Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Carnegie Mellon University

2. **Reporting Period (start and end date of grant award period):** 1/1/10 – 12/31/13

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Jim Osborn

4. **Grant Contact Person's Telephone Number:** 412 268-6553

5. **Grant SAP Number:** 4100050890

6. **Project Number and Title of Research Project:**

   Project 2: Understanding Schizophrenia Through Logical and Empirical Analysis

7. **Start and End Date of Research Project:** /1/10 – 12/31/13

8. **Name of Principal Investigator for the Research Project:** Wayne W. Wu, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $538,215

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Wu, Wayne	Associate Professor	61%	$281,759
Dorney, Barbara	Administrative Associate	12.5%	$ 27,605
Stupka, Melissa	Program Coordinator	12.5%	$ 24,000

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Cho, Raymond	Assistant Professor, Psychiatry	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
n/a		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No_____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
n/a	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No__X_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

We believe that our analysis has led to concrete testable hypotheses about the cortical areas that are the sources of AVH. The next step is to carry out experiments to test these hypotheses.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No____X_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This grant contributed to the university's ability to attract and hire Dr. Wu.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No_____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No_____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The specific aims of this project were:

Specific Aim 1: To test the resultant model of automaticity in cortical network activations during resting state EEG in association with auditory verbal hallucinations (AVH) in schizophrenia subjects with a high degree of AVH.

Progress made on aim 1:

These aims were best hypotheses based on our understanding of AVH at the time of the initial proposal. However, as a result of our discussion, we believe that the best set of experiments are outlined in our discussion below, including stimulation and depression of auditory cortical activity during AVH. We have suggested different predictions to test our model as against the standard self-monitoring model. Accordingly, we did not believe it to be

useful during this period to proceed with the specific proposal. Ray Cho, as well, is leaving the University of Pittsburgh, and as he has the clinical and experimental expertise, there was some slowing of our experimental aims as he needed to sort out his new academic position.

However, our hope is in the next stage to begin targeted experiments using a transcranial magnetic stimulation protocol to test the involvement of auditory processing in the generation of AVH, given that we have now identified concrete differences between the two models. These differences have never been articulated in the literature, and we believe that careful conceptual analysis and inquiry has allowed us to state an experimental goal to understand the underlying basis of AVH.

Indeed, our analysis suggested to us that a simple way to test the model was to make specific predictions about what the phenomenology of AVH should be like. That is, what is the daily experience of AVH for patients? In particular, we surmised that patients who engage in a dialog with their AVH using inner speech provide difficult cases for many forms of self-monitoring. Indeed, we believe that there are likely patients whos inner speech is concomitant with their AVH. Our empirical approach, then, has shifted to first going back to the patients, understanding their experiences, and extracting from that data that can be used to test models. Again, we have felt that starting from the ground up, with a clear theoretical view of the issues but also going back to the patient data (reports of AVH) provide a solid basis for more significant experimental interventions.

Specific Aim 2. To test the resultant model of automaticity in cortical network activations during an auditory stimulation EEG paradigm for schizophrenia subjects with high versus low degrees of AVH.

Progress made on aim 2: We believe that we are in a position to address this specific issue. Certainly, patients with high versus low degrees of AVH will be an interesting sub population to probe.

As in the case of Aim 1, we firmly believe that an adequate theoretical understanding that involves concrete hypotheses, contrasting alternatives, and specific predictions that can test those alternatives is crucial to doing well-informed and likely to be successful experimental interventions. Our initial proposals, while good guesses based on the current state of the literature, were insufficiently concrete to justify the use of limited resources, including patient time and experimenters effort. We feel confident now that the conceptual framework is in place to allow us to ask targeted questions, where answers will allow us to differentiate the two main alternatives we have investigated theoretically.

The aim of the project was to take firm steps towards understanding the underlying mechanisms for two positive symptoms in schizophrenia: auditory verbal hallucination and thought insertion. The concrete steps are: (1) to provide a **conceptual analysis** of the concepts of relevance to formulating theories of the symptoms and their mechanisms and (2) on the basis of that conceptual clarification, to provide **mechanistic proposals** and concrete recommendations for **experimental tests**. We have taken steps in respect of auditory verbal hallucination (AVH). As thought insertion is a more complex and likely heterogeneous

phenomena that has been less well studied (and hence provides less data to begin with), we opted to focus our efforts on AVH.

Conceptual analysis is crucial to formulating adequate theories and hypotheses. Its aim is to provide clear, concrete and consistent definitions of fundamental concepts. Where concepts are not clear, the theories and questions that are posed using them will be equally unclear. Conceptual analysis is especially crucial when talking about *conscious experience* such as AVH. Our approach has been driven by the need to carefully listen to patients and their reports of their phenomenology to inform this analysis.

1. **Patient reports of their phenomenology are of critical important to building and testing adequate models of AVH.**

What is the basis of AVH? As noted in the proposal, a common model for AVH, and indeed for many of the positive symptoms, is the *source*- or *self-monitoring model*. The basic idea is intuitive as applied to AVH: patients are themselves the sources of the voices that they experience, yet they lose track of the source or self-generated basis of these voices. When they lose track of the voices, they experience them as alien, belonging to another. This *description* of the aberrant experience is perfectly accurate, yet it underdetermines the nature of the *mechanism* of AVH. What is true at the level of one's experience might not be reflected at the level of the underlying mechanism.

We believe that the description of conscious experience in AVH makes it seem to theorists studying AVH that its mechanism must also involve self-monitoring. Such theorists then notice that there are similar self-monitoring mechanisms postulated in the domain of motor control. These mechanisms involve the use of *corollary discharge* or *efference copy* signals of the motor command. The general idea is that when the motor system produces a signal that moves the body, there is a correlated signal that carries that same information to "self-monitoring" mechanism whose function it is to make predictions of the outcomes of those commands. Such self-monitoring mechanisms have been fruitfully applied to understanding how the motor system generates accurate and fluid movements and how the visual system compensates for saccadic eye movements so that the world does not look to be moving. These points are not in dispute. What is in dispute is whether the description of AVH phenomenology as failed self-monitoring means that the AVH mechanism involves failed self-monitoring, namely the failure of mechanisms similar to those used in the motor domain but applied to the experience of audible voices. It is important to see, however, that there are *two concepts of self-monitoring* used by theorists: a general one used to describe conscious experience that all theorists of AVH can agree to and a mechanistic one used in the motor control literature. These notions of self-monitoring are not the same.

2. **Inferring the mechanism of failed self-monitoring from the description of AVH consciousness as failed self-monitoring is a faulty inference that trades on two notions of self-monitoring.**

It is an open *empirical question* whether AVH is the result of faulty self-monitoring in the motor control sense (that is the sense in which "self-monitoring" will be used). In the motor control literature, the mechanism involves corollary discharge signals that are used in crucial computations needed for generating movement or for keeping the visual world stable when the eyes move. But what does this have to do with *auditory experience of voices*?

The extrapolation of mechanisms for motor-control to the domain of auditory hallucination is a significant one that is not obvious. That leap might be made more plausible by postulating that AVH is the result of *inner speech* that is not adequately self-monitored, and indeed, that is a very common version of the self-monitoring approach to AVH. The idea is that the patient generates inner speech (talking to oneself in one's head) that is not adequately self-monitored. Since the self-monitoring mechanism fails, the inner speech is not recognized as self-generated. As it is speech and yet taken as not self-generated, then it must be "other"-generated. This leads to AVH. We think this is a reasonable hypothesis, yet we also believe that there is substantial evidence against it. Here, attention to the lived experience of AVH is crucial.

It is important to analyze the nature of normal inner speech mechanisms and several features make themselves apparent:

A) Inner speech is in *one's own voice* with its voice properties.
B) Inner speech is *often not auditory* in nature (in many, it is felt more *'motorically'*).
C) Inner speech often does not show degrees of (audible) *intensity*
D) Inner speech is located within the head.

But if we listen to patients and their experiences of AVH, we can contrast different properties.

a) AVH is almost always of another's voice with its voice properties (e.g. gender).
b) AVH is (by definition) *auditory*
c) AVH involves *different degrees of intensity*
d) AVH is sometimes *located externally*.

The contrast between the two cases raises a challenge for inner speech models of AVH, namely that it is not enough to postulate that the patient's inner speech is misattributed due to defective self-monitoring. *In addition*, inner speech models have to explain the striking transformations of normal inner speech experience to the peculiarities of AVH. For example, how does inner speech, usually in one's own voice with its properties, get transformed into another's voice with its properties (e.g. pitch and timbre associated with gender). So, at a minimum, appeal to defective self-monitoring is not enough to explain the transformed phenomenology of AVH.

3. The inner speech version of the self-monitoring model leaves unexplained how specific AVH phenomenology arises from inner speech.

Our analysis emphasizes that there is a large explanatory hurdle that such models face and which, strikingly, they have largely not confronted. Yet it is the phenomenology of AVH that distinguishes it from other positive symptoms. A crucial feature of the symptom is left unexplained.

Once one focuses on the phenomenology, further challenges arise. Specifically, *many patients respond to their AVH with inner speech*. Here is a sample dialog with one patient that we have interacted with (patient OC with AVH):

> **AVH**: Oh you're going to let him get away with that (this voice is apparently speaking to another entity about OC)
> **OC**: God loves them too
> **AVH**: I got you a 100 times (taunting OC that it affected OC somehow)
> **OC**: yeah, you did.
> **OC**: Judge not and you wouldn't be judged (paraphrased from bible)

The critical point here is that this is a dialog involving interplay between AVH and the patient's inner speech. It is hard to explain this plausibly on the inner speech model of AVH. Recall that AVH is inner speech that is not self-monitored. That is, the normal self-monitoring mechanism is broken. But in this patient, the dialog requires that the self-monitoring mechanism oscillate between being broken and operating normally perfectly in time with a mundane back and forth pattern in a dialog. While this is not impossible, it is highly implausible that the mechanism goes on and off in time with the give and take of a conversation. There are, indeed, other cases of such dialogs that we have discovered in conversation with patients and they provide evidence against inner speech models of self-monitoring.

4. **The dialogs patients often have with their AVH via inner speech are difficult to explain plausibly with the inner speech version of the self-monitoring model.**

In addition, we are currently speaking to more patients to see if their AVH and inner speech *overlap in time*. If this occurs then this might be *fatal* to the inner speech model for the self-monitoring mechanism would have to be *on and off at the same time*: on to explain the subject's own inner speech and simultaneously off to explain the subject's AVH. But this is logically impossible, assuming there is a single self-monitoring mechanism. There are some suggestions by a few patients that indicate this possibility, but we will need to investigate this more directly.

Accordingly, we conclude that if one were to endorse a self-monitoring approach to AVH, the most plausible substrate for AVH is not inner speech. There is a natural alternative, namely that the substrate for AVH is auditory imagination of a voice that is not adequately self-monitored. By moving the substrate for AVH away from inner speech toward auditory imagination, we can (a) explain the distinctively auditory phenomenology of AVH because auditory imagination of a voice has similar phenomenology (one can imagine someone else's voice at different intensities saying different things) and (b) one can explain the dialog involving AVH and inner speech responses.

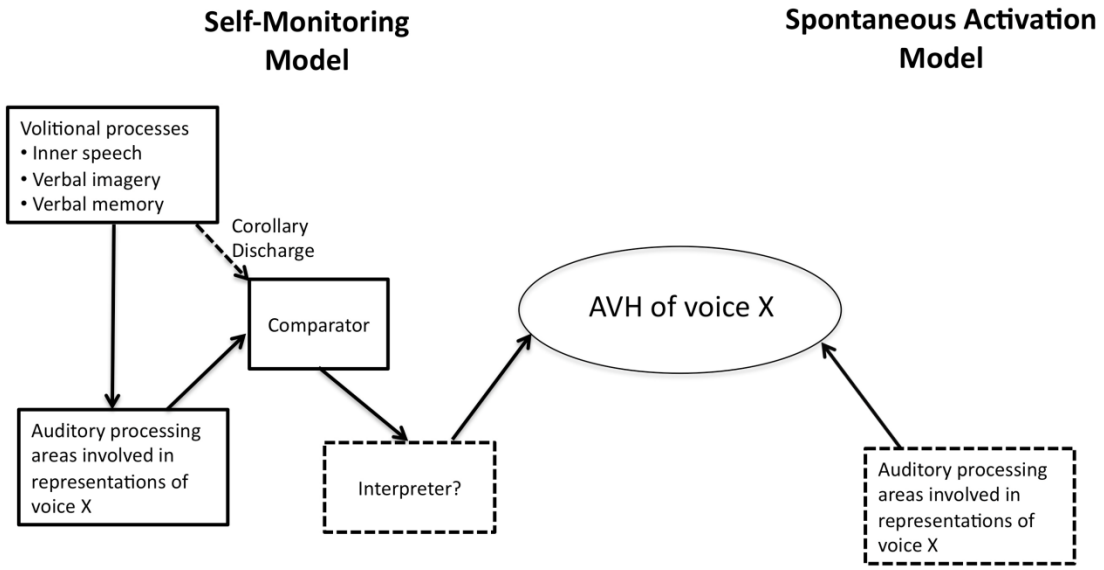
5. **The most plausible self-monitoring model of AVH invokes auditory imagination of a voice and not inner speech as a substrate.**

Notice that these conclusions, backed by analysis of the phenomenological reports of AVH patients and of the conceptual analysis of the implications of self-monitoring accounts are substantive. We have done away with the more abstract and inchoate talk of failed self-monitoring at the level of conscious experience in favor of tying it to a more plausible interpretation of self-monitoring mechanisms in respect of auditory imagination. This is why we contend that conceptual analysis has an important role to play in understanding AVH.

We are not, however, self-monitoring theorists of AVH because there is a more plausible alternative: AVH arises from the *spontaneous-activation* of relevant auditory representations of speech. Both the auditory imagination based self-monitoring model and the spontaneous-activation account that we endorse agree that auditory representations of speech play a central role in explaining AVH. However, they fundamentally disagree on the mechanism. For self-monitoring theorists, AVH is the result of failed top-down control mechanisms, specifically self-monitoring while for spontaneous-activation accounts, it is the overactivity of auditory areas that leads to AVH. Put another way, the self-monitoring account has the subject initiating a round of auditory imagination and losing track of that imagination as self-generated and hence as AVH; the spontaneous activation account has the subject as in fact passive, but with an overactive auditory system that spontaneously generates auditory experiences that are hallucinations. The former then requires a faulty top-down signal; the latter does not.

6. **Spontaneous activation accounts of AVH deny that AVH results from a top-down signal initiating an internal episode with defective self-monitoring; rather, it postulates the spontaneous generation of that episode.**

We can think of the two as differing on whether AVH is top-down or bottom-up in its source. The differences between the two accounts are given in the following figure which demonstrates how much more loaded the self-monitoring account is.



It is also important to see that there is a *proof of concept for the spontaneous activity account* but not for the self-monitoring account. That is, we know from surgical interventions by Wilder Penfield that stimulation of auditory cortex elicits auditory hallucinations of voices. This shows that spontaneous activation (i.e. activation not due to the subject) is sufficient for AVH like symptoms. At the same time, there has not been a similar proof of concept for self-monitoring accounts of AVH. For this reason, we think that the spontaneous activation account should be the *default model* for AVH.

7. **As there is a proof of concept for spontaneous activation accounts of AVH but not for self-monitoring accounts, the spontaneous activation account should be the default model of AVH.**

Of course, this does not demonstrate that the self-monitoring account is false. That is an empirical matter, but the goal of conceptual analysis is to clear the geography of the issues so that we can identify experimental avenues to assess both proposals. The science of AVH would benefit from confronting alternative possibilities and testing them.

One more conceptual point needs to be made, namely some of the evidence that is often given in favor of the self-monitoring account. It has been amply demonstrated in motor tasks that patients with schizophrenia do seem to have defective self-monitoring in correcting motor behavior. We do not dispute this, but we emphasize that this does not provide evidence for the self-monitoring account as *against the spontaneous activation account.* The reason is apparent from the diagram: the absence of self-monitoring is *fully consistent* with the spontaneous activation account, since it does not postulate the deployment of the self-monitoring mechanism. Another way of putting this point: both models we are considering do not require the proper functioning of self-monitoring to explain AVH. On the self-monitoring account it is the absence of or defective self-monitoring that explains (in part)

AVH; on the spontaneous activation account, it is the bottom-up activity of sensory areas (independent of self-monitoring) that yields AVH. On both, normal self-monitoring is absent.

How then can we test these models? Our conceptual work has led to concrete proposals for experimental tests to dissect which model is in play. It is worth emphasizing that both might be true (they are not mutually inconsistent), but this can only be determined by explicit experimental work.

There are many experimental directions that we have detailed in Cho and Wu (2013) and which are provided in the following three tables focusing on proof of concept studies, on testing the self-monitoring mechanism, and on testing the spontaneous activity account. We believe that in seeing the conceptual landscape in this way will improve our grappling with the mechanisms of AVH.

Table 1. AVH Mechanisms: Proof of concept studies

Intervention	Possible Outcomes	Commentary
Disrupt self-monitoring during inner speech	AVH of one's own inner voice (does not reproduce typical schizophrenia AVH)	To date, there have been no reports in the literature of such experiments for self-monitoring.
Disrupt self-monitoring during auditory imagery	AVH of imagined voices	As above.
Stimulate auditory cortices	AVH with typical phenomenology	There are relevant cases for stimulation of auditory cortices, e.g. neurosurgical studies (Penfield & Perot, 1963); 'naturalistic studies' (epilepsy; Elliott et al 2009)

Table 2. AVH Mechanisms: Testing Self-monitoring Account in Schizophrenia

Intervention	Possible Outcomes	Commentary
Disrupt self-monitoring	Worsening of existing AVH Increase in types of experienced AVH (e.g. inner speech).	As self-monitoring posits loss of function, it is unclear that disruption of self-monitoring during discrete AVH episodes provides relevant outcomes. Further disruption of self-monitoring should lead to increase in AVH, but with predicted expansion of the type of AVH experienced (e.g. inner speech).
Remediation of monitoring deficits	Decrease in frequency of AVH	An ideal intervention of targeted remediation of self-monitoring during discrete AVH episodes in patients is currently unavailable.

Table 3. AVH Mechanisms: Testing Spontaneous Activity Account in Schizophrenia

Intervention	Possible Outcomes	Commentary
Inhibition of sensory cortex during discrete AVH episodes	AVH decrease	Demonstrates that a modulation of auditory cortical activity correspondingly modulates AVH severity
During quiescent non-AVH period, stimulation of same cortical region shown to be sensitive for inhibition of AVH	AVH with complete phenomenology	As above.
Generalized inhibition of sensory cortex	Decrease in AVH frequency	Hoffman et al (2003, 2005) have implemented generalized inhibition, demonstrating overall decrease in frequency of AVH A stronger test would be cortical inhibition during discrete AVH episodes as above

We shall mention one experiment here in more detail that we hope to undertake in the near future to test a prediction of the spontaneous activation model, namely the reliance of activity in relevant sensory areas. Our prediction then is that if these sensory areas are disrupted

during AVH, the result will also be disrupted AVH. At the same time, if these sensory areas are activated, whether during or outside of AVH episodes, there will a corresponding activation or exacerbation of AVH. Such suppression and activation of neural activity can be induced by transcranial magnetic stimulation (TMS) of sensory areas. TMS provides a less expensive and non-invasive way of testing the spontaneous activity account. If the results are as predicted, the minimal conclusion would be that sensory areas are critical in the generation of AVH, as the spontaneous activation account suggests.

8. **TMS stimulation of sensory areas can provide a test of spontaneous activity accounts: suppression of these areas during AVH might attenuate the symptom while activation of these areas might exacerbate the symptom.**

A more general therapeutic approach to AVH using TMS has been taken by Ralph Hoffman (Yale University), and we believe that probing the mechanism of AVH via TMS might open avenues for the development of new therapies that target such hallucinations.

As noted, we opted not to pursue this conceptual approach for thought insertion as yet. That symptom is highly complex and in many ways elusive. An important first step will be to gather more phenomenological reports from patients on thought insertion in an effort to delineate the structure of this symptom, one that involves the paradoxical attribution of one's own thought to another. A central issue regarding thought insertion will be whether the self-monitoring account or the spontaneous activation account provides a better explanation of the symptom. These are matters we hope to pursue as well as we aim to begin experimental work on AVH.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?
_____Yes
___X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?
_____Yes
___X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
____X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
____X__ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Explaining Schizophrenia:	Wayne Wu	Mind and Language		☐Submitted ☐Accepted ■Published

Auditory Verbal Hallucination and Self-Monitoring				
2. Mechanisms of auditory verbal hallucination in schizophrenia	Raymond Cho Wayne Wu	Frontiers: Psychiatry	July 25, 2013	☐Submitted ☐Accepted ■Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X_____ No_____

If yes, please describe your plans:

We believe that additional data from patient reports has bearing on our understanding of the mechanisms of AVH. We are currently interviewing patients to gather data relevant to assessing inner speech self-monitoring models of AVH. We hope to submit this in the near future.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No__X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

Wayne Wu is associate professor in and associate director of The Center for the Neural Basis of Cognition (CNBC), Carnegie Mellon University. He received his BS in biology from the Massachusetts Institute of Technology in 1991 and then did his graduate work in Molecular and Cell Biology at the University of California, Berkeley where he worked on protein-protein interactions and structure-function relations in gene regulatory proteins with Peter Schultz, then in the Department of Chemistry. He was a Howard Hughes Medical Institute Predoctoral Fellow and received his MA in Molecular and Cell Biology in 1993. He then changed fields and began studying philosophy including work at the University of Pittsburgh, the University of Oxford (U.K.) and ultimately receiving his PhD in Philosophy from the University of California, Berkeley in 2005. Wu was an assistant professor in the Philosophy Department at The Ohio State University from 2006-10 and then moved to his present position at Carnegie Mellon University.

His work aims to connect relevant empirical work to long-standing philosophical questions about the mind, consciousness and agency. This includes a careful analysis of the philosophical issues so that they can more clearly engage with relevant empirical experiments in psychology and neuroscience. This has led to his collaborations with other scientists on agency, schizophrenia, and visually guided action. His research interests include: (a) the nature of human agency; (b) the visual computations needed for guiding motor behavior; (c) the nature of attention and its role in agency; (d) the function of the primate cortical visual systems in agency and in consciousness; (e) elucidating central but ill defined concepts in cognitive science; and (f) schizophrenia.

As associate director of the CNBC, Wu has played a central role in providing opportunities for scientists doing research at all levels of analysis to come together and share their ideas and results. This integrated approach holds the best hope of making progress in cognitive science. His bridge-building activities include organizing discussion groups such as working groups on attention that involved many faculty, post-doctoral researchers and graduate students, and constituting a recent CNBC panel on the state of the art of vision science where nearly 100 participants engaged in a discussion about current challenges in our understanding of vision. Such bridge building, as evidence in his collaboration with Raymond Cho, detailed in this report, is a further illustration of his work connecting different levels of analysis in the understanding of the mind and brain.

BIOGRAPHICAL SKETCH

NAME Raymond Cho, M.D., M.Sc.	POSITION TITLE Assistant Professor of Psychiatry
eRA COMMONS USER NAME CHORY1	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Toronto, Toronto, Ontario, Canada	BS	1987-1989 1993-1995	Biology, Physics Mathematics
University of Toronto, Toronto, Ontario, Canada	MD	1989-1993	Medicine
University of Toronto, Toronto, Ontario, Canada	MSc	1995-1997	Physiology/Neuroscience
University of Pittsburgh, Pittsburgh, PA	Residency	1998-2002	Psychiatry
Princeton University, Princeton, NJ	Doctoral Program	1999-2000, 2002-2003	Psychology

A. Personal Statement

The goal of this study is to investigate mechanisms of auditory verbal hallucinations. The main focus of my research is understanding basic mechanisms of cognitive control and their impairments in schizophrenia, using neuroimaging, EEG/MEG and computational approaches. I have been collaborating closely with Dr. Wayne Wu in investigations of mechanisms of auditory verbal hallucinations. My clinical background as medical director of the STEP (Services for the Treatment of Early Psychosis) Clinic and clinical neuroscience research expertise provide a synergistic complement to Dr. Wu's philosophical and cognitive expertise.

B. Positions and Honors

Positions and Employment

2002- Assistant Professor, Department of Psychiatry, University of Pittsburgh
2002- Attending Physician, Comprehensive Care Services, Western Psychiatric Institute and Clinic
2003- Associate Director of Clinical Core, Conte Center for Neuroscience of Mental Disorders
2003- Associate Director, Clinical Cognitive Neuroscience Laboratory, University of Pittsburgh
2004- Medical Director, STEP (Services for the Treatment of Early Psychosis) Program
2005- Faculty, Center for the Neural Basis of Cognition, University of Pittsburgh/Carnegie Mellon University
2008- Assistant Professor, Department of Psychology, University of Pittsburgh
2011- Assistant Professor, Department of Neuroscience, University of Pittsburgh
2013- University of Pittsburgh IRB member

Other Experience and Professional Memberships

2002- Member, Society for Neuroscience
2003- Member, Organization for Human Brain Mapping
2004- Member, Cognitive Neuroscience Society
2009- Member, Society of Biological Psychiatry
2010- Associate Member, American College of Neuropsychopharmacology

Honors

1995-97 National Sciences and Engineering Research Council of Canada Postgraduate Scholarship
1997-98 K. M. Hunter Foundation Research Fellowship
1999 APIRE/Janssen Scholars in Research on Severe Mental Illness

2000 APA Kempf Fund Award for Research Development in Psychobiological Psychiatry
2000 NIMH Outstanding Resident Award
2002 APA/Lilly Psychiatric Research Fellowship
2002 Pittsburgh Psychiatric Society Resident's Award
2002 Awardee of Program for Minority Research Training in Psychiatry Fellowship
2002 Resident Golden Apple Teaching Award
2002 McLaughlin Award
2002 Selectee for EU Advanced Course in Computational Neuroscience
2003 NARSAD Young Investigator Award
2004 NARSAD Constance and Stephen Lieber Scholar
2005 APIRE/Astra-Zeneca Young Minds in Psychiatry Award
2005 NARSAD Young Investigator Award
2007 Eighth Biennial Mt. Sinai Conference on Cognition in Schizophrenia Travel Award
2010 University of Pittsburgh School of Medicine Award for Excellence in Clinical Precepting
2010 NCDEU New Investigator Award

C. Selected Peer-reviewed Publications

Cho RY, Nystrom LE, Brown ET, Jones AD, Braver TS, Holmes PJ, Cohen JD: Mechanisms underlying performance dependencies on stimulus history in a two-alternative forced choice task. *Cogn Affect Behav Neurosci* 2(4), 283-299, 2002. PMID 12641174

Kerns JG, Cohen JD, MacDonald AW III, Cho RY, Stenger VA, Carter CS: Anterior cingulate conflict monitoring predicts adjustments in control. *Science* 303, 1023-1026, 2004. PMID 14963333

Cho RY, Ford JM, Krystal JH, Laruelle M, Cuthbert B, Carter CS: Functional neuroimaging and electrophysiology biomarkers for clinical trials for cognition in schizophrenia. *Schizophr Bull* 31: 865-869, 2005. PMID 16166611

Cho RY, Konecky, RO, Carter, CS: Impairments in Frontal Cortical Gamma Synchrony and Cognitive Control in Schizophrenia. Proceedings of the National Academy of the Sciences, 103: 19878-19883, 2006. PMID 17170134

Lewis D, Cho RY, Carter CS, Eklund K, Forster S, Kelly, M, Montrose, D: Subunit-selective modulation of GABAA receptor neurotransmission and cognition in schizophrenia. *American Journal of Psychiatry:* 165(12), 1585-93, 2008. PMID 18923067

Cho RY, Orr JM, Cohen JD, Carter C S. Generalized signaling for control: Evidence from post-conflict and post error performance adjustments. *Journal of Experimental Psychology: Human Perception and Performance*: Aug:35(4):1161-77, 2009. PMID 19653756

Kieffaber PD and Cho RY: Cortical Gamma-band Oscillations Reflect Cognitive Control Elicited by Implicit Probability Cues in the Preparing to Overcome Prepotency (POP) Task. *Cognitive, Affective and Behavioral Neuroscience* 10 (4), 431-40, 2009.

Takahashi T, Cho RY, Mizuno T, Kikuchi M, Murata T, Takahashi K, Wada Y: Antipsychotics reverse abnormal EEG complexity in neuroleptic-naive schizophrenia: A multiscale entropy analysis. *Neuroimage:* 51(1), 173-82, 2010.

Forster SE, Carter CS, Cohen JD, Cho RY: Parametric Manipulation of the Conflict Signal and Control-State Adaptation. *Journal of Cognitive Neuroscience:* 23(4), 923-35, 2011.

Frankle WG, Cho RY, Mason NS, Chen C, Walker C, Lewis DA, Mathis CA: [11C]flumazenil binding is increased in a dose-dependent manner with tiagabine induced elevations in GABA levels. *Plos One*: 7(2), e32443, 2012.

Komek K, Ermentrout GB, Walker, C, Cho RY: Dopamine and gamma band synchrony in schizophrenia: Insights from computational and empirical studies. *European Journal of Neuroscience*: 36(2), 2146-2155, 2012.

Richard, A.E., Carter, C.S. Cohen, J.D., Cho, RY. Persistence, diagnostic specificity and genetic liability for context-processing deficits in schizophrenia. *Schizophrenia Research:* 147(1):75-80, 2013.

Cho, R.Y., Walker, C., Polizzotto, N.R.**, Wozny, T., Fissell, K., Chen, C., Lewis, D.A. (in press). Development of sensory cortical gamma oscillations and cross-frequency coupling from childhood to early adulthood. Cerebral Cortex.

Cho, R.Y., Wu, W. (2013). Mechanisms of auditory verbal hallucination in schizophrenia. Frontiers in Psychiatry 4:155. doi: 10.3389/fpsyt.2013.00155.

Forster, S., Cho, R.Y.* (in press). Modulation of Control Within and Across Tasksets: Context Specificity of Post-conflict and Post-error Adjustments. PLOS ONE.