things), the relevance of this finding to the current study that proposed non-syndromic, non-genetically identified SZ is not apparent and is in some way misleading. Is the data from Fig. 5 also from Disc1?
- Given preliminary data with cultured neurons, what is the rationale for organoid cultures of one expects non-genetically defined SZ to behave similarly to those from patients with DISC1 mutations?
- Running seahorse on organoids is a fascinating idea with great potential impact, but in the Aim 2 feasibility for this is related to Fig. 5, which was conducted on dissociated cultures. As the seahorse platform is designed for monolayers, preliminary data, particularly addressing well to well variability that is a major challenge with seahorse measurements on cultures that are not monolayers, would be helpful to establish feasibility.

- Teratoma assays that are expensive and cause pain to animals are no longer considered necessary relative to profiling for pluripotent markers, and at any rate each line will need to be tested for ability to generate cerebral organoids which can fail to occur despite 3-germ-layer inclusive teratoma formation.
- Since IPSCs will be generated from patients with previously defined higher levels of "lactate" on MRI, how will the workflow proceed to identify these patients then generate the IPSCs to the passage level of their being ready for study in Aim 2?

5. Environment:

Strengths

- It is not ideal to split the aims between 3 locations, but the PIs do a good job explaining how the proposal would proceed, and the environments in each of the locations are outstanding for completing their proposed studies.

Weaknesses

Footnotes for 1 R01 MH121102-01; PI Name: Rowland, Laura M

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

Introduction to the revised application. We appreciate the thoughtful and extensive critiques provided by the reviewers. We have distilled this feedback into 4 major and several other concerns. Importantly, in the revised application we feel we have incorporated all of the feedback, resulting in a markedly improved, highly focused, and compelling proposal. We have also retained all of the elements of the proposal that were found by the reviewers to be "innovative," "fascinating," and potentially of "high impact." The "extraordinarily well-suited" team of investigators also remains in place. Changes to the proposal are indicated by yellow highlights.

Major Concern (All Rs). *The conceptual framework/linkage between bioenergetic abnormalities in limbic regions and schizophrenia (SZ) outcomes (reduced everyday functioning and cognitive abnormalities) is unclear.* We rethought our conceptual framework, leading to the idea that bioenergetic dysfunction impairs synaptic plasticity, changing cellular microcircuits throughout the brain; these changes lead to aberrant macrocircuit function in brain regions containing cells and circuits requiring high energy demands during normal cognitive function and is manifested as impaired cognition in SZ. Within this framework, it follows that our choices of the ACC and thalamus contain cellular elements with high energy demand; we also include parvalbumin positive interneurons (as suggested), as this cell type has particularly high energy requirements. We now posit that bioenergetic defects are present throughout the brain, but may be more impactful (at least in SZ) in cells and synapses in circuits that have particularly high energy requirements during cognitively demanding functions. Finally, this focus has scaled back our dependent measures, addressing the concern that we are "overpromising."

Major Concern. *R3 raises the concern that minibrains only model the first half of brain development, and thus would not provide an analogous substrate to compare to the human imaging (SA1) or postmortem (SA3) studies of adult brain.* We agree with this concern, and have shifted the focus of SA2 to the generation and evaluation of cortical neurons/astrocytes from human iPSCs, which are functional mature and widely used for studying neuropsychiatric disorders including schizophrenia.

Major Concern. *A significant concern was raised regarding integration of data across specific aims, with a particular focus on there being a need for a clear plan for this important element of the proposal.* Working with our bioinformatics consultant, Dr. Jarek Meller (LOS attached), we have clarified our integration plan, and added specific details to the revised application for the multidimensional correlation approach we will use to assess associations between clinical, imaging, cell culture, and postmortem dependent measures.

Major concern. (**All Rs**) *Participant selection for generating IPSCs.* Reviewers presented differing opinions regarding participant selection, therefore we will not preselect participants based on MRS lactate levels, but will included all participants that agree in years 1-3. This will provide a range of lactate levels, and allow additional enrollment in years 4-5 if this is not the case.

Other concerns. (**R1**) *Identifying treatment targets in bioenergetic pathways.* This statement was premature for the current project, but reflects an ultimate goal. (**R1**) *Two theories of bioenergetic dysfunction- pick one.* We now focus on alterations in the neuron-astrocyte lactate shuttle, as this fully overlaps with the spectroscopy outcomes (ie lactate measurements) for SA1. (**R2**) *UPSA is outdated.* We agree and substitute this functional "capacity" assessment with a functional "outcome" assessment. (**R2**) *No potential pitfalls or alternative strategies are provided.* We have included comments for these elements in the revised application. (**R2**) *Sex as a variable in regression analysis.* Examining sex with regression is now included. (**R2**) *Concern for the number of blood draws.* We now plan two bloods draws. (**R3**) *Regarding the environment, three separated locations are not ideal but the PIs do a good job explaining how the proposal would proceed, and the environments in each of the locations are outstanding for completing their proposed studies.* We regularly communicate via phone, skype, and in person (conferences and visits to each lab). The workflow, communication, and logistics are in place for this ongoing collaboration. Highlighting this working relationship, we recently published a lactate study as co-authors in Scientific Reports. (**R1**) *There is no mention of the thalamus and its role in limbic pathology in schizophrenia.* We have incorporated this important concept in the revision. (**R1**) *Details are not provided for assessing between group differences for SA3.* We added details for these standard statistical approaches. (**R2**) *Bioenergetic coupling is not defined.* We now define this important concept. (**R2**) *Interneurons and local circuits were not discussed.* We added comments for this issue in the revision. (**R2**) *No pilot data for lactate for SA3.* We found increased lactate in the ACC in schizophrenia in postmortem brain (Fig 5A). (**R3**) *Regarding the prelim data for SA2, concerns were raised that cells from a subject with schizophrenia with the DISC mutation is of low relevance to the proposed work.* Our prelim data (Figs 5B, 6 and 7) are from cell cultures from a subject with schizophrenia with the DISC mutation. These data show the feasibility of using biochemical assays and the Seahorse approach on cultured neurons derived from iPSCs. We agree that these data do not inform the hypothesis regarding spontaneous cases of schizophrenia, and discovery of cell-specific perturbations of the lactate shuttle in now the primary focus for SA2.

SUMMARY STATEMENT
(Privileged Communication)

Release Date: 08/18/2019
Revised Date:

PROGRAM CONTACT:
VICTORIA Arango
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Application Number: 1 R01 MH121102-01A1

Principal Investigators (Listed Alphabetically):

MCCULLUMSMITH, ROBERT E
ROWLAND, LAURA M (Contact)
WEN, ZHEXING

Applicant Organization: UNIVERSITY OF MARYLAND BALTIMORE

Review Group: ZRG1 BDCN-T (02)
Center for Scientific Review Special Emphasis Panel
Member Conflict: Addictions, Depression, Bipolar Disorder, and Schizophrenia

Meeting Date: 07/25/2019
Council: OCT 2019
Requested Start: 09/01/2019

RFA/PA: PA19-056
PCC: A3-NSS

Project Title: Translational assessment of brain bioenergetic function in schizophrenia

SRG Action: Impact Score:28 Percentile:12 #
Next Steps: Visit https://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Age: 1A-Children, Adults, Older Adults, scientifically acceptable

Project Year	Direct Costs Requested	Estimated Total Cost
1	497,266	775,223
2	497,552	775,669
3	497,552	775,669
4	493,152	768,809
5	493,152	768,809
TOTAL	2,478,674	3,864,178

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R01MH121102-01A1 ROWLAND, LAURA

RESUME AND SUMMARY OF DISCUSSION: This is a resubmitted R01 application to investigate the hypothesis that diminished cognitive functioning in human patients with schizophrenia (SZ) is due to impaired bioenergetic metabolism in limbic circuits and that evidence of this shift away from oxidative phosphorylation can be observed by measuring lactate. Strengths include high significance with the potential to advance our understanding of how cellular energetic abnormalities lead to system-level abnormalities including cognitive dysfunction, outstanding MPIs and investigative team working in a supportive environment, and technical and conceptual innovation. The multipronged approach ranges from awake imaging to iPSC culture from post mortem tissue to bioinformatic. The PIs were responsive to prior critiques. Minor to moderate weaknesses include: 1) It is unclear whether the team proposes that lactate is a marker of cognitive impairment or causal of it. The preliminary data for this project identified a modest elevation in lactate in SZ patients correlated with cognitive impairment. Some saw the omission of correlating regional lactate level and function to be a missed opportunity. 2) The sensitivity of the 3T magnet imaging was questioned because prior data were collected using a 7T magnet, although reviewers acknowledged optimization procedures are in place. 3) Preliminary data from visual cortex as the control tissue were not convincing. 4) The aims were not well integrated. Overall, however, reviewers found much to be excited about with this project and weaknesses did little to reduce enthusiasm.

DESCRIPTION (provided by applicant): Schizophrenia is a devastating illness with no cure, affecting about 1% of the population worldwide, costing billions of dollars annually. The scientific premise for this proposal is based on accumulating imaging, postmortem, animal model, genetic, and bioinformatics data converging on alterations in the production of bioenergetic molecules in myriad brain regions in this illness. We previously reported abnormally high levels of lactate in living patients with schizophrenia that were strongly associated with poor cognitive function. This finding complements our induced pluripotent stem cell (iPSC) and postmortem work showing higher lactate levels in schizophrenia in iPSC-derived cortical neurons and postmortem anterior cingulate cortex in subjects with schizophrenia. Based on this evidence, we hypothesize that diminished cognitive functioning in schizophrenia is due to impaired bioenergetic metabolism in limbic circuits with increased pathological generation or utilization of lactate in schizophrenia. Specifically, we posit that there is increased production and release of lactate from astrocytes, coupled with increased uptake and utilization of lactate, in lieu of glucose uptake and oxidative phosphorylation, to produce ATP in support of neuronal plasticity in limbic circuits. This new R01 project uses complementary, but distinct approaches, to examine abnormalities of bioenergetic function in schizophrenia. For SA1, we will use magnetic resonance spectroscopy (MRS) to quantify lactate levels and comprehensively characterize patients using neuroimaging, clinical, cognitive, functioning, and metabolic assessments. For Aim 2, cultured human neurons/astrocytes derived from iPSCs obtained in SA1 to assess lactate production and utilization challenges. We will further delineate the functional consequences of lactate production on cellular energy metabolism and neuronal development/function at molecular and cellular levels in cultured human iPSC-derived neurons/astrocytes. In Aim 3, we will use a bioinformatics approach to identify lactate-associated targets for cell-subtype specific studies of biochemical/lactate changes in postmortem brain. Taken together, our aims will comprehensively assess perturbations of lactate and lactate associated pathways across clinical, tissue culture, and postmortem substrates in schizophrenia. By developing a more sophisticated understanding of the pathophysiology of schizophrenia, this project will help identify targets in bioenergetic pathways for development of treatment interventions for this debilitating illness.

PUBLIC HEALTH RELEVANCE: This project will investigate brain bioenergetic alterations in schizophrenia using a translational approach that includes brain imaging, cognition, functioning, and clinical assessments in living patients, bioenergetics studies in cultured human iPSC-derived neurons/astrocytes, and biochemical confirmation studies in postmortem brain accompanied with bioinformatics. This project will help identify treatment targets in bioenergetic pathways that may improve cognition and quality of life in those with this devastating illness.

CRITIQUE 1

Significance: 3
Investigator(s): 1
Innovation: 2
Approach: 4
Environment: 1

Overall Impact: The investigators propose to study bioenergetic function in schizophrenia using a combination of methods, including in vivo MRS imaging in humans (Aim 1); human iPSC-derived cortical neurons/astrocytes generated from individuals with schizophrenia and matched healthy controls (Aim 2); and laser microdissection and QPCR in post-mortem brain tissue obtained from individuals with schizophrenia and healthy controls (Aim 3). The premise of the study is based mainly on a recent 7T MRS study from the Principal Investigator's group showing elevated lactate in schizophrenia and is supported by preliminary iPSC and postmortem data including in the proposal. This is a fascinating and innovative proposal- their multi-level approach (i.e. in vivo MRS, iPSCs, postmortem laser microdissection) to investigating elevated lactate in schizophrenia is compelling and highly innovative. The potential impact of the proposed studies is high. While investigators were responsive to the initial reviews, several weaknesses remain that lower the overall impact to medium. They include: 1) unclear link between lactate dysfunction and cognition; 2) confusion as to whether they hypothesize global or regional changes in lactate; 3) large number of dependent variables in Aim 2 and corresponding weakness in statistical plan for this aim; 4) use of 3T for MRS when their prior study used 7T; and 5) concerns about the samples included in Aim 3. Also, the proposal could be improved by better integrating across the three aims and clarifying how the aims inform each other.

1. Significance:

Strengths

- While preliminary, elevated lactate in schizophrenia is interesting and merits further investigation.
- Multi-level approach (i.e. in vivo imaging, iPSCs, postmortem tissue) to investigating elevated lactate in schizophrenia in the context of a compelling biological model.

Weaknesses

- Apart from citing two rodent papers, not much evidence is presented to support their hypothesis that elevated brain lactate will be associated with worse cognitive function. The proposal would benefit from greater exposition of the mechanisms through which elevated lactate leads to brain dysfunction and cognitive impairment.
- The foundation of the proposal- elevated lactate in schizophrenia- is based on just a single prior MRS study that found elevated lactate in a sample of 31 patients. While intriguing, the modest sample does raise concerns about the scientific rigor of prior research.

2. Investigator(s):

Strengths

- Principal Investigator Rowland is an expert in MRS, and neuroimaging more broadly, and has considerable expertise in clinical research of psychotic disorders.
- Principal Investigator is supported by a strong team of MPI/Co-I's that includes individuals with expertise in biomedical engineering related to MRS (Wijtenburg), neuroimaging/neurophysiology (Hong), biostatistics (Shuo), neuroscience (McCullumsmith), and iPSCs (Zhexing).
- Strong record of collaboration between Principal Investigator and numerous members of the team.

Weaknesses

- None noted

3. Innovation:

Strengths

- Several features of the proposal are innovative, including measuring brain lactate in multiple regions using MRS; iPSCs from schizophrenia patients; and laser microdissection of post mortem tissue in patients.
- Translational, multi-level approach (i.e. in vivo imaging, iPSCs, postmortem data) is innovative.

Weaknesses

- Use of 3T instead of 7T MRS.

4. Approach:

Strengths

- Multi-level approach to investigating lactate is a major strength of the proposal.
- Strong preliminary data, especially for Aim 1.
- MRS will look at multiple brain regions.

Weaknesses

- The initial MRS study by the Principal Investigator which found elevated brain lactate was done at 7T. In that paper the authors emphasized the importance of measuring lactate at 7T, noting that lactate is, in their words "barely detectable" at 1.5T and 3T. As such, the decision to use 3T MRS is perplexing and would seem to be a significant limitation.
- In addition to lactate, the investigators proposing measuring several additional, unspecified metabolites, as well as resting-state fMRI, CMRO2, and ASL. These data are not integrated into the proposal and, while convenient to collect, leaves the reader with the sense that this is a bit of fishing expedition.
- Relatedly, Aim 2 includes an exceptionally large number of dependent variables that will be compared between controls and schizophrenia. Seven measures of lactate metabolism alone are listed in section 2.2.2 (i.e. PFK, hexokinase, LDH, PGI, AMPK, fructose-6 phosphate, PFKFB2). Their statistical plan does not appear to account for the large number of dependent variables.

- It appears as though the 15 patients and 15 controls included in Aim 2 will be drawn from the sample included in Aim 1. It would be helpful if the investigators confirmed this and clarified how patients and controls will be selected.
- In Aim 3, the patient sample has an average CDR score of 1.9 +/- 1.2, compared to 0.2 +/-0.5. A CDR of 2 is considered "moderate" dementia. This suggests that a proportion of the schizophrenia sample has dementia. This is not acknowledged by the investigators and would appear to be a major confound.

5. Environment:

Strengths

- Environment at UM and MPRC is excellent for carrying out the proposed studies.

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Acceptable risks and/or adequate protections are in place

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

- Not Applicable (No Clinical Trials)

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

Vertebrate Animals:

- Not Applicable (No Vertebrate Animals)

Biohazards:

- Acceptable

Resubmission:

- The investigators were responsive to the initial reviews, particularly with respective to improving the conceptual framework of the proposal.

Resource Sharing Plans:

- Acceptable

Authentication of Key Biological and/or Chemical Resources:

- Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 2
Investigator(s): 1
Innovation: 1
Approach: 2
Environment: 1

Overall Impact: This is a resubmission. the goal of the proposed study is to understand brain bioenergetic dysfunction in schizophrenia, where the bioenergetic function was defined as the capacity of cells to generate, transport and utilize energy substrates such as ATP, lactate and glucose. The premise for this proposal is based on accumulating imaging, postmortem, animal model, genetic, and bioinformatics data converging on bioenergetic alterations in this illness. The proposal includes an MRS essay of lactate levels in ACC, thalamus, and visual cortex, in 60 schizophrenia (SZ) and 60 healthy controls (HC) coupled with cognitive tests (MCCB), comprehensive characterization of bioenergetic mechanisms in cultured human neural cells derived from a subset of the 60/60 subjects, and post-mortem studies planned as confirmatory relative to results obtained in SA2. The major hypothesis is that lactate will be higher in patients versus controls which will be associated with poorer cognition in SZ. The contact Principal Investigator has been very responsive to reviewers' comments. Specifically, she now focused on the mechanisms related to bioenergetic abnormalities in schizophrenia, explained the motivation behind the inclusion of thalamus as one of the regions of interest, clarified the statistical approach that would relate cognitive and biochemical findings to each other, introduced the distinction between neurons and astrocytes in terms of their relative contribution to SZ dysfunction, included an important section on the methodology of characterizing bioenergetic perturbations in development/function of both glutamatergic neurons and astrocytes, reduced the number of blood draws and discussed some of the pitfalls. Some of the issues remaining is the discussion of the visual cortex as a control region. In the light of the correlation between lactate levels and visual learning in SZ only, it appears that visual cortex probably has a function in SZ abnormal cognition. I think a better way of thinking about the visual cortex would be through the lens a different cognitive function relative to ACC and thalamus. I am also a bit puzzled by a statement that the applicants are interested in what molecular changes are associated with increased lactate and cognitive changes in living patients – at least the way I understand this proposal, a big part of the argument is that abnormal lactate levels LEAD to abnormal cognition – what is not clear is what mechanisms underlie abnormal lactate levels. Another somewhat puzzling statement relates to resting state fMRI for functional connectivity. I don't see how this measure would be used in this proposal. As it is written right now, the measure is not discussed in the statistics section. It is a bit unclear from statistical analysis for SA1 how the correlational analyses between MCCB and lactate will be conducted – as it is written it is not clear what lactate measure will be used – total lactate, lactate from a specific brain region? Given the applicants rationale for using three different brain regions, it would be interesting to see correlations with lactate from each of these regions.

1. Significance:

Strengths

- The in-depth study of bioenergetic abnormalities in SZ including the detailed profiles of both glutamatergic neurons and astrocytes models from iPSC derived from SZ patients has a great potential in advancing our understanding of how cellular energetic abnormalities result in system level abnormalities manifesting as cognitive dysfunction and clinical symptoms.
- The level of detailed, cutting edge analyses of bioenergetic function in SZ has rarely, if ever, been attempted.

Weaknesses

- Somewhat vague relationship between the exquisite cellular level details proposed to be assessed and cognitive/clinical consequences – it is regarded as understandable given a lack of real understanding how cellular level mechanisms translate into abnormal lactate levels.

2. Investigator(s):

Strengths

- This is an exceptionally strong team of investigators.

Weaknesses

- None identified.

3. Innovation:

Strengths

- Successful completion of the proposed studies will lead to important conceptual breakthroughs regarding how bioenergetic function is impaired in SZ brain.
- MRS for detection of lactate levels in three distinct brain regions in SCZ and controls is new.
- iPSCs derived from SZ patients has never been conducted.
- An enhanced iPSC model with state-of the-art specific cell type differentiation techniques, integration of mechanism and spatial information for biomarkers of SZ, and combination of multiple levels of analyses for addressing cellular heterogeneity represents the cutting-edge technologies for investigating biology of human complex diseases.
- The combination of laser microdissection and enzyme assays (SA3) is an innovative application of standard approaches.

Weaknesses

- None identified.

4. Approach:

Strengths

- Concerted focus on the mechanisms of bioenergetic abnormalities in SZ
- Use of multiple approaches to characterize the nature of bioenergetic abnormality on SZ
- Use of post-mortem models to confirm the findings from SA1 and SA2
- Improved integration of data across analytic levels

Weaknesses

- The role of rs-fMRI unclear
- The relationship between cognitive processes and cellular level mechanisms somewhat vague.
- The role of visual cortex as 'control region' unconvincing.

5. Environment:

Strengths

- Excellent environment in both University of Maryland and the Maryland Psychiatric Research Center (MPRC), as well as in the Emory University School of Medicine, for collaborator Dr. Wen.

Weaknesses

- None noted; The Principal Investigator described the plan for collaborating between the two institutions which sounds feasible and convincing.

Protections for Human Subjects:

- Acceptable Risks and/or Adequate Protections
- Acceptable subject protections are in place.

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 18: Including ages < 18 justified scientifically
- The selection of age 18-45 is appropriate for the proposal.

Vertebrate Animals:

- Not Applicable (No Vertebrate Animals)

Biohazards:

- Acceptable

Resubmission:

- The Principal Investigator was very responsive to Reviewers comments and came back with more focused, well designed study.

Resource Sharing Plans:

- Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3

Significance: 2
Investigator(s): 1
Innovation: 1
Approach: 4
Environment: 1

Overall Impact: This is a resubmission for an innovative multi-PI study of bioenergetics in schizophrenia, across levels of analysis, including in vivo quantification of lactate using MRS, cultured human neurons/astrocytes, and postmortem studies/bioinformatics. This enables the study of bioenergetics in schizophrenia across levels of analysis, including behavioral, circuit-based, cellular and molecular. The investigators are experts in each of these areas, including Rowland (MRS), Zhexing Wen (iPSCs) and McCullumsmith (postmortem/bioinformatics). There is a clear mechanistic framework, with bioenergetic dysfunction thought to impair synaptic plasticity, and hence macrocircuit function specifically in brain regions that have high energy demands during cognition. The investigators were responsive to reviewer suggestions, including definition of bioenergetic function, more focus on PV interneurons, shift from minibrains to human iPSCs, broader participant selection, focus on the neuron-astrocyte lactate shuffle, new functional scale, including sex in analyses, reduction of number of blood draws, provision of alternative strategies, new publication among Principal Investigator's, inclusion of thalamus, new pilot data for elevated lactate in ACC postmortem (not accounted for by meds, PMI or tissue pH). A minor point is that recruitment continues into Year 5, leaving little time for analysis. A larger concern is that there are only two sentences at the end that describe the integration of data across the three aims as "multidimensional correlations." Penalized regression with LASSO, sparse modeling, and machine learning/canonical correlations are specific statistical approaches that might be used to handle this large volume of data across the three studies, but as it stands, the analytics for the very important task of integrating the data remain largely unspecified.

1. Significance:

Strengths

- The project addresses the important problem of bioenergetics and its contribution to schizophrenia. Prior research supports this proposal and its level of rigor. The success of this study has important ramifications for therapeutics.
- The study is truly translational and enables the study of bioenergetics in schizophrenia across levels of analysis, including behavioral, circuit-based, cellular and molecular.
- There is a clear mechanistic framework, with the idea that bioenergetic dysfunction impairs synaptic plasticity, and hence microcircuit function, particularly in brain regions with high energy demands during cognition. The more specific mechanism tested is the neuron-astrocyte lactate shuffle.

Weaknesses

- The analytics for integrating the three aims remains underdeveloped.

2. Investigator(s):

Strengths

- Rowland is an expert in MRS.
- Zhexing Wen is an expert in iPSCs.

- McCullumsmith is an expert in bioinformatics/postmortem studies.
- The multiple Principal Investigators have presented together at conferences, and more recently published together.
- The multiple Principal Investigator leadership plan is well-described.

Weaknesses

- None noted.

3. Innovation:

Strengths

- The proposal to study bioenergetics across these different levels of analysis is highly innovative.

Weaknesses

- None noted

4. Approach:

Strengths

- The proposal has an approach and methodology suited to accomplish the three aims of in vivo imaging, analysis of iPSC's and postmortem studies, which are detailed enough that they should be reproducible.
- The proposal addresses potential problems and alternative strategies.
- The proposal evaluates key variables such as gender, and accounts for potential confounds, such as medications.
- The investigators were highly responsive to reviewers' suggestions to improve approach in this resubmission.
- Recruitment and retention plan are well-described.

Weaknesses

- Recruitment continues into Year 5, leaving little time for analysis.
- There are only two sentences at the end that describe the integration of data across aims as "multidimensional correlations." Penalized regression with LASSO, sparse modeling, and machine learning/canonical correlations are specific statistical approaches that might be used to handle this large volume of data across the three studies, but as it stands, the analytics for the very important task of integrating the data across aims remain largely unspecified.

5. Environment:

Strengths

- Excellent

Weaknesses

Protections for Human Subjects:

- Acceptable Risks and/or Adequate Protections

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

- Acceptable

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion Based on Age: Distribution justified scientifically

Vertebrate Animals:

- Not Applicable (No Vertebrate Animals)

Biohazards:

- Acceptable

Resubmission:

- Very responsive to all critiques. Only issue is that integration of the three aims remains largely unspecified in respect to analyses.

Resource Sharing Plans:

- Acceptable
- Will make iPSC lines available.

Authentication of Key Biological and/or Chemical Resources:

- Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE

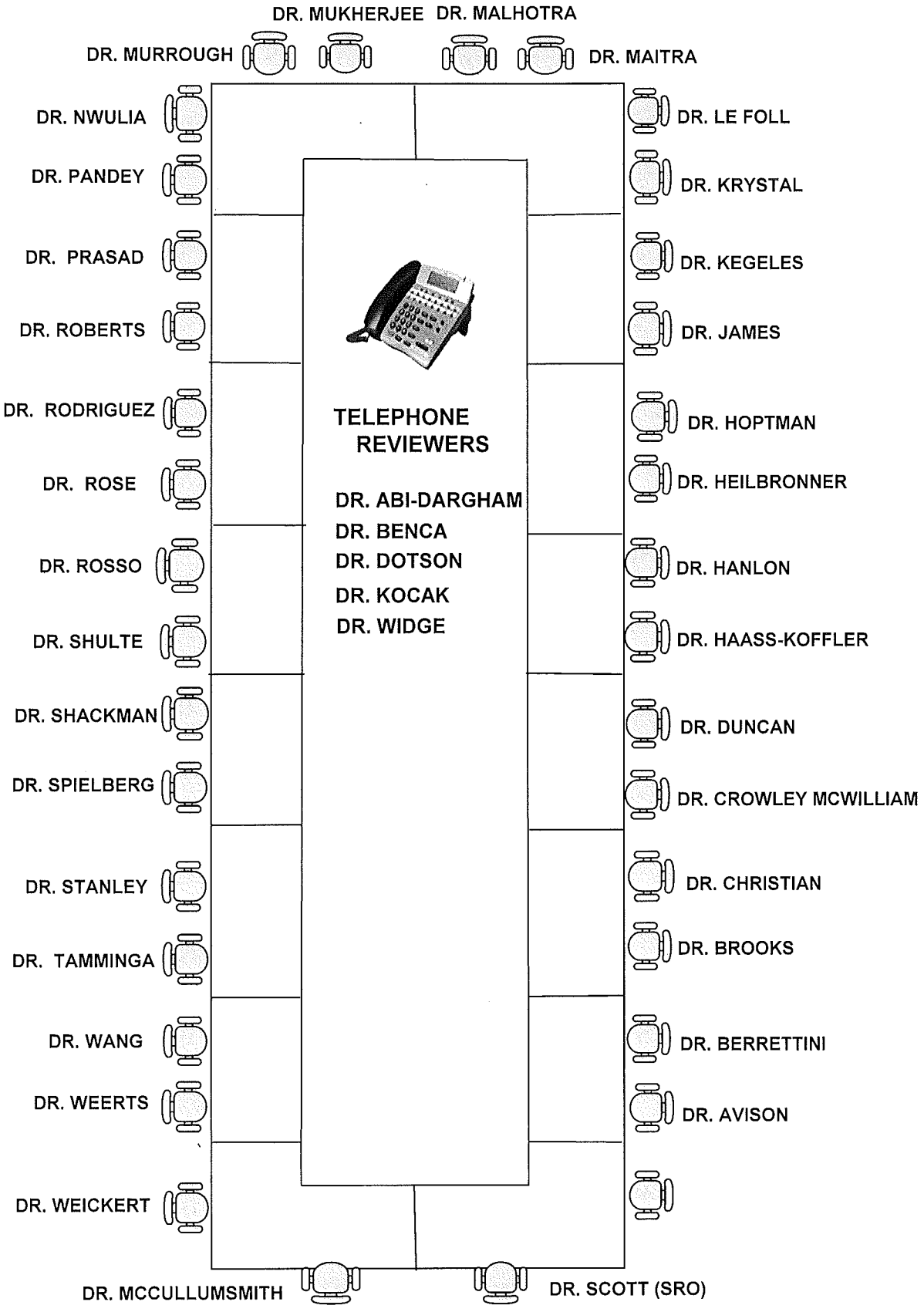
INCLUSION OF WOMEN PLAN: ACCEPTABLE

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

INCLUSION ACROSS THE LIFESPAN PLAN: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NEURAL BASIS OF PSYCHOPATHOLOGY, ADDICTIONS AND SLEEP DISORDERS (NPAS) STUDY SECTION
February 6-7-2020



MEETING ROSTER

Neural Basis of Psychopathology, Addictions and Sleep Disorders Study Section
Brain Disorders and Clinical Neuroscience Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
NPAS
Agenda Seq Num - 385353
02/06/2020 - 02/07/2020

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

Overall Impact:
The likelihood that a project will have a sustained and powerful influence on science (and/or clinical practice and/or technological developments?)

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

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

Evaluating Overall Impact:
Consider the 5 criteria: significance, investigator, innovation, approach, environment (weighted based on reviewer's judgment)

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

Opening Remarks: NPAS

WELCOME/INTRODUCTION:
Good morning, and welcome to the The Neural Basis of Psychopathology, Addictions and Sleep Disorders (NPAS) Study Section. On behalf of all of us at NIH, we thank you for your time and dedication to the peer review process. We'd like to thank our standing members, and the ad hocs who agreed, some on rather short notice, to make the time to participate.

LOGISTICAL ISSUES:

- Wireless EmbassyMtg (no password)
- Restrooms
- Coffee in the lobby, and water in the hallway
- Lunch – pre-ordered box lunches should be submitted by 10, otherwise on your own (lobby or elsewhere)
- Dinner at 7:30 – can still attend. $40 to Carlos, yes I take Venmo. Please do keep your reservation if possible.
- Request corrections to roster
- Date of next meeting: June 11-12 location TBD (preference for earlier in June; more advance notice going forward)

Go around the room for introductions – remember to use your microphones, for the benefit of reviewers participating by phone, and program staff listening in. Push to talk – please turn off.
Around the table – your name, institution, and a short statement about your research interests; Phone reviewers?
Also: CSR staff – our Extramural Support Assistant, Juan Carlos Keene, BDCN (Brain Disorders and Clinical Neuroscience) chief Sam Edwards.
Program Staff from various institutes are listening on the phone. They are the audience...

Certificate for Dr. Elise Weerts

CORE PRINCIPLES OF PEER REVIEW:

Confidentiality:

- No discussion should occur outside the meeting. Everything you've seen in the applications should be considered confidential (unpublished data). Printed materials into box that will be placed by the door.
- No discussion with the applicants or program officials. Your name is on a publicly available roster - if you are approached by a PI, simply decline to discuss the proceedings, and let the SRO know.
- Confidentiality is critical to the credibility of the review process; it protects both the applicant and the reviewer, and NIH takes it very seriously.

Conflict of Interest

- COI identified by now, esp. for assigned applications. But never too late to identify COI and recuse yourself. Simply step out, or if you are on the phone, we mute you (don't hang up).
- Pre-meeting COI form has been eSigned in IAR. (Also post-meeting COI forms). You can sign post when you're done (if leaving early)

Scientific Misconduct

- Plagiarism, falsification of data etc... Let me know in private. We will proceed with the review and deal with it afterwards.

My role as an SRO

- I am the Designated Federal Official charged with ensuring that scientific merit review is conducted fairly, and in accordance with NIH policy. Co-chair of this meeting and I am the government official that must be present to conduct review. While the Chair oversees the *scientific* discussion, the SRO controls the *process*.

REVIEW ESSENTIALS

1. Discussion Procedures

- No funding/payline during the discussion (or in critiques). We are here to rank applications on the basis of scientific merit.
- Discussion should be focused on whether/why the research proposed is worth doing and its potential to impact to the field.
- Significance and Overall Impact should be that of the specific project, not just the general area of research or disease that is covered by the application.
- Your score should reflect only what's in the application in front of you, and all of that application – don't score the application that it *could* be, if only that 3rd aim were fixed...

NIH initiative on enhancing reproducibility of research through Rigor and Transparency. Of course NIH has always recognized the

importance of scientific rigor, and this is not a new review criterion; instead, think of it as a framework to address **four key points** critical to the reproducibility of research findings:

- 1. First, we ask you to consider the **scientific foundation** forming the basis of the proposed research. "Premise" has been officially replaced by "rigor of the prior research", but the idea remains the same. The scientific foundation can be established through preliminary data (in an R01) and citations to peer-reviewed literature. This would fall under the Significance criterion.
- 2. Second, comment on the **Rigor** of the experimental design to obtain robust and unbiased results. This would fall under Approach.
- 3. Consideration of relevant biological variables, such as age and sex. This does not require studies to address sex differences explicitly, but both sexes should be included unless scientifically justified, and data should be disaggregated by sex. This would also fall under Approach.
- 4. Authentication of **key** biological and/or chemical resources (this a non-scorable issue). What is "key" is up to you, but anything that can be a source of variability: mouse lines, antibodies, etc.

It is important that the discussion (and your critiques) include comments on *rigor of the prior research*, and the degree of *rigor* of the experiment design, and SABV where relevant. It is our hope that increasing attention to rigor and transparency will translate to enhanced reproducibility of NIH funded-research.

- **NIH has *not* changed the review criteria by which applications are evaluated**. Your role remains to use your scientific judgement to identify the most promising, highest impact scientific research according to your individual weighting of the 5 NIH criteria (plus vertebrate animals, human subjects, and biohazards).

Translational studies versus basic research

- Still a misperception that NIH is primarily interested in applied research with translational/therapeutic potential rather than basic research with broad applicability and relevance.
- This is not the case. Unless it is a clear stated goal of an application, moderate or even limited relevance to human disease or limited translational potential of an otherwise highly significant topic does not automatically diminish overall impact.

Non-hypothesis driven

- A strong *scientific foundation* does not mean that an application must be hypothesis-driven. Discovery-based research is also important and should not automatically considered as a weakness.

Procedure

- Target time 15 min per applications. Perhaps a good idea to spend less time spent on applications where scoring range is very narrow.
- Reviewer 1 will introduce the application to the rest of the panel. Be concise when summarizing the purpose and hypothesis of the application, including the **rigor of the prior reseach.** Don't spend time with extensive description of the Aims, experimental design and details, etc. unless it informs on *Rigor* and therefore on your score.
- Good idea to move stepwise through the 5 review criteria with specific comments on the strengths and weaknesses. Aim to speak for about 5 minutes.
- Reviewers 2 and 3 should offer additional/complementary points on each of the 5 core review criteria and emphasize issues that inform the score. No need to repeat what has been said already, it's fine to say, "I agree".
- If you are very supportive of an application, please convey this opinion to the rest of the panel. Don't forget to focus on strengths not just weaknesses.
- Please do not forget to address Vertebrate Animals and Human Subjects during the discussion and before voting.
- Our Chair will then open the application for discussion: **try for consensus but not required**; try to delineate area of differences.
- Our Chair will then briefly summarize the main point of the discussion (what he has heard in term of weaknesses and strengths) and ask the assigned reviewers to state their final scores.

Discussion non-scorable issues:

- Plan for Authentication of *key* biological and/or chemical resources must be in place.
- Budget: if changes are recommended, we need to provide specifics to IC especially for non-modular budgets. Not sufficient to just say it is too high (or too low). Remember we can recommend changes in amount or time of support. Issues of scientific overlap with other projects may also be discussed at this point.

2. Scoring & Meeting Procedures

- **Score at IAR and also on your paper scoring sheet (in this case, the agenda) as a backup**
    - **97 applications in 6 clusters: Established PI R01s, NI R01s (Today); R61/33; R21, R03, and K awards tomorrow**

- Our target is to discuss ~ 50% of applications in each cluster. The order of review is not in score order within each cluster. Please don't let an application's position in the sequence bias your scoring.
- Preliminary scores are only preliminary. I am expecting that some scores of discussed applications (currently narrowly restricted in a limited scoring range) will change during the meeting, likely recalibrating downward to use more of the full scoring range.
- 1 is not forbidden and the scoring range 4, 5, 6, 7 is wide open for applications that are discussed. Cannot limit yourself to 2-4. DO NOT consider the preliminary scores that you've given to non-discussed applications to guide your scoring for discussed applications. Non-discussed applications WILL NOT receive an overall impact score. The wider the scoring range you use for discussed applications the better the panel is able to provide a clear ranking of discussed applications.
- Remember that you are doing here is ranking applications using percentiles that are calculated after the meeting using R01 scores over 3 review cycles (the previous two, and this one). You cannot use R21s, R03s to balance the distribution of scores. They have absolutely no impact on our panel's percentile.
- Absolutely OK to score outside of the range provided by the assigned reviewers. Please do not hesitate to do so, but not anonymously – I will ask for a show of hands, and provide a verbal count so that program staff knows how the panel is voting. You may be asked to provide a brief rationale if it is not obvious to the rest of the panel.
- Any reviewer can request an application to be "rescued" from the Not Discussed list and brought back to the table. BUT I would expect that you feel that this application would have a strong potential to end up with a competitive final score. **Please let me know as soon as possible if you'd like to bring an application up for discussion.**

Questions before I turn it over to the Chair?

New/Early Stage Investigators

- New investigator has not received prior R01-level support; ESI is within 10 years of their terminal degree. Consider career stage, less emphasis on preliminary results and more on research feasibility and potential. Premise must still be established, but they may rely on the literature more than preliminary data from their own lab.

After lunch Reminders:
Enter scores in IAR as we go
Established PI median score is 4, remember we can re-calibrate to use more of the range.
Double check the roster

End of Day 1:
Check IAR scores;
Room will be locked, you can leave papers.
Dinner

Tomorrow: 8 AM

Morning:

K01
Mentored Research Scientist Development Award (K01) is to provide support and "protected time" (three to five years) for an intensive, supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research independence.

Unlike R awards, we evaluate the research plan in the context of the candidate's career development goals and path toward independence. Rigor and transparency still apply, but Significance, Innovation, and Approach are all folded into a single criterion, under the Research Plan.

K08
Mentored Clinical Scientist Research Career Development Awards (K08) program is to prepare qualified individuals for careers that have a significant impact on the health-related research needs of the Nation. This program represents the continuation of a long-standing NIH program that provides support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience in the fields of biomedical and behavioral research, including translational research.

K23
NIH Mentored Patient-Oriented Research Career Development Award (K23) is to support the career development of individuals with a clinical doctoral degree who have made a commitment to focus their research endeavors on patient-oriented research.

K24
Midcareer Investigator Award in Patient-Oriented Research (K24) is to provide support to mid-career health-professional doctorates for protected time to devote to patient-oriented research (POR) and to act as research mentors primarily for clinical residents, clinical fellows and/or junior clinical faculty.

K25
Mentored Quantitative Research Career Development Award (K25) is to attract to NIH-relevant research those investigators whose quantitative science and engineering research has thus far not been focused primarily on questions of health and disease. The K25 award will provide support and "protected time" for a period of supervised study and research for productive professionals with quantitative (e.g., mathematics, statistics, economics, computer science, imaging science, informatics, physics, chemistry) and engineering backgrounds to integrate their expertise with NIH-relevant research.

R61/R33
R61/R33 Phased Innovation Award mechanism to support clinical research applications that are exploratory and developmental in nature and focus on understanding the neurobiological mechanisms underlying Substance Use Disorders (SUD), including fundamental brain function relevant to substance use.

R21s (and R03 Small Research Grant)
- R21 applications
    - The R21 grant mechanism is typically intended to promote exploratory/developmental research by providing support for the early and conceptual stages of a future project, e.g R01.
    - Can be high-risk high reward studies that may lead to a breakthrough in a particular area, or result in novel techniques, models or applications etc. Often riskier but risk is NOT a requirement.
    - NO ESI/NI.
    - No Preliminary data are required. Don't ask for it.... other ways to suggested weak prelim support: there no solid ground for the proposed experiments...premise is weak, not well justified...limited evidence in the literature... etc...
    - but if they are included they are subjected to evaluation. It is typically not a mini R01 but many institutes at NIH do not view this as a negative criterion for R21s. So my recommendation is to focus on the science on its potential impact to the field rather than second guessing if the proposed research is appropriate for the R21 program

R03
The NIH Small Research Grant Program supports small research projects that can be carried out in a short period of time with limited resources. This program supports different types of projects including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology.

4. Post-meeting
- Please ND/NP remaining applications
- Sign post-meeting COI forms in IAR
- Please leave your paper scoring sheets with ESA
- Drop any paper materials in the box for shredding; delete application pdfs (save critiques for 30 days)
- Please revisit your critiques - the **Edit Phase closes Tuesday morning at 9** AM
- You can revisit your individual criterion scores during the edit phase. There is no need to change your prelim impact score at IAR. Also, please make sure the value of your individual criterion scores reflect the text; e.g. a 4 or worse should have weaknesses, 3 or better, strengths.
- **Thank you, safe travels, and please provide feedback to me, or Sam Edwards at CSR. See you in June!**
- CHAIR & SRO: sign minutes

NIH Center for Scientific Review

STUDY SECTION CHAIR'S DISCUSSION CHEAT SHEET

1. **Announce application.** PI Name and Project Title

2. **Identify conflicts.** Wait until they leave the room or are put into an electronic subconference room

3. **Announce Assigned Reviewers.** Use Full Name for clarity

4. **Ask reviewers to state Preliminary Overall Impact Scores.** - specific to project

- **Reviewer 1:** Ask to describe Overall Impact, Significance, and Major Score-Driving issues **(4-5 minutes)**
- **Reviewer 2:** Anything to add or emphasize, focusing on overall impact, differences **(2-3 minutes)**
- **Reviewer 3:** Anything to add or emphasize, focusing on overall impact, differences **(2-3 minutes)**

5. **Open discussion.**

- Highlight the assessment of the Significance of the application
- Flesh out differences in opinion remembering consensus is not the goal
- Identify the panel's assessment of overall impact
- Make sure scores align with comments.

6. **Additional Review Criteria.** Prompt as appropriate.

- Human Subject Protections
  *For clinical trials only - ask if proposed Study Timeline is feasible and well justified. Ask about DSMP/DSMB.
- Inclusion of Women, Minorities, and Individuals Across the Lifespan
- Vertebrate Animal Protections
- Biohazards
- Resubmission/Renewal/Revision

MPI plan?

7. **Summarize key issues (should be brief and focus on main points)**

- Restatement of the panel's assessment of the Significance of the application
- Key score driving issues
- Major differences in opinion

8. **Final scores**

- Ask assigned reviewers to state final scores
- Ask if anyone wishes to score Outside the Range (& Why)? Outside Range?

9. **Budget and Other issues: Resource Sharing, Authentication of Key Biological and/or Chemical Resources, Select Agents, Foreign Justification (if applicable)**

10. **Ask Reviewers in conflict back into the room physically or electronically**
(Average discussion for an R01 application should be about 15 minutes.)