SUMMARY STATEMENT

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(Privileged Communication)

Release Date: **04/04/2021**
Revised Date:

Application Number: **1 F31 MH127951-01**

PENSACK,MAX
The Trustees of Columbia University in the City of
3227 Broadway, L6, Quad 6A
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Review Group:	**ZRG1 F02B-E (20)** **Center for Scientific Review Special Emphasis Panel** **Fellowships: Sensory and Motor Neuroscience, Cognition and Perception**
Meeting Date:	**03/04/2021**
Council:	**MAY 2021** ***PCC:*** **7K-TGNBF**
Requested Start:	**07/01/2021**

Project Title:	**Behavioral flexibility and the geometry of neural representations in hippocampus and prefrontal cortex**
	***Requested*: 3 Years**
Sponsor:	**SALZMAN, C. D**
Department:	**Neurobiology and Behavior**
Organization:	**COLUMBIA UNIVERSITY HEALTH SCIENCES**
City, State:	**NEW YORK NEW YORK**
SRG Action:	**Impact Score:54 Percentile:55 +**
Next Steps:	**Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects:	**10-No human subjects involved**
Animal Subjects:	**30-Vertebrate animals involved - no SRG concerns noted**

1F31MH127951-01 Pensack, Max

RESUME AND SUMMARY OF DISCUSSION: In this predoctoral fellowship application, the PI proposes training while investigating the underlying neurophysiology that gives rise to important types of behavioral flexibility such as, rapid context-dependent adjustments in behavior, using a non-human primate (NHP) model. The primary weakness cited by reviewers of this ambitious proposal was that the PI failed to provide evidence of the progress he has made in training the monkey to learn a challenging task that is critical to the success of the project. This raised concerns about the feasibility of the project and diminished overall enthusiasm for the research plan, which was otherwise described as a novel approach with the potential to offer fundamental insights about the neural representation of behavioral flexibility. In addition, although reviewers were highly impressed by the PI's strong scholastic record, his modest record of scientific productivity led to concerns about his ability to transform his rich research experience into publications. The PI's sponsor and co-sponsors were regarded as highly accomplished and well-established scientists with a superb track record of scientific productivity and mentoring trainees. In addition, the mentoring team was viewed to offer the complementary expertise necessary for the PI to accomplish their training goals, and the sponsor was noted to have adequate funds to support the proposed research. The training plan was regarded as well rounded, given the addition of several valuable technical skills such as electrophysiology to the candidate's repertoire, along with opportunities to develop non research skills such as grant writing. However, the plan was noted to lack formal training in advanced data analysis and statistical methods that were considered as crucial for the geometry analysis described in the proposal. For some reviewers, these concerns were somewhat mitigated by the solid mentoring team, while for others, the PI's track record of scientific productivity, the limited demonstration of his progress, and gaps in the training plan, deflated overall training potential. After extensive debate, an enduring mixture of opinions ultimately offset the panel's enthusiasm. Thus, final ratings from the panel were in the modest range for the foundation that this predoctoral training proposal will provide for a future career in studying the neural basis of psychiatric disorders.

DESCRIPTION (provided by applicant): We live in a world that is constantly changing. In order to pursue goals and survive in such a complex environment, one cannot rely on learned stimulus-response associations alone. Rather, we require behavioral flexibility – the ability to rapidly adjust actions and expectations in response to changes in internal and environmental variables. Our ability to engage in flexible behavior breaks down under conditions of stress and in the setting of many neuropsychiatric conditions, including addiction, anxiety, mood, and psychotic disorders. This project aims to characterize the underlying neurophysiology that gives rise to two important types of behavioral flexibility: Type 1, rapid context-dependent adjustments in behavior, and Type 2, rapid decision-making in novel conditions through generalization from past experiences. These types of flexibility make distinct demands on neural representations. The dorsolateral prefrontal cortex (DLPFC) and hippocampus (HPC) are thought to contribute to both types of flexibility but delineating each area's unique computational role has proved difficult. The overarching hypothesis of this grant is that neural representations of variables – considered as the pattern of activity in a population across experimental conditions - must exhibit a particular geometry to support the two types of behavioral flexibility. I will test this hypothesis by comparing the geometry of representations during correct and incorrect behavior on certain trial types. By elucidating the neural basis of flexibility in HPC and DLPFC, this project provides a foundation for understanding the neural basis of deficits seen in stress and neuropsychiatric illness, paving the way for the development of future treatments.

PUBLIC HEALTH RELEVANCE: Pursuing goals in a complex environment requires behavioral flexibility – the ability to rapidly adjust actions and expectations in response to changes in internal and environmental variables. Deficits in flexible behavior are seen in nearly all psychiatric conditions,

including addiction, anxiety, mood, and psychotic disorders. The experiments outlined in this proposal will examine how the geometry of neural representations in the hippocampus and dorsolateral prefrontal cortex correlates with behavioral flexibility in healthy monkeys, laying the groundwork for the development of future psychiatric treatments.

CRITIQUE 1

Fellowship Applicant: 2
Sponsors, Collaborators, and Consultants: 2
Research Training Plan: 3
Training Potential: 2
Institutional Environment & Commitment to Training: 2

Overall Impact/Merit: This is a well written proposal by a promising MD/PhD student in the Neurobiology and Behavior graduate Program at Columbia University, requesting three years of support. The PI is currently enrolled in Columbia's Postbaccalaureate Premed Program and currently assembling his thesis committee to pursue a PhD degree in neuroscience.

The proposed project investigates neuronal mechanisms of flexibility in behavior by investigating neuronal activity in the dorsolateral prefrontal cortex (DLPFC) and the hippocampus in rhesus monkeys. The PI differentiates two types of flexibility: Type 1 is the rapid adjustment of behavior when changes in a familiar context occur. Type 2 uses generalization of past experience to make decisions in a novel context. In Aim 1 two contexts are paired with four stimuli, creating 8 potential combinations and corresponding responses. A learned signal indicates a 50% probability that a change in context will occur in the next trial and the PI argues that the monkey will generate neuronal representations of all 8 possible outcomes, predominantly in the DLPFC and that this will be reflected in the SD measure of neuronal activity. In Aim 2 two new contexts will be introduced and one of the four stimuli will be withheld in training and only presented for the first time with a novel context. This condition tests for generalization and the PI expects hippocampal neuronal activity during the novelty trials to correlate strongly with CCGP.

The sponsor's lab has developed the measures of the "geometry" of neuronal population activity and differentiated two general types: Shattering-geometry (SG) and cross-condition generalization performance (CCGP). The geometry measure is derived from an expression of population activity based on firing rate in an n-dimensional space, with each dimension corresponding to one neuron. Each complex pattern corresponding to a context-stimulus condition results in a single point in this space. SD and CCGP differ in the spatial relationship between the points representing different context-stimulus combinations and how they are separable within the n-dimensional space. The PI proposes to apply the neuronal geometry analysis to the neuronal data collected during Type 1 and 2 flexibility tasks and hypothesizes that Type 1 flexibility correlates more with SD geometry and Type 2 with CCGP.

The behavior is challenging and the PI states that training with monkeys has begun and first signs of successful context switching learning are seen. However, no preliminary data are shown nor are prior published studies using similar paradigms discussed. The lack of training for the PI regarding the complex data analysis is another concern. Will the applicant be fully competent in applying the geometry analysis or limited to running existing algorithms?

All in all, this is a well written project which, if successful, could provide important new insights into neuronal coding, decision making and behavioral flexibility. Training opportunities for the candidate are very good, especially since work with primates is a very rare skill. However, there are concerns regarding feasibility and training of the PI in the crucial but complex data analysis.

1. Fellowship Applicant:

Strengths

- High school valedictorian and recipient of several awards and honors.
- Extensive prior research experience.
- Co-author on one abstract, one peer-reviewed publication.
- Teaching experience abroad (2 years in Japan) shows spirit of adventure and open mindedness.
- Excellent scholastic performance with mostly As and some Bs.
- Provided a very well written description of the research plan.

Weaknesses

- None noted

2. Sponsors, Collaborators, and Consultants:

Strengths

- Sponsor Dr. Salzman is a well-established leader in the field, well-funded and productive.
- Salzman has a good track record as a mentor, with several mentees now in independent academic positions.
- Co-sponsor Dr. Fusi brings complementary expertise and is a well-funded and well-established investigator.

Weaknesses

- Training plan could be more specific. Mostly mentions that the PI “will continue” ongoing training without going into specifics.

3. Research Training Plan:

Strengths

- Addresses a fundamental question of neuronal representation of flexibility and decision making in primates.
- Application of a novel data analytical approach to a new and promising set of combined electrophysiological and behavioral data.
- Work with primates is an increasingly rare and sought-after skill.

Weaknesses

- There is a concern regarding the feasibility of the behavioral training as the tasks are rather complex.
- It is unclear whether and how the PI will be trained in statistics/data analysis relevant for the geometry analysis.

4. Training Potential:

Strengths

- Primate electrophysiology combined with complex behavioral training.
- Cutting edge data analytical tools.

Weaknesses

- Lack of specific description of training for the geometry analysis is a concern.

5. Institutional Environment & Commitment to Training:

Strengths

- The training environment at Columbia University is excellent.

Weaknesses

- None noted

Protections for Human Subjects:

Not Applicable (No Human Subjects)

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

Inclusion Plans:

- Sex/Gender:
- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion Based on Age:

Vertebrate Animals:

YES, all criteria addressed

- All criteria adequately addressed.

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Courses.

Comments on Subject Matter (Required):

- All relevant subjects covered.

Comments on Faculty Participation (Required):

- Faculty participates.

Comments on Duration (Required):

- 2 hrs./course for one semester.

Comments on Frequency (Required):

- Required refresher every 4 years.

Applications from Foreign Organizations:

Not Applicable

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Acceptable

- Adequate plan provided.

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Fellowship Applicant: 4
Sponsors, Collaborators, and Consultants: 1
Research Training Plan: 6
Training Potential: 4
Institutional Environment & Commitment to Training: 1

Overall Impact/Merit: This application comes from a student with an unusual career trajectory. He started in philosophy and theater and then as a teacher abroad. His interests in mind/brain issues brought him back to academia. He first participated in a post-bac program where he started doing research. The experiences are varied and have ranged from electrophysiology to non-human primate (NHP) work. All his training has been at Columbia where his sponsor is a well-stablished researcher (Salzman). From all the different research experiences, there are two publications where he is a co-author. These publications are more on clinical reports and methodology. His co-sponsor is a theoretical neuroscientist (Fusi) who has a strong collaboration with Salzman. There is a concern of how many technical and theoretical skills the applicant will learn, as opposed to only use them. He shows interest in computational/theoretical aspects which should require more than one course and lab interactions to become proficient in. The scientific objective of this proposal is to study the neuronal base of behavioral flexibility in NHPs. He will study context-dependent and generalization in novel conditions behaviors while recording from areas of the brain that might be involved in these tasks. The research is of interest in the field of decision making and could greatly contribute to the training of the

applicant. However, there are concerns regarding his contributions to the development of the project, and how this training will then be incorporated in his MD education.

1. Fellowship Applicant:

Strengths

- Varied experiences and exposure to different research techniques.

Weaknesses

- Not clear to me why the applicant chose to go to Japan to learn about NHP electrophysiology while there is so much work at his home institution. The applicant says this was a rotation, but he was not part of the PhD program at that time, he was in an MD program.
- There are many changes in research trajectory that do not allow me to understand the type of research the applicant wants to pursue.
- It is not clear what the position of the applicant is with respect to the MD program. He is not in a PhD/MD training program, but rather in both independently. There is no indication of how he wants to re-join the MD program after he finishes his PhD.

2. Sponsors, Collaborators, and Consultants:

Strengths

- The sponsor and co-sponsors are currently collaborating and form a strong team.

Weaknesses

- None noted

3. Research Training Plan:

Strengths

- The applicant will learn how to perform research in wake behaving NHP and use machine learning to decode the neuronal activity being recorded.

Weaknesses

- There is some discussion that the applicant uses MonkeyLogic-Matlab to program behavioral tasks. However, there is no evidence of how the applicant will gain skills to program his own analysis algorithms.
- There is a lack of formal training in statistics and advanced methods in data analysis and programming.

4. Training Potential:

Strengths

- There is an enormous training potential in NHP electrophysiology.

Weaknesses

- Given the non-STEM background of the applicant, the theoretical training is not enough to gain insight into the sophisticated tools used in the project.
- Not clear how he will combine his PhD with his MD training, which are independent.

5. Institutional Environment & Commitment to Training:

Strengths

- Columbia is a leading neuroscience place with very strong support for student development.

Weaknesses

- None noted.

Protections for Human Subjects:

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

Inclusion Plans:

- Sex/Gender:
- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion Based on Age:

Vertebrate Animals:

YES, all criteria addressed

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- One semester in first year of PhD program.

Comments on Subject Matter (Required):

- Not described.

Comments on Faculty Participation (Required):

- 14 faculty.

Comments on Duration (Required):

- One semester.

Comments on Frequency (Required):

- Weekly, 14 sessions.

Applications from Foreign Organizations:

Not Applicable

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Unacceptable

- There is no description of releasing any data with the analyst to the increasing number of repositories.

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3

Fellowship Applicant: 3
Sponsors, Collaborators, and Consultants: 1
Research Training Plan: 4
Training Potential: 2
Institutional Environment & Commitment to Training: 1

Overall Impact/Merit: Max Pensack is an MD/PhD candidate and a polymath with impressively broad academic and research history and interests. Although his academic record is strong (good grades at an excellent school), his publication record in research is thin, perhaps due to his jack-of-all-trades tendencies preventing the duration of work to complete some research. The proposed research would employ a nice combination of experiments and theory: non-human primate experiments and population-geometry computational methods. The work would illuminate the neural basis of behavioral flexibility. The proposed work is very exciting and likely to generate substantial advances in basic cognitive systems neuroscience. The public health relevance is indirect, but potentially interesting. The sponsor (Salzman) and co-sponsor (Fusi) are superb choices, uniquely suited to the research goals and clearly describing training plans and involvement specific to Pensack. Pensack is on a good starting track, learning challenging experiment techniques in monkeys and challenging theoretical tools. The proposal would have been stronger if some of the preliminary data – mentioned, but not shown – was included as a more solid demonstration of skills already obtained.

Protections for Human Subjects:

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

Inclusion Plans:

- Sex/Gender:

- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion Based on Age:

Training in the Responsible Conduct of Research:

Comments on Format (Required):

Comments on Subject Matter (Required):

Comments on Faculty Participation (Required):

Comments on Duration (Required):

Comments on Frequency (Required):

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

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:

VERTEBRATE ANIMALS: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 F31 MH127951-01; PI Name: Pensack, Max Jacob

+ Derived from the range of percentile values calculated for the study section that reviewed this application.

NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.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.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
Fellowships: Sensory and Motor Neuroscience, Cognition and Perception
ZRG1 F02B-E (20)
03/04/2021 - 03/05/2021

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

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