

Response Form for the Final Performance Review Report*

1. Name of Grantee: Carnegie Mellon University
2. Year of Grant: 2008 Formula Grant

A. For the overall grant, briefly describe your grant oversight process. How will you ensure that future health research grants and projects are completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) are submitted to the Department in accordance with Grant Agreements? If any of the research projects contained in the grant received an “unfavorable” rating, please describe how you will ensure the Principal Investigator is more closely monitored (or not funded) when conducting future formula funded health research.

Grant oversight for this award consisted of each PI reviewing the individual annual reports from funded investigators to assess yearly research progress and monthly financial reviews by the PI with the cognizant Carnegie Mellon Business Manager for this award to ensure that expenditures tracked the budget.

The Carnegie Mellon Office of Sponsored Programs tracks reporting deadlines and assists with compliance.

* Please note that for grants ending on or after July 1, 2007, grantees' Final Performance Review Reports, Response Forms, and Final Progress Reports ***will be made publicly available on the CURE Program's Web site.***

Project Number: 0862701
Project Title: Mellon Institute Vivarium - Research Infrastructure
Investigator: Gilman, Frederick

B. Briefly describe your plans to address each specific weakness and recommendation in Section B of the Final Performance Summary Report using the following format. As you prepare your response please be aware that the Final Performance Review Summary Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

Reviewer Comment on Specific Weakness and Recommendation (*Copy and paste from the report the reviewers' comments listed under Section B - Specific Weaknesses and Recommendations*):

Response (*Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts*):

Reviewer 1:

Ensure that a qualified laboratory animal veterinarian is involved in the design process of future vivarium renovation or construction. These individuals have thorough knowledge of regulatory requirements and animal needs and are vital to this process.

Response:

We actually did have consultations by local animal veterinarians. CMU doesn't currently have enough research involving animals to warrant a staff veterinarian. We did consider, but were not successful in obtaining NIH support.

Reviewer 2:

The proposal, progress, and final reports were well written and complete for an infrastructure project.

Response:

None

Reviewer 3:

None

C. If the research project received an "unfavorable" rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive "unfavorable" ratings.

Response:

D. Additional comments in response to the Final Performance Review Report (OPTIONAL):

Response:

Project Number: 0862702
Project Title: Computational and Neural Basis of Visual Inference
Investigator: Olson, Carl

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Response (*Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts*):

Reviewer 1:

1. Greater emphasis on the translational aspect of the work is recommended, with greater attempts to identify partners who can facilitate translation of the findings into human populations.

Response:

The PI has established a collaboration with a clinical group at the University of Pittsburgh Department of Psychiatry. This group, headed by Dr. Raymond Cho, uses EEG to study brain function in healthy humans and those with neuropsychiatric disorders. One project, now complete, demonstrated that phenomena observed in monkey studies conducted with TS support also occur in humans. The paper is under review.

2. Emphasis on enhancements in infrastructure is desirable, including leveraging of funds for facilities improvements.

Response: Duly noted.

3. Expansion of the research program to include permanent personnel would be desirable, which might require leveraging of Pennsylvania funds with other grant monies.

Response: Duly noted.

4. From the point of view of Pennsylvania, community involvement would be desirable in developing lines of work which are of direct interest to the local communities in Pennsylvania. There does not appear to have been thought given to such issues.

Response: Duly noted.

5. Greater emphasis on dissemination is recommended, including publications and conference presentations.

Response: Duly noted.

Reviewer 2:

1. A weakness is that there is little specific interaction between the computational and neurophysiological branches of the project. The potential to combine such approaches is great, and the research outcomes demonstrate how strong the researchers are in such domains. I recommend that the research team emphasize studies where computational and neurophysiological approaches are combined, or where specific predictions or principles that arise from one domain are directly applied to the other.

Response:

Computational and neurophysiological studies tend to be carried out independently but we strive to bring them into register. To the degree that the PI has mainly neurophysiological expertise and the co-PI has mainly computational expertise, one way in which to achieve register is through active collaboration. The PI and the co-PI have at this point established an active collaboration that will culminate in at least one joint publication. This collaboration involves recording from V2 with multiple chronically implanted electrodes while monkeys undergo statistical learning of a sort known from our prior studies to produce strong changes in IT.

2. It is unclear why the proposed neurophysiological study was not undertaken. It appears particularly appropriate to the project objectives.

Response:

This was a tactical decision based on feasibility. The ideal way in which to carry out this experiment is with simultaneous chronic recording in V1, V4 and IT. We have successfully accomplished simultaneous chronic recording in a single area but not in multiple areas. We are in process of designing a system for multiple areas. This approach is at the cutting edge in our field.

Reviewer 3:

1. The most major weakness is that very little direct research has been carried out for Aims 1 and 3, and only modest progress has been reported for Aim 2.

Recommendation: A much greater amount of direct work needs to be carried out on each of three original aims to justify this project. If the original aims are now considered overly ambitious or certain difficult/insurmountable problems emerge, then these problems should be openly discussed. A proposal with modified aims would need to provide a clear rationale and justification for any proposed changes to the aims.

Response:

See response to Reviewer 2, Comment 2.

2. A second major weakness is the lack of evidence of direct collaboration between the PI and co-PI. Based on the progress report, it appears that the two research groups are pursuing their independent research programs and conducting the types of experiments that they would otherwise carry out in the absence of this collaborative grant.

Recommendations: Regular meetings (e.g., monthly) between the two researchers and their labs should be implemented to foster a better integrated and interdisciplinary project. A specific set of goals and attainables for improving integration of the experiments, data, and analytic approaches should be clearly spelled out; and progress on attaining those targets should be evaluated throughout the project, if continued funding occurs.

Response:

The two laboratories have weekly joint meetings. See response to Reviewer 2, Comment 1.

3. Another weakness is that Aim 3 of the project seemed overly ambitious yet vague. There was minimal specification of how specific goals and experiments would be carried out; and there was no description of how data recorded from various levels of the visual hierarchy (V1, V4, IT) would be combined or analyzed to test specific hypotheses, such as feed forward or feedback interactions between these recorded areas. The proposal also lacked a strategic plan for how the experiments and data would be integrated across the two research groups to facilitate the collaborative goals of the proposed research. The lack of specific experiments, designs, and collaborative strategic planning has led to a vague and overly ambitious aim with no clear road map.

Recommendation: Revise Aim 3 to include a more clearly articulated set of plans and experiments with specific achievable goals.

Response:

Duly noted. See response to Reviewer 2, Comment 2.

4. A final weakness is that the current funds have been used to provide partial support for the PI, co-PI and administrative staff. However, these funds could be used to attract new talent to the research institution and to foster the training of pre- and post-doctoral trainees.

Recommendation: Re-budget the project to enhance the support of new trainees and to attract new talent to the institution.

Response:

Duly noted. It is worth mentioning that the PI and co-PI do support a considerable group of pre-doctoral and postdoctoral researchers.

5. Of note also is that many of the cited publications are only tangentially related to the original aims of the grant proposal.

Response:

Duly noted.

C. If the research project received an “unfavorable” rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive “unfavorable” ratings.

Response: This project was given an overall review of outstanding.

D. Additional comments in response to the Final Performance Review Report (OPTIONAL):

Response: We take note below of weaknesses and recommendations made by the reviewers with the qualification that, inasmuch as the project is complete, we cannot act on the recommendations in the body of project.

Project Number: 0862703
Project Title: Memory-Based Neural Activity in the Hippocampus
Investigator: Touretzky, David

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Response (*Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts*):

Reviewer 1:

1. They need to publish findings from Result 2.

Response:

As explained in our final report, further work on the model showed that by relaxing the assumption that LTP does not occur when the pre-synaptic and postsynaptic cells' firing *crosses* a theta cycle, the learning of both forward and backward sequences can be obtained using ordinary STDP (spike-timing dependent plasticity). Thus, the phase gradient along the longitudinal axis of the hippocampus may not be a prerequisite for backward sequence learning as we originally thought. If that is the case, then our simplified model is so straightforward it does not seem to us to be an advance over earlier LTP-based models of sequence learning. On the other hand, if further experimental work shows that LTP *cannot* occur across a theta cycle, then the hippocampal phase gradient might be necessary for backward sequence learning, but certain other technical difficulties arise, acknowledged in our original manuscript, that would have to be resolved before the model was fully satisfactory. We do not at present know a good way to resolve these difficulties. For this reason, we decided to devote our remaining time to additional statistical analyses of the experimental data rather than further work on the model. However, the modeling results we did obtain are reported in Anoopum Gupta's doctoral thesis.

2. They needed to articulate clear next steps as a follow-up to their interesting work.

Response:

We continued to work on analysis of the experimental data and published a second journal paper, in Nature Neuroscience:

Gupta, A. S., van der Meer, M. A. A., Touretzky, D. S., and Redish, A. D. (2012)
Segmentation of spatial experience by hippocampal theta sequences.
Nature Neuroscience, 15(7):1032-1039

Dr. Gupta has completed his M.D. degree and is currently doing a residency in neurology.

Dr. Touretzky is presently focusing on his other major research area, cognitive robotics, and therefore has not pursued further computational neuroscience funding. He hopes to return to computational neuroscience work at some point in the future.

Reviewer 2:

Excellent training program and facilities.

Response:

We appreciate the positive feedback.

Reviewer 3:

Although the overall progress made was excellent, the modeling component was less successful than it could have been. I would encourage Dr. Touretzky to consider all of the assumptions made in the models to identify broader classes of models that could explain the data.

Response:

We agree with this reviewer's observation in Section A that "The absence of a deep understanding of the actual learning rules *in vivo* makes developing well-constrained and testable models very difficult." Modelers are frequently forced to make simplifying assumptions when the true anatomical or physiological facts are not yet known. STDP is a useful abstraction for current modeling efforts, but the real synaptic learning story is admittedly more complex, and not yet well understood.

As explained in our response to Reviewer 1, if we assume that STDP can cross theta cycles, the sequence learning results we reported can be explained by a straightforward (but abstract) synaptic learning model. To replace this with a more physiologically realistic version of synaptic learning would be an interesting path to pursue, but progress might be limited by the rate at which new experimental data become available. We do not have the expertise to perform such experiments ourselves. Given the limited time and resources available before Dr. Gupta left for his residency, we chose to focus our efforts on further analyses of the experimental data, which resulted in a Nature Neuroscience paper.

C. If the research project received an "unfavorable" rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive "unfavorable" ratings.

Response:

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